REVIEWS AND NOVEL CLINICAL PERSPECTIVES ON SEMAGLUTIDE: A GLP-1 RECEPTOR AGONIST WITH BOTH INJECTABLE AND ORAL FORMULATIONS

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REVIEWS AND NOVEL CLINICAL PERSPECTIVES ON SEMAGLUTIDE: A GLP-1 RECEPTOR AGONIST WITH BOTH INJECTABLE AND ORAL FORMULATIONS

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EDITORIAL
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Editorial: Reviews and Novel Clinical Perspectives on Semaglutide: A GLP-1 Receptor Agonist With Both Injectable and Oral Formulations

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Editorial on the Research Topic

Reviews and Novel Clinical Perspectives on Semaglutide: A GLP-1 Receptor Agonist With Both Injectable and Oral Formulations

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The potential of glucagon-like peptide-1 (GLP-1) as a therapeutic target in type 2 diabetes (T2D) was first realized with the discovery that GLP-1 plays a key role in augmenting insulin secretion in response to nutrient intake (1). Subsequently, GLP-1 receptor agonists (GLP–1RAs) have been shown to increase insulin and decrease glucagon secretion in a glucose-dependent manner, resulting in reduced blood glucose levels, but with a low risk of hypoglycemia. GLP-1RAs also improve multiple pathophysiological defects in T2D beyond glycemic control, including reduction of body weight. Several cardiovascular (CV) outcomes studies have also shown that some GLP-1 RAs, namely liraglutide, semaglutide, and dulaglutide, can effectively prevent CV events, such as acute myocardial infarction or stroke, and associated mortality (2).

Although GLP-1RAs act *via* the same overall mechanism, they vary structurally and in their pharmacokinetic and clinical effects. Early GLP-1RAs needed to be administered subcutaneously (s.c.) once or twice daily. To reduce the injection burden and improve convenience, molecules and formulations were modified to create GLP-1RAs that require less frequent administration. Semaglutide is one such long-acting GLP-1RA – it shares 94% sequence homology with GLP-1, but three structural modifications extend its half-life to ~1 week, which permits once-weekly s.c. administration (3, 4).

An oral GLP-1RA formulation may be preferred by some patients; however, oral delivery of peptides is difficult due to extensive degradation by proteolytic enzymes in the gastrointestinal tract and poor absorption across the gastrointestinal epithelium. By co–formulating semaglutide with the absorption enhancer, sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC), a novel oral formulation of semaglutide has been developed. SNAC protects semaglutide against enzymatic degradation *via* a local pH buffering effect and promotes absorption of semaglutide across the gastric epithelium in a concentration-dependent manner by effects on transcellular pathways, which are transient and fully reversible (5). The long half-life of semaglutide helps maintain exposure in the event of any variation in day-to-day absorption of the oral formulation.

This Research Topic discusses the efficacy, general safety, CV effects, and additional clinical perspectives related to semaglutide, in both its s.c. and oral formulations. The review article by Meier describes data on glucose-lowering and body-weight reductions from the SUSTAIN and PIONEER global clinical trial programs that established the efficacy of s.c. and oral semaglutide, respectively, in a range of clinical settings. Factors that may influence the choice of formulation in individual patients are also discussed. In the SUSTAIN and PIONEER programs, s.c. and oral semaglutide were well tolerated, with a long-term safety profile consistent with other GLP−1RAs. The most common adverse events and selected adverse events of interest are described by Smits and Van Raalte, alongside a discussion of mechanistic studies.

The CV safety of s.c. and oral semaglutide have been confirmed in specific CV outcomes trials. The review article by Nauck and Quast summarizes data on CV safety and discusses mechanisms responsible for the CV benefits seen with some GLP-1RAs, including semaglutide, with particular focus on effects related to reversing atherosclerosis, inflammation, and endothelial dysfunction.

Although early use is advocated by international diabetes guidelines, GLP-1RAs are often underutilized. The article by Gallwitz and Giorgino reviews the current place of GLP−1RAs in therapy, and recommendations by medical and scientific societies such as the American Diabetes Association and the European Association for the Study of Diabetes. In addition, the article highlights some clinical considerations related to the use of semaglutide, such as dosing considerations, use in special populations, and ongoing large-scale studies that will add to the evidence base of s.c. and oral semaglutide in T2D, and potentially contribute to new indications.

AUTHOR CONTRIBUTIONS

The authors were involved with drafting and/or critically reviewing all drafts during the development of the article, and provided final approval for submission. All authors contributed to the article and approved the submitted version.

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REVIEW
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Cardiovascular Safety and Benefits of Semaglutide in Patients With Type 2 Diabetes: Findings From SUSTAIN 6 and PIONEER 6

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To exclude an excess risk of cardiovascular (CV) events, CV outcomes trials (CVOTs) have assessed the effects of new glucose-lowering therapies, including glucagon-like peptide-1 receptor agonists (GLP-1RAs), in patients with type 2 diabetes and established CV disease or CV risk factors. The CV safety of semaglutide vs. placebo, when added to standard care, was evaluated in the SUSTAIN 6 trial for the formulation administered once-weekly subcutaneously and in PIONEER 6 for the new once-daily oral formulation. In SUSTAIN 6 and PIONEER 6, both powered to demonstrate noninferiority (upper 95% confidence interval [CI] of the hazard ratio [HR] <1.8), there were fewer first major adverse CV events with semaglutide vs. placebo, with HRs of 0.74 (95% CI 0.58–0.95) and 0.79 (0.57–1.11), respectively. In SUSTAIN 6, the results were significant for noninferiority and superiority, although the latter was not prespecified. Surprisingly, CV and all-cause mortality were significantly reduced by oral semaglutide in PIONEER 6. The ongoing SOUL CVOT will further inform about CV outcomes with oral semaglutide vs. placebo (NCT03914326). Findings from SUSTAIN 6 and PIONEER 6 fall within the spectrum reported with other GLP-1RA CVOTs: noninferiority vs. placebo for major CV events was seen with lixisenatide and exenatide extended-release, while superiority was demonstrated with liraglutide, albiglutide, and dulaglutide. Beneficial outcomes have been recognized in international guidelines, which recommend subcutaneous liraglutide, semaglutide, and dulaglutide to reduce the risk of CV events in high-risk patients. Both indirect mechanisms *via* risk factor modification and direct effects *via* GLP-1 receptors in the CV system have been proposed to be responsible for CV event reductions. The exact mechanism(s) remains to be characterized, but appears to be mainly linked to anti-atherosclerotic effects. Further research is needed to elucidate the relevant mechanisms for CV benefits of GLP-1RAs.

Keywords: glucagon-like peptide 1 receptor agonist, type 2 diabetes, cardiovascular, safety, semaglutide

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INTRODUCTION

Independent of other conventional risk factors, diabetes confers an approximately two-fold increased risk for cardiovascular (CV) disease (CVD) compared with individuals without diabetes (1). The elevated risk of CVD begins at fasting glucose levels below the cut-off point for diabetes (<7 mmol/L [126 mg/dL]) and increases with increasing glucose levels (1). Approximately one-third of all individuals with type 2 diabetes (T2D) are or will be affected by CVD and it is a major cause of mortality, accounting for around half of all deaths (2).

Previously, concern was raised about the CV safety of glucose-lowering treatments for T2D, leading the US Food and Drug Administration to issue guidance for industry to ensure that evaluation of new therapies excluded an excess in CV risk (3). Since then, several CV outcomes trials (CVOTs) have been conducted, either with approved medications or with agents in development as part of the regulatory process.

In large prospective, randomized clinical trials, the CV safety of glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs) was studied in comparison with placebo (both on a background of standard care); either neutral effects or reductions in CV events have been reported (4–10). The present article will review the Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) 6 trial and the Peptide InnOvatioN for Early diabEtes tReatment (PIONEER) 6 trial, which were designed to evaluate the CV safety of subcutaneous and oral semaglutide, respectively (6, 10). For reference, the effects of other GLP-1RAs on CV events will also be compared. Potential mechanisms explaining reductions in CV events with GLP-1RAs in general, and with semaglutide in particular, will be discussed.

SUSTAIN 6 – ESTABLISHING THE CARDIOVASCULAR SAFETY OF SUBCUTANEOUS SEMAGLUTIDE

The preapproval SUSTAIN 6 trial aimed to prove noninferiority of subcutaneous semaglutide as compared with placebo for the primary endpoint of time to the first occurrence of a major adverse CV event (MACE), which was defined as death from CV causes, nonfatal myocardial infarction (MI), or nonfatal stroke (6). The trial was designed such that noninferiority of subcutaneous semaglutide to placebo was confirmed if the upper bound of the 95% confidence interval (CI) of the hazard ratio (HR) for the primary endpoint was below 1.8 (ruling out an 80% elevation in risk with an error margin of 5%). The trial was both time-driven (minimum duration of 104 weeks) and event-driven, with at least 122 primary outcome events needed for sufficient power to determine noninferiority.

SUSTAIN 6 was conducted in patients with T2D with HbA_{1c} >7% and at high risk of CV events, defined as: i) aged ≥50 years with established CVD (previous CV, cerebrovascular, or peripheral vascular disease), chronic heart failure (HF) (New York Heart Association [NYHA] class II or III), or chronic kidney disease (CKD) stage ≥3; or ii) aged ≥60 years with at least one CV risk factor (persistent microalbuminuria or proteinuria, hypertension with left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction, or an ankle–brachial index <0.9) (6).

Patients were randomized (1:1:1:1) to receive either 0.5 mg or 1.0 mg of once-weekly subcutaneous semaglutide or volume-matched placebo in addition to their standard care for 104 weeks (6). A fixed-dose escalation procedure was used to minimize the gastrointestinal adverse events seen with GLP-1RAs, with a starting dose of subcutaneous semaglutide of 0.25 mg for 4 weeks, which was escalated to 0.5 mg for 4 weeks until the maintenance dose (0.5 mg or 1.0 mg) was reached.

Of the 3,297 patients enrolled, 83.0% were aged ≥50 years and had established CVD or CKD: 58.8% had established CVD without CKD (**Table 1**), 10.7% had CKD only, and 13.4% had both CVD and CKD (6). In total, 17% of the participants were aged ≥60 years and had at least one CV risk factor. The overall mean duration of T2D was 13.9 years, and the mean glycated hemoglobin (HbA_{1c}) level was 8.7%. Background standard-of-care at baseline included metformin for 73% of patients, insulin for 58%, and sulfonylureas for 43%. Most patients were receiving antihypertensive medication (93%), lipid-lowering therapy (76%), and antithrombotic/antiplatelet drugs (76%).

Over 104 weeks, a first MACE was reported in 6.6% of patients who received subcutaneous semaglutide (both semaglutide doses combined) vs. 8.9% with placebo (both placebo groups combined), with a HR of 0.74 and a 95% CI of 0.58–0.95, confirming noninferiority to placebo ($p < 0.001$) (**Figure 1**) (6). As a preapproval trial, the main aim of SUSTAIN 6 was to confirm CV safety. As such, the trial was not powered to demonstrate superiority and such testing was not prespecified. However, the treatment effect of subcutaneous semaglutide and the accrual of more events than estimated resulted in a nominally significantly lower risk of MACE among patients receiving subcutaneous semaglutide ($p = 0.02$), as assessed *post-hoc*.

When the individual components of the primary endpoint were analyzed, nonfatal MI occurred in 2.9% of patients receiving subcutaneous semaglutide and in 3.9% of those receiving placebo (HR 0.74; 95% CI 0.51–1.08; $p = 0.12$), while

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; EASD, European Association for the Study of Diabetes; eGFR, estimated glomerular filtration rate; eNOS, endothelial nitric oxide synthase; ER, extended release; GLP-1, glucagon-like peptide-1; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; HF, heart failure; HR, hazard ratio; ICAM, intercellular adhesion molecule; IL, interleukin; KLF-2, Krüppel-like factor 2; LDL, low-density lipoprotein; MACE, major adverse cardiovascular event (s); MCP, monocyte chemoattractant protein; MI, myocardial infarction; NNT, number needed to treat; NO, nitric oxide; NYHA, New York Heart Association; oxLDL, oxidized low-density lipoprotein; PIONEER, Peptide InnOvatioN for Early diabEtes tReatment; ROS, reactive oxygen species; SGLT2i, sodium-glucose co-transporter-2 inhibitor; SOUL, A Heart Disease Study of Semaglutide in Patients with Type 2 Diabetes; SUSTAIN, Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes; T2D, type 2 diabetes; TM, thrombomodulin; TNF-α, tumor necrosis factor alpha; VCAM, vascular cell adhesion protein; VSMC, vascular smooth muscle cells.

nonfatal stroke occurred in 1.6% and 2.7%, respectively (HR 0.61; 95% CI 0.38–0.99; $p = 0.04$). Rates of death from CV causes were similar for subcutaneous semaglutide and placebo (2.7% vs. 2.8%, respectively; HR 0.98; 95% CI 0.65–1.48; $p = 0.92$), as was death from any cause (3.8% vs. 3.6%, respectively; HR 1.05; 95% CI 0.74–1.50; $p = 0.79$). An expanded composite endpoint of MACE plus revascularization (coronary or peripheral), and hospitalization for unstable angina or HF, occurred in 12.1% of patients receiving subcutaneous semaglutide and in 16.0% of patients receiving placebo (HR 0.74; 95% CI 0.62–0.89; $p = 0.002$). Thus, among patients with T2D at high CV risk, noninferiority was confirmed, and in a *post-hoc* non-prespecified analysis, the rate of MACE was shown to be significantly lower in those receiving subcutaneous semaglutide than in those receiving placebo.

TABLE 1 | Baseline characteristics of patients in the SUSTAIN 6 and PIONEER 6 trials [Marso (6); Husain (10)].

Trial	SUSTAIN 6 [Marso 2016a]	PIONEER 6 [Husain 2019]
Comparison	Once-weekly subcutaneous semaglutide 0.5/1.0 mg vs. placebo	Once-daily oral semaglutide 14 mg vs. placebo
N	3,297	3,183
Age, y	65 ± 7	66 ± 7
Female sex, %	39.3	31.6
Diabetes duration, y	13.9 ± 8.1	14.9 ± 8.5
HbA_{1c}, %	8.7 ± 1.5	8.2 ± 1.6
Body weight, kg	92.1 ± 20.6	90.9 ± 21.2
Body mass index, kg/m²	32.8 ± 6.2	32.3 ± 6.5
Age ≥50 years and presence of CVD and/or CKD*, %	83.0	84.7
Age ≥60 years and presence of CV risk factors only, %	17.0	15.3
Established CVD without CKD, %	58.8	NA
CKD without CVD, %	10.7	NA
Established CVD with CKD, %	13.4	NA
Prior myocardial infarction, %	32.5	36.1
Prior heart failure (NYHA class II or III), %	23.6	12.2
Prior moderate renal impairment, %	25.2	28.2

Mean values ± standard deviation unless otherwise stated.
**CKD was taken as an equivalent to existing CVD.*
CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; HbA_{1c}, glycated hemoglobin; NA, not available; NYHA, New York Heart Association; y, years.

SELECT – ASSESSING THE CARDIOVASCULAR BENEFIT OF SUBCUTANEOUS SEMAGLUTIDE IN PATIENTS WITH OVERWEIGHT OR OBESITY

Following the confirmation that subcutaneous semaglutide is associated with CV safety and preliminarily, even some evidence of benefit, a definitive CVOT is ongoing to assess the effects of subcutaneous semaglutide on CV events in patients at high CV risk who are overweight or obese (NCT03574597) (12). In the ongoing Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT) trial, approximately 17,500 people with pre-existing CVD and with overweight or obesity (body mass index ≥27 kg/m^2) but without diabetes will receive either subcutaneous semaglutide (up to 2.4 mg) or placebo in addition to standard care for up to 5 years. This will be the first clinical trial to assess the superiority of a GLP-1 RA versus placebo for reduction of CV events in patients with established CVD and overweight or obesity but without established T2D. By excluding patients with T2D, the aim is to reduce the extent to which improved glycemic control is the driver of improved CV outcomes. This could potentially show

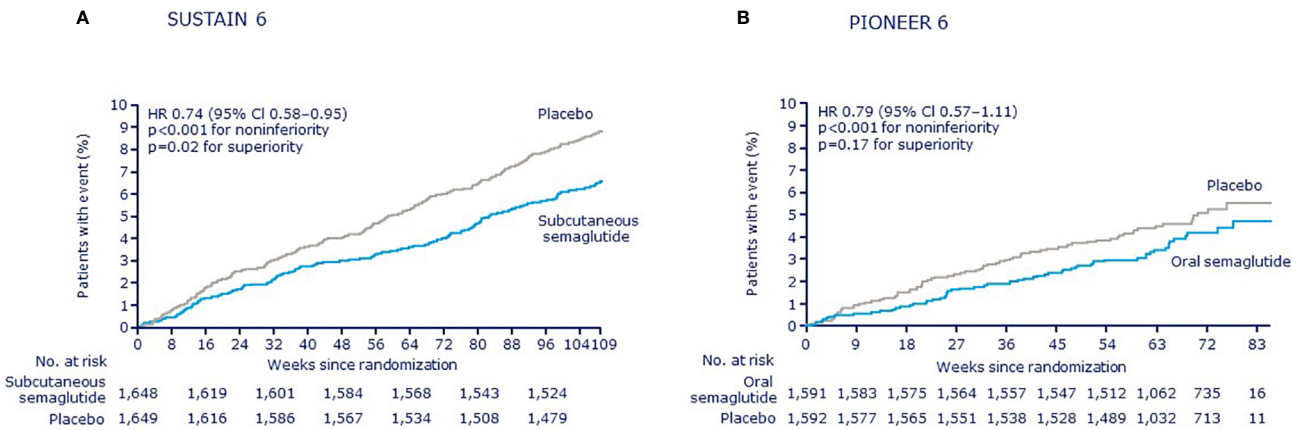

FIGURE 1 | Kaplan–Meier plots of the primary outcome (a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) in SUSTAIN 6 and PIONEER 6 (11). **(A)** SUSTAIN 6 **(B)** PIONEER 6; CI, confidence interval; HR, hazard ratio. **(A)** From Marso SP, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med (2016) 375:1834-44. Copyright © (2016) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. **(B)** From Husain M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med (2019) 381:841-51. Copyright © (2019) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

the benefit or early intervention in patients with normoglycemia or pre-diabetes even before the development of T2D and a positive outcome could indicate a new approach to CV risk reduction in obese or overweight patients. The primary endpoint of the SELECT trial is time to the first occurrence of MACE and the trial is powered to show superiority (semaglutide vs. placebo). Secondary endpoints include several composite CV endpoints, individual components, all-cause mortality, glycemic parameters, and changes in weight-related patient-reported outcomes.

PIONEER 6 – ESTABLISHING THE CARDIOVASCULAR SAFETY OF ORAL SEMAGLUTIDE

Similar to SUSTAIN 6, PIONEER 6 aimed to establish the CV safety of oral semaglutide before regulatory approval and was not powered to prove superiority and, thus, CV benefit (10). As with SUSTAIN 6, PIONEER 6 was designed to establish noninferiority by ruling out an 80% excess in CV risk with oral semaglutide for noninferiority relative to placebo for an identical MACE primary outcome, but was driven by events only (at least 122 events needed to be accrued) and there was no minimum duration.

The eligibility criteria were almost identical to those of the SUSTAIN trial except there was no requirement for HbA_{1c} >7% in PIONEER 6 and different restrictions on permitted background glucose-lowering medication. PIONEER 6, but not SUSTAIN 6, excluded patients with estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 and patients with proliferative retinopathy or maculopathy requiring acute treatment.

In PIONEER 6, patients were randomized (1:1) to receive once-daily oral semaglutide or placebo, both in addition to standard care. Slow dose escalation was used to minimize adverse events. Oral semaglutide was initiated at 3 mg and dose-escalated every 4 weeks, to 7 mg and then 14 mg. Once the maximum 14 mg daily dose was reached, patients remained at this dose unless a reduction was warranted due to adverse events.

Of the 3,183 patients enrolled in PIONEER 6, 85% were aged ≥50 years with established CVD and/or CKD and 15% were aged ≥60 years with CV risk factors only (**Table 1**). In total, 26% had moderate renal impairment (30 to <60 mL/min/1.73 m^2). The mean HbA_{1c} level was 8.2%, which is lower than in SUSTAIN 6, perhaps reflecting the lack of a HbA_{1c} threshold in the inclusion criteria for PIONEER 6. The overall mean duration of T2D was comparable with SUSTAIN 6 at 14.9 years. Background standard-of-care at baseline included metformin for 77% of patients, insulin for 61%, and sulfonylureas for 32%. Compared with SUSTAIN 6, PIONEER 6 included a greater proportion of patients receiving sodium-glucose co-transporter-2 inhibitors (SGLT2is; 10% vs. <1%), reflecting the increased use of this drug class at the time of this trial.

In PIONEER 6, over a median follow-up of 15.9 months, the composite primary endpoint of MACE was reported in 3.8% of patients in the oral semaglutide group vs. 4.8% in the placebo group, with a HR of 0.79 and a 95% CI of 0.57–1.11, confirming noninferiority of oral semaglutide to placebo ($p < 0.001$) (**Figure 1**) (10). PIONEER 6 was not powered to assess superiority and a significant difference for the obvious trend between treatment groups was not detected ($p = 0.17$). When the individual MACE components were analyzed, a nominally statistically significant reduction in the risk of death from CV causes was observed (0.9% vs. 1.9%; HR 0.49; 95% CI 0.27–0.92) although the study was not sufficiently powered to establish superiority for individual outcomes. No significant differences were seen for other components: nonfatal MI occurred in 2.3% of patients in the oral semaglutide group and in 1.9% in the placebo group (HR 1.18; 95% CI 0.73–1.90), while nonfatal stroke occurred in 0.8% and 1.0%, respectively (HR 0.74; 95% CI 0.35–1.57). Rates of death from any cause were 1.4% with oral semaglutide and 2.8% with placebo (HR 0.51; 95% CI 0.31–0.84). An expanded composite endpoint of MACE plus unstable angina resulting in hospitalization or HF resulting in hospitalization occurred in 5.2% of the patients receiving subcutaneous semaglutide and in 6.3% of those receiving placebo (HR 0.82; 95% CI 0.61–1.10). The PIONEER 6 study investigators therefore concluded that the CV safety profile of oral semaglutide was noninferior to placebo, when both were administered with a background of standard care.

Whether oral semaglutide significantly reduces the risk of MACE is the subject of the ongoing CVOT, A Heart Disease Study of Semaglutide in Patients with Type 2 Diabetes (SOUL; NCT03914326) (13). Larger and longer than PIONEER 6, SOUL is evaluating the effects of once-daily oral semaglutide (up to 14 mg) vs. placebo in around 9,640 patients with T2D and CVD, cerebrovascular disease, symptomatic peripheral artery disease, or CKD over a period of 3.5–5 years. The primary endpoint is time to the first occurrence of MACE and the trial is powered for an assessment of superiority (vs. placebo), which is part of the prespecified statistical analysis plan. Secondary endpoints include several composite endpoints, all-cause mortality, CKD-related endpoints, major adverse limb events, and individual components of the composite outcomes. The trial size and study duration of SOUL are similar to the LEADER CVOT, which compared liraglutide with placebo as described below (5).

POOLED ANALYSIS OF SUSTAIN AND PIONEER TRIALS

Insights from the individual trials are complemented by a recent *post-hoc* patient-level analysis that combined data from the SUSTAIN 6 and PIONEER 6 trials, which was made possible by their similar designs (11). In terms of glycemic and body weight control, once-daily oral and once-weekly subcutaneous semaglutide display very similar actions at corresponding doses (14). When data were combined, the overall HR for MACE with semaglutide vs. placebo was 0.76 (95% CI 0.62–0.92). The HRs for each individual component of MACE were <1.0 and the upper limit of the 95% CI was <1.0 for nonfatal stroke.

While these are *post-hoc* analyses, they suggest a potential for beneficial effects for semaglutide on CV outcomes regardless of the route of administration.

The effect of semaglutide on MACE was consistent across several clinically relevant subgroups, including those with established CVD and/or CKD vs. those with CV risk factors only, and in patients with and without prior MI or stroke. In patients with prior HF (NYHA class II–III), no effect of semaglutide vs. placebo on MACE was observed, although the overall incidence of prior HF was low. When considering HF hospitalization as an endpoint, the pooled analysis found no effect, with a HR of 1.03 (95% CI 0.75–1.40).

The lack of an increased CV risk in SUSTAIN 6 and PIONEER 6 is consistent with evidence from a meta-analysis summarizing data from SUSTAIN and PIONEER glycemic efficacy trials, which included patients with T2D at relatively low CV risk (11). When MACE were analyzed in the SUSTAIN 1–5 and two SUSTAIN Japanese trials and in PIONEER 1–5, 7–8 and two PIONEER Japanese trials, the pooled incidence rates were low at 0.7 and 0.9 events per 100 subject-years with semaglutide and comparator, respectively. The HR for MACE was 0.85, with broad 95% CIs (95% CI 0.55–1.33) due to the low numbers of events accrued.

CARDIOVASCULAR SAFETY OF OTHER GLP-1RAS

To date, seven CVOTs have been conducted with GLP-1RAs (4–10) and results for effects on MACE are shown in **Figure 2**. The trials varied in their ambitions (striving for noninferiority or superiority) and therefore had different population sizes and durations. There was also some variation in the population characteristics studied.

The first CVOT with GLP-1RAs was the ELIXA trial with the short-acting agent, lixisenatide, administered by once-daily subcutaneous injection (4). In 6,068 patients who had had a recent acute coronary event (within 180 days), the primary endpoint of MACE plus hospitalization for unstable angina occurred with a HR of 1.02 (95% CI 0.89–1.17) over approximately 2 years of follow up, demonstrating noninferiority of lixisenatide to placebo ($p < 0.001$) but with no positive effects, despite adequate power for superiority testing ($p = 0.81$). There was no significant difference in the risk of all-cause mortality (0.94; 95% CI 0.78–1.13).

The next CVOT to be published, the post-approval LEADER trial with once-daily subcutaneous liraglutide, gave the first indications that GLP-1RAs could be capable of exerting CV benefits. The rate of MACE was significantly lower with liraglutide than with placebo (HR 0.87; 95% CI 0.78–0.97; $p < 0.001$ for noninferiority; $p = 0.01$ for superiority) over ~4 years in 9,340 patients with established CVD or CV risk factors (5). The risk of all-cause mortality was also lower in the liraglutide group than the placebo group (HR 0.85; 95% CI 0.74–0.97; $p = 0.02$).

The EXSCEL trial was a large trial of 14,752 patients with established CVD or CV risk factors followed for a median of 3.2 years, which studied the effects of subcutaneous once-weekly exenatide extended release (ER) (7). The HR for MACE with exenatide vs. placebo was 0.91 (95% CI 0.83–1.00), demonstrating noninferiority vs. placebo ($p < 0.001$), but not superiority ($p = 0.06$). The HR for all-cause mortality was 0.86 (95% CI 0.77–0.97), which was not considered significant based on the hierarchical testing plan.

Superiority in MACE was subsequently shown for once-weekly subcutaneous albiglutide vs. placebo in the Harmony Outcomes trial (HR 0.78; 95% CI 0.68–0.90; $p < 0.0001$ for noninferiority; $p = 0.0006$ for superiority), which studied 9,463 patients aged ≥40 years with established CVD over a median of 1.6 years (8). The HR for all-cause mortality was 0.95 (95% CI 0.79–1.16; $p = 0.644$). However, albiglutide had been withdrawn

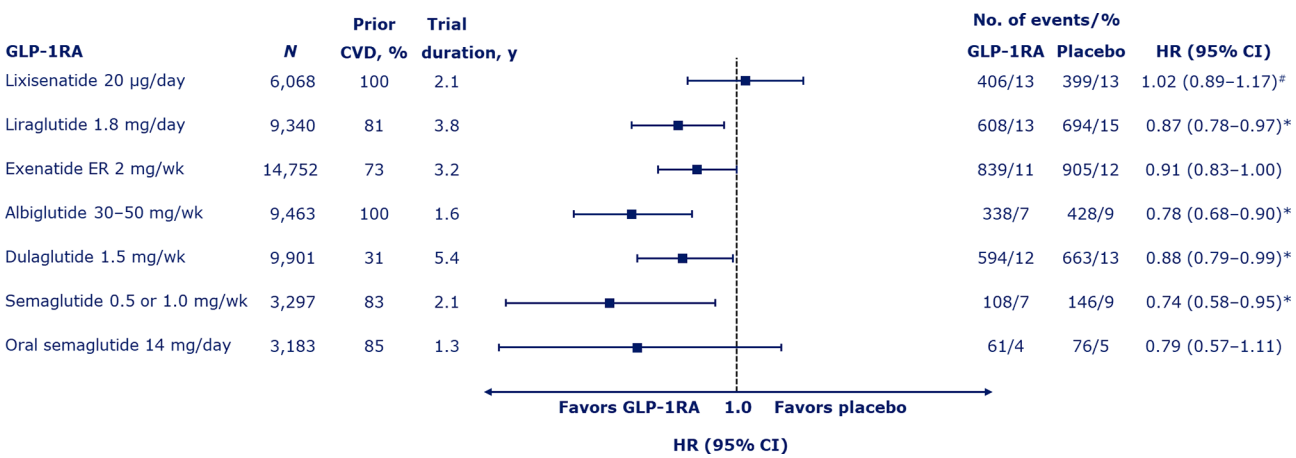

FIGURE 2 | Risk of major adverse cardiovascular events (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) with GLP-1RAs (4–10). Median duration of the trials shown. #Also includes hospitalization for unstable angina. *Denotes significant difference (p < 0.05) vs. placebo. CI, confidence interval; CVD, cardiovascular disease; ER, extended release; GLP-1RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; wk, week; y, years.

from the market due to limited prescribing prior to analyzing this CVOT and has since not been available.

Superiority was also demonstrated with once-weekly subcutaneous dulaglutide vs. placebo in the REWIND trial over a long median follow-up period of 5.4 years (HR for MACE of 0.88; 95% CI 0.79–0.99; $p = 0.026$ for superiority) (9). All-cause mortality did not differ significantly between the dulaglutide and placebo groups (HR 0.90; 95% CI 0.80–1.01; $p = 0.067$). The REWIND trial was noteworthy as, from its total of 9,901 participants, the majority (68.5%) had CV risk factors only at baseline and fewer than one-third (31.5%) had established CVD. In contrast, the prevalence of established CVD was 73–100% in other CVOTs (4–10). The authors of REWIND concluded that GLP-1RAs should be considered for the management of glycemic control in people with T2D with either previous CVD or CV risk factors.

Thus, overall, GLP-1RAs appear to have the potential for beneficial effects on adverse CV outcomes, especially concerning ischemic events and related mortality. A recent meta-analysis of the seven CVOTs indicated that GLP-1RA treatment reduced MACE by 12% (HR 0.88; 95% CI 0.82–0.94; $p < 0.001$) (15). In addition, CV mortality was reduced by 12% (HR 0.88; 95% CI 0.81–0.96; $p = 0.003$), fatal or nonfatal stroke by 16% (HR 0.84; 95% CI 0.76–0.93; $p < 0.001$), and fatal or nonfatal MI by 9% (HR 0.91; 95% CI 0.84–1.00; $p = 0.043$). Another meta-analysis of the same seven trials similarly reported that GLP-1RAs significantly reduced MACE, with a number needed to treat (NNT) to prevent one MACE of 73 (95% CI 45–212) (16). GLP-1RAs also reduced total mortality by 11%, with an NNT to prevent one death of 118, reduced CV mortality by 12% (NNT 170), and reduced stroke by 16% (NNT 211). However, they are less effective regarding hospitalization due to HF, with a reduction shown of 8% (NNT 300).

Reasons that have been postulated to account for the lack of positive effect in the ELIXA trial are the different trial populations (such that biological processes after an acute coronary event may be less amenable to modification than those relating to general atherosclerosis) and the short duration of action of lixisenatide (insufficient GLP-1 receptor stimulation over the 24-hour dosing period) (17). The effect of exenatide ER was also less positive than the other GLP-1RAs across a large population; this may be as a result of the dose of 2 mg per week, which may not be competitive compared with the doses of other GLP-1RAs (17). Also, a relatively high number of patients discontinued treatment in EXSCEL, which may have prevented determination of a treatment difference between exenatide ER and placebo (7).

WHAT IS THE PLACE OF GLP-1RAS IN THE GUIDELINES FOR PATIENTS WITH DIABETES AND CARDIOVASCULAR DISEASE?

Based on these CVOTs, the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) have provided updated guidance (18). They recommend that for patients with T2D and established atherosclerotic CVD (such as those with prior MI, ischemic stroke, unstable angina with electrocardiogram changes, myocardial ischemia on imaging or stress test, or revascularization of coronary, carotid, or peripheral arteries) where 'MACE is the gravest threat', the level of evidence for MACE benefit is greater for GLP-1RAs than other glucose-lowering classes, in particular, SGLT2is (18). To reduce the risk of MACE, the consensus update states that GLP-1RAs can also be considered in patients with T2D without established CVD but with indicators of high risk, specifically, patients aged ≥55 years with coronary, carotid, or lower extremity artery stenosis >50%, left ventricular hypertrophy, eGFR <60 mL/min/1.73 m^2, or albuminuria.

As GLP-1RAs do not appear to have a consistent effect on HF hospitalization, SGLT2is are recommended if HF predominates; however, if SGLT2is are not tolerated or are contraindicated, or if eGFR is less than adequate, a GLP-1RA with proven CV benefit can be added (18). SGLT2is are also recommended first for patients where CKD predominates (18). Nevertheless, some beneficial effects of GLP-1RAs on albuminuria and reducing the progressive loss of kidney function have been demonstrated in LEADER, SUSTAIN 6, and REWIND (5, 6, 9, 19) and a GLP-1RA with proven CVD benefit is recommended in patients with CKD if SGLT2is are not tolerated or are contraindicated, or if eGFR is less than adequate (18).

In recent guidelines on diabetes, prediabetes, and CVD from the European Society of Cardiology, in collaboration with the EASD, GLP-1RAs with proven CV benefit (liraglutide, semaglutide, and dulaglutide) are recommended as an add-on therapy to metformin (20). GLP-1RAs with proven benefit are even recommended as a first-line therapy in people with T2D and atherosclerotic CVD or at high/very high CV risk without prescribing metformin (20), despite the fact that CVOTs testing GLP-1RAs have mainly been performed in metformin-treated patients. The high-risk category is defined by ≥10 years of (known) diabetes duration, without target organ damage, but one (or more) other associated risk factor (such as obesity, hypertension, dyslipidemia, or smoking). GLP-1RAs with proven CV benefit are recommended in patients with T2D and CVD or at very high/high CV risk to reduce CV events (class I, level A), while liraglutide is also recommended to reduce the risk of death (class I, level B) (20). Many diabetologists still favor a combination of a GLP-1RA or SGLT2i with metformin (if not contraindicated and if no intolerance precludes the use of metformin), even if these combinations do not lead to achievement of glycemic targets. More research is needed to guide first-line recommendations.

MECHANISMS FOR THE CARDIOVASCULAR BENEFITS OF GLP-1RAS

Different mechanisms have been proposed to explain the CV benefits elicited by some GLP-1RAs (21). GLP-1RAs have

positive effects on several CV risk factors (glycemic control, body weight, blood pressure, fasting, and postprandial lipoproteins) and it appears that the GLP-1RAs that induced the largest reductions in HbA_{1c}, body weight, and systolic blood pressure were also those associated with CV-event reduction. However, not all glucose-lowering and risk-factor management trials have shown a positive effect on CV events over the relatively short timeframe of CVOTs and therefore, risk-factor modification alone cannot explain the magnitude of the benefits observed (21). GLP-1RAs may exert additional mechanisms involving directly influencing GLP-1 receptors in the CV system, potentially leading to anti-atherosclerotic/anti-inflammatory effects and improved endothelial function/vasodilation (**Figure 3**) (21).

In atherogenesis, low-density lipoprotein (LDL) cholesterol is transported into the intima layer of arterial blood vessels where reactive oxygen species (ROS) can lead to the formation of oxidized LDL (oxLDL) particles. In an environment characterized by oxidative stress and mitochondrial dysfunction, the presence of oxLDL further increases the secretion of proinflammatory cytokines (e.g., tumor necrosis factor α, interleukin [IL]-6 and IL-1β) and the expression of

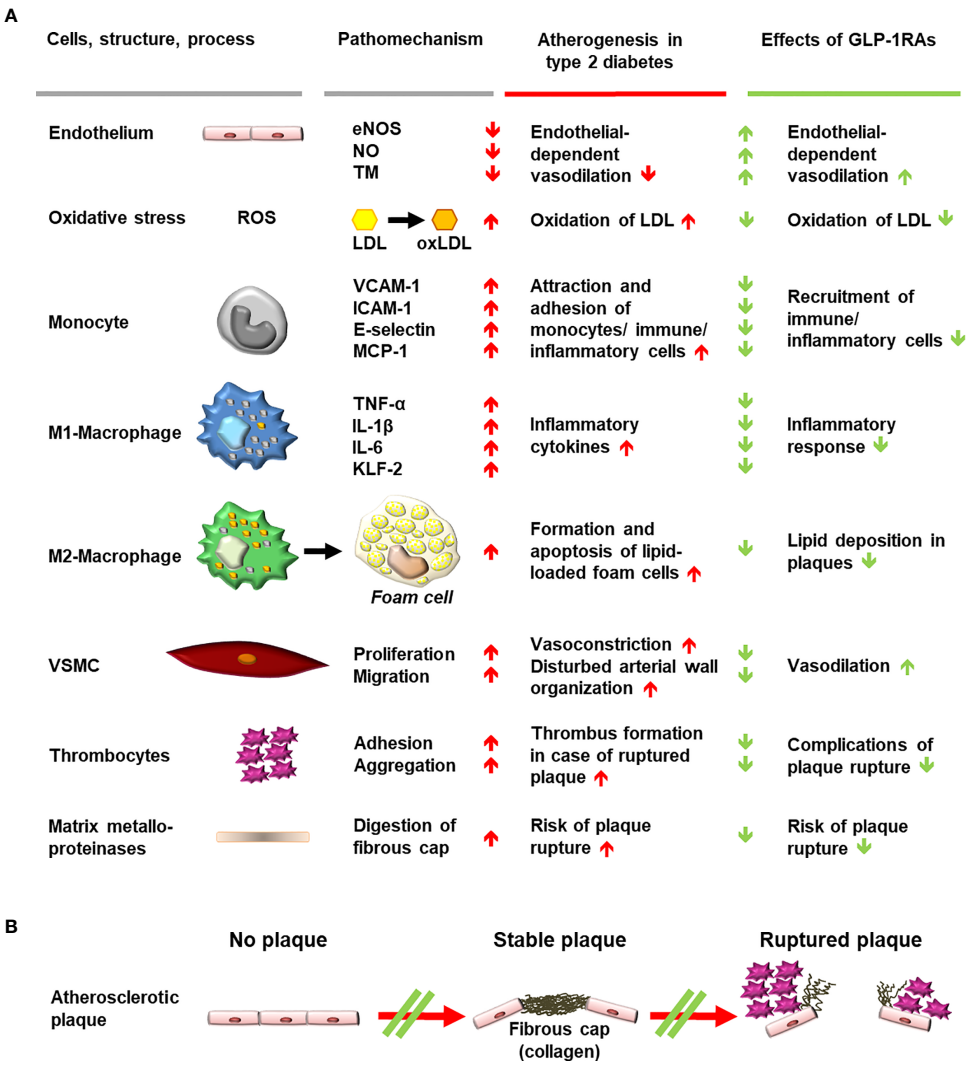

FIGURE 3 | Schematic diagram of mechanisms involved in generating atherosclerotic lesions in patients with type 2 diabetes and anti-atherosclerotic effects of stimulating GLP-1 receptors with GLP-1RAs. **(A)** Cells, structures, and processes involved in atherogenesis, for which evidence suggests an interference of GLP-1 receptor stimulation with pro-atherogenic mechanisms. Findings worsening the progression of atherogenesis are depicted as red arrows, while beneficial effects of GLP-1RAs on pathomechanisms and atherogenesis are shown as green arrows. **(B)** Progression of plaque formation towards an increased likelihood of rupture is shown with red arrows. Interference with the formation of plaques or with progression towards plaque rupture is shown as a green double line crossing a red arrow. eNOS, endothelial nitrous oxide synthase; GLP-1, glucagon-like peptide-1; GLP-1RA, glucagon-like peptide-1 receptor agonist; 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; TM, thrombomodulin; TNF-α, tumor necrosis factor alpha; VCAM-1, vascular cell adhesion protein 1; VSMC, vascular smooth muscle cell.

adhesion molecules (including vascular cell adhesion protein [VCAM]-1, monocyte chemoattractant protein [MCP]-1, intercellular adhesion molecule [ICAM]-1 and E-selectin) by monocytes and macrophages (22). In addition, the Krüppel-like factor 2 pathway is suppressed, leading to decreased endothelial nitric oxide (NO)-synthase (eNOS) activity, reduced NO production, vasoconstriction, vascular smooth muscle cells (VSMC) proliferation, and intima-media thickening (22, 23).

GLP-1 receptor stimulation appears to attenuate these processes in preclinical models and human studies in various ways. GLP-1 receptor stimulation (e.g., through GLP-1 (24–27), exenatide (28), liraglutide (26, 29–32), or semaglutide (33) prevents ROS and reduces vascular oxidative stress. The secretion of adhesion molecules including VCAM-1, MCP-1, ICAM-1, and E-selectin is also reduced by GLP-1 (34), exenatide (34–36), liraglutide (37), and dulaglutide (22). Furthermore, increased eNOS activity and NO production have been observed with GLP-1 (23, 26), exenatide (23), and liraglutide (26, 30, 37). In addition, liraglutide has been reported to reduce oxLDL uptake into macrophages (38), inhibit VSMC proliferation (39), and reduce carotid intima-media thickness in patients with the metabolic syndrome (40).

GLP-1RAs [lixisenatide (41) and liraglutide (42)] may also modulate the ROS- and oxLDL-mediated differentiation of macrophage phenotype away from the inflammatory pattern of M1-macrophages and towards anti-inflammatory M2-macrophages. Furthermore, GLP-1 (43, 44) and liraglutide (45) may suppress oxLDL-induced foam-cell formation from M2-macrophages, retarding atherosclerotic lesion development in experimental models (45). Evidence suggests that GLP-1 (46) and lixisenatide (47) may also stabilize atherosclerotic plaques, reducing plaque macrophage infiltration, increasing collagen content, and increasing fibrous cap thickness. In addition, the activity of matrix metalloproteinases, which destabilize the dense fibrous cap of stable plaques through proteolysis, is reduced by GLP-1RAs [GLP-1 (46), exenatide (48) or semaglutide (49)]. Plaque hemorrhage is reduced by semaglutide (49), which, like GLP-1 (50), also inhibits caspase-mediated apoptosis (51). The integrity of endothelial cells was shown to be stabilized by exenatide, suggesting further protective effects of GLP-1 receptor stimulation (52, 53).

FUTURE CLINICAL TRIALS EXAMINING SEMAGLUTIDE EFFECTS ON CARDIOVASCULAR DISEASE

To provide further insight, the effect of subcutaneous semaglutide vs. placebo on coronary atherosclerosis progression is currently being measured by multidetector computed tomography angiography over 1 year in ~140 patients with T2D and CVD or at least one CV risk factor in the Semaglutide Treatment On Coronary Progression (STOP; NCT03985384) trial (54, 55). Secondary endpoints include quantitative changes in different coronary plaque types and morphology. In addition, the LIRA-FLAME trial (NCT03449654) is examining the effects of liraglutide vs. placebo on vascular inflammation in 102 patients with T2D over 26 weeks as assessed by fluorodeoxyglucose-positron emission tomography/computed tomography (primary outcome), and also to evaluate endothelial function, coronary artery calcium, and carotid-intima thickness (56).

CONCLUSIONS

The CV safety of semaglutide, administered subcutaneously or orally, has been established in the SUSTAIN 6 and PIONEER 6 trials. These findings are consistent with the results of CVOTs conducted for different GLP-1RAs. The beneficial effects of liraglutide, semaglutide, and dulaglutide have been recognized in international guidelines and these GLP-1RAs are now recommended to reduce the risk of CV events in high-risk patients. The ongoing SOUL trial will confirm whether oral semaglutide provides significant reductions in CV events as seen with subcutaneous semaglutide. The SELECT trial will assess whether subcutaneous semaglutide improves CV outcomes in obese or overweight patients without T2D. A CV benefit in this trial may indicate the need for earlier intervention in CV risk reduction, even before the development of T2D. The mechanisms responsible for the reduced risk of adverse CV events with GLP-1RAs may be related to inhibition of the progression of atherosclerotic lesions by multiple pathways, primarily involving reduced inflammatory processes within the atherosclerotic plaque. Additional studies are warranted, and ongoing studies will provide further mechanistic information into how some GLP-1RAs are able to provide CV benefits.

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All authors contributed to the article and approved the submitted version.

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REVIEW
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Efficacy of Semaglutide in a Subcutaneous and an Oral Formulation

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Despite the benefits of early and effective glycemic control in the management of type 2 diabetes (T2D), achieving glycated hemoglobin (HbA_{1c}) targets is challenging in some patients. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) provide effective reductions in HbA_{1c} and body weight. Semaglutide is the only GLP-1RA that is available in both an injectable and oral formulation. The efficacy of once-weekly subcutaneous semaglutide and once-daily oral semaglutide has been investigated in the global SUSTAIN and PIONEER phase III clinical trial programs in a range of clinical settings, including early T2D managed with diet and exercise only, more established T2D uncontrolled on one to three oral antidiabetic drugs, and advanced disease treated with insulin. Across the SUSTAIN program, once-weekly subcutaneous semaglutide 1.0 mg reduced HbA_{1c} by 1.5–1.8% after 30–56 weeks, which was significantly more than sitagliptin, liraglutide, exenatide extended release, dulaglutide, canagliflozin, or insulin glargine. Across the PIONEER program, once-daily oral semaglutide 14 mg reduced HbA_{1c} by 1.0–1.4%, significantly more than sitagliptin or empagliflozin, and to a similar extent as liraglutide after 26 weeks. In addition, subcutaneous semaglutide reduced body weight significantly more than all active comparators tested, while oral semaglutide reduced body weight more than sitagliptin and liraglutide, and to a similar extent as empagliflozin. Neither formulation of semaglutide has been associated with an increased risk of hypoglycemia and both improve various measures of health-related quality of life. Semaglutide offers the benefits of a highly effective GLP-1RA in both injectable and oral formulations. Selection of the most appropriate formulation can be made on an individual basis to best suit the patient's preferences and needs.

Keywords: body weight, glycated hemoglobin (HbA_{1c}), efficacy, glucagon-like peptide-1 receptor agonist (GLP-1RA), oral, semaglutide, subcutaneous, type 2 diabetes

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Abbreviations: Cana, canagliflozin; C_{avg}, median semaglutide concentration; DTSQ, Diabetes Treatment Satisfaction Questionnaire; Dula, dulaglutide; Empa, empagliflozin; ER, extended release; Exe, exenatide; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated hemoglobin; IGlar, insulin glargine; Lira, liraglutide; Met, metformin; OAD, oral antidiabetic drug; OD, once daily; OW, once weekly; Pbo, placebo; PIONEER, Peptide InnOvatioN for the Early diabEtes tReatment; s.c., subcutaneous; Sema, semaglutide; SF-36, 36-item Short-Form; SGLT2i, sodium-glucose co-transporter-2 inhibitor; Sita, sitagliptin; SU, sulfonylurea; SUSTAIN, Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes; T2D, type 2 diabetes; TZD, thiazolidinedione.

INTRODUCTION

Evidence from trials and real-world studies in patients with type 2 diabetes (T2D) indicates that the risk of complications may be reduced by providing sustained glycemic control and that near-normal glycated hemoglobin (HbA_{1c}) levels should be achieved as early as possible in the T2D trajectory (1, 2). However, achieving and sustaining optimum glycemic control remains challenging in many patients (3), despite treatment advances and the availability of new classes of glucose-lowering agents. In a recent study of 28,315 patients with incident T2D, around half of patients spent the 10 years after diagnosis with HbA_{1c} above desired targets: mean percent time spent with HbA_{1c} ≥7% was 40% in the first 2 years and 61% after 6–10 years (3).

Reasons that may be responsible for the lack of improvement in glucose levels over time include failure to address the complex pathophysiology of T2D, therapeutic inertia leading to delayed treatment intensification, insufficient implementation of lifestyle changes, and poor adherence to and persistence with treatment (4, 5). Most patients should receive metformin initially, but if control is suboptimal after 3–6 months, treatment intensification with another glucose-lowering therapy is required, and selection of subsequent therapies should be made on an individualized basis to meet the specific needs of the patient (4).

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a well-established class of glucose-lowering agents that induce glucose-mediated stimulation of insulin secretion, reduce glucagon release, reduce hepatic glucose output, delay gastric emptying, increase satiety, and improve cardiovascular risk factors (6–9). By correcting multiple pathophysiological defects in T2D, GLP-1RAs provide effective glycemic control, with a low risk of hypoglycemia, while reducing body weight, blood pressure, and in some cases, cardiovascular events (6).

Semaglutide is the only GLP-1RA that is available in both an injectable and an oral formulation (10). Once-weekly subcutaneous semaglutide was approved by the US Food and Drug Administration in December 2017 (11) and by the European Medicines Agency in February 2018 (12), while once-daily oral semaglutide was approved in the US in September 2019 (13) and in Europe in April 2020 (14). It was thought that an oral formulation may improve convenience, acceptance, and adherence with GLP-1RA therapy, and may provide an additional option to help increase glycemic target achievement, particularly in patients who are reluctant to initiate injectable medications (10).

This article describes results from global clinical trial programs that established the efficacy of subcutaneous and oral semaglutide in a range of clinical settings and discusses factors that may influence the choice of formulation in individual patients. The safety of subcutaneous and oral semaglutide will be covered in a separate article in this issue (15).

DESIGN OF THE SUSTAIN AND PIONEER PROGRAMS

Both formulations of semaglutide were investigated in comprehensive international clinical development programs. As part of the Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) program, the efficacy of once-weekly subcutaneous semaglutide was evaluated in over 7,000 patients in six global phase IIIa trials (SUSTAIN 1–6) across the wide spectrum of the T2D disease course (16–21) and in nearly 3,000 patients in four phase IIIb trials (SUSTAIN 7–10) (22–25) (**Table 1**). Oral semaglutide was then investigated in eight global Peptide InnOvatioN for the Early diabEtes tReatment (PIONEER) phase IIIa trials in over 8,000 patients, with similarly broad evaluation in different patient populations who were receiving a range of background medications (26–33) (**Table 1**). Further SUSTAIN and PIONEER trials were conducted in Japanese subjects and are not described in detail here.

Patients with early T2D (mean diabetes duration 3–4 years) managed on diet and exercise only were studied in SUSTAIN 1 and PIONEER 1 (16, 27). Effects in patients with more established T2D (mean diabetes duration 7–10 years) already receiving one to three oral antidiabetic drugs (OADs) and in need of treatment intensification were studied in seven SUSTAIN trials and four PIONEER trials (17–19, 22–25, 28–30, 33). Patients with advanced disease (mean diabetes duration 13–15 years) on insulin who required additional treatment were studied in SUSTAIN 5 and PIONEER 8 (20, 26). Typical inclusion criteria for the SUSTAIN and PIONEER trials were age ≥18 years, a diagnosis of T2D at least 90 days prior to screening, and inadequate glycemic control within a specified HbA_{1c} range (**Table 1**).

In both trial programs, initial dose escalation of semaglutide was implemented to mitigate gastrointestinal adverse events. The SUSTAIN trials assessed final once-weekly doses of 1.0 mg only, or 0.5 mg and 1.0 mg, of subcutaneous semaglutide (16–25). Once-daily doses of oral semaglutide (14 mg only or 3 mg, 7 mg, and 14 mg) were assessed in most trials in the PIONEER program (26–32); however, the 3 mg dose is not approved as a maintenance dose and data are not included here. PIONEER 7 evaluated a flexible dosing approach by which the oral semaglutide dose was adjusted (3 mg, 7 mg, or 14 mg) depending on the patient's glycemic response and gastrointestinal tolerability, to mimic the individualized approach that may be used in clinical practice (33).

Once-weekly subcutaneous semaglutide was compared with placebo (16, 24), as well as commonly used glucose-lowering agents from drug classes recommended for patients who require further treatment intensification: the dipeptidyl peptidase-4 inhibitor sitagliptin (17); other GLP-1RAs (exenatide extended release [ER], dulaglutide and liraglutide) (18, 22, 25); the sodium-glucose co-transporter-2 inhibitor (SGLT2i) canagliflozin (23); and basal insulin (insulin glargine) (19). In the PIONEER program, four trials compared once-daily oral semaglutide with the active comparators sitagliptin, the SGLT2i empagliflozin, and liraglutide (28–30, 33).

Across the SUSTAIN program, the primary and confirmatory secondary endpoints for most trials were change from baseline in HbA_{1c} and body weight, respectively, to the end of treatment (30, 40, 52, or 56 weeks) (16–25). In the PIONEER program, most trials had the primary and confirmatory secondary endpoints at week 26 of change from baseline in HbA_{1c} and body weight,

TABLE 1 | Summary of the designs of the global glycemic efficacy SUSTAIN and PIONEER trials (16–26).

Trial	Treatment arms	Key inclusion criteria	Trial duration; blinding	Primary endpoint
Trials in early T2D (mean duration 3–4 years)				
SUSTAIN 1 (*N* = 388)	• s.c. semaglutide 0.5 mg OW • s.c. semaglutide 1.0 mg OW • Placebo OW	• Treated with diet and exercise • HbA_{1c} 7.0–10.0%	30 weeks; blinded	Change in HbA_{1c} from baseline to week 30
PIONEER 1 (*N* = 703)	• Oral semaglutide 3 mg OD • Oral semaglutide 7 mg OD • Oral semaglutide 14 mg OD • Placebo OD	• Treated with diet and exercise • HbA_{1c} 7.0–9.5%	26 weeks; blinded	Change in HbA_{1c} from baseline to week 26
Trials in established T2D (mean duration 6–10 years)				
SUSTAIN 2 (*N* = 1,231)	• s.c. semaglutide 0.5 mg OW • s.c. semaglutide 1.0 mg OW • Sitagliptin 100 mg OD	• Treated with met, TZD, or both • HbA_{1c} 7.0–10.5%	56 weeks; blinded	Change in HbA_{1c} from baseline to week 56
PIONEER 3 (*N* = 1,864)	• Oral semaglutide 3 mg OD • Oral semaglutide 7 mg OD • Oral semaglutide 14 mg OD • Sitagliptin 100 mg OD	• Treated with met ± SU • HbA_{1c} 7.0–10.5%	78 weeks; blinded	Change in HbA_{1c} from baseline to week 26
PIONEER 7 (*N* = 504)	• Oral semaglutide (flexible dose adjustment: 3, 7, or 14 mg) OD • Sitagliptin 100 mg OD	• Treated with 1–2 from met, TZD, SU, SGLT2i • HbA_{1c} 7.5–9.5%	52 weeks; open-label*	Proportion of patients with HbA_{1c} <7.0% at week 52
SUSTAIN 3 (*N* = 813)	• s.c. semaglutide 1.0 mg OW • Exenatide ER 2.0 mg OW	• Treated with 1–2 from met, SU, TZD • HbA_{1c} 7.0–10.5%	56 weeks; open-label	Change in HbA_{1c} from baseline to week 56
SUSTAIN 7 (*N* = 1,201)	• s.c. semaglutide 0.5 mg OW • s.c. semaglutide 1.0 mg OW • Dulaglutide 0.75 mg OW • Dulaglutide 1.5 mg OW	• Treated with met • HbA_{1c} 7.0–10.5%	40 weeks; open-label	Change in HbA_{1c} from baseline to week 40
SUSTAIN 10 (*N* = 577)	• s.c. semaglutide 1.0 mg OW • Liraglutide 1.2 mg OD	• Treated with 1–3 from met, SU, SGLT2i • HbA_{1c} 7.0–11.0%	30 weeks; open-label	Change in HbA_{1c} from baseline to week 30
PIONEER 4 (*N* = 711)	• Oral semaglutide 14 mg OD • Liraglutide 1.8 mg OD • Placebo OD	• Treated with met ± SGLT2i • HbA_{1c} 7.0–9.5%	52 weeks; blinded	Change in HbA_{1c} from baseline to week 26
SUSTAIN 9 (*N* = 302)	• s.c. semaglutide 1.0 mg OW • Placebo OW	• Treated with SGLT2i ± (met or SU) • HbA_{1c} 7.0–10.0%	30 weeks; blinded	Change in HbA_{1c} from baseline to week 30
SUSTAIN 8 (*N* = 788)	• s.c. semaglutide 1.0 mg OW • Canagliflozin 300 mg OD	• Treated with met • HbA_{1c} 7.0–10.5%	52 weeks; blinded	Change in HbA_{1c} from baseline to week 52
PIONEER 2 (*N* = 822)	• Oral semaglutide 14 mg OD • Empagliflozin 25 mg OD	• Treated with met • HbA_{1c} 7.0–10.5%	52 weeks; open-label	Change in HbA_{1c} from baseline to week 26
SUSTAIN 4 (*N* = 1,089)	• s.c. semaglutide 0.5 mg OW • s.c. semaglutide 1.0 mg OW • Insulin glargine OD	• Treated with met ± SU • HbA_{1c} 7.0–10.0%	30 weeks; open-label	Change in HbA_{1c} from baseline to week 30
Trials in advanced T2D (mean duration 13–15 years)				
SUSTAIN 5 (*N* = 397)	• s.c. semaglutide 0.5 mg OW • s.c. semaglutide 1.0 mg OW • Placebo OW	• Treated with basal insulin ± met • HbA_{1c} 7.0–10.0%	30 weeks; blinded	Change in HbA_{1c} from baseline to week 30
PIONEER 8 (*N* = 731)	• Oral semaglutide 3 mg OD • Oral semaglutide 7 mg OD • Oral semaglutide 14 mg OD • Placebo OD	• Treated with basal, basal-bolus, or premixed insulin ± met • HbA_{1c} 7.0–9.5%	52 weeks; blinded	Change in HbA_{1c} from baseline to week 26
PIONEER 5 (*N* = 324)	• Oral semaglutide 14 mg OD • Placebo OD	• Moderate renal impairment • Treated with met or SU, or both, or basal insulin ± met • HbA_{1c} 7.0–9.5%	26 weeks; blinded	Change in HbA_{1c} from baseline to week 26

**With 52-week extension study.*

ER, extended release; HbA_{1c}, glycated hemoglobin; met, metformin; N, number of randomized patients; OD, once daily; OW, once weekly; s.c., subcutaneous; SGLT2i, sodium-glucose co-transporter-2 inhibitor; sita, sitagliptin; SU, sulfonylurea; T2D, type 2 diabetes; TZD, thiazolidinedione.

respectively (26–32). An exception was PIONEER 7, in which the primary endpoint was the proportion of patients achieving HbA_{1c} <7.0% at week 52 (33).

The effects of semaglutide were investigated in certain special populations. SUSTAIN 6 and PIONEER 6 assessed the effects of semaglutide vs. placebo on cardiovascular outcomes in patients with T2D at high risk of cardiovascular events (21, 32), and are discussed in a separate article (34). The PIONEER 5 trial was conducted to explore the efficacy and safety of oral semaglutide 14 mg vs. placebo in patients with T2D (most commonly at an advanced stage) and moderate renal impairment (estimated glomerular filtration rate of 30–59 mL/min per 1.73 m^2) (31).

In the SUSTAIN program, analyses were performed on data obtained before the initiation of any rescue medication or before premature treatment discontinuation (16–25). The PIONEER program adopted a different approach, with two scientific questions related to the efficacy objectives being addressed through the definition of two estimands (35). The primary estimand was the treatment policy estimand, presented here, which evaluated the treatment effect for all randomized patients regardless of trial product discontinuation or use of rescue medication. The trial product estimand evaluated the treatment effect, assuming that all patients remained on the trial product for the entire planned trial duration and did not use rescue medication.

HBA_{1C} REDUCTIONS WITH SEMAGLUTIDE

Results for HbA_{1c} reductions from baseline are shown in **Figure 1**. It should be noted that the SUSTAIN and PIONEER trials differed in their inclusion criteria (e.g., baseline HbA_{1c} and background medication), duration, and analysis approach, therefore the magnitude of HbA_{1c} reduction cannot be directly compared.

Patients with Early T2D Being Treated With Diet and Exercise

In trials of patients with early T2D insufficiently controlled with diet and exercise alone, who had baseline HbA_{1c} levels of 8.0–8.1%, the highest doses of subcutaneous semaglutide (1.0 mg) or oral semaglutide (14 mg) given as monotherapy were able to reduce HbA_{1c} by 1.6% (at 30 weeks) and 1.4% (at 26 weeks), respectively, and were superior to placebo (both $p < 0.001$) (**Figure 1A**) (16, 27).

Patients With Established T2D Being Treated With One to Three OADs

Considerable HbA_{1c} reductions (1.0–1.6%) were seen with semaglutide in patients with established T2D who were already receiving one to two OADs in SUSTAIN 2 (metformin ± a thiazolidinedione) and PIONEER 3 (metformin ± a sulfonylurea) (**Figure 1B**) (17, 29). In these trials, subcutaneous semaglutide (0.5 mg and 1.0 mg over 56 weeks) and oral semaglutide (7 mg and 14 mg over 26 weeks) reduced HbA_{1c} significantly more than the active comparator, once-daily sitagliptin 100 mg (all $p < 0.001$) (17, 29). A similar result was observed when flexibly dosed oral semaglutide was compared with sitagliptin over 52 weeks in PIONEER 7 (–1.3 vs. –0.8%; $p < 0.001$) (**Figure 1B**) (33).

When compared with other GLP-1RAs in patients with established T2D already receiving one to three OADs, subcutaneous semaglutide 1.0 mg reduced HbA_{1c} significantly more than once-weekly exenatide ER 2.0 mg (–1.5% vs. –0.9%), once-weekly dulaglutide 1.5 mg (–1.8% vs. –1.4%), and once-daily liraglutide 1.2 mg (–1.7% vs. –1.0%) (all $p < 0.001$) (18, 20, 25) (**Figure 1B**). With oral semaglutide, similar HbA_{1c} reductions were seen as with once-daily liraglutide 1.8 mg when patients were on a background of metformin ± an SGLT2i in PIONEER 4 (–1.2% vs. –1.1%) (30).

When added to an SGLT2i ± metformin or sulfonylurea, subcutaneous semaglutide reduced HbA_{1c} by 1.5% compared with 0.1% with placebo ($p < 0.001$) at 30 weeks in SUSTAIN 9 (**Figure 1C**) (24). When compared with SGLT2i as second-line therapy, subcutaneous semaglutide 1.0 mg reduced HbA_{1c} significantly more than canagliflozin 300 mg after 52 weeks (–1.5% vs. –1.0%; $p < 0.001$), while oral semaglutide 14 mg reduced HbA_{1c} significantly more than empagliflozin 25 mg after 26 weeks (–1.3% vs. –0.9%; $p < 0.001$) (**Figure 1C**) (23, 28). Subcutaneous semaglutide has also been compared with basal insulin. In SUSTAIN 4, in patients uncontrolled on metformin ± a sulfonylurea, subcutaneous semaglutide 0.5 mg and 1.0 mg produced greater HbA_{1c} reductions than insulin glargine over 30 weeks (–1.2% and –1.6% vs. –0.8%; both $p < 0.0001$) (19).

Patients With Advanced T2D

For patients with advanced uncontrolled T2D already receiving insulin, subcutaneous semaglutide (0.5 mg and 1.0 mg) and oral semaglutide (7 mg and 14 mg) both reduced HbA_{1c} significantly more than placebo ($p < 0.001$) (**Figure 1D**) (20, 26). In SUSTAIN 5, insulin dose decreased from baseline to week 30 with subcutaneous semaglutide 0.5 mg, semaglutide 1.0 mg, and placebo (geometric means from 39.3 to 35.4, from 37.4 to 31.5, and from 36.6 to 35.2 IU, respectively) (20). In PIONEER 8, total daily insulin dose significantly decreased from baseline to week 26 with oral semaglutide 7 mg and 14 mg compared with placebo (–8 IU and –9 IU vs. –1 IU; both $p < 0.001$) (26).

In patients with mean T2D duration of 14 years and with moderate renal impairment in PIONEER 5, oral semaglutide 14 mg was significantly more effective than placebo in reducing HbA_{1c} at 26 weeks (–1.0% vs. –0.2%; $p < 0.001$) (**Figure 1D**) (31).

Achievement of Glycemic Targets

For both formulations, effective HbA_{1c} reductions allowed the majority of patients to achieve glycemic targets. In the SUSTAIN program, 66–80% achieved HbA_{1c} <7% with subcutaneous semaglutide 1.0 mg, while 55–77% achieved HbA_{1c} <7% with oral semaglutide 14 mg in the PIONEER program (16–20, 22–31, 33).

BODY WEIGHT REDUCTIONS WITH SEMAGLUTIDE

Patients With Early T2D Being Treated With Diet and Exercise

In patients with early T2D, subcutaneous semaglutide 1.0 mg and oral semaglutide 14 mg monotherapy were able to reduce body weight by 4.5 kg and 3.7 kg, respectively, which were superior to the reductions seen with placebo (1.0 and 1.4 kg, respectively) ($p < 0.001$) (**Figure 2A**) (16, 27).

Patients With Established T2D Being Treated With One to Three OADs

In the SUSTAIN 2, PIONEER 3, and PIONEER 7 trials in patients with established T2D receiving one or two OADs, subcutaneous

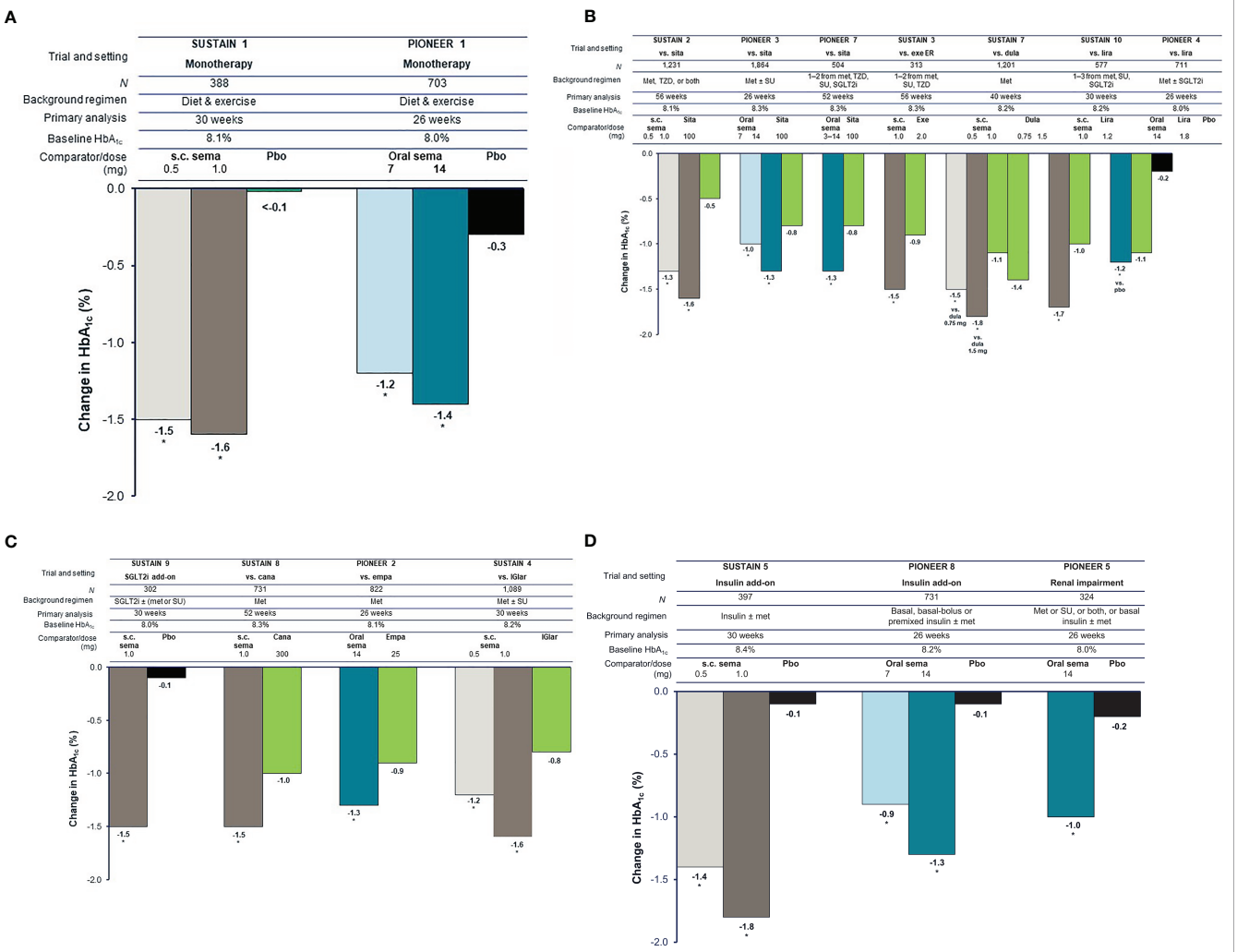

FIGURE 1 | Reduction in HbA_{1c} with semaglutide and comparators in global glycemic efficacy trials (16–20, 22–26, 31, 33). **(A)** Trials in early T2D (mean duration 3–4 years). **(B)** Trials in established T2D (mean duration 6–10 years) with incretin-based therapies as comparators. **(C)** Trials in established T2D (mean duration 6–10 years) with other comparators. **(D)** Trials in advanced T2D (mean duration 13–15 years). For the SUSTAIN trials shown, HbA_{1c} reduction at study end (weeks 30, 40, 52, or 56) was the primary endpoint. Estimated mean changes from baseline in HbA_{1c} included only data obtained before initiation of any rescue medication or before premature treatment discontinuation. For the PIONEER trials shown, HbA_{1c} reduction at week 26 was the primary endpoint, except for PIONEER 7 where the primary endpoint was achievement of HbA_{1c} <7.0% (53 mmol/mol) at week 52. Estimated mean changes from baseline in HbA_{1c} are regardless of trial product discontinuation or rescue medication (treatment policy estimand). Oral semaglutide 3 mg daily was also tested in PIONEER 1, PIONEER 3, and PIONEER 8; however, this dose is not recommended as a maintenance dose [Rybelsus SPC] and data are not shown (except for in PIONEER 7 as part of a flexible dosing approach in which investigators could increase or decrease the dose of oral semaglutide between 3, 7 and 14 mg according to efficacy and tolerability criteria and clinical judgment). *$p < 0.05$ for the estimated treatment difference with semaglutide vs. comparator. Cana, canagliflozin; dula, dulaglutide; empa, empagliflozin; ER, extended release; exe, exenatide; HbA_{1c}, glycated hemoglobin; IGlar, insulin glargine; lira, liraglutide; met, metformin; N, number of randomized patients; pbo, placebo; s.c., subcutaneous; sema, semaglutide; SGLT2i, sodium-glucose co-transporter-2 inhibitor; sita, sitagliptin; SU, sulfonylurea; T2D, type 2 diabetes; TZD, thiazolidinedione.

semaglutide (0.5 mg and 1.0 mg) and oral semaglutide (7 mg, 14 mg, and flexibly dosed) reduced body weight significantly more than sitagliptin (all $p < 0.001$) (**Figure 2B**) (17, 29, 33). When compared with other GLP-1RAs in patients with established T2D, subcutaneous semaglutide 1.0 mg significantly reduced body weight more than once-weekly exenatide ER 2.0 mg (–5.6 kg vs. –1.9 kg), once-weekly dulaglutide 1.5 mg (–6.5 kg vs. –3.0 kg), and once-daily liraglutide 1.2 mg (–5.8 kg vs. –1.9 kg) (all $p < 0.001$) (**Figure 2B**) (18, 22, 25). Oral semaglutide 14 mg reduced body weight significantly more than liraglutide 1.8 mg in PIONEER 4 (–4.4 kg vs. –3.1 kg; $p < 0.001$) (30).

When added to SGLT2i background therapy, subcutaneous semaglutide 1.0 mg reduced body weight by 4.7 kg compared with 0.9 kg with placebo ($p < 0.001$) in SUSTAIN 9 (24) (**Figure 2C**). When compared with SGLT2i as second-line therapy, subcutaneous semaglutide 1.0 mg reduced body weight significantly more than canagliflozin 300 mg at 52 weeks (–5.3 kg vs. –4.2 kg; $p < 0.01$), while oral semaglutide 14 mg produced similar

body weight reductions as empagliflozin 25 mg at 26 weeks (–3.8 kg vs. –3.7 kg) (**Figure 2C**) (23, 28). In SUSTAIN 4, patients on one or two OADs who received subcutaneous semaglutide 1.0 mg lost 5.2 kg compared with weight gain of 1.2 kg with insulin glargine after 30 weeks ($p < 0.001$) (19).

Patients With Advanced T2D

In advanced T2D, both subcutaneous semaglutide (0.5 mg and 1.0 mg) and oral semaglutide (7 mg and 14 mg) reduced body weight significantly more than placebo in patients inadequately controlled on insulin ($p < 0.001$) (**Figure 2D**) (20, 26). In PIONEER 5, patients with moderate renal impairment treated with oral semaglutide 14 mg lost 3.4 kg, while those on placebo lost 0.9 kg at 26 weeks ($p < 0.001$) (**Figure 2D**) (31).

PATIENT-REPORTED OUTCOMES

Patient-reported outcomes assess psychological aspects such as treatment satisfaction, patient wellbeing, health status, and quality of life to complement clinical outcomes and provide an understanding of the physical, social, and emotional impact of treatment regimens (36).

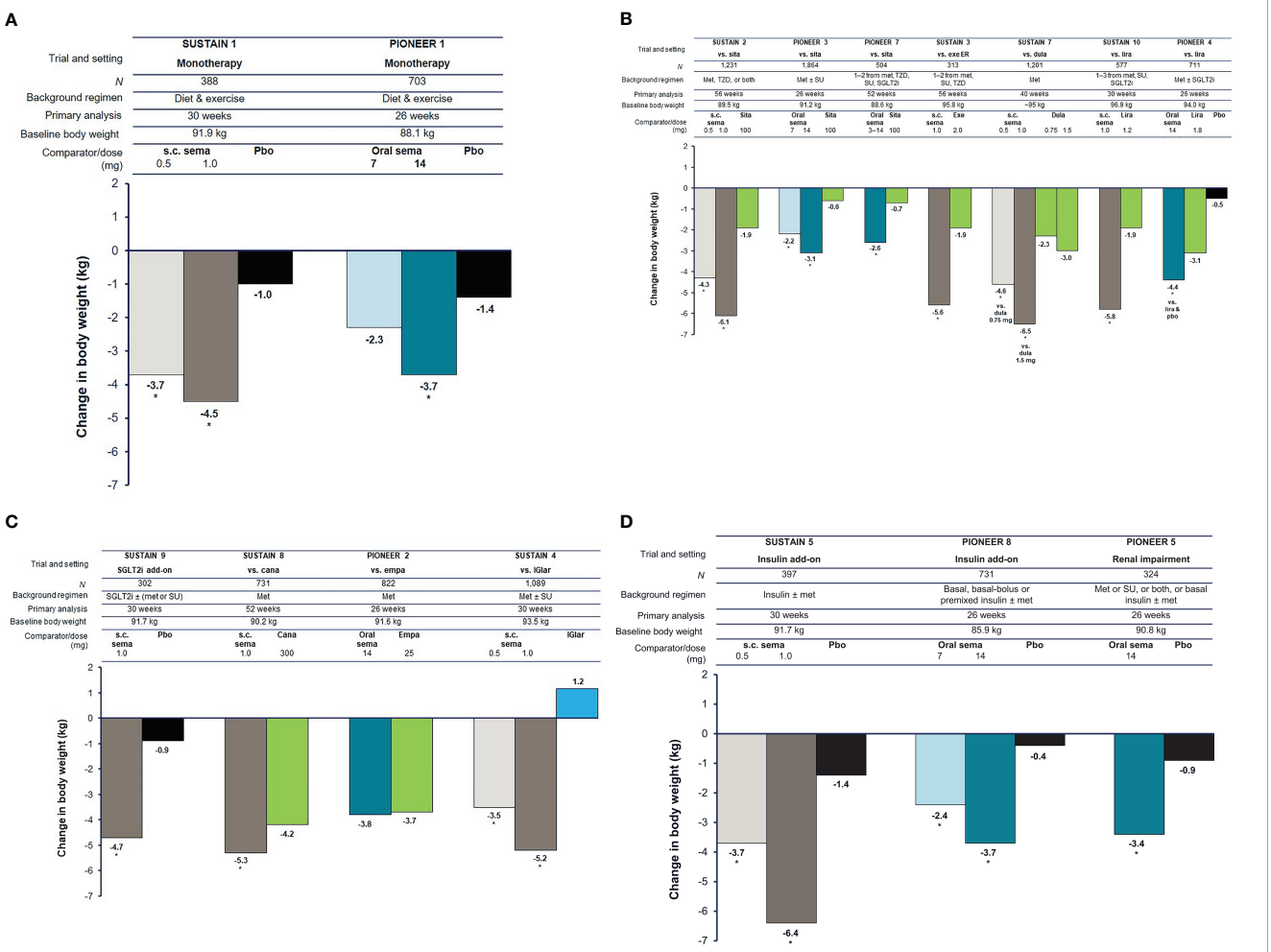

FIGURE 2 | Reduction in body weight with semaglutide and comparators (16–20, 22–26, 31, 33). **(A)** Trials in early T2D (3–4 years). **(B)** Trials in established T2D (6–10 years) with incretin-based therapies as comparators. **(C)** Trials in established T2D (6–10 years) with other comparators. **(D)** Trials in advanced T2D (13–15 years). For the SUSTAIN trials shown, estimated mean changes from baseline in body weight included only data obtained before initiation of any rescue medication or before premature treatment discontinuation. For the PIONEER trials shown, estimated mean changes from baseline in body weight are regardless of trial product discontinuation or rescue medication (treatment policy estimand). Oral semaglutide 3 mg daily was also tested in PIONEER 1, PIONEER 3, and PIONEER 8; however, this dose is not recommended as a maintenance dose [Rybelsus SPC] and data are not shown (except for in PIONEER 7 as part of a flexible dosing approach in which investigators could increase or decrease the dose of oral semaglutide between 3, 7 and 14 mg according to efficacy and tolerability criteria and clinical judgment). *$p < 0.05$ for the estimated treatment difference with semaglutide vs. comparator. Cana, canagliflozin; dula, dulaglutide; empa, empagliflozin; ER, extended release; exe, exenatide; IGlar, insulin glargine; lira, liraglutide; met, metformin; pbo, placebo; s.c., subcutaneous; sema, semaglutide; SGLT2i, sodium-glucose co-transporter-2 inhibitor; sita, sitagliptin; SU, sulfonylurea; T2D, type 2 diabetes; TZD, thiazolidinedione.

When treatment satisfaction was measured by the Diabetes Treatment Satisfaction Questionnaire (DTSQ) in patients treated with subcutaneous semaglutide in SUSTAIN 2–5, improvements were significantly greater vs. comparators/placebo (all $p < 0.05$) and were generally greater in patients who achieved vs. did not achieve weight loss and glycemic targets (37). In SUSTAIN 7, improvements in overall treatment satisfaction were generally similar between semaglutide and dulaglutide, irrespective of weight loss or glycemic control.

When the DTSQ was used in PIONEER 4, 7, and 8, total treatment satisfaction scores with oral semaglutide were similar to active comparators and better than with placebo (except in PIONEER 5 in which scores for oral semaglutide and placebo were similar) (26, 30, 31, 33). In PIONEER 4, DTSQ scores favored oral semaglutide over placebo for all items at weeks 26 and 52 except 'feeling of unacceptably low blood sugars' (weeks 26 and 52) and 'flexibility of treatment' (week 52), which were similar (30). There were no differences in treatment satisfaction between oral semaglutide and liraglutide 1.8 mg.

In PIONEER 7, change from baseline to week 52 in DTSQ scores for satisfaction with treatment, convenience and flexibility of treatment, and total treatment satisfaction appeared similar for oral semaglutide and sitagliptin despite the specific dosing instructions needed with oral semaglutide (33). In PIONEER 5 and 8 in advanced T2D, the frequency of patient-perceived hyperglycemia was significantly lower in the oral semaglutide group than in the placebo group (26, 31).

The 36-item Short-Form Survey (SF-36) version 2 was used to assess physical function, pain, general health, mental health, emotional function, and social function in SUSTAIN 2, 4, and 7 (17, 19, 22). In SUSTAIN 2, several aspects on the SF-36 improved with subcutaneous semaglutide vs. sitagliptin and none worsened (17). In SUSTAIN 4, subcutaneous semaglutide 1.0 mg demonstrated significant improvement compared with insulin glargine in the role-emotional (measure of role limitations due to emotional problems) and general health domains of the SF-36, but not in other domains (19). In SUSTAIN 7, SF-36 scores were similar between subcutaneous semaglutide and dulaglutide (22).

SF-36 version 2 scores were similar between oral semaglutide and sitagliptin in PIONEER 3 and PIONEER 7 (29, 33). In PIONEER 2, scores using the SF-36 were broadly similar with oral semaglutide 14 mg and empagliflozin 25 mg; however, scores were significantly better for oral semaglutide than empagliflozin for the domains of general health and social functioning at week 26, but favored empagliflozin for the role-physical domain and physical component summary scores at week 52 (28). In patients with renal impairment in PIONEER 5, SF-36 scores at week 26 significantly favored oral semaglutide over placebo for the physical component summary and the role-physical, bodily pain, and social functioning domains (31).

For patients with more advanced disease in PIONEER 8, oral semaglutide 14 mg significantly improved general health at week 52 and mental health at week 26 compared with placebo (26). Furthermore, significant improvements in the psychosocial domain and total score of the Impact of Weight on Quality of Life-Lite Clinical Trial Version were observed with oral semaglutide 14 mg vs. placebo at weeks 26 and 52.

EXPOSURE–RESPONSE RELATIONSHIPS

In pharmacokinetic studies, lower bioavailability with oral administration of semaglutide appeared to result in more variable plasma concentrations compared with subcutaneous administration (38, 39). Using data from the SUSTAIN and PIONEER trials, population pharmacokinetic and exposure–response analyses were used to investigate if the oral route of administration changed the efficacy and tolerability of semaglutide compared with subcutaneous administration (39). Exposure–response analyses showed greater HbA_{1c} reductions with increasing semaglutide exposure and the same relationship was observed with body weight reductions. The exposure range with oral semaglutide was found to be wider than for subcutaneous semaglutide, consistent with the more variable plasma concentrations with oral treatment, but there was considerable overlap between oral semaglutide 7 and 14 mg and subcutaneous semaglutide 0.5 and 1.0 mg. The authors concluded that similar exposure–response relationships were observed for efficacy (HbA_{1c} and body weight) and also for tolerability (nausea and vomiting) of semaglutide, regardless of the route of administration.

SELECTION OF THE MOST APPROPRIATE FORMULATION

With the efficacy of both formulations established and approval granted, healthcare professionals and patients are in a position to choose the formulation that best suits the needs of the individual patient (**Figure 3**).

Regarding efficacy, a network meta-analysis showed that once-daily oral semaglutide 14 mg was associated with numerically greater HbA_{1c} reductions than once-weekly subcutaneous semaglutide 0.5 mg and also dulaglutide 1.5 mg and liraglutide 1.8 mg (40). No statistical difference in efficacy was observed between oral semaglutide 14 mg and once-weekly subcutaneous semaglutide 1.0 mg at week 26, although HbA_{1c} reductions were numerically greater with subcutaneous semaglutide 1.0 mg. Oral semaglutide provided a significantly greater reduction in body weight than all GLP-1RA comparators studied except subcutaneous semaglutide 0.5 mg and 1.0 mg (40). No head-to-head studies have compared approved doses of oral semaglutide (7 mg and 14 mg) vs. once-weekly subcutaneous semaglutide (0.5 mg and 1.0 mg). Doses of oral semaglutide of 2.5 mg, 5 mg, 10 mg, 20 mg, and 40 mg were studied in the phase II trial (41). The phase II trial included an arm in which patients received subcutaneous semaglutide 1.0 mg; however, the primary endpoint of glycemic efficacy was only statistically significant compared with placebo, not between active oral vs. injectable treatment groups (41). In the exposure analyses, average exposure for once-weekly subcutaneous

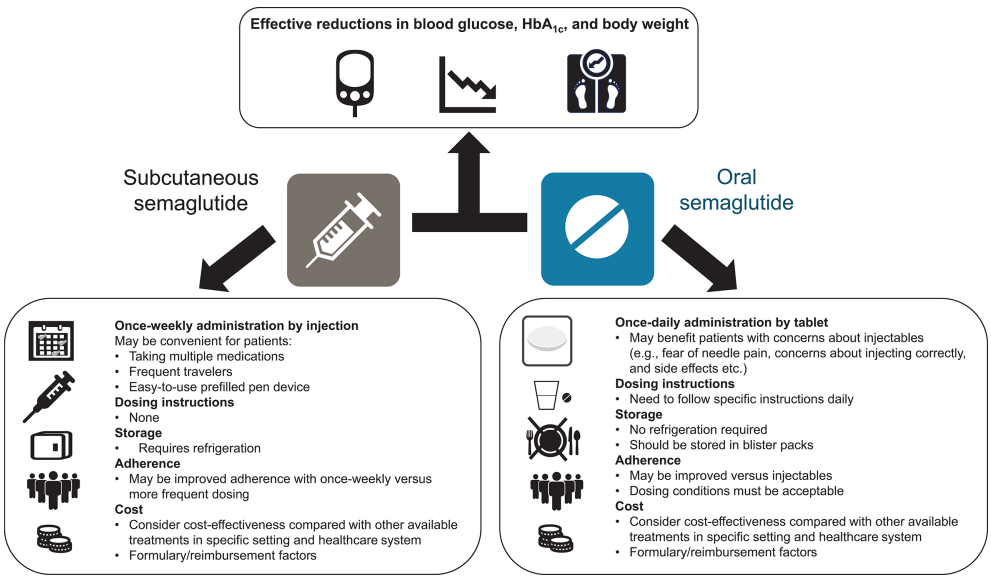

FIGURE 3 | Overview of considerations related to the use of subcutaneous and oral formulations of semaglutide. HbA_{1c}, glycated hemoglobin.

semaglutide 1.0 mg was higher than with oral semaglutide 14 mg, but as mentioned, the exposure range with oral semaglutide was wider than for subcutaneous dosing, with a considerable overlap between oral semaglutide 7 and 14 mg and subcutaneous semaglutide 0.5 and 1.0 mg (39).

As discussed in detail in (15), the risk of hypoglycemia is low with both formulations of semaglutide, despite the effective HbA_{1c} reductions (16–20, 22–31, 33), which may be due to the glucose-dependent mechanism of action of GLP-1RAs. The safety profile is very similar for both formulations (16–20, 22–31, 33). Injection-site reactions are uncommon with the subcutaneous formulation (18). Subcutaneous semaglutide has proven cardiovascular benefit (21); this has not been demonstrated for oral semaglutide, although cardiovascular safety has been shown (32, 34).

Given the generally similar efficacy and safety profiles of the two formulations, other considerations may need to be taken into account when selecting the most appropriate formulation to use. Many patients are reluctant to initiate injectable treatment and barriers to their use include fear of injection pain, feelings of failure related to disease progression, embarrassment/concerns about injecting in public, being nervous about injecting correctly, and adverse events (42, 43). Physicians may also be reluctant to start injectable therapy due to concerns over patient adherence, perceived fear of injection pain, and lack of knowledge of newer therapies (44). For patients who are reluctant to initiate injectable therapy and have a preference for oral administration, oral semaglutide may represent the more appropriate choice. However, the effective use of oral semaglutide depends on the patient following certain dosing instructions. Patients are instructed to swallow the oral semaglutide tablet whole on waking and on an empty stomach, with a sip of water (up to half a glass of water equivalent to 120 mL), and to wait at least 30 minutes before eating, drinking, or taking other oral medications that day (13, 14). The beneficial effects of oral semaglutide may be attenuated if this guidance is not followed.

In a survey for more than 500 patients presented with hypothetical drug profiles, a greater proportion of respondents preferred a once-daily oral treatment with fewer dosing requirements, similar to empagliflozin (41%) or sitagliptin (31%), than a profile corresponding to that of oral semaglutide (11%), citing factors such as fasting and potential gastrointestinal effects (45). However, in an actual clinical trial setting (PIONEER 7), patient-reported satisfaction and treatment convenience were similar between oral semaglutide and sitagliptin (33). Another survey of 600 patients compared preferences regarding once-daily oral semaglutide and a once-weekly injectable GLP-1RA. Three times as many patients preferred the oral to the injectable treatment when initially asked (77% vs 24%), but after they were given more detail on the actual dosing requirements, just over half of respondents indicated a preference for oral semaglutide (46). However, preferences may vary according to factors such as geographical region. For example, a survey of Japanese patients (n=500) found that approximately 90% of patients preferred the profile of once-daily oral semaglutide to that of once-weekly injectable dulaglutide (47).

Some patients may prefer the less frequent once-weekly administration of subcutaneous semaglutide over the need to take a tablet with specific dosing instructions each morning, e.g., those with multiple concomitant medications. Patients generally report a preference for less frequent dosing with injectable GLP-1RAs (48–51), and adherence and persistence rates are improved with once-weekly injectable GLP-1RAs compared with more frequently dosed treatments (52–56). In addition, the subcutaneous version of semaglutide might be preferred for patients prescribed levothyroxine, which should itself be taken

in the morning on an empty stomach, half an hour before breakfast (57). The use of an injection pen may also be considered more convenient and less burdensome than the need for daily tablets by some patients, e.g., those who travel frequently. The subcutaneous formulation requires refrigeration, unlike tablets, which may be a factor for some patients.

Cost-effectiveness is also likely to be a consideration. The relative cost-effectiveness of the two semaglutide formulations has not been directly compared. However, both subcutaneous and oral semaglutide have been reported to be more cost-effective and offer lower cost-of-control compared with other injectable GLP-1RAs and oral glucose-lowering drugs, although this may vary between different patient cohorts and healthcare settings (58–64). In addition, switching may be dependent on non-medical decisions outwith the physician's choice, with a recent expert consensus indicating that non-medical triggers for switching to subcutaneous semaglutide from other GLP-1RAs also included formulary changes and insurance mandates, as well as cost considerations (65).

To conclude, when treatment intensification is needed to improve glycemic control, semaglutide offers the benefits of an effective GLP-1RA in both an injectable and an oral formulation. Selection of the most appropriate formulation can be made on an individual basis to best suit the patient's preferences and needs.

AUTHOR CONTRIBUTIONS

The author was involved with drafting and/or critically reviewing all drafts during the development of the article, and provided final approval for submission.

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REVIEW
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Clinical Perspectives on the Use of Subcutaneous and Oral Formulations of Semaglutide

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Early and effective glycemic control can prevent or delay the complications associated with type 2 diabetes (T2D). The benefits of glucagon-like peptide-1 receptor agonists (GLP-1RAs) are becoming increasingly recognized and they now feature prominently in international T2D treatment recommendations and guidelines across the disease continuum. However, despite providing effective glycemic control, weight loss, and a low risk of hypoglycemia, GLP-1RAs are currently underutilized in clinical practice. The long-acting GLP-1RA, semaglutide, is available for once-weekly injection and in a new once-daily oral formulation. Semaglutide is an advantageous choice for the treatment of T2D since it has greater efficacy in reducing glycated hemoglobin and body weight compared with other GLP-1RAs, has demonstrated benefits in reducing major adverse cardiovascular events, and has a favorable profile in special populations (e.g., patients with hepatic impairment or renal impairment). The oral formulation represents a useful option to help improve acceptance and adherence compared with injectable formulations for patients with a preference for oral therapy, and may lead to earlier and broader use of GLP-1RAs in the T2D treatment trajectory. Oral semaglutide should be taken on an empty stomach, which may influence the choice of formulation. As with most GLP-1RAs, initial dose escalation of semaglutide is required for both formulations to mitigate gastrointestinal adverse events. There are also specific dose instructions to follow with oral semaglutide to ensure sufficient gastric absorption. The evidence base surrounding the clinical use of semaglutide is being further expanded with trials investigating effects on diabetic retinopathy, cardiovascular outcomes, and on the common T2D comorbidities of obesity, chronic kidney disease, and non-alcoholic steatohepatitis. These will provide further information about whether the benefits of semaglutide extend to these other indications.

Keywords: glucagon-like peptide-1 receptor agonist (GLP-1RA), oral, subcutaneous, semaglutide, type 2 diabetes

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INTRODUCTION

For patients with type 2 diabetes (T2D), early control of hyperglycemia after diagnosis is important to prevent debilitating long-term complications and to reduce diabetes-related mortality (1, 2). This is illustrated by the results from a recent registry analysis including 34,737 patients, which showed that glycated hemoglobin (HbA_{1c}) levels between 7.0% and <8.0% (53 to <64 mmol/mol) for the

first year after diagnosis were associated with a greater risk of future microvascular complications (hazard ratio [HR] 1.39; 95% confidence interval [CI] 1.23–1.58), macrovascular events (HR 1.29; 95% CI 1.20–1.38), and mortality (HR 1.29; 95% CI 1.10–1.51) compared with levels of <6.5% (<48 mmol/mol) (2).

Glycemic management in patients with T2D has become more individualized, and there are now several different treatment options available, with various factors influencing the most appropriate choice for individual patients. Glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs) are a well-established class of glucose-lowering agents that act on multiple pathophysiological defects in T2D, providing effective glycemic control, weight loss, and a low risk of hypoglycemia, with a well-characterized safety profile (3). In addition, as described by Smits and van Raalte in this supplement (4), certain GLP-1RAs have also been shown to reduce the risk of cardiovascular (CV) events, as well as some renal-related endpoints, in CV outcomes trials (CVOTs) (5–8).

This article will review the place of GLP-1RAs in therapy and, within this class, specifically discuss some clinical considerations around the use of the long-acting GLP-1RA, semaglutide, when given subcutaneously or *via* its new oral formulation.

WHAT IS THE PLACE OF GLP-1RAS IN THERAPY?

Metformin is the first-line therapy of choice for most patients with T2D; however, if patients do not achieve their individualized HbA_{1c} target after 3–6 months, another glucose-lowering medication should be added (9). In 2018, the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) consensus for the management of hyperglycemia in T2D presented a new decision algorithm and, as part of this, key patient characteristics should be assessed including the existence of comorbidities, such as atherosclerotic CV disease (CVD), chronic kidney disease (CKD), or heart failure (HF), which necessitate the preferential use of certain classes of glucose-lowering agents as second-line therapy (9, 10).

In patients who have established atherosclerotic CVD or evidence of high atherosclerotic CVD risk, the ADA/EASD consensus now recommends either a GLP-1RA or a sodium-glucose co-transporter-2 inhibitor (SGLT2i) (if estimated glomerular filtration rate [eGFR] is adequate) with proven efficacy to reduce the risk of CV events (9, 11). This change represents a shift in diabetes management beyond glycemic control alone and was based on CVOTs, which demonstrated that several GLP-1RAs and SGLT2is reduced the risk of major adverse CV events (MACE; CV death, nonfatal myocardial infarction, and nonfatal stroke) compared with placebo (5–8, 12, 13). A 2019 update to the ADA/EASD consensus, based on results from the REWIND CVOT with dulaglutide, suggests that a GLP-1RA or SGLT2i should also be considered in high-risk T2D patients without established CVD but with indicators of high CV risk, such as age ≥55 years with coronary, carotid, or lower-extremity artery stenosis >50%, left ventricular hypertrophy, an eGFR <60 mL/min/1.73 m^2, or albuminuria (8, 11). Of note, beneficial outcomes observed in CVOTs do not appear to be restricted to patients with elevated HbA_{1c}, and the 2019 update of the ADA/EASD consensus suggests that GLP-1RAs or SGLT2is should be considered independently of baseline HbA_{1c} or the individualized HbA_{1c} target in patients at high CV risk (11). In recent guidelines from the European Society of Cardiology on diabetes, prediabetes, and CVD, in collaboration with the EASD, a GLP-1RA or SGLT2i with proven CVD benefit is recommended as an add-on therapy to metformin and even as a first-line therapy in drug-naïve or metformin-intolerant patients with T2D and CVD or at high or very high CV risk (14).

For patients in which HF or CKD predominates, the ADA/EASD consensus recommends an SGLT2i with evidence of reducing HF and/or CKD progression, or if SGLT2is are not tolerated or contraindicated or if eGFR is less than adequate, a GLP-1RA with proven CV benefit can be added (11). If further treatment intensification is needed after second-line SGLT2i therapy, a GLP-1RA may be added (11). Recent results from a meta-analysis indicate greater reductions in HbA_{1c}, body weight, and systolic blood pressure with a lower requirement of rescue therapy when a GLP-1RA was added in combination with an SGLT2i vs. SGLT2i monotherapy alone (15).

For patients without CVD, the ADA/EASD consensus advocates involving specific factors that could impact on the choice of treatment, including the need to avoid weight gain and/or hypoglycemia, in the decision cycle (9, 11). In addition, the importance of choosing treatment regimens to optimize adherence and persistence is emphasized (9). For patients without established CVD but with a compelling need to minimize weight gain or promote weight loss, either a GLP-1RA with good efficacy for weight loss or an SGLT2i is recommended (9, 11). For patients without established CVD but with a compelling need to minimize hypoglycemia, a GLP-1RA, an SGLT2i, a dipeptidyl peptidase-4 inhibitor, or a thiazolidinedione are the recommended options. A sulfonylurea or a thiazolidinedione should be considered when cost is a major issue.

Current Underutilization

Despite being effective glucose-lowering therapies with CV and renal benefits, GLP-1RAs are often underutilized. A nationwide analysis in Denmark found that, while the use of GLP-1RAs has increased since their introduction in 2005, they still only accounted for 8% of all glucose-lowering drugs used in 2017 (16). In a survey of patients who initiated a GLP-1RA in Northern Italy over the period 2010 to 2018 (N = 5,408), it appeared that over time GLP-1RAs were being prescribed to patients with progressively more advanced disease, with significant increases in baseline age, diabetes duration, presence of CVD, and insulin use in patients receiving GLP-1RA therapy during the study period (17).

This apparent delay in prescribing GLP-1RAs and intensifying treatment, despite poor glycemic control in a substantial proportion of patients, was also seen in a UK survey of 113 physicians who contributed data for 1,096 patients (18). The median time from diagnosis to GLP-1RA initiation was

6.1 years and patients had HbA_{1c} values above 7.0% for a median of 13.5 months prior to switching from their last oral regimen to a GLP-1RA. In a UK physician perceptions survey completed in 2014, factors that most commonly caused hesitation when prescribing GLP-1RAs included that they were not considered first-line therapy according to guidelines, their injectable mode of administration, cost, and the potential for gastrointestinal (GI) adverse effects (19). The most common reasons reported for prescribing GLP-1RAs were weight loss, good efficacy, and low hypoglycemia risk.

DEVELOPMENT OF GLP-1RAS AND SEMAGLUTIDE

Although GLP-1RAs act *via* the same overall mechanism, they vary structurally, and differ in their pharmacokinetics and clinical specifics (**Table 1**), with some degree of heterogeneity in respect to their ability to reduce HbA_{1c} and body weight, and evidence of cardiorenal protection (27, 28). The first GLP-1RAs to be developed needed to be administered subcutaneously twice daily (exenatide (20)) or once daily (lixisenatide (21) and liraglutide (22)). Subsequent developments led to the approval of longer-acting GLP-1RAs that could be administered once weekly (exenatide extended release [ER] (23), dulaglutide (24), and semaglutide (25)) to reduce the injection burden and improve convenience. Indeed, once-weekly regimens have been associated with better adherence than more frequently dosed agents (exenatide vs. liraglutide) (29), and this may lead to improved outcomes.

Semaglutide has 94% sequence homology with native GLP-1, with three key structural differences that prolong its half-life to approximately one week, without compromising GLP-1 receptor binding (25, 30). In the SUSTAIN program, subcutaneous semaglutide consistently demonstrated superior and sustained glycemic control and weight loss compared with comparators across the T2D disease continuum (31). As reviewed by Meier in this supplement (32), in head-to-head trials with other long-acting GLP-1RAs, subcutaneous semaglutide 1.0 mg produced superior HbA_{1c} and weight reductions compared with exenatide ER 2.0 mg (estimated treatment difference [ETD] –0.62% and 3.78 kg; both $p < 0.0001$, respectively) (33) and with dulaglutide 1.5 mg (ETD –0.41% and 3.55 kg; both $p < 0.0001$, respectively) (34). Since the approval of once-weekly subcutaneous semaglutide in 2017/2018, further information is being gathered through an ongoing series of prospective, noninterventional real-world studies across 10 different countries, which aim to determine its efficacy, safety, and treatment satisfaction in patients in local clinical practice over approximately 30 weeks of treatment (35–43).

It is known that some patients prefer oral over injectable medications (44, 45), and lower treatment adherence has been reported with more frequent administration or when patients perceive the treatment as difficult or inconvenient (45, 46). Oral medication may also help to overcome the clinical inertia seen in the frequent reluctance to initiate injectable medicines. For this reason, an oral formulation of semaglutide was developed and was approved for the treatment of adults with T2D by the U.S. Food and Drug Administration in September 2019 and by the European Medicines Agency in April 2020. In Europe, subcutaneous semaglutide and oral semaglutide are indicated as adjuncts to diet/exercise either as monotherapy, when metformin is considered inappropriate due to intolerance or contraindications, or in combination with other glucose-lowering medication(s), for patients who do not have sufficient glycemic control (25, 26). As the first oral formulation of a GLP-1RA, oral semaglutide represents a useful option to help improve acceptance and adherence compared with injectable formulations in those patients with a preference for oral therapy, and may contribute to the reversal of current underutilization, potentially leading to earlier initiation of GLP-1RAs in the T2D disease continuum.

DOSING CONSIDERATIONS WITH SUBCUTANEOUS AND ORAL SEMAGLUTIDE

Dose Escalation

As a class, GLP-1RAs have a well-defined safety profile. The most commonly reported adverse events (AEs) are GI-related effects, including nausea, diarrhea, and vomiting, which are generally mild-to-moderate in severity and transient in nature (47). In general, GI AEs are most frequent shortly after treatment initiation and therefore slow up-titration of the dose is recommended for most GLP-1RAs (**Table 1**). For subcutaneous semaglutide, the starting dose is 0.25 mg once weekly, and after 4 weeks, the dose should be increased to 0.5 mg once weekly (25). After at least 4 weeks on a dose of 0.5 mg once weekly, the dose can be increased to 1 mg once weekly to further improve glycemic control. For oral semaglutide, patients should start treatment with the 3 mg dose once daily for 1 month, then increase to 7 mg once daily (26). After at least 1 month on a dose of 7 mg once daily, the dose can be increased to a maintenance dose of 14 mg once daily if needed to further improve glycemic control. When starting semaglutide, patients should be reassured that GI AEs do not affect the majority of patients and are likely to be only mild-to-moderate in severity and transient (25, 26). To help minimize any nausea, patients could be advised to eat smaller meals and stop when they feel full, and to avoid meals with a high fat content (48–50).

Dosing Instructions

Subcutaneous semaglutide can be dosed at any time on the day of the weekly injection, with or without meals (25). For oral semaglutide, the presence of food in the stomach impairs absorption (51, 52). Patients are advised to swallow the oral semaglutide tablet on an empty stomach, with a sip of water (up to half a glass of water equivalent to 120 mL), and to wait at least 30 minutes before eating, drinking, or taking other oral medications (26). This may be problematic for some patients, and may influence their preferred choice of formulation.

TABLE 1 | Summary of the clinical particulars of available GLP-1RAs (20–26).

	Exenatide	Lixisenatide	Liraglutide	Exenatide ER	Dulaglutide	Semaglutide	
Route	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Oral
Frequency	Twice daily	Once daily	Once daily	Once weekly	Once weekly	Once weekly	Once daily
Timing of administration	Within 60 mins of the morning and evening meal	Within 60 mins of any meal (preferably the same meal each day)	Any time (independent of meals) but preferably the same time each day	Any time of day, with or without meals	Any time of day, with or without meals	Any time of day, with or without meals	On an empty stomach 30 mins before eating, drinking, or taking other oral medications
Dosage regimens	Starting: 5 μg	Starting: 10 μg	Starting: 0.6 mg	No up-titration	No up-titration	Starting: 0.25 mg	Starting: 3 mg
	Maintenance: 10 μg	Maintenance: 20 μg	Maintenance: 1.2 mg & 1.8 mg	Maintenance: 2 mg	Maintenance: 0.75 mg for monotherapy or 1.5 mg as add-on (a starting dose of 0.75 mg may be used in vulnerable patients)	Maintenance: 0.5 mg & 1.0 mg	Maintenance: 7 mg & 14 mg
Are dose adjustments needed in special populations?							
Elderly	Exercise caution and proceed conservatively with escalation to 10 μg if >70 years	None needed based on age	None needed based on age	None needed based on age	None needed based on age	None needed based on age	None needed based on age
Renal impairment							
Mild	None	None	None	None	None	None	None
Moderate	Proceed conservatively with escalation to 10 μg	None	None	None	None	None	None
Severe	Not recommended	Not recommended	None	Not recommended	None	None	None
ESRD	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
Hepatic impairment	None	None	Not recommended with severe impairment	None	None	Exercise caution with severe impairment	Exercise caution with severe impairment

ER, extended release; ESRD, end-stage renal disease; GLP-1RA, glucagon-like peptide-1 receptor agonist.

In pharmacokinetic studies, subcutaneous or oral semaglutide did not have clinically relevant effects on the exposure of other widely used medications, such as warfarin, metformin, digoxin, atorvastatin/rosuvastatin (53–55), or the combined oral contraceptive, ethinylestradiol/levonorgestrel (**Figure 1**) (56, 57). In addition, oral semaglutide did not have clinically relevant effects on the exposure of lisinopril or furosemide (53, 54). When tested with omeprazole, which increases gastric pH, no clinically relevant interactions were observed on the exposure of oral semaglutide (58).

In a drug–drug interaction study, levothyroxine exposure was increased by 33% when co-administered with oral semaglutide 14 mg, which may be due to delayed gastric emptying and increased levothyroxine absorption (59). Monitoring of thyroid parameters should therefore be considered when treating patients with oral semaglutide at the same time as levothyroxine (26). When co-administering other oral medications, it is important to adhere to the administration instructions for oral semaglutide, and consider increased monitoring for medications that have a narrow therapeutic index or that require clinical monitoring (60).

In population pharmacokinetic and exposure–response analyses, the exposure range following oral semaglutide was wider than for subcutaneous dosing but with a considerable overlap between oral semaglutide 7 and 14 mg and subcutaneous semaglutide 0.5 and 1.0 mg (61). The effect of switching between oral and subcutaneous semaglutide cannot easily be predicted because of the high pharmacokinetic inter-individual variability of oral semaglutide; however, exposure after 14 mg oral semaglutide once daily appears comparable with 0.5 mg subcutaneous semaglutide once weekly (26). It is recommended that patients switching from once-weekly subcutaneous semaglutide at a dose of 0.5 mg can be transitioned onto oral semaglutide at a dose of 7 or 14 mg once daily, up to 7 days after their last injection of subcutaneous semaglutide; however, there is no equivalent oral dose for those switching from subcutaneous semaglutide 1 mg (60).

SEMAGLUTIDE IN RENAL IMPAIRMENT

CKD is a common complication of T2D and a major cause of morbidity and mortality (62). The exendin-4-based GLP-1RAs, exenatide (immediate-release and ER) and lixisenatide are partially renally eliminated and are not recommended in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2)

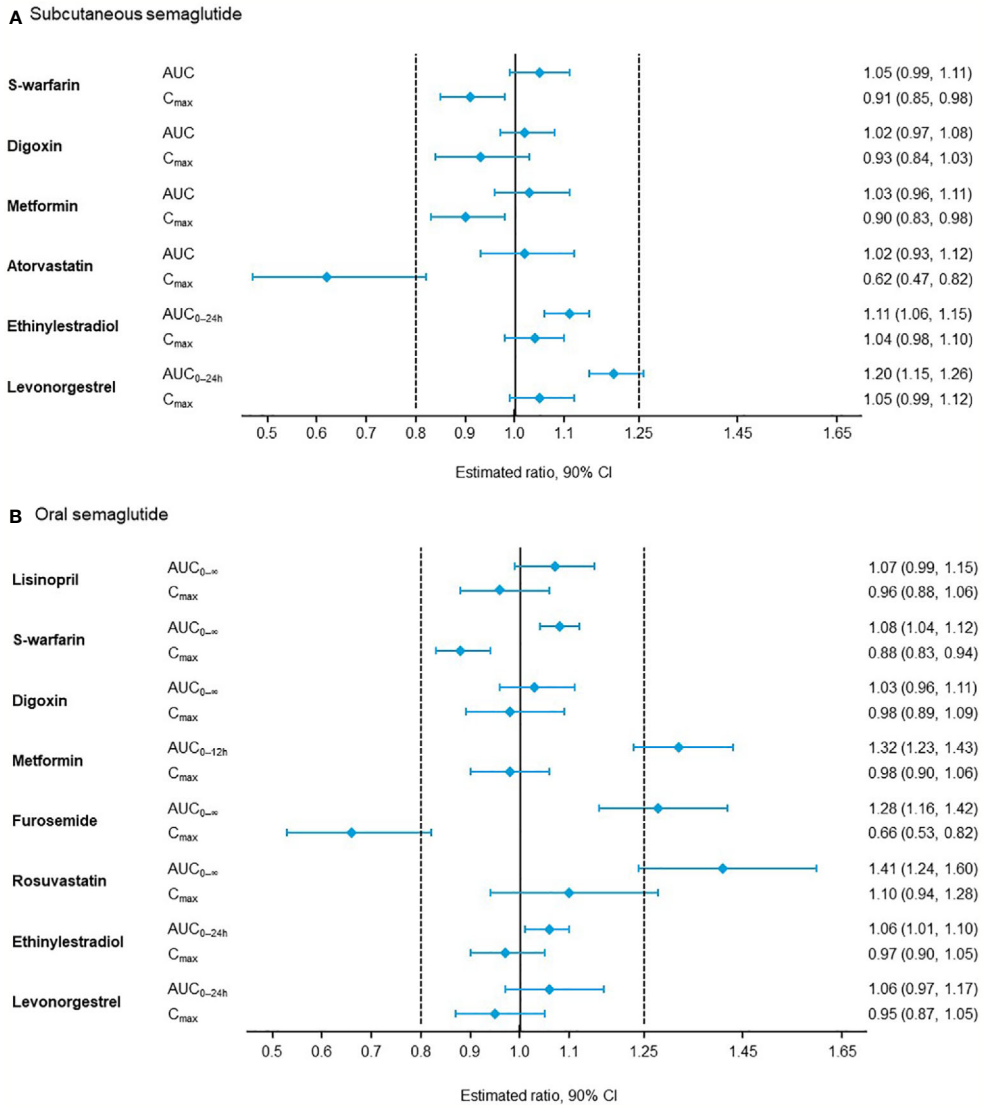

FIGURE 1 | Effect of **(A)** subcutaneous semaglutide and **(B)** oral semaglutide on the pharmacokinetics of co-administered drugs (53–57). AUC, area under the curve; CI, confidence interval; C_{max}, maximum concentration.

(20, 21, 23) (**Table 1**). Furthermore, dose escalation of immediate-release exenatide should proceed conservatively in patients with moderate renal impairment (eGFR 30–50 mL/min/1.73 m^2) (21). Results from pharmacokinetic studies have established that dose adjustments are not necessary when semaglutide (subcutaneous or oral) is used in patients with different levels of renal impairment (25, 26, 63, 64). Like all other GLP-1RAs, semaglutide is not recommended in patients with end-stage renal disease (ESRD) (eGFR <15 mL/min/1.73 m^2) (25, 26).

To provide further data on the use of semaglutide in patients with renal dysfunction, the PIONEER 5 trial evaluated the efficacy and safety of once-daily oral semaglutide 14 mg vs. placebo in 324 patients with T2D and moderate renal impairment (eGFR 30–59 mL/min/1.73 m^2) (65). Superior and significant reductions in HbA_{1c} and body weight were observed with oral semaglutide vs. placebo over 26 weeks, and renal function was unchanged throughout the study in both treatment groups. Patients with CKD were also included in the SUSTAIN 6 and PIONEER 6 CVOTs (6, 66). Indeed, in SUSTAIN 6, the CKD-related endpoint of new or worsening nephropathy was found to occur in significantly fewer patients in the subcutaneous semaglutide group compared with the placebo group (3.8% vs. 6.1%; HR 0.64; 95% CI 0.46–0.88; $p = 0.005$) (6).

GLP-1RAs may exert beneficial actions on the kidneys through reductions in blood glucose, blood pressure, and weight, as well as *via* possible direct cardio-nephroprotective mechanisms, such as improved endothelial dysfunction, reduced oxidative stress, and reduced inflammation (62). The phase III

FLOW trial (NCT03819153) is ongoing to determine the effect of once-weekly subcutaneous semaglutide 1.0 mg vs. placebo on the progression of renal impairment in over 3,000 patients with T2D and CKD (eGFR 50–75 mL/min/1.73 m^2 and urinary albumin-to-creatinine ratio [UACR] >300–<5,000 mg/g or eGFR 25–50 mL/min/1.73 m^2 and UACR >100–<5,000 mg/g) (67). The primary endpoint is the time to the first occurrence of a composite primary outcome event, defined as persistent eGFR decline of ≥50% from trial start, reaching ESRD, death from kidney disease, or death from CVD for up to 5 years.

SEMAGLUTIDE IN HEPATIC IMPAIRMENT

There is a complex interplay between T2D and liver disease, particularly non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), which are common in patients with T2D (68). The mechanisms responsible for the link between NAFLD and T2D are not completely understood but could include genetic factors, insulin resistance, dysfunctional adipose tissue, chronic hyperglycemia, altered gut microbiome, and changes in hepatokines, among others (68, 69).

GLP-1RAs appear to be well-tolerated in patients with hepatic impairment, and dose adjustments are not necessary (**Table 1**) (20–26). Consistent with this, pharmacokinetic studies have established no apparent effect of hepatic impairment on the exposure of semaglutide when each formulation was tested (25, 26, 70, 71).

Novel therapies are in demand for the treatment of NAFLD, and early studies suggested that GLP-1RAs may reduce liver inflammation and fibrosis (72). Potential mechanisms for the GLP-1RAs' benefit in the context of NAFLD include: reduced body weight and body fat through central regulation of satiety; reduced hepatic, skeletal muscle, and adipose tissue insulin resistance due to decrease in body weight; modified intestinal lipoprotein metabolism; and amelioration of dysfunctional adipose tissue and enhancement of insulin release (72, 73). The safety and efficacy of liraglutide 1.8 mg once daily for 48 weeks were tested in a phase II trial in 52 patients with NASH, in which this drug was found to be well-tolerated (74). Furthermore, there was evidence of histological resolution in the end-of-treatment biopsy in 39% of patients in the liraglutide group compared with only 9% in the placebo group.

A phase II trial recently evaluated the effects of once-daily subcutaneous semaglutide (0.1 mg, 0.2 mg, and 0.4 mg) vs. placebo in 320 patients with NASH (75). Treatment with semaglutide 0.4 mg resulted in a significantly higher percentage of patients achieving the primary endpoint of NASH resolution and no worsening of fibrosis than placebo after 72 weeks (59% vs. 17%; $p < 0.001$).

Given the lack of hepatic GLP-1 receptor expression, the potential mechanism of action by which semaglutide results in NASH resolution may be mediated *via* weight loss. However, semaglutide is also associated with improvements in insulin resistance, hepatic lipotoxicity, and hepatic inflammation. In pre-clinical models, improvements in inflammation with liraglutide were shown to be independent of weight reduction, as was prevention of initiation of fibrosis (76). Thus, it appears unlikely that improvements in NASH with GLP-1 receptor agonists are solely mediated *via* weight reduction.

SEMAGLUTIDE IN OBESITY

Compared with other GLP-1RAs, the capability for weight loss appears to be higher with semaglutide, and the ADA/EASD consensus provides the following ranking for weight-loss efficacy: subcutaneous semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide (9). The mechanisms responsible for weight loss have been investigated for both subcutaneous and oral semaglutide (77, 78). In 30 patients with obesity, *ad libitum* energy intake was substantially lower with once-weekly subcutaneous semaglutide (dose escalated to 1.0 mg) vs. placebo for 12 weeks, and this was associated with reduced appetite and food cravings, better control of eating, and lower preference for fatty, energy-dense food (77). Subcutaneous semaglutide induced a 5.0 kg reduction in mean body weight after 12 weeks, which was found to be derived predominantly from body fat mass reduction, assessed by air displacement plethysmography. Consistent results have been observed with once-daily oral semaglutide (dose escalated to 14 mg) vs. placebo in a similar study in 15 patients with T2D (78).

A phase II dose-finding trial evaluated the efficacy and safety of once-daily subcutaneous semaglutide in promoting weight loss (79). In total, 957 patients with obesity (body mass index [BMI] ≥30 kg/m^2) but without T2D were randomized to once-daily subcutaneous semaglutide (dose escalated to 0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg, or 0.4 mg), once-daily subcutaneous liraglutide (dose escalated to 3.0 mg), or placebo, in combination with dietary and physical activity counseling, with the primary endpoint of percentage weight loss at week 52. Estimated mean weight change was –2.3% for the placebo group and ranged from –6.0% with subcutaneous semaglutide 0.05 mg to –13.8% with subcutaneous semaglutide 0.4 mg after 52 weeks (all $p \leq 0.001$). Furthermore, mean body weight reductions with semaglutide at a dose of 0.2 mg or higher were significantly greater than with liraglutide (–7.8%).

These findings paved the way for the phase III STEP (Semaglutide Treatment Effect in People with obesity) program, which is currently investigating body weight changes following treatment with once-weekly 2.4 mg subcutaneous semaglutide (80). This global clinical program has enrolled approximately 5,000 adults with overweight or obesity. The main eligibility criteria for weight in the STEP 1, 3, 4, and 5 trials were BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 with at least one weight-related comorbidity (hypertension, dyslipidemia, obstructive sleep apnea, or CVD), while patients in STEP 2 had to have a BMI ≥27 kg/m^2 and T2D. The primary endpoint of STEP 1–5 is the change from baseline to end of treatment in body weight; the proportion of patients achieving a body weight reduction of ≥5% is a co-primary endpoint in STEP 1–3 and 5. In the completed STEP trials, semaglutide 2.4 mg as an adjunct

to lifestyle intervention led to mean body weight losses of ~15–17% over 68 weeks in patients without T2D (STEP 1, 3 and 4), with a smaller mean weight loss of 9.6% seen in patients with T2D over the same period (STEP 2). At week 68, 86–89% of patients without T2D achieved ≥5% body weight loss (STEP 1, 3 and 4), with 69% of patients with T2D achieving this threshold (STEP 2). Across all studies, semaglutide 2.4 mg also demonstrated benefits beyond weight loss on cardiometabolic parameters and patient-reported outcomes (81–84).

In addition to the STEP program, the effect of semaglutide treatment on CV outcomes is being assessed in adults aged ≥45 years with overweight or obesity. The SELECT phase III trial (NCT03574597) is investigating whether once-weekly subcutaneous semaglutide (up to 2.4 mg) can reduce MACE vs. placebo in approximately 17,500 people with overweight or obesity and established CVD with a follow-up of approximately 5 years (85).

ADDITIONAL LARGE-SCALE ONGOING STUDIES WITH SEMAGLUTIDE

Following the phase III programs for subcutaneous and oral semaglutide, additional questions remain that are being investigated in ongoing studies. In the CVOT, SUSTAIN 6, subcutaneous semaglutide was associated with a higher risk of diabetic retinopathy complications than placebo after 2.1 years (6). Most events occurred early in the trial, and this has been suggested to be attributable to the magnitude and rapidity of the HbA_{1c} reduction in patients with pre-existing diabetic retinopathy (86). Patients with proliferative retinopathy or maculopathy resulting in active treatment were excluded from the PIONEER 6 CVOT, in which no apparent imbalance was observed between oral semaglutide and placebo in the AE reporting of diabetic retinopathy over 16 months (66). The long-term FOCUS phase III trial (NCT03811561) is currently ongoing to specifically investigate the effects of subcutaneous semaglutide on diabetic retinopathy complications (87). Approximately 1,500 patients with T2D and Early Treatment Diabetic Retinopathy Study (ETDRS) level of 10–75 in both eyes and no ocular or intraocular treatment for diabetic retinopathy or diabetic macular edema in the 6 months prior to screening will receive once-weekly subcutaneous semaglutide 1.0 mg or placebo for up to 5 years, with the primary endpoint of progression of 3 steps or more in ETDRS level.

Subcutaneous semaglutide significantly reduced the rate of MACE vs. placebo in a *post-hoc* non-prespecified analysis of SUSTAIN 6, but it is unknown whether oral semaglutide can also reduce CV events (6). In PIONEER 6, oral semaglutide significantly reduced the rate of MACE and decreased all-cause mortality vs. placebo. However, while oral semaglutide was demonstrated to be noninferior to placebo in PIONEER 6, the trial was not powered to assess any potential CV benefit (66).

SOUL (NCT03914326) is an ongoing CVOT evaluating the effects of once-daily oral semaglutide (up to 14 mg) vs. placebo in 9,642 patients with T2D and CVD, cerebrovascular disease, symptomatic peripheral artery disease, or CKD (88). The primary endpoint is time to the first occurrence of MACE, with a follow-up of approximately 5 years. Secondary endpoints will explore the effects of oral semaglutide on other CV endpoints and assess any improvements in additional diabetic complications, including CKD and limb ischemia.

CONCLUSIONS

The benefits of GLP-1RAs are becoming increasingly recognized in international T2D recommendations and, along with other agents targeted at T2D pathophysiology, such as SGLT2is, their initiation early in the disease trajectory is advocated. The higher efficacy of semaglutide in reducing HbA_{1c} and body weight compared with other GLP-1RAs and favorable clinical characteristics make semaglutide, either subcutaneous or oral, an advantageous choice for T2D treatment. Oral semaglutide provides an additional treatment option for patients and physicians who may be reluctant to initiate or intensify therapy by injection, and this may also help to increase earlier GLP-1RA utilization.

Where unanswered questions remain about the impact of semaglutide on outcomes, ongoing trials are underway to provide additional clarity. Effects on diabetic nephropathy and retinopathy are being assessed for subcutaneous semaglutide, and whether there are any positive CV benefits of oral semaglutide will also be determined. The management of comorbidities that are increasingly common in patients with T2D, such as obesity and liver disease, need to be better addressed; in this respect, ongoing trials will provide further information about whether the benefits of semaglutide extend to these other indications.

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All authors contributed to the article and approved the submitted version.

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REVIEW
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Safety of Semaglutide

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The glucagon-like peptide-1 receptor agonist (GLP-1RA) semaglutide is the most recently approved agent of this drug class, and the only GLP-1RA currently available as both subcutaneous and oral formulation. While GLP-1RAs effectively improve glycemic control and cause weight loss, potential safety concerns have arisen over the years. For semaglutide, such concerns have been addressed in the extensive phase 3 registration trials including cardiovascular outcome trials for both subcutaneous (SUSTAIN: Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes) and oral (PIONEER: Peptide InnOvatioN for the Early diabEtes tReatment) semaglutide and are being studied in further trials and registries, including real world data studies. In the current review we discuss the occurrence of adverse events associated with semaglutide focusing on hypoglycemia, gastrointestinal side effects, pancreatic safety (pancreatitis and pancreatic cancer), thyroid cancer, gallbladder events, cardiovascular aspects, acute kidney injury, diabetic retinopathy (DRP) complications and injection-site and allergic reactions and where available, we highlight potential underlying mechanisms. Furthermore, we discuss whether effects are specific for semaglutide or a class effect. We conclude that semaglutide induces mostly mild-to-moderate and transient gastrointestinal disturbances and increases the risk of biliary disease (cholelithiasis). No unexpected safety issues have arisen to date, and the established safety profile for semaglutide is similar to that of other GLP-1RAs where definitive conclusions for pancreatic and thyroid cancer cannot be drawn at this point due to low incidence of these conditions. Due to its potent glucose-lowering effect, patients at risk for deterioration of existing DRP should be carefully monitored if treated with semaglutide, particularly if also treated with insulin. Given the beneficial metabolic and cardiovascular actions of semaglutide, and the low risk for severe adverse events, semaglutide has an overall favorable risk/benefit profile for patient with type 2 diabetes.

Keywords: glucagon-like peptide-1 receptor agonist (GLP-1RA), oral, subcutaneous, semaglutide, type 2 diabetes, safety

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INTRODUCTION

With an alarming increase in type 2 diabetes (T2D) prevalence as well as its associated complications (1), the need for adequate treatment strategies for this devastating disease has never been higher. However, apart from studying the potential beneficial effects of new glucose-lowering agents, regulators and clinicians are increasingly focusing on long-term safety aspects. One of the newer antihyperglycemic drug classes receiving such scrutiny on safety are the glucagon-like

peptide-1 (GLP-1) receptor agonists (GLP-1RAs). These agents are based on the gut-derived incretin hormone GLP-1, which is a potent stimulator of insulin, while suppressing glucagon secretion (2). In combination with inhibiting effects on gastric emptying and hepatic gluconeogenesis (3), GLP-1RA effectively reduce glucose levels (4). Several agents are now available after the first agent received marketing approval in 2005. Within the class of GLP-1RAs, substantial differences exist in drug structure, efficacy, dosing interval and even adverse effects (5). Nevertheless, in general, a decrease in HbA_{1c} of 1–1.5% is observed, as well as beneficial effects on body weight, blood pressure and lipid profile (4). However, partly due to the widespread presence of GLP-1 receptors, several adverse effects have been observed, of which pancreatitis, pancreatic cancer and thyroid cancer were initially flagged as safety alerts (6).

The most recently approved GLP-1RAs is semaglutide. This agent is somewhat special among GLP-1RAs given that it is the only drug available as both subcutaneous injection (similar to all other GLP-1RAs) and as an oral formulation. Moreover, with years of development after marketing approval of the first GLP-1RA, the registration trials with semaglutide could focus on the already known potential safety risks of this drug class. In this review, as part of a supplement on semaglutide, we will detail the safety aspects of this drug.

SEMAGLUTIDE

Semaglutide has been developed based on the vast body of research behind the development of liraglutide (7). Compared to liraglutide, which is administered once daily, semaglutide has an even longer half-life, allowing for once weekly administration. While a significant improvement over once or twice daily subcutaneous administration, the injecting route could be a barrier for some potential users. An absorption enhancer was discovered (sodium *N*-[8-(2-hydroxybenzoyl) aminocaprylate] or SNAC), which, when co-administered with semaglutide, was demonstrated to give therapeutic levels of the latter (8). SNAC helps to protect semaglutide from proteolytic degradation in the stomach and facilitates its absorption across the gastric mucosa by transient effects on transcellular pathways (8). At equivalent levels of exposure, similar glycemic and weight responses have been seen with both oral and subcutaneous semaglutide (9).

Both the subcutaneous and oral formulations of semaglutide have undergone extensive phase 3 clinical testing (**Table 1**). For the once-weekly subcutaneous formulation, the SUSTAIN program (Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes) included 13 separate randomized clinical phase 3a and 3b trials (10–13, 22, 25–32) SUSTAIN 1 through 10 were global international trials, while three additional trials were specific for China and Japan. In four studies, semaglutide was compared with placebo, with differing patient populations. SUSTAIN-6 is the cardiovascular outcome trial (CVOT) of subcutaneous semaglutide (28).

The PIONEER program (Peptide InnOvatioN for the Early diabEtes tReatment) comprised 10 individual trials comparing once-daily oral semaglutide with placebo (six studies) or active comparator in different populations (14–21, 23, 24). Similar to the SUSTAIN program, PIONEER 6, was the CVOT (19). PIONEER 9 and 10 are specific to the Japanese population (12, 13). The SOUL (A Heart Disease Study of Semaglutide in Patients with Type 2 Diabetes) study is a larger CVOT with oral semaglutide that is currently ongoing (NCT03914326).

Combining all individual studies, the SUSTAIN program contained almost 12,000 participants, with over 9,500 subjects in the PIONEER program. With treatment duration of at least 26 weeks, this accounts of many patient years of follow-up, allowing an adequate review of the safety of semaglutide.

ADVERSE EFFECTS OF SEMAGLUTIDE

Semantically, the on-target effects of GLP-1RAs are those effects leading to a reduction in glucose levels. Any other effect can be considered as a pleiotropic, off-target effect, or in the case of unwanted actions, adverse effects (**Figure 1**). Many of the (adverse) class effects are shared among the different GLP-1RA, however, differences do occur. For semaglutide, one could expect a different side-effect profile for the oral *versus* the subcutaneous formulation. Apart from the obvious—tablets will not induce injection-site reactions—it could be suggested that higher portal levels induce more gastrointestinal disturbances. Moreover, with the maximum oral dosage plasma levels are lower compared with the maximal subcutaneous dose (oral 20 mg yields plasma levels of ~25 nM, subcutaneous 1 mg yields plasma levels of ~45 nM (33, 34)). Worth noting is that no data comparing the pharmacokinetic profile of both formulations against each other are available. In the following sections, the adverse reactions and safety issues of semaglutide, both oral and subcutaneous, will be discussed. We will discuss the risk of hypoglycemia, gastrointestinal side effects including previous reports on increased risk for pancreatitis and pancreas cancer, thyroid cancer, gallbladder stones, effects on the cardiovascular system, acute kidney injury, diabetic retinopathy risks and allergies/injection-site reactions (**Table 2**).

Hypoglycemia

Given that the aim of GLP-1RA therapy is mainly to reduce blood glucose levels, it is conceivable that these agents could cause hypoglycemia. However, since GLP-1RA mainly lower blood glucose by stimulating glucose-dependent insulin secretion, hypoglycemia is an infrequent problem. In addition, the inhibition of glucagon release does not occur under hypoglycemic conditions (35). In SUSTAIN-6, severe or plasma glucose-confirmed (<56 mg/dl [3.1 mol/L]) hypoglycemia occurred in similar rates between patients with semaglutide (23.1% in the 0.5 mg group and 21.7% in the 1 mg group) and placebo (21.2%) (28). In comparison, in SUSTAIN-4, severe or confirmed hypoglycemia occurred in 11% of insulin glargine-treated patients, compared with 4–6% in the semaglutide-treated patients (26). Importantly, in SUSTAIN-4 it is reported that hypoglycemia predominantly occurred in subjects using sulfonylurea agents (26). To illustrate: in the group of subjects randomized to semaglutide 1 mg, 9% of subjects using a s sulfonylurea had a severe or blood-glucose

TABLE 1 | Overview of Phase 3 studies of oral semaglutide (PIONEER) and subcutaneous semaglutide (SUSTAIN) (10–32).

Trial	Treatment arms		Key inclusion criteria	Trial duration; blinded or open-label	Primary endpoint/ outcome	Key baseline characteristics (mean values)	Trial product discontinuation/ rescue medication use (proportion of patients)
PIONEER 1	Oral semaglutide 3 mg	n=175	Treated with diet and exercise, HbA_{1c} 7.0–9.5%	26-week; blinded	Change in HbA_{1c} from baseline to week 26	Age: 55 years, HbA_{1c}: 8.0% (63 mmol/mol), duration of T2D: 3.5 years	3% / 7%
	Oral semaglutide 7 mg	n=175					8% / 2%
	Oral semaglutide 14 mg	n=175					7% / 1%
	Placebo	n=178					5% / 15%
PIONEER 2	Oral semaglutide 14 mg	n=410	Treated with metformin, HbA_{1c} 7.0–10.5%	52-week; open-label	Change in HbA_{1c} from baseline to week 26	Age: 58 years, HbA_{1c}: 8.1% (65 mmol/mol), duration of T2D: 7.4 years	18% / 8%
	Empagliflozin 25 mg	n=409					11% / 11%
PIONEER 3	Oral semaglutide 3 mg	n=466	Treated with metformin ± sulfonylurea, HbA_{1c} 7.0–10.5%	78-week; blinded	Change in HbA_{1c} from baseline to week 26	Age: 58 years, HbA_{1c}: 8.3% (67 mmol/mol), duration of T2D: 8.6 years	17% / 34%
	Oral semaglutide 7 mg	n=464					15% / 22%
	Oral semaglutide 14 mg	n=465					19% / 10%
	Sitagliptin 100 mg	n=466					13% / 28%
PIONEER 4	Oral semaglutide 14 mg	n=285	Treated with metformin ± SGLT2i, HbA_{1c} 7.0–9.5%	52-week; blinded	Change in HbA_{1c} from baseline to week 26	Age: 56 years, HbA_{1c}: 8.0% (64 mmol/mol), duration of T2D: 7.6 years	15% / 7%
	Liraglutide 1.8 mg (s.c.)	n=284					13% / 6%
	Placebo	n=142					12% / 30%
PIONEER 5	Oral semaglutide 14 mg	n=163	Moderate renal impairment, treated with metformin ± sulfonylurea; or basal insulin ± metformin, HbA_{1c} 7.0%-9.5%	26-week; blinded	Change in HbA_{1c} from baseline to week 26	Age: 70 years, HbA_{1c}: 8.0% (64 mmol/mol), duration of T2D: 14.0 years	18% / 4%
	Placebo	n=161					12% / 10%
PIONEER 6 (CVOT)	Oral semaglutide 14 mg	n=1591	Age ≥50 years with CVD/CKD or age ≥60 years with CV risk factors	Event-driven; blinded	3-point composite MACE	Age: 66 years, HbA_{1c}: 8.2% (66 mmol/mol), duration of T2D: 14.9 years	15% / NR
	Placebo	n=1592					10% / NR
PIONEER 7	Oral semaglutide (flexible 3, 7 or 14 mg)	n=253	Treated with 1–2 OADs, HbA_{1c} 7.5–9.5%	52-week; open-label	Proportion of patients with HbA_{1c} <7.0% at week 52	Age: 57 years, HbA_{1c}: 8.3% (67 mmol/mol), duration of T2D: 8.8 years	17% / 3%
	Sitagliptin 100 mg	n=251					9% / 16%
PIONEER 8	Oral semaglutide 3 mg	n=184	Treated with insulin ± metformin, HbA_{1c} 7.0–9.5%	52-week; blinded	Change in HbA_{1c} from baseline to week 26	Age: 61 years, HbA1c: 8.2% (66 mmol/mol), duration of T2D: 15.0 years	13% / 29%
	Oral semaglutide 7 mg	n=181					19% / 18%
	Oral semaglutide 14 mg	n=181					20% / 17%
	Placebo	n=184					12% / 36%
PIONEER 9	Oral semaglutide 3 mg	n=49	Treated with diet and exercise or stable dose of 1 OAD, HbA_{1c} 7.0–10.0% if on diet and exercise or HbA_{1c} 6.5–9.5% if on 1 OAD	52-week; open-label	Change in HbA_{1c} from baseline to week 26	Age: 59 years, HbA_{1c}: 8.2% (66 mmol/mol), duration of T2D: 7.6 years	8% / 14%
	Oral semaglutide 7 mg	n=49					2% / 10%
	Oral semaglutide 14 mg	n=48					6% / 8%
	Liraglutide 0.9 mg (s.c.)	n=48					8% / 6%
	Placebo	n=49					0% / 31%
PIONEER 10	Oral semaglutide 3 mg	n=131	Treated with stable doses of 1 OAD, HbA_{1c} 7.0–10.5%	52-week; open-label	Number of treatment-emergent adverse events at week 57	Age: 58 years, HbA_{1c}: 8.3% (67 mmol/mol), duration of T2D: 9.4 years	5% / 17%
	Oral semaglutide 7 mg	n=132					7% / 6%
	Oral semaglutide 14 mg	n=130					12% / 2%
	Dulaglutide 0.75 mg (s.c.)	n=65					6% / 9%
SUSTAIN 1	S.c. semaglutide 0.5 mg	n=128	Treated with diet and exercise, HbA_{1c} 7.0–10%	30-week; blinded	Change in HbA_{1c} from baseline to week 30	Age: 54 years, HbA_{1c}: 8,1% (65 mmol/mol), duration of T2D: 4.2 years	13% / 5%
	S.c. semaglutide 1 mg	n=130					12% / 5%
	Placebo	n=129					11% / 21%
SUSTAIN 2	S.c. semaglutide 0.5 mg	n=409	Treated with metformin ± thiazolidinediones, HbA_{1c} 7.0–10.5%	56-week; blinded	Change in HbA_{1c} from baseline to week 56	Age: 55 years, HbA_{1c}: 8.1% (65 mmol/mol), duration of T2D: 6.6 years	6% / 5%
	S.c. semaglutide 1 mg	n=409					5% / 2%
	Sitagliptin 100 mg	n=407					5% / 20%
SUSTAIN 3	S.c. semaglutide 1 mg	n=404	Treated with 1-2 OADs, HbA_{1c} 7–10.5%	56-week; open-label	Change in HbA_{1c} from baseline to week 56	Age: 57 years, HbA_{1c}: 8.3 (68 mmol/mol), duration of T2D: 9.2 years	20% / 7%
	Exenatide ER 2.0 mg	n=405					21 % / 12%

(Continued)

TABLE 1 | Continued

Trial	Treatment arms		Key inclusion criteria	Trial duration; blinded or open-label	Primary endpoint/ outcome	Key baseline characteristics (mean values)	Trial product discontinuation/ rescue medication use (proportion of patients)
SUSTAIN 4	S.c. semaglutide 0.5 mg S.c. semaglutide 1 mg Insulin glargine	n=362 n=360 n=360	Treated with metformin ± sulfonylurea, HbA_{1c} 7.0–10.0%	30-week; open-label	Change in HbA_{1c} from baseline to week 30	Age: 57 years, HbA_{1c}: 8.2 (66 mmol/mol), duration of T2D: 8.6 years	14% / 17% 16% / 18% 9% / 9%
SUSTAIN 5	S.c. semaglutide 0.5 mg S.c. semaglutide 1 mg Placebo	n=132 n=131 n=133	Treated with insulin ± metformin, HbA_{1c} 7.0–10.0%	30-week; blinded	Change in HbA_{1c} from baseline to week 30	Age: 59 years, HbA_{1c}: 8.4% (68 mmol/mol), duration of T2D: 13.3 years	11% / 2% 13% / <1% 10% / 14%
SUSTAIN 6 (CVOT)	S.c. semaglutide 0.5 mg S.c. semaglutide 1 mg Placebo	n=826 n=822 n=1649	Age ≥50 years with CVD/CKD or age ≥60 years with CV risk factors	Duration (104-week) and event-driven; blinded	3-point composite MACE	Age: 65 years, HbA_{1c}: 8.7%, duration of T2D: 13.9 years	19.9% / NR 22.6% / NR 18.8% / NR
SUSTAIN 7*	S.c. semaglutide 0.5 mg S.c. semaglutide 1 mg Dulaglutide 0.75 mg (s.c.) Dulaglutide 1.5 mg (s.c.)	n=301 n=300 n=299 n=299	Treated with metformin, HbA_{1c} 7.0–10.5%	10-week; open-label	Change in HbA_{1c} from baseline to week 40	Age: 66 years, HbA_{1c}: 8.2% (66 mmol/mol), duration of T2D: 7.4 years	16% / 1% 17% / 2% 9% / 5% 12% / 2%
SUSTAIN 8*	S.c. semaglutide 1 mg Canagliflozin 300 mg	n=394 n=394	Treated with metformin, HbA_{1c} 7.0–10.5%	52-week; blinded	Change in HbA_{1c} from baseline to week 52	Age: 57 years, HbA_{1c}: 8.3% (67 mmol/mol), duration of T2D: 7.4 years	16% / 7% 13% / 7%
SUSTAIN 9*	S.c. semaglutide 1 mg Placebo	n=151 n=151	Treated with metformin ± SGLT2i, HbA_{1c} 7.0–10%	30-week; blinded	Change in HbA_{1c} from baseline to week 30	Age: 57 years, HbA_{1c}: 8.0% (64 mmol/mol), duration of T2D: 9.7 years	15% / 0.7% 8% / 5.3%
SUSTAIN 10*	S.c. semaglutide 1 mg liraglutide 1.2 mg (s.c.)	n=290 n=287	Treated with 1–3 OADs, HbA_{1c} 7.0–11.0%	30-week; blinded	Change in HbA_{1c} from baseline to week 30	Age: 60 years, HbA_{1c}: 8.2%, duration of T2D: 9.3 years	14.1% / 1.4% 9.1% / 4.2%
SUSTAIN JAPAN 'Sitagliptin'	S.c. semaglutide 0.5 mg S.c. semaglutide 1 mg Sitagliptin 100 mg	n=103 n=102 n=103	Treated with diet and exercise with HbA_{1c} 7.0–10.5%, or OAD monotherapy with HbA_{1c} 6.5–9.5%	30-week; open-label	Number of treatment-emergent adverse events at week 30	Age: 58 years, HbA_{1c}: 8.1%, duration of T2D: 8.0 years	2.9% / 0.9% 14.7% / 0 2.9% / 4.9%
SUSTAIN JAPAN 'individual'	S.c. semaglutide 0.5 mg S.c. semaglutide 1 mg Additional OAD (investigators discretion)	n=239 n=241 n=120	Treated with diet and exercise, or OAD monotherapy, HbA_{1c} 7.0–10.5%	56-week; open-label	Number of treatment-emergent adverse events at week 56	Age: 59 years, HbA_{1c}: 8.1% (65 mmol/mol), duration of T2D: 8.8 years	6.3% / 0% 14.1% / 0.4% 5.9% / 6.7%
SUSTAIN China	S.c. semaglutide 0.5 mg S.c. semaglutide 1 mg Sitagliptin 100 mg	n=287 n=290 n=290	Treated with metformin, HbA_{1c} 7.0–10.5%	30-week; blinded	Change in HbA_{1c} from baseline to week 30	Age: 53 years, HbA1c 8.1%, Duration of T2D: 6.4 years	NR / 3.1% NR / 1.4% NR / 6.6%

**Phase 3b trials all others are phase 3a trials CKD, chronic kidney disease; CV, cardiovascular; CVOT, cardiovascular outcomes trial; CVD, cardiovascular disease; ER, extended release; MACE, major adverse cardiovascular event; NR, not reported; OAD, oral antidiabetic drug; s.c, subcutaneous; SGLT2i, sodium-glucose co-transporter-2 inhibitor; T2D, type 2 diabetes.*

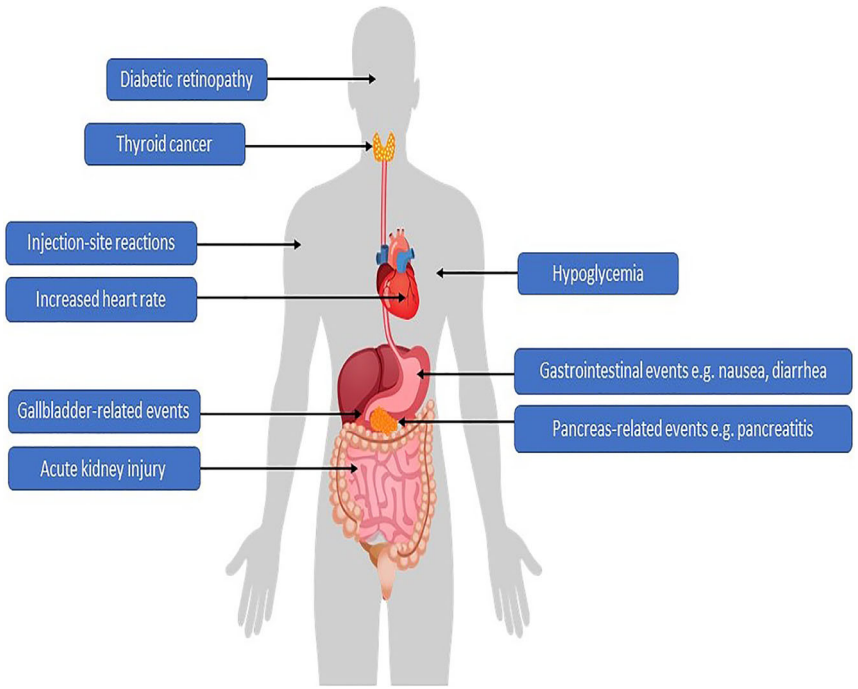

FIGURE 1 | Potential adverse effects associated with GLP1-RAs.

confirmed hypoglycemia, *versus* 2% in those not using a sulfonylurea. Similarly, in SUSTAIN-3, the majority of hypoglycemic events were reported in subjects concomitantly receiving sulfonylureas in both the semaglutide 1.0 mg and exenatide ER 2.0 mg groups. For oral semaglutide, the percentage of patients with severe hypoglycemia was 1.4% with oral semaglutide and 0.8% with placebo in PIONEER 6 (19). Here all severe hypoglycemic events occurred in patients receiving concomitant insulin or sulfonylurea therapy at the time of the event. In other phase 3 trials, no increase in hypoglycemia risk was observed *versus* comparator groups, including other GLP-1RAs (18–21, 23, 33–36).

Real world data with respect to hypoglycemia are limited to a single observational cohort from Canada (36). In 815 individuals who started semaglutide therapy and were followed for 6 months, there was no change in overall reported hypoglycemia. Although the group of concomitant insulin users also reported no change in hypoglycemia occurrence, this could have been mitigated by the on average 10–20% reduction in total daily insulin dosage (36). Sulfonylurea users did not experience an increase in hypoglycemia events.

Thus, the risk of hypoglycemia appears to be low with subcutaneous and oral semaglutide by themselves, yet the risk is increased when combined with sulfonylurea and/or insulin therapy. Several experts advise to lower the dose of sulfonylurea and short-acting and low-acting insulin analogues prior to or during titration of GLP-1RA therapy, to reduce the risk of (severe) hypoglycemia (37).

Gastrointestinal (GI) Adverse Effects

In the phase 3 trials, both oral and subcutaneous semaglutide were associated with gastrointestinal disturbances, such as nausea, vomiting and diarrhea, well-known effects from this drug class. When compared with placebo, subcutaneous semaglutide for 30 weeks induced nausea in 11.4 to 20% of the semaglutide-treated patients (placebo 3.3–8%), vomiting in 4 to 11.5% (placebo 2–3%) and diarrhea in 4.5 to 11.3% (placebo 1.5–6%) (10, 27, 31). In SUSTAIN 6, where generally older patients with comorbid conditions were treated for 104 weeks, the incidence of GI disturbances was somewhat higher (28). For oral semaglutide, the placebo-controlled trials found nausea ranged between 5.1 and 23.2% (placebo 5.6–7.1%), vomiting between 2.9 and 9.9% (placebo 2.2–3.8%) and diarrhea between 5.1 and 15% (placebo 2.2–8%) during the on-treatment period (14, 17, 21). These rates were not different when focusing on Japanese patients [PIONEER 9 (23)], but appeared higher in patients with T2D, reduced kidney function (estimated glomerular filtration rate [GFR] of 30–59 ml/min) and comorbidities in PIONEER 5 (18).

In one phase 2 trial, subcutaneous and oral semaglutide were compared with each other (38). Here, patients were randomized to oral semaglutide (at a dose of 5, 10, 20 or 40 mg once daily), subcutaneous semaglutide (1 mg once weekly) or placebo. As discussed below, this study also assessed the effect of dose escalation in two additional groups. Unfortunately, the currently advocated oral treatment doses of 7 and 14 mg were not included. When comparing oral 20 mg to subcutaneous 1

TABLE 2 | Adverse effects and safety risks in phase 3 trials (10–32).

Treatment arms	Incidence of AE, n (%)											% of patients with AE leading to trial product discontinuation	
	Any	Severe or confirmed symptomatic hypoglycemic episode*	Gastrointestinal			Pancreas		Gallbladder	Thyroid	Diabetic retinopathy	Acute kidney Injury	Any AE, n (%)	Gastrointestinal, %
			Nausea	Vomiting	Diarrhea	Pancreatitis	Pancreatic cancer						
PIONEER 1													
Oral semaglutide 3 mg	101 (57.7)	5 (2.9)	14 (8.0)	5 (2.9)	15 (8.6)	0		NR	0	1 (0.6%)	0	4 (2.3)	75
Oral semaglutide 7 mg	93 (53.1)	2 (1.1)	9 (5.1)	8 (4.6)	9 (5.1)	0		NR	0	6 (3.4%)	0	7 (4.0)	57
Oral semaglutide 14 mg	99 (56.6)	1 (0.6)	28 (16.0)	12 (6.9)	9 (5.1)	0		NR	0	2 (1.1%)	1 (0.6)	13 (7.4)	69
Placebo	99 (55.6)	1 (0.6)	10 (5.6)	4 (2.2)	4 (2.2)	0		NR	0	3 (1.7%)	1 (0.6)	4 (2.2)	25
PIONEER 2													
Oral semaglutide 14 mg	289 (70.5)	7 (1.7)	81 (19.8)	30 (7.3)	38 (9.3)	1 (0.2)	0	NR	0	14 (3.4)	2 (0.5)	44 (10.7)	75
Empagliflozin 25 mg	283 (69.2)	8 (2.0)	10 (2.4)	7 (1.7)	13 (3.2)	1 (0.2)	0	NR	0	5 (1.2%)	1 (0.2)	18 (4.4)	17
PIONEER 3													
Oral semaglutide 3 mg	370 (79.4)	23 (4.9)	34 (7.3)	13 (2.8)	45 (9.7)	1 (0.2)	0	NR	0	27 (5.8)	3 (0.6)	26 (5.6)	42
Oral semaglutide 7 mg	363 (78.2)	24 (5.2)	62 (13.4)	28 (6.0)	53 (11.4)	1 (0.2)	0	NR	0	24 (5.2)	2 (0.4)	27 (5.8)	56
Oral semaglutide 14 mg	370 (79.6)	36 (7.7)	70 (15.1)	42 (9.0)	57 (12.3)	1 (0.2)	1 (0.2)	NR	0	16 (3.4)	5 (1.1)	54 (11.6)	59
Sitagliptin 100 mg	388 (83.3)	39 (8.4)	32 (6.9)	19 (4.1)	37 (7.9)	1 (0.2)	1 (0.2)	NR	0	27 (5.8)	3 (0.6)	24 (5.2)	50
PIONEER 4													
Oral semaglutide 14 mg	229 (80)	2 (1)	56 (20)	25 (9)	43 (15)	0	0	NR	1 (0.4)	8 (3)	0	31 (11)	71
Liraglutide 1.8 mg (s.c.)	211 (74)	7 (2)	51 (18)	13 (5)	31 (11)	1 (0.4)	1 (0.4)	NR	1 (0.4)	4 (1)	1 (0.4)	26 (9)	65
Placebo	95 (67)	3 (2)	5 (4)	3 (2)	11 (8)	1 (0.7)	0	NR	0	2 (1)	1	5 (4)	60
PIONEER 5													
Oral semaglutide 14 mg	122 (75)	9 (6)	31 (19)	19 (12)	17 (10)	0	0	NR	0	5 (3)	3 (1.8)	24 (15)	79
Placebo	109 (68)	3 (2)	12 (7)	6 (4)	6 (4)	0	0	NR	0	2 (1)	1 (0.6)	8 (5)	38
PIONEER 6													
Oral semaglutide 14 mg	NR	NR	NR	NR	NR	1 (0.1)	0	NR	2 (0.1)	93 (5.8)	32 (2.0)	184 (11.6)	59
Placebo	NR	NR	NR	NR	NR	3 (0.2)	0	NR	0	76 (4.8)	37 (2.3)	104 (6.5)	25
PIONEER 7													

(Continued)

TABLE 2 | Continued

Treatment arms	Incidence of AE, n (%)											% of patients with AE leading to trial product discontinuation	
	Any	Severe or confirmed symptomatic hypoglycemic episode*	Gastrointestinal			Pancreas		Gallbladder	Thyroid	Diabetic retinopathy	Acute kidney Injury	Any AE, n (%)	Gastrointestinal, %
			Nausea	Vomiting	Diarrhea	Pancreatitis	Pancreatic cancer						
Oral semaglutide (flexible 3, 7 or 14 mg)	197 (78)	14 (5.5)	53 (21)	14 (6)	22 (9)	0	0	NR	0	6 (2.4)	1 (0.4)	22 (9)	64
Sitagliptin 100 mg	172 (69)	14 (5.6)	6 (2)	3 (1)	8 (3)	0	0	NR	0	6 (2.4)	0	8 (3)	25
PIONEER 8													
Oral semaglutide 3 mg	137 (74.5)	52 (28.3)	21 (11.4)	11 (6.0)	16 (8.7)	0	0	NR	0	7 (3.8)	2 (1.1)	13 (7.1)	69
Oral semaglutide 7 mg	142 (78.5)	47 (26.0)	30 (16.6)	14 (7.7)	22 (12.2)	0	0	NR	0	8 (4.4)	1 (0.6)	16 (8.8)	75
Oral semaglutide 14 mg	151 (83.4)	48 (26.5)	42 (23.2)	18 (9.9)	27 (14.9)	0	0	NR	0	9 (5.0)	0	24 (13.3)	79
Placebo	139 (75.5)	54 (29.3)	13 (7.1)	7 (3.8)	11 (6.0)	0	0	NR	0	8 (4.3)	0	5 (2.7)	20
PIONEER 9													
Oral semaglutide 3 mg	37 (76)	0	2 (4)	NR	4 (8)	0	0	NR	0	0	0	1 (2)	100
Oral semaglutide 7 mg	37 (76)	0	5 (10)	NR	1 (2)	0	0	NR	1	1 (2.0)	0	1 (2)	100
Oral semaglutide 14 mg	34 (71)	0	4 (8)	NR	3 (6)	0	0	NR	0	1 (2.1)	0	2 (4)	100
Liraglutide 0.9 mg (s.c.)	32 (67)	2 (4.2)	0	NR	2 (4)	0	0	NR	0	0	0	0	0
Placebo	39 (80)	0	1 (2)	NR	1 (2)	0	0	NR	0	2 (4.1)	0	0	0
PIONEER 10													
Oral semaglutide 3 mg	101 (77)	3 (2)	7 (5)	3 (2)	2 (2)	0	0	2 (2)	0	9 (7)	0	4 (3)	50
Oral semaglutide 7 mg	106 (80)	3 (2)	11 (8)	6 (5)	2 (2)	0	0	1 (1)	0	12 (9)	0	8 (6)	50
Oral semaglutide 14 mg	111 (85)	4 (3)	12 (9)	9 (7)	10 (8)	0	0	0	0	7 (5)	0	8 (6)	63
Dulaglutide 0.75 mg (s.c.)	53 (82)	0	6 (9)	1 (2)	4 (6)	0	0	1 (2)	0	3 (5)	0	2 (3)	50
SUSTAIN 1													
S.c. semaglutide 0.5 mg	82 (64)	0	26 (20)	5 (4)	16 (13)	0	0	3 (2)	0	NR	0	8 (6)	63
S.c. semaglutide 1 mg	73 (56)	0	31 (24)	9 (7)	14 (11)	0	0	1 (<1)	0	NR	0	7 (5)	57
Placebo	69 (53)	3 (2)	10 (8)	2 (2)	3 (2)	0	0	0	0	NR	0	3 (2)	33
SUSTAIN 2													
S.c. semaglutide 0.5 mg	306 (75)	7 (2)	73 (18)	33 (8)	54 (13)	3 (1%)	NR	1 (<1)	0	1 (<1)	NR	33 (8)	82
S.c. semaglutide 1 mg	292 (71)	2 (<1)	72 (18)	41 (10)	53 (13)	1 (<1)	NR	7 (2)	1	0	NR	39 (10)	79
Sitagliptin 100	292 (72)	5 (1)	30 (7)	11 (3)	29 (7)	0	NR	6 (1)	0	3 (1)	NR	12 (3)	25
SUSTAIN 3													
S.c. semaglutide 1 mg	303 (75)	33 (8.2)	90 (22.3)	29 (7.2)	46 (11.4)	2 (<1)	NR	6 (1%)	NR	NR	NR	38 (9.4)	NR

(Continued)

TABLE 2 | Continued

Treatment arms	Incidence of AE, n (%)											% of patients with AE leading to trial product discontinuation	
	Any	Severe or confirmed symptomatic hypoglycemic episode*	Gastrointestinal			Pancreas		Gallbladder	Thyroid	Diabetic retinopathy	Acute kidney Injury	Any AE, n (%)	Gastrointestinal, %
			Nausea	Vomiting	Diarrhea	Pancreatitis	Pancreatic cancer						
Exenatide ER 2.0 mg	309 (76.3)	33 (8.1)	48 (11.9)	25 (6.2)	34 (8.4)	3 (<1)	NR	2 (<1)	NR	NR	NR	29 (7.2)	NR
SUSTAIN 4													
S.c. semaglutide 0.5 mg	253 (70)	16 (4)	77 (21)	24 (7)	59 (16)	2 (1)	1 (<1)	1 (<1)	NR	1 (<1)	NR	20 (6)	55
S.c. semaglutide 1 mg	264 (73)	20 (6)	80 (22)	37 (10)	69 (19)	0	0	2 (1)	NR	0	NR	27 (8)	70
Insulin glargine	235 (65)	38 (11)	13 (4)	11 (3)	16 (4)	0	0	0	NR	1 (<1)	NR	4 (1)	0
SUSTAIN 5													
S.c. semaglutide 0.5 mg	91 (68.9)	11 (8.3)	15 (11.4)	8 (6.1)	6 (4.5)	0	0	3 (2.3)	0	(3.0)	NR	6 (4.5)	NR
S.c. semaglutide 1 mg	84 (64.1)	14 (10.7)	22 (16.8)	15 (11.5)	9 (6.9)	0	0	1 (0.8)	0	(0.8)	NR	8 (6.1)	NR
Placebo	77 (57.9)	7 (5.3)	6 (4.5)	4 (3.0)	2 (1.5)	0	0	0	0	0	NR	1 (0.8)	NR
SUSTAIN 6													
S.c. semaglutide 0.5 mg	740 (89.6)	191 (23.1)	143 (17.3)	14 (1.7)	15 (1.8)	6 (0.7)	0	25 (3)	0	50 (3.0)	42 (5.1)	95 (11.5)	49
S.c. semaglutide 1 mg	732 (89.1)	178 (21.7)	180 (21.9)	23 (2.8)	19 (2.3)	3 (0.4)	1 (0.1)	17 (2.1)	0	23 (2.8)	119 (14.5)	65	
Placebo	1484 (90)	350 (21.2)	129 (7.8)	5 (0.3)	7 (0.4)	12 (0.7)	4 (0.2)	39 (2.3)	0	29 (1.8)	34 (4.1)	110 (6.7)	16
SUSTAIN 7													
S.c. semaglutide 0.5 mg	204 (68)	2 (1)	68 (23)	31 (10)	43 (14)	0	0	2 (1)	1 (<1)	2 (1)	NR	24 (8)	67
S.c. semaglutide 1 mg	207 (69)	5 (2)	63 (21)	31 (10)	41 (14)	0	0	4 (1)	0	2 (1)	NR	29 (10)	62
Dulaglutide 0.75 mg (s.c.)	186 (62)	3 (1)	39 (13)	12 (4)	23 (8)	0	0	4 (1)	0	2 (1)	NR	14 (5)	43
Dulaglutide 1.5 mg (s.c.)	221 (74)	5 (2)	60 (20)	29 (10)	53 (18)	0	0	8 (3)	1 (<1)	3 (1)	NR	20 (7)	70
SUSTAIN 8													
S.c. semaglutide 1 mg	298 (76)	53 (14)	89 (23)	50 (13)	60 (15)	NR	NR	NR	NR	9 (2)	4 (1)	38 (10)	68
Canagliflozin 300 mg	283 (72)	32 (8)	26 (7)	9 (2)	37 (9)	NR	NR	NR	NR	15 (4)	0	20 (5)	20
SUSTAIN 9													
S.c. semaglutide 1 mg	104 (69.3)	17 (11.3)	29 (19.3)	14 (9.3)	17 (11.3)	0	0	NR	NR	3 (2.0)	1 (0.7)	13 (8.7)	77

(Continued)

TABLE 2 | Continued

Treatment arms	Incidence of AE, n (%)											% of patients with AE leading to trial product discontinuation	
	Any	Severe or confirmed symptomatic hypoglycemic episode*	Gastrointestinal			Pancreas		Gallbladder	Thyroid	Diabetic retinopathy	Acute kidney Injury	Any AE, n (%)	Gastrointestinal, %
			Nausea	Vomiting	Diarrhea	Pancreatitis	Pancreatic cancer						
Placebo	91 (60.3)	3 (2.0)	5 (3.3)	3 (2.0)	9 (6.0)	0	0	NR	NR	8 (5.3)	0	3 (2.0)	0
SUSTAIN 10													
S.c. semaglutide 1 mg	204 (70.6)	5 (1.7)	63 (21.8)	30 (10.4)	45 (15.6)	0	NR	NR	NR	3 (1.0)	NR	33 (11.4)	67
Liraglutide 1.2 mg (s.c.)	190 (66.2)	7 (2.4)	45 (15.7)	23 (8.0)	35 (12.2)	2 (0.7%)	NR	NR	NR	4 (1.4)	NR	19 (6.6)	58
SUSTAIN JAPAN 'SITA'													
S.c. semaglutide 0.5 mg	77 (74.8)	0	(10.7)		(6.8%)	0	0	1 (1.0)	0	4 (3.9)	NR	3 (2.9)	NR
S.c. semaglutide 1 mg	73 (71.6)	1 (1.0)	(12.7)		(8.8%)	0	0	3 (2.9)	0	2 (1.9)	NR	11 (10.8)	NR
Sitagliptin 100 mg	68 (66.0)	0	0		(1.9%)	0	1 (1.0)	0	0	4 (3.9)	NR	2 (1.9)	NR
SUSTAIN JAPAN 'INDIVIDUAL'													
S.c. semaglutide 0.5 mg	206 (86.2)	3 (1.3)	29 (12.1)	13 (5.4)	24 (10.0)	0	0	4 (1.7%)	0	11 (4.6)	NR	14 (5.9)	NR
S.c. semaglutide 1 mg	212 (88)	6 (2.5)	46 (19.1)	14 (5.8)	38 (15.8)	0	0	2 (0.8%)	0	16 (6.6)	NR	26 (10.8)	NR
Additional OAD (investigators discretion)	86 (71.7)	2 (1.7)	1 (0.8)	2 (1.7)	8 (6.7)	0	0	0	0	6 (5.0)	NR	4 (3.3)	NR
SUSTAIN China													
S.c. semaglutide 0.5 mg	209 (72.8%)	2 (0.7%)	22 (7.7%)	14 (4.9%)	58 (20.2%)	0	0	NR	NR	19 (6.6%)	NR	17 (5.9%)	59
S.c. semaglutide 1 mg	216 (74,5%)	6 (2.1%)	39 (13.4%)	19 (6.6%)	49 (16.9%)	1 (0.3%)	0	NR	NR	14 (4.8%)	NR	31 (10.7%)	68
Sitagliptin 100 mg	199 (68,6%)	4 (1.4%)	5 (1.7%)	3 (1.0%)	20 (6.9%)	0	0	NR	NR	10 (3.4%)	NR	6 (2.1%)	17

AE, adverse event; ER, extended release; NR, not reported; OAD, oral antidiabetic drug; s.c. subcutaneous.

An independent external adjudication committee (EAC) validated prespecified categories of adverse events (including deaths, selected cardiovascular events, malignant neoplasms, thyroid diseases [malignant thyroid neoplasms and C-cell hyperplasia], acute kidney injury, acute pancreatitis, and lactic acidosis) except in SUSTAIN 10 where there was no adjudication.

**An episode that was severe according to the ADA classification (requires assistance of another person to actively administer carbohydrate, glucagon, or other corrective action) or an episode with confirmed blood glucose value <56 mg/dL and symptoms consistent with hypoglycemia.*

mg, the total amount of gastrointestinal disturbances was similar (56% *versus* 54%, respectively). This was also true for nausea (34% *versus* 32%), vomiting (16% *versus* 9%) and diarrhea (20% *versus* 14%). The proportion of patients with premature discontinuation because of adverse events appeared higher for oral semaglutide 20 mg (27%) than for subcutaneous semaglutide 1 mg (14%). All numbers were similar between the 10 and 20 mg oral dose, except for treatment discontinuation, which was 12% for the lower dosage.

Importantly, for both formulations, higher doses are often associated with more frequent GI adverse effects. For this reason, a dose escalation scheme is advised, starting with a low dose (3 mg). As a clear example in the abovementioned phase 2 study (38), 77% of patients experienced GI adverse effects when a fast 2-week dose escalation was used to reach 40 mg compared with 54% in the slower 8-week dose-escalation group. Generally, the GI complaints with semaglutide occur in the first 8–12 weeks of treatment during dose escalation [in contrast to for example liraglutide, where they occur within 2 weeks (17, 32)], and wane over time (**Figure 2**). Overall, the adverse effects are mild to moderate in severity and often self-limiting.

Nevertheless, GI complaints are the main adverse-event related cause of drug discontinuation in the phase-3 trials, with rates up to 12% (**Table 2**). Moreover, cohorts with real-world data show similar numbers. In one retrospective study where 189 patients with T2DM starting subcutaneous semaglutide, 9.5% discontinued therapy because of GI complaints, while in 5.8% such adverse effects limited uptitration (39). In another cohort where 164 T2DM patients were switched from a different GLP-1RA therapy to semaglutide, 10.4% discontinued semaglutide because of adverse GI effects (40). Combined, data from clinical trials and clinical practice suggest that approximately 10% of patients will discontinue semaglutide because of GI complaints, which may be a bit higher compared to other GLP-1 analogues.

Apart from gradual dose titration, data on how to prevent or treat GI disturbances with GLP-1RA are limited. Patients can be counseled to eat slowly with reduced portion size per meal, stop eating when they experience satiety, and to avoid high-fat food (41). Anti-emetic therapy has been found effective in healthy subjects (42), but are not common practice since long-term data are not available. Interestingly, in one systematic analysis, background use of metformin was associated with more nausea and vomiting when using a GLP-1RA (43). However, whether this is also true for the combination with semaglutide, or whether lowering the dose of metformin has effect, has not been studied.

The mechanisms behind nausea/vomiting and diarrhea are incompletely understood. For nausea, a relation with the inhibiting effects on gastric emptying seems plausible. However, nausea also occurs in the fasting state (44), and is not related to measures of gastric emptying speed after meal ingestion (45). An effect on the central nervous system has been suggested as a recent study with modified exenatide—with reduced brain penetrance—showed less vomiting in musk shrews, despite retaining effects on glucose control (46). For diarrhea, studies are lacking. In one study, osmotic diarrhea occurred 8 h after infusion of GLP-1 peptide (47), and GLP-1RAs have been shown to reduce intestinal uptake of glucose and lipids (48, 49). Also, in patients with type 1 diabetes, liraglutide reduced colon transit time (50). So, hypothetically, semaglutide could induce diarrhea by altering nutrient absorption or intestinal motility.

Finally, although nausea and vomiting are perhaps unwanted effects, they may also be partly responsible for aspects of the drug's efficacy as indicated above. As such, in some studies, nausea induced by GLP-1RAs is linked to weight loss (51, 52). For example, obese subjects treated with high-dose liraglutide who experienced (transient) nausea had on average 2.9 kg (95%-CI 0.5–5.3) more weight loss compared to those without GI events (51). In a mediation analysis of the SUSTAIN 1 to 5 trials,

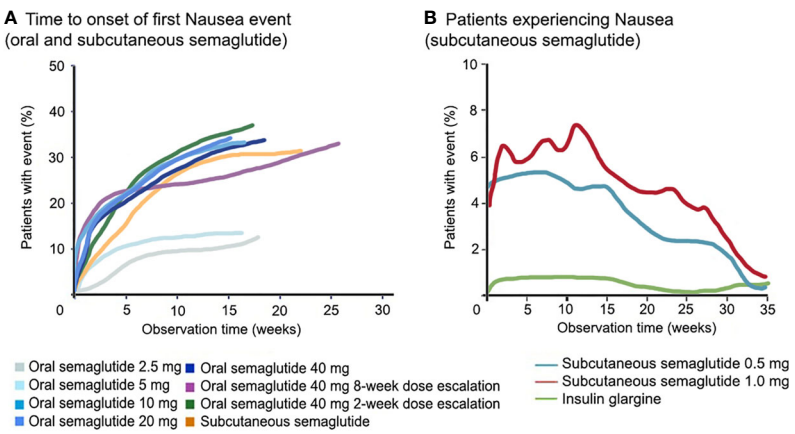

FIGURE 2 | Course of nausea with semaglutide. GLP-1RA, including semaglutide, cause nausea in about one third of treated patients, which is both dose- and time-dependent. In panel **(A)**, a direct comparison between subcutaneous and oral semaglutide is shown, as well as different doses of oral semaglutide, for the first occurrence of nausea. In panel **(B)**, the course of the occurrence of nausea is shown for subcutaneous semaglutide. Data for panel **(A)** are derived from the phase-2 trial (38), for panel **(B)** data are shown from (26). GLP-1RA, glucagon-like peptide-1 receptor agonist.

a small component (0.07 to 0.5 kg) of the total treatment difference in weight loss was explained by nausea or vomiting (52). In contrast, when combining data from SUSTAIN 3, 7 and 10, the occurrence of nausea and vomiting was not associated with superior weight loss (53). Whether this route plays a role in the beneficial effects of GLP-1RA on body weight needs further studying.

Pancreatic Adverse Events: Pancreatitis and Pancreatic Cancer

Within years of the introduction of GLP-1RAs, these agents were linked to the occurrence of acute pancreatitis, and suggested to potentially cause pancreatic cancer (6). In the subsequent years, many pharmacovigilance and database studies followed, with conflicting results (54–60). Given the nature of observational studies, data could have been confounded, since patients with diabetes whom have an indication for GLP-1RA therapy often have concomitant risk factors for pancreatitis (notably obesity, longer diabetes duration and co-medication). As such, the longer term CVOTs were a welcome addition to the discussion. When focusing on semaglutide, no signals of pancreatic AEs were present with blinded adjudication. In SUSTAIN 6, acute pancreatitis occurred in 9 semaglutide-treated patients, and in 12 placebo-treated patients. Pancreatic cancer occurred in one and four patients, respectively (28). In PIONEER 6, acute pancreatitis occurred in one semaglutide-treated patient, and in three placebo-treated patients (19). The incidence of pancreatic cancer was not reported. When combining all phase 3a data, pancreatitis occurred in five semaglutide-treated patients in PIONEER (six in the comparator group), and in 15 patients in SUSTAIN (13 in the comparator group). However, it is possible that for a relatively rare complication (the background incidence of pancreatitis and pancreatic cancer in T2D patients is 422 and 15–24 per 100,000 person-years, respectively (61, 62)), the CVOTs and phase 3 studies are of insufficient power to show differences between groups. When combining all available CVOT data (including those from non-semaglutide GLP-1RAs) in a meta-analysis, a hazard ratio of 1.05 (95% confidence interval [CI] 0.78–1.40) was found for pancreatitis and 1.12 (95% CI 0.77–1.63) for pancreatic cancer (63). These data thus argue against an effect of GLP-1RA on pancreatitis and pancreatic cancer incidence. However, one can wonder whether the follow-up duration in the CVOTs (ranging from a median of 1.3 to 5.4 years) is long enough for patients to develop pancreatic cancer.

While establishing (the absence of) a link with pancreatitis and pancreatic cancer in large clinical studies was one aspect in this field of research, others focused on animal studies and more mechanistic findings. One consistent finding is a subtle and asymptomatic increase in plasma lipase and amylase level (64, 65), which occurs within hours of administration (66). In a 26-week randomized controlled trial, oral semaglutide dose-dependently increased lipase levels by 9 to 55% and subcutaneous semaglutide by 36% (38). An increase in enzyme levels was not associated with occurrence of pancreatic events in trials with liraglutide (67, 68). Moreover, our group previously demonstrated that the liraglutide-induced increase in pancreatic enzymes is not associated with changes in pancreatic exocrine function or pancreas size measured by magnetic resonance imaging (69). Such studies have not yet been conducted for semaglutide.

A handful of preclinical studies showed that GLP-1RAs induce pancreatic inflammation, cellular proliferation and intra-epithelial neoplasia (PanIN) (70–72). However, the majority of animal studies did not find any effect of GLP-1RAs on pancreatic physiology, even with doses up to 240 the normal human dose (73–76). Preclinical studies with semaglutide also found no adverse signals in pancreatic tissue (76). Although pancreatic adverse events are difficult to completely rule out, an assessment by the FDA and the EMA concluded that a causal association between incretin-based drugs and pancreatitis or pancreatic cancer is inconsistent with the current data (77).

Thyroid Cancer

Both formulations of semaglutide have received an official box warning for thyroid C-cell tumors in the US. This caution is solely based on data from rodent studies and is not unique for semaglutide amongst the GLP-1RA. In rodents, the thyroid C-cells (neuroendocrine parafollicular cells which secrete calcitonin) highly express the GLP-1 receptor (78). Stimulation leads to upregulation of the calcitonin gene expression, calcitonin synthesis, C-cell hyperplasia, and increased risk of medullary adenomas and carcinomas (78). Initial studies found expression of the GLP-1 receptor in healthy human thyroid tissue, as well as in medullary thyroid carcinoma (MTC) and C-cell hyperplasia (79, 80). However, these studies were later refuted, as incompletely validated GLP-1 receptor antisera were used (81). When using validated antibodies, the GLP-1 receptor is only marginally expressed in thyroids of non-human primates and humans (78, 82). Supporting this is the observation that monkeys treated with >60 times the human dose of liraglutide do not develop C-cell abnormalities after 20 months (78).

In the SUSTAIN program, three adjudicated events of malignant thyroid neoplasm were identified, two in semaglutide-treated patients (combined n = 5,933), and one in the comparator group (n = 4,736) (10–13, 22, 26–32). None of these were medullary carcinoma. Serum calcitonin was measured during these trials, and no notable difference in mean levels was seen between the treatment arms. In the PIONEER program, four thyroid malignancies occurred in semaglutide-treated patients, *versus* one in the comparator group (14–21, 23, 24). In one instance, a MTC developed in a patient with preexisting nodules and elevated calcitonin at baseline (19). When looking at long-term data from the LEADER trials, the CVOT for liraglutide, there was no difference between liraglutide and placebo regarding calcitonin levels and C-cell malignancies (83).

It should be noted that MTC is rare (estimated incidence of 0.2 cases per 100,000 patient-years), and as such, it is very difficult to definitively rule out an association between GLP-1RA and thyroid malignancies. Therefore, regulatory authorities required additional pharmacovigilance activities, by systematically monitoring the annual incidence of MTC in the US for at least 15 years (MTC-

22341, results expected by 2035–2037). In the meantime, semaglutide is contraindicated in patients with a personal or family history of MTC, as well as in patients with multiple endocrine neoplasia (MEN) type 2 in the US.

Gallbladder

In the SCALE-trial, high-dose liraglutide for the treatment of obesity was associated with an increased risk of gallbladder events compared to placebo (2.5% *versus* 1.0% of patients, respectively) (84). Based on AEs as reported in the European EudraVigilance database, gallbladder disease is likely not limited to liraglutide, but affects all incretin-based therapies (85). A recent meta-analysis observed an increased risk of 28% for cholelithiasis with GLP-1RA treatment (86), but a breakdown for each agent was not given. In the SUSTAIN program, 83 patients (1.4%) treated with semaglutide developed a gallbladder event, compared with 39 patients (1.9%) in the placebo group (10, 27, 28, 31, 32). The events mainly included cholelithiasis. In the PIONEER program, cholelithiasis occurred more often in the semaglutide-treated group (0.6% *versus* 0.1% with placebo), while the risk of cholecystitis was similar (data derived from the summary of product characteristics (SmPC) (87), as the manuscripts did not describe these data). Importantly, none of the gallbladder events have been linked to mortality. Cholelithiasis has been included in the SmPC of both subcutaneous and oral semaglutide).

Initially the gallbladder events were attributed to GLP-1RA-induced weight loss, as for example in the SCALE and LEADER trials, the patients with gallbladder events had more than average weight loss (84, 88). However, as gallbladder disease is not an issue with sodium-glucose co-transporter-2 (SGLT-2) inhibitors (with similar weight loss) (89), and gallbladder events also occurred in GLP-1RA-treated patients well after weight reduction (90), other mechanisms are possibly in play. One option could be lower gallbladder motility, which enhances biliary sludge formation and bile stones. In acute intervention studies, exenatide and albiglutide reduced cholecystokinin-induced gallbladder emptying (91, 92). However, after 12-week liraglutide intervention, we were unable to demonstrate an effect on gallbladder emptying (93), while Nexøe-Larsen et al. observed that liraglutide prolonged the time to reach maximum gallbladder emptying (94). Another mechanism is a change in bile salts, leading to supersaturated bile. While we observed changes in deoxycholic acid levels in plasma and fecal samples after liraglutide treatment, the clinical relevance remains unclear (93). Fascinatingly, exendin-4 appears to stimulate cholangiocyte proliferation through the GLP-1 receptor, hereby preventing cholangiocyte apoptosis in models of bile acid-induced damage and models of ductopenic cholangiopathies (95, 96). Although these data are considered beneficial, it also indicates that GLP-1RA could have direct adverse effects on the biliary tree. What the exact mechanism is behind the gallbladder events requires further study, but probably encompasses a combination of factors.

Cardiovascular

All GLP-1RAs increase heart rate, and this is not different for semaglutide. In SUSTAIN 6, a placebo-corrected heart rate increase of 2.75 beats per minute (bpm) was observed for semaglutide 0.5 mg, and 3.2 bpm for the 1.0 mg dosage (97). This increase was not associated with adverse cardiac events.

In addition, no increase in cardiovascular outcomes were observed in SUSTAIN 6 and PIONEER 6, which is reassuring given the initial fear of adverse cardiac events with increased resting heart rates. Large epidemiological studies have found that an increase in 5 bpm is associated with an increase of 17% in mortality (98). It is unclear whether this association holds true for drug-induced heart-rate acceleration. The α-blocking agent doxazosin increases heart rate by ~25% (99), and is associated with an increase in heart failure incidence (compared with the diuretic agent chlorthalidone) (100). In contrast, lowering heart rate by approximately 10 bpm using the cardiac funny-channel inhibitor ivabradine did not affect mortality in patients with stable coronary artery disease. At this point, it is clear that the beneficial effects of GLP-1RA on cardiovascular risk factors and physiology outweigh a potential risk of the associated heart rate increase. Liraglutide has been on the market for 10 years, but cardiovascular safety beyond this has not been studied yet.

The increase in heart rate is also of importance in patients with heart failure (HF). While the semaglutide CVOTs did not show an increased incidence of hospitalization for HF compared to placebo (101), in earlier smaller studies with liraglutide in patients with HF with reduced left ventricular ejection fraction, the GLP-1RA was associated with increased incidence of serious cardiac events (rhythm disorders, worsening of HF) (102, 103). Since patients with HF with New York Heart Association class IV were excluded from the CVOTs, it is unclear whether safety risks could occur in semaglutide-treated patients. However, a recent meta-analysis of all current CVOTs, showed that GLP-1RAs as a group were associated with a (non-significant) reduction in HF (104).

Several clinical mechanistic trials provided conflicting evidence while aiming to understand the GLP-1RA-induced heart rate-increase. Some studies found systemic vasodilation (with likely consequent reflex tachycardia), while others failed to show this (105–107). Similarly, discrepant findings are available for activation of the (cardiac) sympathetic nervous system (106, 108–111). Our own group previously hypothesized a direct effect of GLP-1RAs on sino-atrial cells (106), after exclusion of other potential causes. This postulation was later confirmed in a mouse model, where stimulation of GLP-1 receptors on atrial cells induced a chronotropic effect, but only when neuronal input was present (112).

Most novel drugs also undergo testing for their effect on the QT interval, as QT prolongation is a marker for potential ventricular fibrillation. Compared with placebo, subcutaneous semaglutide had no effect on this ECG measure in healthy volunteers, with doses above what is used in daily practice (113).

Acute Kidney Injury

Initial case reports suggested that GLP-1RA treatment could cause acute kidney injury (AKI) in some patients (114). Mechanistically, this was explained by dehydration caused by nausea, vomiting and diarrhea (see above). Also, very recently it was shown that the GLP-1RA, dulaglutide decreased fluid

intake (115). Furthermore, GLP-1RA potentially further compromise fluid homeostasis by increasing renal sodium excretion (116). Combined, this could induce renal failure, especially in frail patients or those with medication such as renin–angiotensin–aldosterone system inhibitors, non-steroidal anti-inflammatory drugs or diuretic drugs.

In the SUSTAIN program, acute kidney failure was only reported in SUSTAIN 6, where its occurrence was similar between semaglutide and placebo (28). In PIONEER, AKI was a safety event of interest, and reported in all papers (14, 17–19, 21, 23). In PIONEER 6, AKI occurred in 2.0% of patients treated with oral semaglutide and 2.3% of placebo-treated patients (19). Whether this is statistically or clinically significant has not been evaluated yet.

In contrast to the incidental cases of AKI, the CVOTs mainly demonstrate a beneficial effect on renal outcomes, likely because of effects on cardiovascular risk factors (117). As recently reviewed, GLP-1RAs reduce progression to macro-albuminuria and lead to (subtle) reductions in the decline in renal function (118). In a recent post-hoc analysis of SUSTAIN 6, semaglutide was associated with less events of nephropathy, independent of baseline blood pressure (119). Thus, while it is conceivable yet not statistically confirmed that semaglutide could cause AKI in selected patients, there is plenty of evidence that it reduces nephropathy in the long term. A dedicated kidney trial (the FLOW study; NCT03819153) is currently ongoing, studying the effects of subcutaneous semaglutide on renal outcomes in people with T2D and chronic kidney disease.

Diabetic Retinopathy

In the SUSTAIN-6 trial, an increase in DRP complications, defined as a composite of need for retinal photocoagulation or treatment with intravitreal agents or vitreous hemorrhage or diabetes-related-blindness, was reported for semaglutide compared to placebo (hazard ratio 1.76; 95% CI 1.11–2.78). In a large systemic review and network analysis, including several GLP-1RAs, subcutaneous semaglutide was the only glucose-lowering drug for which this signal was observed (120). However, in the LEADER trial, a non-significant trend towards DRP was observed for liraglutide (121). In PIONEER 6, unadjudicated DRP occurred in 5.8% of oral semaglutide-treated patients and in 4.8% of the placebo-treated patients (19).

Villsbol and colleagues further investigated the DRP signal in the SUSTAIN program (122). In SUSTAIN-6, nearly 30% of patients had previous documented DRP, with 6% proliferative DRP. This percentage was not surprising given the inclusion of patients with previous cardiovascular disease, usually associated with long-standing diabetes. In semaglutide-treated patients, 3% (*versus* 1.8% in the placebo group) of patients reached an adjudicated endpoint of DRP. Across all DRP categories as indicated above, more events with semaglutide were noted. Participants that were prone to develop DRP had pre-existing DRP, longer diabetes duration, higher HbA_{1c} levels at baseline, and more often used insulin therapy. Particularly, participants with pre-existing DRP who were using insulin therapy had the highest risk for a new DRP event.

This analysis further assessed whether the increase in DRP was a GLP-1 specific effect, or rather caused by a robust and early glucose lowering as suggested by several other studies, where acute and large reductions in glucose concentrations may initially and transiently worsen DRP, yet prevent or delay onset or progression of DRP in the long term (123–128). Patients that met a DRP endpoint had strongest glucose lowering during the trial, independent of their randomization to semaglutide or placebo. A *post-hoc* mediation analysis adjusting for HbA_{1c} reduction at week 16 showed that glucose reduction at this time point explained the increased incidence. Limitations of DRP assessment during the trial were the absence of assessment of retinal changes over time, while the severity was not graded on baseline. Nevertheless, based on the data brought forward, it seems safe to conclude that the phenomenon of early worsening of pre-existing DRP was secondary to the initial and rapid improvement in glycemic control that occurred in SUSTAIN-6. This was confirmed in the recent AngioSafe study which showed no effect of GLP-1RA therapy on angiogenesis and no association between GLP-1 exposure and severe DRP was shown (129).

Currently, a large trial is ongoing assessing the long-term effects of semaglutide on DRP in patients with T2D as primary outcome (FOCUS trial, NCT03811561). This study will provide important data with respect to semaglutide safety on the retina. Until that time, caution should be exercised when using semaglutide in patients with DRP. It may be sensible to perform a fundoscopy prior to semaglutide therapy, and existing DRP should be treated where necessary. In addition, given the strong effects of semaglutide on glucose levels, down titrating insulin will prevent rapid decreases in glucose concentrations thereby reducing the risk of acute DRP worsening.

Injection-Site and Allergic Reactions

Although every subcutaneous injection can induce injection-site reactions, there are no signals that this is higher with semaglutide compared with placebo (130). In phase 3 studies, any site reaction was present in 0.6% of patients on the 0.5 mg dose, 0.3% on the 1 mg dose, and 0.8% in the comparator groups. The local site reaction includes bruising, discoloration, induration, and pain (130). In SUSTAIN-6, none of these injection site-reactions was considered severe, and it was never a reason to withhold therapy.

Given the immunogenic potential of protein-based drugs, it is important to monitor allergic reactions with GLP-1RAs. Allergic reactions were reported in four patients in the SUSTAIN program. However, at closer inspection, these reactions were more likely caused by the (concomitant) use of angiotensin-converting enzyme inhibitors or an infection (130). Across the phase 3a PIONEER trials, less subjects with oral semaglutide (2.9%) had allergic reactions compared with the comparators (4.6%) (131). No cases of anaphylactic reactions have yet been attributed to semaglutide; one patient using semaglutide had an anaphylactic shock attributed to cefazolin in SUSTAIN-6.

EFFECTS OF SEMAGLUTIDE COMPARED TO OTHER GLP-1 RECEPTOR AGONISTS

The group of GLP-1RA contains several agents, and their adverse effect profile is not identical. This could be due to differences in pharmacokinetic profile (short- *vs* long-acting) and due to structural differences. Exendin-derived agents, i.e. exenatide and lixisenatide, are based on a protein derived from saliva of the Gila monster, and only share roughly 50% of the homology of GLP-1, which could trigger immunogenicity. The more frequent injection site reactions with exenatide once weekly (22%) compared with semaglutide (1.2%) in SUSTAIN-3 could be a consequence of this (22).

The head-to-head studies within the SUSTAIN and PIONEER programs allow some comparison of the adverse effect profile (**Table 2**). With these data, the safety profiles of rare potential events (e.g. pancreatitis, thyroid cancer, kidney injury, etc.) and hypoglycemia risk are comparable for semaglutide, dulaglutide, exenatide once weekly and liraglutide. However, semaglutide appears to be associated with more frequent nausea and vomiting. In SUSTAIN-3, 41.8% of patients with subcutaneous semaglutide had GI adverse effects, compared with 33.3% in exenatide once weekly (22). In SUSTAIN-7, nausea or vomiting occurred similarly for semaglutide 0.5 mg and 1 mg and dulaglutide 1.5 mg (43–48%), yet less frequent with dulaglutide 0.75 mg (33%) (29). In SUSTAIN-10, 21.8% of semaglutide-patients had nausea, compared to 15.7% of liraglutide-patients (32).

For oral semaglutide, the data are similar. In PIONEER-9, oral semaglutide induced nausea in up to 10% of patients, whereas none of the liraglutide patients had nausea (liraglutide was low-dose however) (23). Compared with dulaglutide in PIONEER-10, nausea rates were similar, yet oral semaglutide was more frequently associated with vomiting (14 mg dose semaglutide: 7%, dulaglutide 0.75 mg 2%) (24).

Finally, in a network meta-analysis, several short- and long-acting GLP-1RA were compared regarding efficacy and side effect profile. Compared with lixisenatide, exenatide twice daily, liraglutide, albiglutide and dulaglutide, semaglutide is associated with highest nausea and vomiting rates, yet also with highest rates of improvement in glycemic control and weight loss (132).

Whether the more rare adverse events differ between the different agents can only be answered by using observational cohort data from a very large group of patients and a longer follow-up time. Since semaglutide is relatively new, these data are not available yet. It should be stressed that guidelines do not favor the prescription of one GLP-1 RA over another, although clinicians are advised to select a compound with proven cardiovascular benefit.

DISCUSSION

Since the finding that the thiazolidinedione rosiglitazone increased cardiovascular events, much weight has been placed on the safety of novel glucose-lowering drugs. For all new drugs, a thorough safety profile needs to be established, with particular emphasis on cardiovascular safety. While safety within the phase 3 program is sufficient for marketing authorization (although the risk of cardiovascular events should not exceed a hazard ratio of 1.8 according to a guidance document that was released by the FDA at that time), it is the post-marketing phase in which rare adverse events and any other potential safety risks are identified or resolved. The same FDA document mandates post-marketing trials to demonstrate that the novel agent does not increase cardiovascular risk by more than 30% compared to placebo (henceforth these trials were named 'cardiovascular outcome trial'), if premarketing studies did not already demonstrate this.

Although designed for cardiovascular safety, other safety aspects may also be assessed in CVOTs. Moreover, after marketing approval, several databases can be employed to understand safety risks. In this regard, case reports and studies using adverse event databases (such as the FDA Adverse Event Reporting System and European Eudravigilance) frequently are the first signals of potential safety risks. With GLP-1RA, these encompassed AKI, pancreatitis, pancreatic cancer and thyroid cancer (6, 114). While awaiting the CVOTs, results from several health care database studies (insurance claims, hospital registry, etc.) were published, and were somewhat conflicting. With the totality of the evidence, many of the feared safety risks were nuanced or refuted.

As semaglutide is one of the youngest GLP-1RA, it was possible to prospectively monitor for the rarer adverse events in the phase 3 program and CVOT. As detailed in the current review, semaglutide appears not to increase the risk of pancreatitis (yet nevertheless it has been added to the SmPC to align with health authorities expectations on class labeling), but it is associated with more events of cholelithiasis. Although current data argue against an increased risk of pancreatic cancer and thyroid cancer with semaglutide, it can be debated whether the background incidence of these disorders is too low to fully conclude the absence of an association.

Even though the route of administration, their drug formulation and the dosage differ, the AE profile appears not to be very different between subcutaneous and oral semaglutide. One important co-product in oral semaglutide, SNAC, can be toxic at high doses (133). However, at the SNAC dosage of 300 mg per tablet of oral semaglutide, it is well below the toxic dose of 1.8 g/kg/day observed in monkeys, where it caused nausea and diarrhea (133). Post-marketing surveillance will help to elucidate whether the subcutaneous and oral variant differ in their real-world safety profile.

Most data reported in this review are from phase 3 clinical trials. Whether all of these data can be extrapolated to clinical practice remains a matter of debate. In RCTs, there are tightly regulated cohorts based on stringent in- and exclusion criteria, thereby reducing generalizability. Moreover, the frequent visits and calls during a study could improve patient coherence. However, real-world evidence—where available—has not shown major differences in for example hypoglycemia rate or drug discontinuation (36, 39, 40).

CONCLUSION

Over the years, the use of GLP-1RAs has first been associated with several adverse events, which were later mostly nuanced or refuted. As one of the newer agents within the class, the safety of semaglutide—both the subcutaneous and oral formulation—has been scrutinized in the phase 3 programs and CVOTs. Compared with placebo and active comparator, semaglutide induces mostly mild and transient gastrointestinal disturbances, and increases the risk of cholelithiasis. However, no major safety concerns have arisen to date, although definitive conclusions for pancreatic cancer, thyroid cancer and DRP complications cannot be drawn at this point. When compared with the beneficial effects of these drugs on glucose metabolism, blood pressure, body weight and cardiovascular (and potentially even renal) endpoints, these agents have an overall beneficial risk/benefit-profile for treatment of patients with T2D.

AUTHOR CONTRIBUTIONS

The authors drafted all versions of the article, and provided final approval for submission. All authors contributed to the article and approved the submitted version.

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