ISSN 2450–7458
e-ISSN 2450–8187

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Expert Opinion on the Cardio-Renal-Metabolic Approach to Management of Adults with Type 2 Diabetes Using Oral Semaglutide: An Indian Perspective

ABSTRACT

Objective: This study aims to evaluate the efficacy and safety of oral semaglutide in managing type 2 diabetes (T2D) through a cardio-renal-metabolic approach tailored for the Indian context.

Materials and methods: A literature review was conducted using PubMed and Google Scholar, focusing on systematic reviews, meta-analyses, and randomized controlled trials related to oral semaglutide. Findings were discussed at the 16th National Insulin and Incretin Summit (NIIS) on November 19, 2022, where an expert panel developed guidelines based on collective insights and live opinion polls.

Results/Key findings: The expert committee recommends oral semaglutide for adults with T2D due to its effectiveness in lowering blood glucose and promoting weight loss. It can be used alone or with other oral anti-diabetic agents, except dipeptidyl peptidase 4 inhibitors (DPP-4i). The drug is safe for those with cardiovascular disease or chronic kidney disease (CKD). Common gastrointestinal side effects are typically mild. Administration requires fasting for 30 min after dosing. Gradual dose escalation is advised to minimize side effects, and patients should be counseled on potential interactions with other medications and pregnancy considerations.

Keywords: semaglutide, type 2 diabetes, glucagon 1 receptor agonist

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Clinical Diabetology
DOI: 10.5603/cd.103785
Received: 28.12.2024 Accepted: 8.01.2025
Early publication date: 14.03.2025

Introduction

Burden of type 2 diabetes

According to the 10th edition of the Diabetes Atlas released by the International Diabetes Federation (IDF) in 2021, diabetes mellitus (DM) affects 8.8% of the adult population in the world [1]. India has the dubious distinction of having the second-largest number of adults living with diabetes after China [2]. The 2023 ICMR-INDIAB national cross-sectional study (ICMR-INDIAB-17) reported an estimated prevalence of diabetes in India among individuals aged 20 years and above of 11.4%. Additionally, it has been estimated that almost 57% of adults living with diabetes in India remain undiagnosed [3]. The 2018 Indian Council of Medical Research (ICMR) guideline specifies a target glycated hemoglobin (HbA1c) value of ≤ 7% for non-pregnant adults with diabetes [4]. However, despite the availability of a plethora of oral antidiabetic drugs (OADs) and insulin preparations, the overall glycemic control of adults living with diabetes in India remains dismal: the reported mean HbA1c value of 9.0% is far higher than the target of ≤ 7% [5]. Clinical inertia (failure to initiate or intensify therapy when warranted) and non-adherence to treatment pose significant challenges in achieving glycemic targets. Early initiation of treatment, followed by timely intensification, is recommended to achieve glycemic targets [6, 7].

People with type 2 diabetes (T2D) are at increased risk of developing microvascular complications, such as nephropathy, retinopathy, and neuropathy, and/or macrovascular complications, such as cardiovascular disease (CVD), cerebrovascular disease, and peripheral vascular disease. Poor glycemic control significantly contributes to the risk of microvascular and macrovascular complications [8]. Moreover, a prospective cohort study including 18,961 subjects reported in the year 2022 that a 5-year increase in the duration of diabetes resulted in an excess risk of approximately 20% for CVD and stroke [9]. According to the Framingham risk score, people with diabetes face a 2- to 4-fold higher risk of cardiovascular (CV) mortality [10]. The Swedish Heart Registry reported a 37% increased risk of mortality in people with diabetes and heart failure (HF) [11]. Chronic kidney disease (CKD) has been reported in 48.4% of people with T2D [12]. The presence of CKD increases the risk of major adverse cardiovascular events (MACE), HF, and all-cause mortality among people with T2D [13].

Several non-insulin-based therapies are available for the management of T2D, including metformin, sulfonylureas, thiazolidinediones, dipeptidyl peptidase 4 inhibitors (DPP-4i), sodium-glucose co-transport-2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP-1RA), amylin analogues, and alpha-glucosidase inhibitors. Among these, SGLT2 inhibitors and GLP-1RAs with proven CVD benefits have been recommended by several national and international associations, including the European Association for the Study of Diabetes (EASD), the American Diabetes Association (ADA), the AACE, RSSDI, ESC, and AHA, for use in people with T2D with established atherosclerotic cardiovascular disease (ASCVD) and/or CKD, to reduce the risk of CV events or CKD progression, independent of baseline HbA1c or metformin use.

Role of GLP-1RA in the management of type 2 diabetes

Glucagon-like peptide-1 (GLP-1) is a peptide released from the L-cells of the small intestine in response to food intake. It stimulates glucose-dependent insulin secretion and inhibits release of glucagon. GLP-1 also decreases gastric emptying and reduces appetite. In many people with T2D, it has been shown that the effects of GLP-1 are blunted, and the administration of pharmacological doses of GLP-1 overcomes this. In people with T2D, GLP-1RAs target 6 of the 8 core pathophysiological defects of T2D (Tab. 1) [14].

Table 1. Pharmacological Targets of GLP-1RAs [16–20]

Organ	Pathophysiology	Effect of GLP-1RA
Pancreas	Impaired insulin secretion from pancreatic β-cells	Enhances glucose-dependent secretion of insulin and amylin
	Increased glucagon secretion from pancreatic α-cells	Suppresses secretion of glucagon
Liver	Increased hepatic glucose output	Reduced hepatic glucose output
Satiety Centre	Dysfunction of central neurotransmitters	Increases satiety (central action)
GI tract	Decreased incretin effect	Slows gastric emptying
Kidney	Increased glucose absorption, activation of the cAMP-protein kinase A pathway	Increased natriuresis, protection from oxidative injury
Cardiac	Oxidative stress, increased inflammation, hypercoagulability, reduced endothelial function, impaired LV function	Increased myocardial contractility, increased heart rate, increased myocardial glucose update, decreased ischemia-induced myocardial damage

cAMP — cyclic adenosine 3′,5′-monophosphate; GI — gastrointestinal; GLP-1RA — glucagon-like peptide-1 receptor agonist; LV — left ventricle

Table 2. Comparison of Short-Acting versus Long-Acting GLP-1RAs [17, 22]

Parameters	Short-acting GLP-1RAs	Long-acting GLP1-RAs
Compounds	Exenatide, lixisenatide	Albiglutide, dulaglutide, exenatide LAR, liraglutide, semaglutide
Half-life	2–5 h	12 h-several days
Control of fasting glycemia	Modest reduction	Strong reduction
Control of postprandial glycemia	Strong reduction	Modest reduction
Frequency of dosage	OD/BID	OD/QW
Fasting insulin secretion	Modest stimulation	Strong stimulation
Gastric emptying rate	↓↓	↓
Heart rate	Slight increase (0–2 bpm) or no effect	Moderate increase (2-5 bpm)

BID — twice daily; GLP-1RA — glucagon-like peptide-1 receptor agonist; OD — once daily; QW — once weekly

Table 3. Recommendations of Salient Guidelines for Use of GLP1-RA in the Management of People with T2D

Guideline	Recommendation
ADA 2024 standards of care [23]	For adults with T2D and established or high risk of ASCVD, HF, and/or CKD, treatment should include GLP-1RAs and/or SGLT2is to reduce CV and kidney disease risk, regardless of HbA1c values (Grade A). GLP-1RAs are preferred over insulin for glycemic management in adults with type 2 diabetes (Grade A). If insulin is used, combining it with a GLP-1RA is recommended for better glycemic control, weight benefits, and reduced hypoglycemia risk. Insulin dosing should be reassessed with the addition or dose escalation of a GLP-1RA (Grade A).
ADA EASD 2019 [24]	GLP-1RAs with proven CV benefits should be preferred in people with T2D who have established ASCVD or multiple high-risk CVD factors. Among people with type 2 diabetes and established CKD, GLP-1RA with proven CVD benefit should be considered when SGLT2i is contraindicated or not tolerated.
Research society for the study of diabetes in India (RSSDI) 2022 [25]	GLP-1RAs with proven CV benefits should be considered in people with T2D with ASCVD, with multiple risk factors for ASCVD, and those with CKD (when a SGLT2i is contraindicated or not tolerated). GLP-1RAs can be considered a viable second- or third-line option for managing glycemia in people with T2D and hyperglycemia. GLP-1RAs are preferred for the management of glycemia in people with T2D when weight loss is a desired outcome.

A1c — glycated hemoglobin; ADA — American Diabetes Association; ASCVD — atherosclerotic cardiovascular disease; CKD — chronic kidney disease; CV — cardiovascular; CVD; cardiovascular disease; DKD — diabetic kidney disease; DM — diabetes mellitus; eGFR — estimated glomerular filtration rate; EASD — European Association for the Study of Diabetes; GLP-1 glucagon-like peptide-1; GLP-1 RAs — glucagon-like peptide-1 receptor agonists; HF — heart failure; MACE — major adverse cardiovascular events; RSSDI — research society for the study of diabetes in India; SGLT2 — sodium-glucose cotransporter-2; T2D — type 2 diabetes

GLP-1RAs like albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, and semaglutide bind to, and activate, the GLP-1RA. Pharmacologically, GLP-1RAs enhance insulin secretion, slow gastric emptying, suppress apoptotic cell death, and increase proliferation of pancreatic β-cells [15]. A comparison of the different GLP-1 RAs approved for use in people with T2D is presented in Table 2 [16–20]. Clinically, GLP-1RAs significantly reduce HbA1c and body weight with a very low risk of hypoglycemia. Overall, all GLP-1RAs are CV-safe, including a few that have been shown to have proven CV benefit [21].

Recommendations of various guidelines on the use of GLP-1 RA in the management of T2D

Most guidelines recommend using a GLP-1RA across the entire spectrum of disease in people with T2D unless there is a specific contraindication. GLP-1RAs with proven CV benefit are specifically recommended for use in people with T2D with high risk for cardiorenal disease or in those with established ASCVD; they are also preferred in people with T2D with CKD when the use of a SGLT2i is contraindicated or is not tolerated. GLP-1RAs are also indicated in people with T2D without ASCVD or CKD for glycemic control and are preferred in people with T2D where weight loss is a desired therapeutic outcome (Tab. 3).

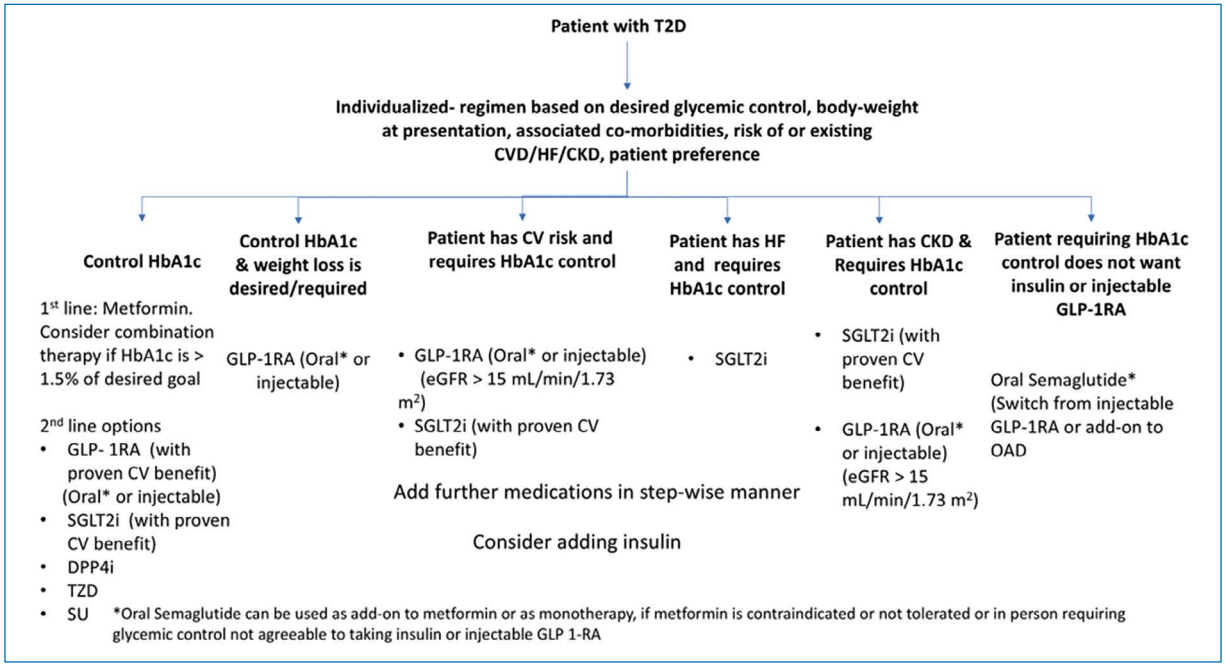

Figure 1. Use of GLP-1RA in the Management of Person with T2D [21]
CKD — chronic kidney disease; CV — cardiovascular; CVD; cardiovascular disease; DPP-4i — dipeptidyl peptidase-4 inhibitors; eGFR — estimated glomerular filtration rate; GLP-1 RAs — glucagon-like peptide-1 receptor agonists; HbA1c — hemoglobin A1c; HF — heart failure; SGLT2 — sodium-glucose cotransporter-2; SU — sulfonylureas; T2D — type 2 diabetes mellitus; TZD — thiazolidinediones

Role of "oral" GLP-1RA in the management of people with T2D (Fig. 1)

Despite the manifold benefits of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in the management of people with T2D, their use is somewhat limited globally. Among the many reasons for this limited use, including the fact that GLP-1 RAs are very expensive, the route of administration is an added hindrance because most GLP-1 RAs marketed initially had to be administrated as a subcutaneous injection. The need to administer medication by injection is a deterrent for many adults with T2D, presenting a challenge not only during initiation of therapy but also for long-term adherence. The advent of the first oral GLP-1RA, oral semaglutide, which was approved for use for glucose control in people with T2D by the US FDA in 2019, opens up exciting new possibilities by overcoming the fear of injection among adults with T2D [21].

Need for expert opinion

Oral semaglutide was approved in India in January 2022 for glycemic management in people with T2D. However, several critical practical aspects of its use in people with T2D in the Indian context need elucidation to ensure its effective and safe use. In the first instance, there is a pressing need for a simple dosing and administration schedule to reap maximal benefits. Secondly, there are no practical recommendations for modifications that need to be made when using oral semaglutide with other commonly used medications, including other oral anti-diabetic agents, statins, levothyroxine, anticoagulants, and anti-hypertensive drugs. The third practical concern relates to transitioning from an injectable GLP-1RA to oral semaglutide in people with T2D who want to switch from an injectable GLP-1RA to oral semaglutide. Finally, the dosing of oral semaglutide is complex in people with T2D with special situations and with comorbidities, especially CKD, HF, CVD, and stroke. In the absence of definitive information on these practical clinical challenges, a committee was constituted to review the available evidence and provide an expert opinion on the cardio-renal-metabolic approach to the management of T2D using oral semaglutide.

Methodology

A literature review of PubMed and Google Scholar was performed to obtain available evidence on the efficacy and safety of oral semaglutide and its recommendations. Systematic reviews, meta-analyses, randomized controlled trials, and key cited articles relating to oral semaglutide were reviewed by doctors, and

guidance relevant to the cardio-renal-metabolic approach for the Indian scenario was framed. The recommendations were discussed at the 16th National Insulin and Incretin Summit (NIIS), held on November 19, 2022 by an expert panel of physicians, endocrinologists, and key opinion leaders. At this summit, live opinion polls were used to capture the views of participants, followed by an expert panel discussion. A consensus was reached on the guidelines and general suggestions on the use of oral semaglutide for cardio-renal-metabolic approach in T2D management in the Indian context. The recommendations were based on experience, judgement, and expert opinions.

Current evidence and practical recommendations for the use of oral semaglutide in people with T2D

Glycemic benefits of oral semaglutide

Use of oral semaglutide in drug-naïve people with T2D

The PIONEER 1 trial established the efficacy and safety of oral semaglutide in drug-naïve adults with T2D. This was a 26-week, phase 3a, randomized, double-blind, placebo-controlled, parallel-group trial, which evaluated the efficacy and safety of oral semaglutide compared to placebo in people with T2D managed only by diet and exercise. Adults with T2D (mean age 55 years, mean baseline HbA1c 8.0%) were randomized to once-daily oral semaglutide 3 mg (N = 175), 7 mg (N = 175), 14 mg (N = 175), or placebo (N = 178). At week 26, oral semaglutide reduced HbA1c and body weight in all doses versus placebo. The placebo-adjusted reduction in HbA1c was 0.6%, 0.9%, and 1.1% with the 3 mg, 7 mg, and 14 mg doses of semaglutide, respectively (treatment policy estimand) ($p < 0.001$ for all). Placebo-adjusted reduction in weight at week 26 was –0.1 kg ($p = 0.87$), –0.9 kg ($p = 0.09$), and –2.3 kg ($p < 0.001$) with 3 mg, 7 mg, and 14 mg doses of semaglutide, respectively (treatment policy estimand). The safety profile of oral semaglutide was consistent with other GLP-1 RAs. The most common adverse events observed were gastrointestinal (GI) in nature, mostly mild to moderate in severity, and transitory. The drop-out rate was 2.3–7.4% in the semaglutide group and 2.2% among those on placebo [26].

Oral semaglutide as an add-on to oral anti-diabetic agents

In the PIONEER 2 trial, oral semaglutide, given together with metformin, resulted in a significantly greater reduction in HbA1c and body-weight when compared to empagliflozin [27]. Oral semaglutide is effective and safe when added to other anti-diabetic agents, as seen in the PIONEER 3, 4, 5, 7, and 8 trials [28–32]. Oral Semaglutide, at both 7 and 14 mg/day, as an add-on to metformin and sulfonylurea, resulted in significantly greater reduction in HbA1c when compared to sitagliptin after 26 weeks ($p < 0.001$ for both) [30]. Oral semaglutide is effective and safe when added to metformin and sulfonylurea (PIONEER 3), metformin, SGLT2i (PIONEER 4), and sitagliptin (PIONEER 7) [30–32].

In the PIONEER 2 trial, a greater proportion of adults with T2D on oral semaglutide had a > 10% reduction in body weight when compared to empagliflozin at week 26 (12.5% vs. 6.8%, $p = 0.0066$). At week 26, the reduction in waist circumferences were significantly greater with oral semaglutide than with empagliflozin [27]. In the PIONEER 3 trial, oral semaglutide showed superior effects in reducing body weight when compared to sitagliptin [30]. Oral semaglutide reduced body weight in people with T2D on insulin with/without metformin (PIONEER 8) [29]. In the PIONEER 4 trial, oral semaglutide, compared with once-daily subcutaneously administered Liraglutide and placebo, showed a superior reduction in body weight when compared to both liraglutide and placebo at week 26 [31].

Oral semaglutide as an add-on to insulin

PIONEER 8, a 52-week, double-blind trial, investigated the efficacy and safety of oral semaglutide in addition to insulin, with or without metformin. Uncontrolled adults with T2D on insulin, with or without metformin, were randomized to oral semaglutide 3 mg (N = 184), 7 mg (N = 182), or 14 mg (N = 181) or to placebo (N = 184). The results concluded that oral semaglutide was superior to placebo in reducing HbA1c ($p < 0.001$) and body weight ($p \leq 0.0001$) at week 26. Significantly greater dose-dependent HbA1c and body weight reductions versus placebo were achieved with oral semaglutide at weeks 26 and 52. Moreover, better glycemic control was achieved with oral semaglutide in people who had reduced insulin daily doses compared to baseline doses. In conclusion, oral semaglutide can be used safely and effectively even in the late stage of T2D for treatment intensification in people with T2D who remain uncontrolled on insulin therapy [29].

The PIONEER trial program showed that 7 out of 10 subjects achieved their glycemic target of HbA1c < 7.0% [21]. The details of the PIONEER trials are described in Table 4.

Table 4. Summary of Clinical Studies for Oral Semaglutide in T2D

Trial	Study design	N	Inclusion criteria	Intervention	Results
As monotherapy and first-line drug after diet and exercise					
PIONEER 1 Aroda et al. [26]	Phase 3a, randomized, double-blind, placebo-controlled, parallel-group trial	703	T2D HbA1c 7.0–9.5% Drug naïve; On lifestyle modification	Oral semaglutide 3 mg, 7 mg, 14 mg or Placebo	Reduction in HbA1c: 3 mg: 0.6% 7 mg: 0.9% 14 mg: 1.1% ($p < 0.001$ for all) Reduction in body weight: 3 mg: 0.1 kg ($p = 0.87$) 7 mg: 0.9 kg ($p = 0.09$) 14 mg: 2.3 kg ($p < 0.001$) Percentage of patients achieving HbA1c < 7%: 3 mg: 55.1 % 7 mg: 68.8 % 14 mg: 76.9 % ($p < 0.001$ for all) Percentage of patients achieving HbA1c ≤ 6.5%: 3 mg: 35.9 % 7 mg: 47.5% 14 mg: 63.8 % ($p < 0.001$)
As an add-on to OHAs/insulin					
PIONEER 2 Rodbard et al. [27]	Randomized, open-label, multinational 52-week trial	822	T2D HbA1c of 7.0–10.5% Receiving a stable dose of metformin (≥ 1,500 mg or maximum tolerated)	Oral semaglutide 14 mg OD or Empagliflozin 25 mg OD	Reduction in HbA1c (week 26): Semaglutide: 1.3% Empagliflozin: 0.9% ($p < 0.0001$) Reduction in body weight (week 52) Semaglutide: 4.7 kg Empagliflozin: 3.8 kg ($p = 0.0114$) (Trial product estimand) HbA1c ≤ 6.5% (week 26): Semaglutide: 47.4 % Empagliflozin: 17.2 % ($p < 0.0001$) HbA1c ≤ 6.5% (week 52): Semaglutide: 47.4 % Empagliflozin: 21.7 % ($p < 0.0001$) Body weight reduction ≥ 10% (week 26): Semaglutide: 12.5 % Empagliflozin: 6.8 % ($p = 0.0066$) Body weight reduction ≥ 10% (week 52): Semaglutide: 15.0 % Empagliflozin: 7.8 % ($p = 0.0028$)

PIONEER 3 Rosenstock et al. [30]	Randomized, double-blind, double-dummy, parallel-group, phase 3a trial	1864	T2D HbA1c levels of 7.0% to 10.5% Taking a stable dosage of metformin with or without sulfonylurea	Oral semaglutide 3 mg, 7 mg, 14 mg or Sitagliptin 100 mg	Reduction in HbA1c (week 26): (estimated treatment differences) Semaglutide 3 mg: 0.2 % ($p = 0.09$) Semaglutide 7 mg: 0.3 % ($p < 0.001$) Semaglutide 14 mg: 0.5 % ($p < 0.001$) Reduction in body weight (week 26) Semaglutide 3 mg: 1.2 kg ($p = 0.02$) Semaglutide 7 mg: 2.3 kg ($p < 0.001$) Semaglutide 14 mg: 3.4 kg ($p < 0.001$) Sitagliptin: 0.6 kg HbA1c < 7.0% (week 26): Semaglutide 3 mg:27% ($p = 0.07$) 7 mg: 42% ($p < 0.001$) 14 mg: 55% ($p < 0.001$) Sitagliptin: 32% Weight loss ≥ 5% (week 26): Semaglutide 3 mg: 13% ($p = 0.15$) 7 mg: 19% ($p < 0.001$) 14 mg: 30% ($p < 0.001$) Sitagliptin: 10%
PIONEER 4 Pratley et al. [31]	Randomized, double-blind, double-dummy, phase 3a trial	711	T2D HbA1c of 7.0–9.5% On a stable metformin dose (≥ 1500 mg or maximum tolerated) with or without an SGLT2-i.	Oral semaglutide 14 mg or SC Liraglutide or Placebo	Reduction in HbA1c (week 26): Oral semaglutide: 1.2 % SC Liraglutide: 1.1 % ($p < 0.0001$)(Trial product estimand) Reduction in body weight (week 26): Oral semaglutide: 4.4 kg SC Liraglutide: 3.1 kg ($p < 0.0001$) HbA1c < 6.5% (week 26): Oral semaglutide: 48% SC Liraglutide: 43% ($p = 0.2687$) Bodyweight loss ≥ 10% (week 26): Oral semaglutide: 14% SC Liraglutide: 6% ($p = 0.0032$)
PIONEER 5 Mosenzon et al. [28]	Randomized, double-blind, phase 3a trial	324	T2D HbA1c of 7.0–9.5% eGFR 30–59 mL/min/1.73 m^2 Receiving a stable dose of metformin or sulfonylurea, or both, or basal insulin with or without metformin for the past 90 days	Oral Semaglutide 14 mg OD or Placebo	Reduction in HbA1c (week 26) Semaglutide: 1.0% Placebo: 0.2% ($p < 0.0001$) Reduction in body weight (week 26) Semaglutide: 3.4 kg Placebo:0.9 kg ($p < 0.0001$) At least a 1.0% decrease in HbA1c: Semaglutide: 60% Placebo: 20% ($p < 0.0001$) Weight loss ≥ 5%: Semaglutide: 36% Placebo: 10% ($p < 0.0001$)

PIONEER 6 Husain et al. [33]	Randomized, double-blind, placebo-controlled trial	3183	T2D Age ≥ 50 years at screening and presence of CVD, or age ≥ 60 years at screening and presence of at least one CV risk factor	Oral semaglutide 14 mg or Placebo Median time: 15.9 months	Reduction in HbA1c: Semaglutide: 1.0% Placebo: 0.3% Reduction in body weight: Semaglutide: 4.2 kg Placebo: 0.8 kg Major CV events Semaglutide: 3.8% Placebo: 4.8% (HR = 0.79, p < 0.001 for non-inferiority) Death from CV causes Semaglutide: 0.9% Placebo: 1.9% (HR = 0.49, 95% CI, 0.27 to 0.92) Non-fatal MI Semaglutide: 2.3% Placebo: 1.9% (HR = 1.18) Nonfatal stroke Semaglutide: 0.8% Placebo: 1.0% (HR = 0.74) Death from any cause Semaglutide: 1.4% Placebo: 2.8% (HR = 0.51)
PIONEER 7 Pieber et al. [32]	Multicenter, randomized, open-label, phase 3a trial	504	T2D (diagnosed ≥ 90 days before screening) HbA1c of 7.5–9.5% Patients receiving stable doses of one or more of metformin, sulphonylureas, SGLT2 inhibitors, or thiazolidinediones.	Semaglutide initial 3 mg, titrating up to 7 or 14 mg or Sitagliptin 100 mg	HbA1c < 7% (week 52): Semaglutide: 58% Sitagliptin: 25% (p < 0.0001) Reduction in body weight (week 52): Semagutide: 2.6 kg Sitagliptin: 0.7 kg (p < 0.0001)
PIONEER 8 Zinman et al. [29]	Randomized, double-blind, placebo-controlled, parallel-group trial	731	Patients with T2D uncontrolled on insulin with or without metformin	Oral semaglutide 3, 7, or 14 mg Or Placebo	Reduction in HbA1c (week 52): Semaglutide 3 mg: 0.5% Semaglutide 7 mg: 0.9% Semaglutide 14 mg: 1.2% (p < 0.001 for all doses) Reduction in body weight (week 52): Semaglutide 3 mg: 0.9 kg (p = 0.0392) Semaglutide 7 mg: 2 kg (p ≤ 0.0001) Semaglutide 14 mg: 3.3 kg (p ≤ 0.0001)

CVD — cardiovascular disease; HbA1c — hemoglobin; HR — hazard ratio; MI — myocardial infarction; OD — once daily; OHA — oral hypoglycemic agents; SC — subcutaneous; SGLT2 — sodium-glucose cotransporter-2; T2D — type 2 diabetes

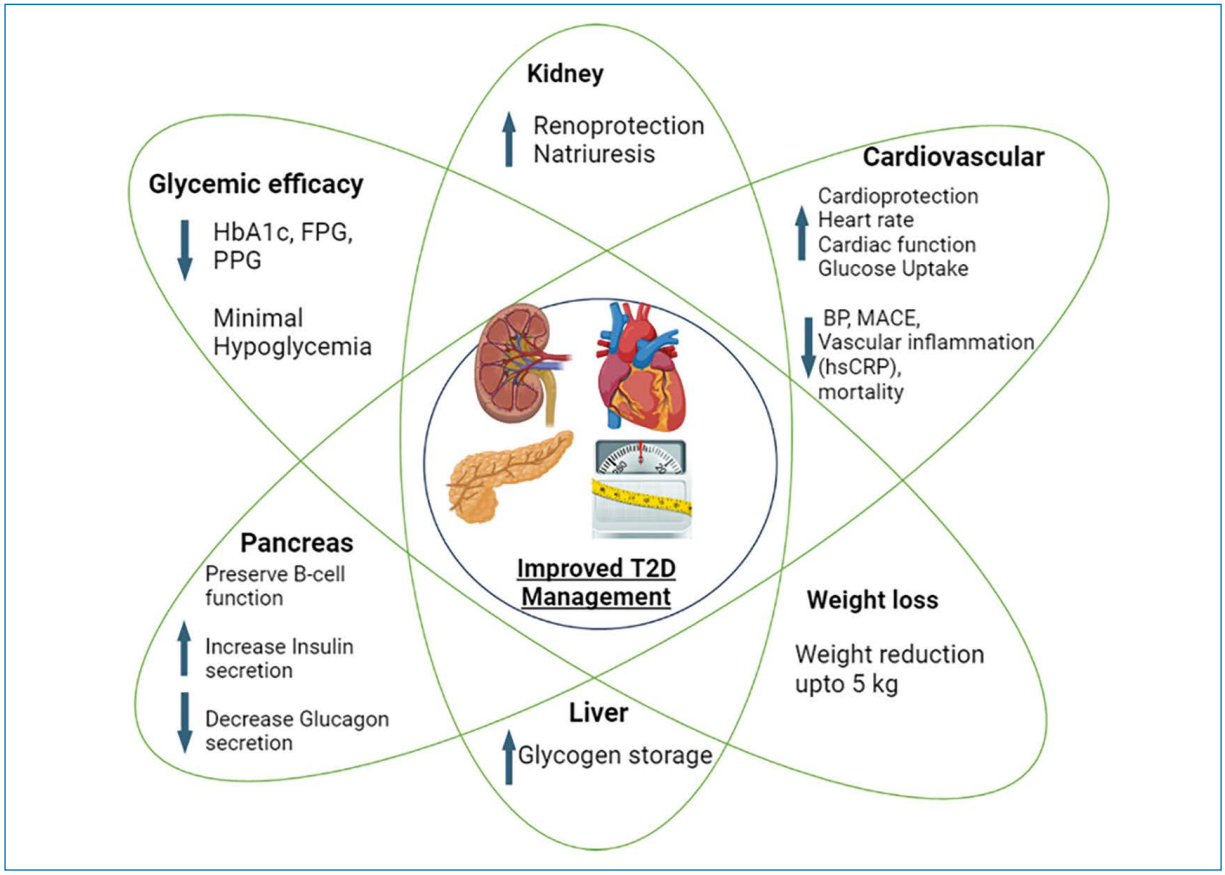

Figure 2. Cardio-Renal-Metabolic Approach for Management of T2D [34]
BP — blood pressure; FPG — fasting plasma glucose; HbA1c — hemoglobin; MACE — major adverse cardiovascular events; PPG — postprandial glucose; T2D — type 2 diabetes

Expert opinion:

The PIONEER trials demonstrated the superiority of oral semaglutide when compared to empagliflozin and sitagliptin in reducing HbA1c and body weight. Moreover, oral semaglutide was seen to be effective and safe when combined with other oral antidiabetic agents, including metformin, sulfonylurea, and SGLT2 inhibitors. In people with long-standing T2D on insulin, addition of oral semaglutide reduces HbA1c, body weight, waist circumference, and insulin requirement.

Taken together, the PIONEER studies highlight the potential of oral semaglutide in the management of adults with T2D, achieving not only an improvement in glycemic control in most but also a clinically significant reduction in body weight in many.

Pleiotropic benefits of oral semaglutide

The management of T2D is gradually shifting from a predominant glucocentric focus to organ protection: the cardio-renal-metabolic outcome-oriented approach (Fig. 2) [29]. In addition to improving glycemic status and reducing body weight, oral semaglutide reduces blood pressure and lipids. Moreover, it has been shown to have a positive impact on CV and clinically significant renal outcomes.

Expert opinion:

Oral semaglutide is safe with respect to cardiovascular events. A dedicated cardiovascular outcomes trial using oral semaglutide is currently underway. Interestingly, subcutaneously administered (SC) once weekly semaglutide has been shown to be statistically superior to placebo in reducing 3P-MACE events, independent of glycemic control. Semaglutide reduces albuminuria and slows the rate of decline of eGFR. Once-weekly SC administered Semaglutide has been shown to significantly reduce clinically relevant renal outcomes; moreover, it reduced the risk of CV events and all-cause mortality in people with CKD.

Safety of oral semaglutide

In the PIONEER trials, oral semaglutide had a tolerability profile consistent with other GLP-1RAs. The most common adverse events were GI-related, mainly nausea,

Table 5. Overview of the Incidence of Adverse Effects of Oral Semaglutide and the Number of Patients Who Withdrew from the PIONEER Trials

Study	Adverse effects	Incidence (%)			No. of patients who withdrew from the trial [N, (%)]		
		3 mg	7 mg	14 mg	3 mg	7 mg	14 mg
PIONEER 1 [26]	GI disorders	1.7	2.3	5.1	4 (2.3)	7 (4.0)	13 (7.4)
	Nausea	8.0	5.1	16.0			
	Diarrhea	8.6	5.1	5.1			
	Vomiting	2.9	4.6	6.9			
PIONEER 2 [27]	Nausea	NA	NA	19.8	NA	NA	44 (10.7)
	Diarrhea			9.3			
	Vomiting			7.3			
	Thyroid-related events (including malignant thyroid neoplasms)			0			
PIONEER 3 [30]	Nausea	7.3	13.4	15.1	26 (5.6)	27 (5.8)	54 (11.6)
	Diarrhea	9.7	11.4	12.3			
	Vomiting	2.8	6.0	9.0			
PIONEER 4 [31]	Nausea	NA	NA	20	NA	NA	31 (11)
	Diarrhea			15			
	Vomiting			9			
	Nasopharyngitis			14			
PIONEER 5 [28]	Nausea	NA	NA	19	NA	NA	24 (15)
	Diarrhea			10			
	Vomiting			12			
	Dyspepsia			10			
	Constipation			12			
PIONEER 6 [38]	GI disorders	NA	NA	1.5	NA	NA	184 (11.6)
	Neoplasms (benign, malignant and unspecified)			1.9			
	Acute pancreatitis			0.1			
PIONEER 7 [32]	Nausea	NA	NA	21	NA	NA	22 (9)
	Diarrhea			9			
	Vomiting			6			
	Nasopharyngitis			10			
PIONEER 8 [29]	Nausea	11.4	16.6	23.2	13(7.1)	16 (8.8)	24 (13.3)
	Diarrhea	8.7	12.2	14.9			
	Vomiting	6.0	7.7	9.9			

vomiting, and diarrhea, which generally occurred early in treatment, and mostly resolved during continuous use. There were no unexpected safety concerns across the PIONEER trials, including in T2D adults with moderate renal impairment (PIONEER 5). As per clinical studies, nausea, vomiting, and diarrhea occurred in 11–20% (7 mg) and 6–8% (14 mg) of people, typically early in treatment, and most of them did not require treatment discontinuation. Overall, oral semaglutide is well-tolerated and is comparable to other GLP-1 receptor agonists, including the once-weekly subcutaneously administered semaglutide [26–33, 35, 36].

Additionally, across the PIONEER trials, there was a low incidence of severe or blood glucose-confirmed symptomatic hypoglycemia (1.7% in PIONEER 2; 0.7% in PIONEER 4). However, the incidence was higher in adults with T2D who were concomitantly receiving SU and insulin [37]. The incidence of adverse effects and patient withdrawals in the PIONEER trials are summarized in Table 5.

Expert opinion:

The most common adverse effect of oral semaglutide is gastrointestinal in nature, which includes nausea, vomiting, and diarrhea, typically occurring early during initiation of oral semaglutide; the frequency of nausea, vomiting, and diarrhea has been reported to range from 11%, 6%, and 9%, respectively, with use of 7 mg oral semaglutide per day to 20%, 8%, and 10%, respectively, with use of 14 mg oral semaglutide per day. The GI adverse effects are mostly mild to moderate in intensity and are self-resolving in many. On average, approximately 4–8% of adults with T2D receiving 7 mg and 8–15% receiving 14 mg per day of oral semaglutide discontinue treatment due to gastrointestinal adverse events. It is essential to discuss these side-effects when initiating oral semaglutide, highlighting the fact that most people with T2D develop tolerability towards these GI side effects over a period of time.

Switching to oral semaglutide from injectable GLP-1 RAs

While switching from an injectable GLP-1RA to oral semaglutide, it is prudent to revisit any contraindications for, or warnings against, the use of a GLP-1RA, followed by deciding on the correct initiation dose of oral semaglutide [39]. In people with T2D taking once-weekly injectable GLP-1RA, the first dose of oral semaglutide should be administered 7 days after the last dose of the once-weekly injectable GLP-1RA. Similarly, in people with T2D taking once-daily injectable GLP-1RA, the first dose of oral semaglutide should be administered 24 hours after the last dose of the once-daily injectable GLP-1RA. Initiation of oral Semaglutide should be with 3 mg once daily (OD) irrespective of the dose of injectable GLP-1RA, increasing to 7 mg OD after 30 days, and 14 mg OD after a further 30 days (maintenance dose) [40]. Escalation of doses could be made faster if the person tolerated the previously administered injectable GLP-1RA well [41, 42].

Expert opinion:

People with T2D can switch from an injectable GLP-1RA to oral semaglutide, either for the convenience of the oral route of administration or for improved efficacy. For those on once-weekly injectable GLP-1RAs, the first dose of oral semaglutide should be administered 7 days after the last dose of the once-weekly injectable GLP-1RA.

For those on once-daily injectable GLP-1RAs, the first dose of oral semaglutide should be administered 24 hours after the last dose of the once-daily injectable GLP-1RA.

Irrespective of the dose of injectable GLP-1RA in use, it is prudent to initiate with 3 mg oral semaglutide once daily and gradually titrate the dose up to 7 mg and then 14 mg once daily. Consider a faster escalation of doses in individuals tolerating the injectable GLP-1RA well.

Patient profiles for oral semaglutide

Elderly people with T2D

The efficacy and safety of oral semaglutide are not impacted by age. It can be used safely in patients up to 75 years of age without any dose modification [38].

Adults with T2D with existing ASCVD or at high risk for ASCVD

SUSTAIN 6 (compared once-weekly subcutaneously administered semaglutide with placebo) and PIONEER 6 (compared once-daily orally administered semaglutide with placebo) investigated the cardiovascular effects of semaglutide, the primary composite outcome being the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (3P-MACE). The SUSTAIN 6 trial, which included adults with T2D at a higher risk of cardiovascular disease, showed a statistically significant 26% reduction in 3P-MACE compared to placebo (hazard ratio, 0.74; 95% CI, 0.58 to 0.95; $p < 0.001$ for noninferiority; $p = 0.02$ for superiority). In the PIONEER 6 trial, which included 206 patients from India, 14 mg of orally administered semaglutide resulted in a 21% reduction in 3P-MACE (hazard ratio, 0.79; 95% CI, 0.57 to 1.11; $p < 0.001$ for noninferiority). Among the individual components of the primary outcome, death from cardiovascular causes was lesser in the oral semaglutide group when compared to that in the placebo group (hazard ratio, 0.49; 95% CI, 0.27 to 0.92). Death from any cause was also lower in the oral semaglutide group when compared to that in the placebo group (hazard ratio, 0.51; 95% CI, 0.31 to 0.84) [43].

A post-hoc analysis of the SUSTAIN 6 and PIONEER 6 trials demonstrated that semaglutide reduced the incidence of any first stroke compared to placebo in people with T2D at high cardiovascular risk (hazard ratio, 0.68, 95% CI, 0.46–1.00; $p = 0.048$), primarily driven by prevention of small-vessel occlusion. Semaglutide treatment, versus placebo, lowered the risk of stroke irrespective of prior stroke at baseline [43].

Based on current evidence, oral semaglutide is CV safe. While once-weekly subcutaneously administered semaglutide has shown superiority over placebo in reducing 3-P MACE, such data are not yet available with oral semaglutide [44]. The ongoing SOUL (semaglutide cardiovascular outcomes trial), which has enrolled 9650 participants, aims to assess the effects of oral semaglutide on the occurrence of cardiovascular events in adults with T2D and eASCVD and/or CKD; it will provide clarity as to whether, similar to once-weekly subcutaneously administered semaglutide, once-daily orally administered semaglutide also provides superiority over placebo in reducing cardiovascular events [45].

Adults with T2D and renal impairment

The PIONEER 5 trial demonstrated the effectiveness of oral semaglutide in treating adults with type 2 diabetes and moderate renal impairment [estimated glomerular filtration rate (eGFR) of 30–59 mL/min/ 1.73 m²]. At week 26, oral semaglutide was superior to placebo in decreasing HbA1c (estimated mean change of –1.0% vs. –0.2%; estimated treatment difference: –0.8% 95% CI –1.0 to –0.6; $p < 0.0001$) and bodyweight (estimated mean change of –3.4 kg vs. –0.9 kg; [SE 0.3]; estimated treatment difference, –2.5, 95% CI –3.2 to –1.8; $p < 0.0001$) by the treatment policy estimand. Overall, renal function, as assessed by eGFR estimation, remained stable throughout the trial [28, 46]. Oral semaglutide is not recommended for use in people with T2D with eGFR < 15 mL/min/1.73 m^2 [47].

Semaglutide, by reducing glucose load, body weight, NADPH oxidase, and reactive oxygen species, can potentially benefit people with T2D with chronic kidney disease. Smaller studies have shown that oral semaglutide can reduce albuminuria and decrease the rate of decline of eGFR [48]. The evaluate renal function with semaglutide once weekly (FLOW) trial assessed (FLOW) trial assessed the effect of subcutaneous (SC) once-weekly semaglutide vs. placebo on clinically relevant renal endpoints in people with T2D and CKD. The primary outcome was a composite of major kidney disease events (composite of onset of dialysis, transplantation, or an eGFR of < 15 mL/min), at least a 50% reduction in eGFR from baseline, or death from kidney-related or CV causes. There was a 24% lower risk of primary outcome events in the semaglutide group when compared to placebo (HR 0.76; 95% CI: 0.66 to 0.88; $p = 0.0003$). Kidney-specific components of the primary outcome (HR 0.79; 95% CI: 0.66 to 0.94) and CV death (HR 0.71; 95% CI: 0.56 to 0.89) also favored semaglutide.

Adults with T2D and hepatic impairment

As per pharmacokinetic studies, hepatic impairment does not appear to impact the exposure of semaglutide. Bækdal et al. [49] in 2018 investigated whether hepatic impairment affects the pharmacokinetics, safety, and tolerability of oral semaglutide. Child-Pugh classification was used to categorize patients into 4 groups: normal hepatic function (N = 24), mild [(N = 12; Child-Pugh class A (5–6 points)], moderate [(N = 12), Child-Pugh class B (7–9 points)], or severe [(N = 8), Child-Pugh class C (10–15 points)] hepatic impairment. The patients received once-daily oral semaglutide (5 mg for 5 days and 10 mg for the next 5 days). Semaglutide plasma concentrations were measured during dosing, and up to 21 days post-last dose. The area under the semaglutide plasma concentration-time curve from 0 to 24 h after the 10th dose, and maximum semaglutide concentration after the 10th dose, were similar across groups. Hepatic impairment did not affect time to maximum semaglutide concentration and half-life. Semaglutide was found to be safe in patients with hepatic impairment. The authors concluded that no dose adjustment of oral semaglutide is warranted in subjects with hepatic impairment. However, clinical data on the use of oral semaglutide in people with T2D with advanced liver disease is limited; as such, prescribing oral semaglutide to people with T2D with hepatic impairment should be as per individual patient's demographics and clinician's judgment.

Adults with T2D at high risk for hypoglycemia

Hypoglycemia risk is one of the critical considerations when selecting pharmacological therapy for people with T2D. There is a need to avoid both mild-to-moderate episodes of hypoglycemia (and their associated impact on quality of life) and the more severe episodes that carry the risk of increased patient morbidity, including hospitalization, CV events, and death. Older patients, those with cognitive dysfunction, those who have renal impairment, and those with longer duration of diabetes are at particular risk of experiencing severe hypoglycemia. Across the PIONEER trials, oral semaglutide was shown to be associated with a low risk of hypoglycemia, and particularly a very low incidence of severe blood glucose-confirmed symptomatic hypoglycemia (Tab. 6).

The incidence of hypoglycemia was observed to range from 1.4% to 37.1% in adults with T2D on oral semaglutide with SU and/or insulin as background therapy (PIONEER 3, 5, 6, 7, and 8), which is higher when compared to people with T2D on only oral semaglutide. PIONEER 1 is the only study in which the subjects were on semaglutide monotherapy, with no other background therapy: the incidence of hypoglycemia due to orally administered once-daily semaglutide was reported at 2.9%, 1.1%, and 0.6%, respectively, for 3 mg, 7 mg, and 14 mg doses of semaglutide (Tab. 6).

People with T2D during fasting (Ramadan/ Navratri)

It is recommended that oral semaglutide be initiated at least 6–8 weeks before the month of Ramadan to allow up-titration to an effective dose of at least 7 mg once daily. It is advisable to avoid dose escalation within 2–4 weeks before, and during, Ramadan.

Table 6. The Incidence of Hypoglycemia in the PIONEER Trials

Trial	Background therapy	Intervention	Hypoglycemia		
			Oral semaglutide 3 mg	Oral semaglutide 7 mg	Oral semaglutide 14 mg
PIONEER 1	Diet and exercise	Oral semaglutide 3 mg, 7 mg, 14 mg or placebo	2.9%	1.1%	0.6%
PIONEER 2	Metformin (≥ 1500 mg or maximum tolerated)	Oral semaglutide 14 mg OD or empagliflozin 25 mg OD	–	–	11%
PIONEER 3	Metformin with or without sulfonylurea	Oral semaglutide 3 mg, 7 mg, 14 mg or Sitagliptin 100 mg	4.9%	5.2%	7.7%
PIONEER 4	Metformin (≥ 1500 mg or maximum tolerated) with or without an SGLT2 inhibitor	Oral semaglutide 14 mg or SC liraglutide or placebo	–	–	1%
PIONEER 5	Metformin (≥ 1500 mg or maximum tolerated dose), sulfonylurea, or both; or basal insulin with or without metformin	Oral semaglutide 14 mg OD or placebo	–	–	6%
PIONEER 6	Majority were on metformin, Insulin, and/or sulfonylurea	Oral semaglutide 14 mg or placebo	–	–	1.4%
PIONEER 7	One or two OHA — majority on either metformin alone or metformin + sulfonylurea	Semaglutide initial 3 mg, titrating up to 7 or 14 mg or sitagliptin 100 mg		Oral semaglutide (weeks 0–104), i.e. durability	Oral semaglutide (weeks 52–104), i.e. switch
			Patients on SU (n = with at least 1 hypoglycemic event	46 (37.1%) (n = 124)	6 (11.8%) (n = 51)
			Patients not on SU with at least 1 hypoglycemic event	12 (9.3%) (n = 129)	3 (6.1%) (n = 49)
PIONEER 8	Insulin with or without metformin	Oral semaglutide 3, 7, or 14 mg or placebo	28.3%	26.0%	26.5%

OD — once daily; OHA — oral hypoglycemic agents; SC — subcutaneous; SGLT2 — sodium-glucose co-transport-2 inhibitors; SU — sulfonylureas

It is recommended that people with T2D, who are on a maintenance dose of oral semaglutide (either 7 mg or 14 mg), continue with it during Ramadan. It is preferable to take oral semaglutide when breaking the fast after sunset (Iftar). The medication should be administered on an empty stomach with not more than 120 mL of water, and one should wait for 30 min before eating, drinking, or taking any other medication. While following these dosing instructions is advisable, individual and/or local variations in Ramadan observance should be considered when discussing the timing of oral semaglutide administration. Infrequent deviations from the recommended dosing schedule (once or twice per week) are unlikely to affect the efficacy of oral semaglutide significantly, but more persistent deviations may impact its efficacy over time [50].

People with T2D working in shifts

Administration of semaglutide is a challenge for shift workers because it is usually recommended that it be taken on an empty stomach in the morning. In such situations, people could consider taking oral semaglutide either after 6 hours of fasting and half an hour before the primary meal of the day or before the meal preceded by the longest inter-meal gap (6 hours or more). The timing of administration can be changed every day according to the shift duty and meal pattern because the half-life of oral semaglutide is 7 days [51].

People with T2D who are overweight/obese

The PIONEER trials have shown that in people with T2D, use of semaglutide can result in a mean reduction in HbA1c of up to 1.5% and weight loss of up to 5 kg when compared to placebo [PIONEER 3: mean change in body weight (treatment policy estimand): −1.2 (3 mg), −2.3 (7 mg), −3.4 (14 mg); mean change in body weight (trial policy estimand): −1.3 (3 mg), −2.4 (7 mg), −3.6 (14 mg); PIONEER 5: mean change in body weight: −3.4 kg (SE 0.3)] [27, 28, 30, 31]. The PIONEER 2 study revealed a significantly greater weight reduction with oral semaglutide when compared to empagliflozin 25 mg at week 52 (−0.9 kg [95% CI: −1.6, −0.2 kg]). Empagliflozin did not show weight loss after 26 weeks, whereas oral semaglutide showed a consistent weight reduction even at week 38. A significant decrease in waist circumference was also seen in those on oral semaglutide when compared to empagliflozin at week 52 [−4.2 cm in the semaglutide group and −2.9 cm in the empagliflozin group ($p = 0.0030$)]. The PIONEER 2 and 4 studies both revealed that body weight reduction with oral semaglutide 14 mg continued to accrue until approximately 38 weeks and plateaued after that. In contrast, the results of PIONEER 3 suggested that reduction in body weight may continue to accrue for up to 52 weeks [44].

A significant portion of the weight loss due to semaglutide can be attributed to body fat loss [27]. In a small retrospective study involving 25 Japanese patients, it was seen that therapy with oral semaglutide for 24 weeks resulted in significant loss of body fat (28.3 ± 1.52 kg at baseline; 26.8 ± 1.59 kg at 12 weeks; 25.5 ± 1.57 kg at 24 weeks; mean ± SE) with no significant change in whole-body lean mass (48.1 ± 1.92 kg at baseline; 47.7 ± 1.93 kg at 12 weeks; 47.6 ± 1.89 kg at 24 weeks; mean ± SE). The appendicular skeletal muscle index (SMI) also remained unchanged [52].

People with T2D and gastrointestinal disease

The predominant adverse events of GLP-1RAs, including oral semaglutide, are GI in nature. The common symptoms include bloating, dyspepsia, eructation, nausea, vomiting, flatulence, diarrhea, and constipation. GI side effects typically occur early during the initiation of oral semaglutide. On average, approximately 4−8% of adults with T2D receiving 7 mg, and 8%-15% receiving 14 mg per day of oral semaglutide discontinued treatment due to GI adverse events. It is essential to avoid dose escalation when GI adverse effects persist. If an adverse GI effect occurs during up-titration, then the dose of oral semaglutide should be lowered and maintained for a few days to weeks at the lower dose before attempting to increase it again. If the adverse GI events are intolerable, then treatment should be temporarily withheld until adverse effects are resolved. Symptomatic treatment should be tailored to the specific GI AE experienced. For nausea and vomiting, anti-emetic and/or prokinetic medications can be considered. Domperidone (10–20 mg 3 to 4 times daily, oral dosage, not recommended for children under 12 years old) is preferred over metoclopramide, particularly in older patients, to minimize the risk of extrapyramidal side effects. A minimum of 30 min should elapse between the administration of oral semaglutide and antiemetic/prokinetic medications. Constipation symptoms may persist longer than other GI adverse effects. Patients should be advised to increase their mobility, and water and fiber intake, and consider using stool softeners [53].

A meta-analysis of 21 large trials in 2022 reported that, compared with placebo, GLP1-RAs were associated with significantly higher risks of gastric ulcer hemorrhage, pancreatitis, acute cholangitis, and acute cholecystitis but were not significantly associated with the occurrences of the other 87 digestive diseases assessed. As such, it is prudent to avoid oral semaglutide in people with T2D with active peptic ulcer disease, active or past history of pancreatitis, and acute cholecystitis [54].

The pharmacokinetics of oral semaglutide was not affected in people with T2D suffering from upper GI diseases, including chronic gastritis, gastroesophageal reflux disease (GERD), or both. As such, oral semaglutide can be used in people with T2D with underlying gastritis and GERD without any dose adjustment [55]; however, one should be cautious while using it in people with established chronic gastritis or GERD, considering the known GI AE profile of oral semaglutide [56].

Injectable GLP1-RAs have been reported to induce gastroparesis [57]. However, there are no reports of clinically significant oral semaglutide-induced gastroparesis. The exact mechanism by which semaglutide may cause gastroparesis is unknown. It is well-recognized that GLP-1 receptors regulate stomach emptying and motility; the stimulation of these receptors may cause gastroparesis. Occasionally, clinically silent diabetic gastroparesis might be triggered following the introduction of a GLP-1RA. Thus, GLP-1RA, including oral semaglutide, is not recommended for people with T2D with symptoms suggestive of gastroparesis.

In a 2021 Danish nationwide population-based cohort study, the authors concluded that in adults

with inflammatory bowel disease (IBD) and T2D there was a lower risk of adverse clinical events amongst people treated with GLP-1-based therapies compared with those treated with other antidiabetic agents, suggesting that treatment with GLP-1RAs improves the disease course of IBD [58]. However, in the absence of sufficient clinical data, it is advisable to avoid using oral semaglutide in people with T2D with active ulcerative colitis and Crohn's disease.

Rare reports of oral semaglutide-induced intestinal obstruction, necessitating withdrawal of treatment, have been identified, but these have not been conclusively confirmed [59–62]. The European Medicines Agency has added an update to the product label to include intestinal obstruction as a potential adverse event for GLP-1 Ras [60].

Proper assessment for any pre-existing GI conditions is crucial before initiating treatment with semaglutide. Educating patients about potential adverse effects, preventive measures, and appropriate management strategies is critical. Adherence to specific dietary recommendations can help alleviate these symptoms [53]. Clinicians should educate patients that although GI AEs may occur, they are generally transient and of mild to moderate severity. However, very occasionally, there might be a more sinister underlying GI pathology, and as such, it is imperative to educate the person with T2D being initiated on oral semaglutide to report back promptly should the symptoms be severe or bothersome and not responding to simple measures. As discussed above, it is best to avoid oral semaglutide in people with T2D with active ongoing GI pathology, including peptic ulcer disease, pancreatitis, cholecystitis, obstructive jaundice, gastroparesis, and IBD.

People with T2D who prefer oral medications over injectables

Patient preference is an important consideration when selecting an add-on anti-diabetic agent for the intensification of therapy of T2D. Among other causes, a delay in intensification due to the injectable nature of the add-on medication (injectable GLP-1RA or insulin) contributes to clinical inertia and poor glycemic control. In such situations, an oral GLP-1RA like semaglutide may help ameliorate the resistance to intensification of therapy. Oral semaglutide offers broadly similar benefits to injectable semaglutide in terms of reductions in HbA1c and body weight and is, therefore, a viable oral option for intensification before progressing to injectables [44].

Expert opinion:

Patient preference plays an essential role while selecting pharmacological agents for intensification of therapy in T2D, especially when transitioning from OADs to injectables. Oral semaglutide, administered once daily in a dose of 14 mg, provides comparable benefits in terms of HbA1c reduction and weight loss to once-weekly subcutaneously administered 1 mg semaglutide, thereby offering a valuable non-injectable alternative to consider for intensification before progressing to injectables.

Dosing of oral semaglutide in a person with T2D already on insulin therapy

People with T2D who are prescribed oral semaglutide when already on insulin injections have an increased risk of experiencing hypoglycemia. Under such circumstances, consider reducing the dose of insulin [42]; it is prudent to reduce the total daily dose of insulin by 20% if the baseline HbA1c value is less than 8%. However, if the baseline HbA1c value is greater than 8%, then there is possibly no need to reduce the dose of insulin when initiating oral semaglutide (Fig. 3) [29].

Administration of semaglutide (Fig. 4)

Oral semaglutide should be taken once daily in a fasting state (at least 6, preferably 8 hours of fasting). The tablet should be taken with up to 120 mL water. No food, beverages, or medications should be consumed for at least 30 min after taking oral semaglutide [49]. The tablet should be swallowed intact.

The factors that decrease semaglutide exposure are taking it with an excess amount of water (> 120 mL), or ingesting food or beverages within 30 min of taking oral semaglutide. An 8-armed, parallel-group, open-label, randomized controlled trial evaluated the impact of ingesting the tablet with varying volumes of water and the effect of duration of fasting after taking the tablet on the pharmacokinetics of oral semaglutide. It concluded that administering oral semaglutide in the fasting state with up to 120 mL water [48], and a post-dose fasting period of at least 30 min, resulted in a clinically relevant semaglutide exposure. While longer post-dose fasting (60 min or 120 min) further increases absorption, 30 min appears to be sufficient for optimal levels in the bloodstream [55].

Buckley et al. concluded from a food-effect study in healthy patients that a fed state hinders semaglutide absorption. A fasting state is required for clinically relevant absorption of oral semaglutide. Alternate-day dosing of oral semaglutide is not supported because plasma level concentrations are not maintained [61].

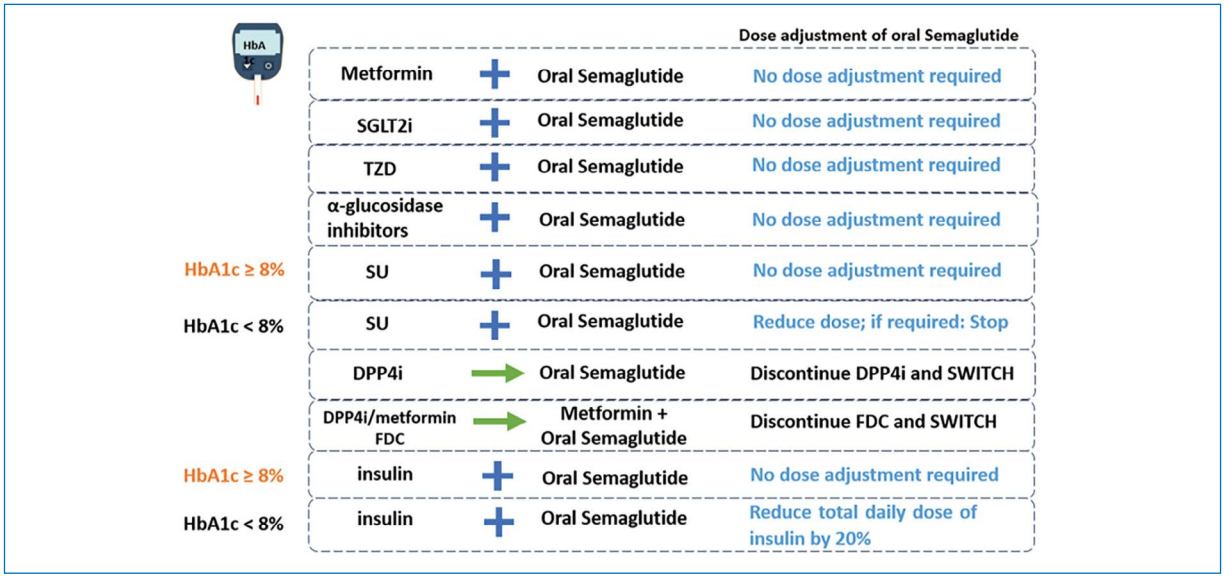

Figure 3. Recommendations for Dose Adjustment of Other OADs when Initiating Oral Semaglutide for the Management of T2D
DPPi — inhibitors of dipeptidyl peptidase-4; FDC — fixed dose combination; HbA1c — glycated hemoglobin; OAD — oral antidiabetic drugs; SGLT2 — sodium-glucose co-transport-2 inhibitors; SU — sulfonylureas; T2D — type 2 diabetes; TZD — thiazolidinediones

Patient counselling for administration of Oral Semaglutide:

- ❑ Take the tablet first thing in the morning (on an empty stomach), with a sip of water (up to 120 mL)
- ❑ Swallow the tablet as it is.
- ❑ Do not split/crush/chew the tablet.
- ❑ Take the tablet >30 min before first food, beverage, or other oral medications of the day.
- ❑ In case of missed dose, take the next dose as scheduled the next day.
- ❑ Alternate day dosing is not recommended.

Figure 4. Administration of Oral Semaglutide [45]

Expert opinion:

Oral semaglutide must be taken on an empty stomach, first thing in the morning, with up to 120 mL of water. Because food affects the absorption of semaglutide, a minimum post-dose fasting period of 30 min is recommended. Up-titration to a higher dose is recommended for most people after 4 weeks to reduce the risk of GI adverse effects. The oral semaglutide tablet should not be broken because this adversely affects its absorption. Alternate-day dosing is not recommended.

For people who are already on, and tolerating, an injectable GLP-1RA, or for those who are able to tolerate the lower dose of oral semaglutide without any GI side effects, a more rapid dose escalation schedule from 3 to 7 to 14 mg per day may be considered by the treating physician on an individual basis.

Guidance on co-administration of commonly used drugs (Fig. 5)

Oral semaglutide is safe when used concomitantly with most commonly used drugs. No clinically significant increase in exposure to semaglutide was observed whilst on omeprazole. Similarly, commonly used drugs like lisinopril, warfarin, metformin, digoxin, ethinylestradiol/levonorgestrel, rosuvastatin, and furosemide when administered together with oral semaglutide did not result in any clinically relevant changes in the exposure to semaglutide [21].

Drugs with a low therapeutic index like warfarin need to be closely monitored upon introduction of oral semaglutide [21]. In healthy adults, a 33% increase in exposure of levothyroxine, when administered at a dose of 600 mcg, was observed when taken together with oral semaglutide. Both oral semaglutide and levothyroxine are to be taken in a fasting condition, followed by a minimum of 30 min of post-dose fasting. One option could be to take levothyroxine 30 min after ingesting oral semaglutide, followed by another 30 min of post-dose fast. However, under most circumstances, it is not feasible to wait for 60 min on an empty stomach in the morning, and as an alternative, levothyroxine could be taken before going to bed (possibly at least 3 hours after the last meal of the day). Monitoring of thyroid parameters is recommended after 4–6 weeks, followed by periodic long-term assessment as dictated by the clinical parameters [63, 64].

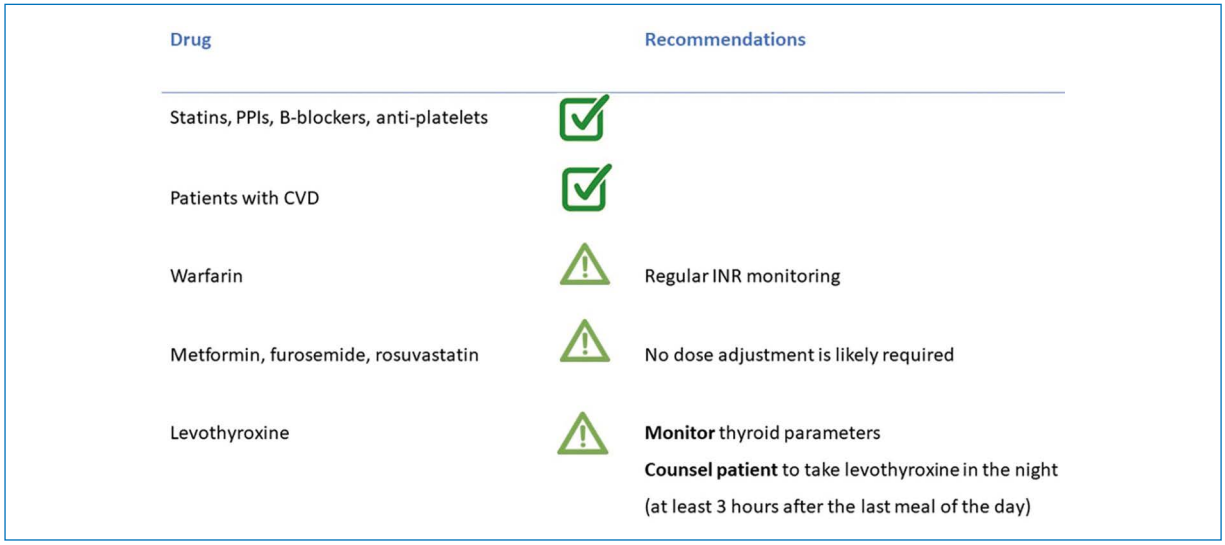

Figure 5. Recommendations for Co-Administration of Oral Semaglutide with Commonly Used Drugs
CVD — cardiovascular disease; INR — international normalized ratio; PPIs — proton pump inhibitors

Expert opinion:

Oral Semaglutide possibly has no effect on the overall exposure to commonly used medications in adults with T2D, including lisinopril, warfarin, metformin, digoxin, ethinyl estradiol, levonorgestrel, furosemide, and rosuvastatin.

Levothyroxine can be administered in the morning on empty stomach 30 min after having ingested oral semaglutide; however, if a one-hour period of staying empty stomach on waking is not feasible, then advice the patient to take levothyroxine at bedtime, two-three hours after dinner. People on thyroid hormone replacement, when initiated on oral semaglutide, should have their thyroid function test checked after 4–6 week. It is prudent to administer a PPI either before breakfast, 30 min after ingesting oral semaglutide or before lunch/dinner.

Oral bisphosphonates should be taken on empty stomach in the morning at least 30 min after ingesting oral semaglutide. Alternatively, an annual intravenous administration of bisphosphonate is also a viable option depending upon patient preference.

Although there are no drug interaction studies with a number of commonly used anti-diabetic medications, it is prudent to maintain a minimum gap of 2 hours from ingestion of oral semaglutide.

Inform that the dose could temporarily be reduced by one step until the GI side-effects resolve.

Explain that centrally acting anti-emetics, which are preferred to mitigate nausea, can be used for symptomatic relief if required.

Counsel to stay hydrated, and to drink cold water if feeling nauseous. Eating slowly, taking smaller portions, avoiding fatty and spicy foods, avoiding smoking, and minimizing alcohol intake help reduce nausea.

Advise women of child-bearing age to stop taking oral semaglutide 2 months prior to planned pregnancy and to avoid taking it during pregnancy and breast feeding.

Contraindications (see Fig. 6)

Oral semaglutide has not undergone studies in people with T2D with a history of pancreatitis, so it is prudent to avoid its use in this group of people. Oral semaglutide is not recommended in women who are pregnant or lactating. It is contraindicated in people with T2D with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2. It should not be used in adults with eGFR < 15 mL/min. It is prudent to avoid oral semaglutide in adults with proliferative diabetic retinopathy, advanced heart failure, and documented gastroparesis [42].

Monitoring and follow-up

For adults with T2D prescribed oral semaglutide, specific monitoring recommendations include periodic assessment for GI side-effects, regular monitoring for diabetic retinopathy, close monitoring of renal function should people with underlying CKD report GI adverse events, observation for any signs/symptoms of pancreatitis, and closer monitoring of use of concomitant medications with a narrow therapeutic index [44].

Patient education

Beyond adherence to the recommended gradual dose-escalation regimen, potential approaches to minimizing/managing GI adverse events with oral semaglutide are similar to those suggested for injectable GLP-1RAs [44].

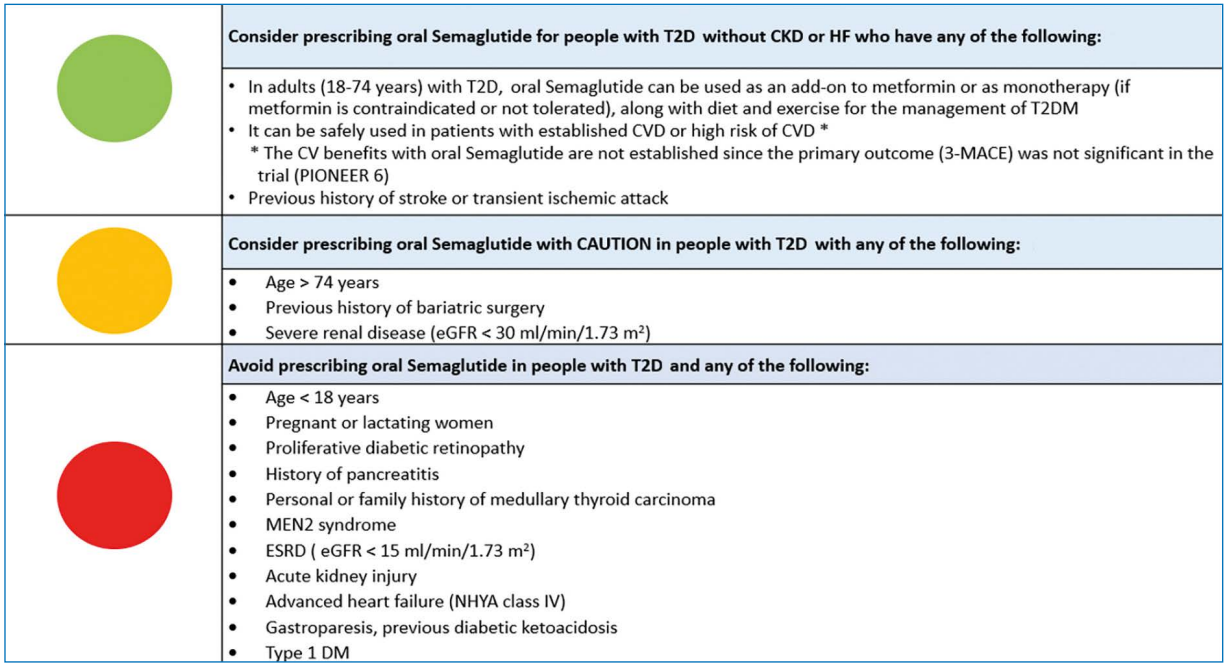

Figure 6. Guidance for Using Oral Semaglutide in People with T2D [64]
CKD — chronic kidney disease; CVD — cardiovascular disease; DM — diabetes mellitus; eGFR — estimated glomerular filtration rate; ESRD — end stage renal disease; HF — heart failure; MACE — major adverse cardiovascular events; MEN2 — multiple endocrine neoplasia syndrome type 2; T2D — type 2 diabetes

Expert opinion:

Counselling of adults with T2D being initiated on oral semaglutide should include the following:

Explain the need for gradual dose escalation. Explain that the 3 mg dose is intended for initiation of treatment to help mitigate GI adverse events and is not the intended maintenance dose.

Counsel regarding common side effects of GLP-1RAs, mostly GI, which typically include upper-GI (e.g., bloating, nausea or vomiting) and/or lower-GI side effects (diarrhea or constipation).

Inform that GI side-effects may occur not only following initiation of therapy with 3 mg of oral semaglutide but also during up-titration from 3 mg to 7 mg, and from 7 mg to 14 mg; however, highlight that under most circumstances the symptoms are mild to moderate in severity, transient, and typically resolve over a period of 2–4 weeks.

Inform that the dose could temporarily be reduced by one step until the GI side-effects resolve.

Explain that centrally acting anti-emetics, which are preferred to mitigate nausea, can be used for symptomatic relief if required.

Counsel to stay hydrated, and to drink cold water if feeling nauseous. Eating slowly, taking smaller portions, avoiding fatty and spicy foods, avoiding smoking, and minimizing alcohol intake help reduce nausea.

Advise women of child-bearing age to stop taking oral semaglutide 2 months prior to planned pregnancy and to avoid taking it during pregnancy and breast feeding.

Conclusions

Oral semaglutide can be used as an add-on therapy to metformin or as monotherapy if metformin is either contraindicated or not tolerated, along with diet and exercise, for the management of adults with T2D. The expert committee recommendations concerning the use of oral semaglutide in adults with T2D are as follows:

Oral semaglutide is effective in reducing blood glucose values. It is safe for use both in adults with early onset as well as in those with a longer duration of T2D.

Oral semaglutide can be used as an add-on to metformin or as monotherapy (if metformin is contraindicated or not tolerated), along with diet and exercise for the management of T2D.

Oral semaglutide can be used in combination with all oral anti-diabetic agents, including insulin, except DPP-4i. Background therapy with metformin, SGLT2i, and thiazolidinediones (TZD) can be continued without any dose adjustments. The dose of sulfonylurea and insulin needs modification to avoid hypoglycemia.

People with T2D can switch from an injectable GLP-1 receptor agonist to oral semaglutide for convenience or enhanced efficacy. The first dose of oral semaglutide should be administered 7 days after the last once-weekly injectable GLP-1RA dose or 24 hours after the last once-daily injectable GLP-1RA dose. It is prudent to start with 3 mg of oral semaglutide, with

up-titration to the higher therapeutic dose of 7 mg and 14 mg, based on the tolerability of the lower dose over a period of 10–20 days.

The common GI adverse effects (nausea and vomiting) of oral semaglutide are mild to moderate in intensity in most and are self-resolving in many.

Oral semaglutide is safe with respect to cardiovascular events. Subcutaneously administered once-weekly semaglutide has been shown to be statistically superior to placebo in reducing 3P-MACE events, independent of glycemic control. Semaglutide has been shown to reduce albuminuria and slow the rate of decline of eGFR.

Oral semaglutide can be safely used in elderly people with T2D with established CV disease or with CV risk factors.

Oral semaglutide should be considered in adults with T2D without ASCVD and/or CKD (eGFR $\geq$ 15) when there is a need to minimize weight gain or promote weight loss, or when there is a need to minimize the risk of hypoglycemia.

Oral semaglutide can be used in adults with T2D with CKD with an eGFR $\geq$ 15 mL/min/1.73 m^2 without any dose adjustment. Among adults with type 2 diabetes and established CKD, GLP-1RA with proven CVD benefit should be considered when SGLT2i is contraindicated or not tolerated.

Oral semaglutide may be used in T2D adults with hepatic impairment with Child-Pugh scores A and B without any dose adjustment. Such use should be at the discretion of the physician and in consultation with the patient.

In the management of people with T2D, considering the person's preferences is crucial, particularly when transitioning from OADs to injectables. Oral semaglutide, which provides comparable benefits in HbA1c reduction and weight loss to injectable GLP-1 receptor agonists, is a valuable non-injectable alternative to consider before progressing to injectables.

Oral semaglutide should be taken on an empty stomach in the morning with up to 120 mL of water, followed by a 30-min post-dose fasting period before consuming food, beverages, or other medications. The tablet should not be broken, to avoid adversely affecting the absorption dynamics of the medication. The dose should be up-titrated slowly from 3 to 7 to 14 mg, using each dose for 4 weeks before up-titration for most people with T2D to minimize GI adverse events. For people who are already taking an injectable GLP-1RA with good tolerability, rapid dose escalation may be considered at the discretion of the treating physician.

Oral semaglutide has minimal impact on the exposure of many commonly prescribed medications including lisinopril, warfarin, and metformin. Levothyroxine can be taken in the morning, but 30 min after having taken oral semaglutide; alternatively, if a one-hour wait on an empty stomach is not feasible, then levothyroxine can be taken at bedtime, maintaining as great a time gap as possible post-dinner. Co-administration with PPIs or oral bisphosphonates requires specific timing recommendations, and a 2-hour gap is generally advisable for other T2D medications.

Patients should be informed about gradual dose escalation of oral semaglutide, starting with 3 mg, especially to avoid GI side effects. It is essential to counsel on common GI effects during the first few weeks, including bloating, nausea, and vomiting, with the instruction to temporarily reduce the dose if necessary. Additionally, guidance on symptom relief strategies must be provided, including avoiding fatty food and taking small meals. Child-bearing age women should be informed to discontinue oral semaglutide two months before planning pregnancy and during breastfeeding.

Article information

Authors contribution

Rajesh Rajput, JJ Mukherjee, Manoj Chawla, Sujoy Majumdar, Sonali Patange, Supratik Bhattacharyya, and Rajeev Chawla substantially contributed to the conception and design of the article. JJ Mukherjee, K N Manohar, Rakhi Malhotra, Sandeep Suri, Vivek Raskar, AH Zargar, Sanjeev Phatak, Banshi Saboo, and AK Das revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Acknowledgement

The authors would like to thank Intellimed Healthcare Solutions Pvt Ltd for their assistance in medical writing.

Conflict of interest

The authors declare no conflict of interest.

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