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GLP-1 Receptor Agonists Critical Review: Revisiting Its Positioning for Type 2 Diabetes Mellitus in Routine Clinical Practice in India

ABSTRACT

Objective: Despite the benefit–risk ratio favoring glucagon-like peptide-1 receptor agonists (GLP-1 RAs), knowledge and awareness is lacking among patients and physicians, particularly in India. The current review provides an overview of GLP-1 RAs and the opinion of a group of healthcare practitioners (HCPs) and independent consultants across India on the evidence for using GLP-1 RAs and its applicability to the Indian population.

Materials and methods: A panel of eight HCPs met virtually on December 12–13, 2020 met as part of the Diabetes Research Society (DIABAID). They examined and critically discussed the current research on the use of GLP-1 RAs in the management of T2DM.

Results: The panel observed that recent diabetes guidelines and recommendations have shifted toward a more individualised and CV risk-focused approach to T2DM management. They proposed that 1) GLP-1 RAs are ideal cardio-metabolic drugs that address multiple aspects of the T2DM; 2) to bring up GLP-1 RAs as early treatment option in discussions with patients; 3) in T2DM patients with a high CV risk or established ASCVD, CKD, or HF, GLP-1 RAs with proven CVD benefits should be initiated; 4) including oral semaglutide in international treatment recommendation guidelines to improve patient and HCP understanding and adaptability; and 5) patient-physician dialogues will be critical in incorporating GLP-1 RAs earlier in the treatment paradigm for effective T2DM management.

Conclusions: The recommendations on using GLP-1 RAs and the associated benefits and risks of these drugs comprise essential considerations for using such medications in the Indian population. (Clin Diabetol 2022, 11; 4: 269–293)

Keywords: glucagon-like peptide-1 receptor agonists, India, opinion, oral semaglutide, type 2 diabetes mellitus

Introduction

Globally, diabetes is one of the evolving epidemics of the 21st century. As per the 9th edition of the International Diabetes Federation Atlas [1], over 463 million adults aged 20–79 years worldwide (9.3% of all adults in this age group) have type 1 or 2 diabetes. In 2019, India had the second largest number of patients aged 20–79 years with diabetes (77.0 million) among all countries and was anticipated to retain this ranking

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by 2030 (101 million) and 2045 (134.2 million). Over 90% of diabetes cases worldwide are due to type 2 diabetes mellitus (T2DM) [1], and its prevalence is rising exponentially across all regions, including India.

Cardiovascular diseases (CVD) pose a higher mortality risk and are a leading cause of death in patients with T2DM worldwide. Common CVD manifestations include heart failure (HF), coronary heart disease, stroke, myocardial infarction (MI), and peripheral arterial disease [2]. In India, awareness on T2DM and its complications remains alarmingly poor. Identifying patients at risk of developing diabetes earlier and increased patient engagement via disease awareness and management practices could narrow the gap for effective management of T2DM in India, which was observed recently in a multicenter screening study for diabetes across all states and union territories of India [3].

Over the years, treatment safety in connection with diabetes-related CVD and CV complications has gained prominence, and novel treatments have targeted underlying disease-specific pathophysiology [4]. Effective glucose control in patients with T2DM has demonstrated a modest impact on CV benefit in the past, but the negative effects of rosiglitazone on CV outcomes in some studies [5] had resulted in the Food and Drug Administration (FDA) mandate all new glucose-lowering medications to verify CV safety and mortality. The safety of medications should be further examined in T2DM populations with a high CV risk, including, but not limited to, CV mortality and stroke [6]. Nevertheless, the therapeutic strategy should be individualized by considering the presence of comorbidities, treatment objectives, and patient preferences [7].

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have been an important treatment option for T2DM over the last decade. Several clinical and real-world evidence scenarios with GLP-1 RAs have demonstrated effective glycemic control, weight loss, and a lower risk of hypoglycemia [8, 9]. Furthermore, GLP-1 RAs helped in achieving modest control of systolic blood pressure (SBP) and lipid concentration reductions in a subset of patients [10] and minimized major adverse cardiovascular events (MACEs) risk in patients with T2DM or those with established CVD, thereby making them suitable contenders for patients with T2DM having an underlying CVD risk. Their use in the South Asian T2DM population, in whom there is a high prevalence of comorbidities, including obesity, CV risk, and renal issues [11], has demonstrated benefits extending beyond glycemic control. Several other GLP-1 RAs have been approved to date for subcutaneous (s.c.) use to treat T2DM, including liraglutide in 2009 (Europe) and 2010 (USA), exenatide ER in 2012, lixisenatide in 2013 (Europe) and 2016 (USA), dulaglutide in 2014, albiglutide in 2014 (Europe and USA), and semaglutide in 2017 (USA) and 2019 (Europe). In South Asia, the available GLP-1 RAs include dulaglutide (0.75 or 1.5 mg once weekly [q.w.]), liraglutide (1.2 or 1.8 mg once daily [o.d.]), lixisenatide (20 mcg o.d.), and semaglutide (0.5 or 1 mg q.w.), administered s.c. Of the GLP-1 RAs available globally, albiglutide is withdrawn from the market as of 2018. Semaglutide is the first GLP-1 RA to receive FDA approval for oral administration across the US, Canada, Australia, Switzerland, and Japan [12]. In India, oral semaglutide is prescribed only by a registered endocrinologist or a qualified physician.

The guidelines by the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) [13] recommend GLP-1 RA and/or sodium–glucose cotransporter 2 inhibitors (SGLT2i) for treating high-risk individuals (those with CVD and chronic kidney disease [CKD]) independent of baseline or individualized glycated hemoglobin (HbA1c) target. Likewise, the European Society of Cardiology (ESC) guidelines recommend GLP-1 RAs (or SGLT2is) as first-line treatment in patients with atherosclerotic cardiovascular disease (ASCVD) or those with an extremely high risk for ASCVD [14]. The ADA recommends GLP-1 RAs as a first line in ASCVD or high risk for ASCVD with or without metformin [7] and lifestyle management in T2DM patients, including those with or without a high risk of CVDs and those looking to reduce the risk of hypoglycemia or promote weight loss. Worldwide, diabetes associations recommend metformin monotherapy as the first-line drug to treat newly diagnosed T2DM and in combination with other treatments when glycemic targets are not achieved. Consensus recommendations from the South Asian Task Force endorse GLP-1 RAs as primary treatment options to manage patients with T2DM [11]. The Indian Council of Medical Research (ICMR) guidelines and algorithm recommends managing T2DM patients using various antidiabetic agents [15]. Nevertheless, there is a lack of consensus on specific treatment guidelines for GLP-1 RAs in the management of T2DM in India. Hence, there is room to decipher the therapeutic role and potential benefits of GLP-1 RAs in the Indian T2DM population to manage such patients more efficiently.

This report intends to explore the potential therapeutic benefits of GLP-1 RA in the Indian population with T2DM by formulating a critical appraisal of clinical evidence-based recommendations. These proposals will provide a first-hand guide and reference for primary-care physicians, clinicians, and healthcare professionals (HCPs), including diabetologists and endocrinology experts, in India to effectively manage T2DM patients with or without an underlying CVD risk.

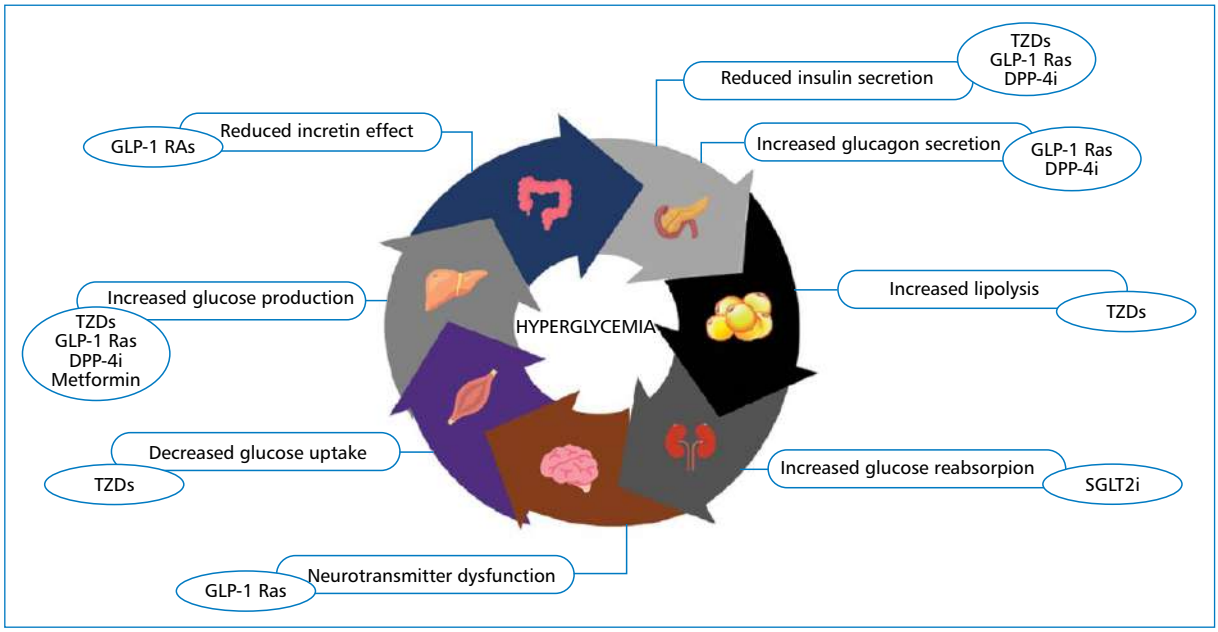

Figure 1. The Ominous Octet
DPP-4i — dipeptidyl peptidase-4 inhibitors; GLP-1 RA — glucagon-like peptide-1 receptor agonist; SGLT2i — sodium–glucose cotransporter-2 inhibitors; TZD — thiazolidinedione

Materials and methods

A panel consisting of eight HCPs converged during a 2-day National Insulin Summit organized virtually by the Diabetes Research Society (DIABAID) from December 12–13, 2020, at Hyderabad, India, to revisit and review evidences on GLP-1 RAs in managing T2DM patients. The HCPs included endocrinologists, pediatric endocrinologists, diabetologists, primary-care physicians, clinicians, and independent consultants, including a project coordinator/manager. The opinions of the panel members were considered in developing the document, which was based on their relevant expertise (at least 10 years of clinical experience), years of clinical practice, publications, and congress records of the panel members who were experts across the South, West, East, and North Indian regions and territories, ensuring pan-Indian coverage.

Panel opinions and discussions of published clinical evidence from randomized clinical trials (RCTs), systematic reviews, meta-analyses, diabetes guidelines and recommendations, opinion documents, position statements, and real-world clinical practice data on the use of GLP-1 RAs in the management of T2DM were used to develop the recommendations. The panel critically discussed, reviewed, and agreed upon the clinical and real-life evidence and recommendations based on their potential applicability to the Indian population.

The sponsor did not have any formal voting authority for the final recommendations and exercised no influence on the development of opinion statements by the experts.

Compliance with Ethics Guidelines

The panelists expressed their consent to participate in the opinion statement development via verbal communication or email. The recommendations were based on a virtual panel discussion without human subjects' involvement, data, or animal experiments. Consequently, there was no ethical approval needed. The panelists were informed of the objective to formulate an opinion recommendation on the topic and the likelihood of a peer-reviewed journal publication.

Role of GLP-1 Ras — the medication we should know

This section summarizes the role of GLP-1 RAs and their standing among incretin-based therapies for managing patients with T2DM.

Being a multifactorial disease, it is well established that the effective management of T2DM depends on targeting the "ominous octet" of pathophysiological abnormalities causing hyperglycemia in such patients (Fig. 1) [16].

Incretins, the gastrointestinal (GI) tract hormones, regulate body weight and maintain glucose homeostasis and energy balance. Released from the intestine after nutrient consumption, they perform a critical role by stimulating insulin secretion and suppressing

glucagon secretion by the pancreas [17]. Incretin-based therapies are being rapidly explored for T2DM treatment, including GLP-1 analogs and receptor agonists, and dipeptidyl peptidase-4 inhibitors (DPP-4i). GLP-1 is one of the two known incretins produced by the L cells of the lower intestine after food intake. Their action, however, may be significantly impaired in the β-cells of T2DM patients compared with those without diabetes [18]. GLP-1 is rapidly degraded by DPP-4 after 1–2 min. Therefore, synthetic GLP-1 RAs resistant to DPP-4 degradation have been developed. In patients with T2DM, GLP-1 RAs have been shown to inhibit gastric emptying, thereby contributing to the blood-glucose-lowering properties of GLP-1 alongside insulin stimulation and suppression of glucagon secretion [19]. Compared with other DPP-4i, GLP-1 RAs are more effective in lowering blood glucose and help in reducing weight [20]. Furthermore, long-acting GLP-1 RAs induce prolonged exposure with effective GLP-1 RA concentrations and maintained over 24h or a week [21], reduce HbA1c more efficiently and cause similar weight reduction compared with short-acting GLP-1 RAs [20], incretins that cause a sharp rise in drug concentrations postinjection that decrease to lower levels after reaching the maximum limit within a few hours [22]. GLP-1 RAs are recommended by the ADA and EASD for T2DM management, along with DPP-4i. GLP-1 RAs are highly recommended in patients with CVD or high CV risk or those who need to lose weight [13]. Thus, GLP-1 RAs are considered effective in promoting insulin secretion and inhibiting glucagon secretion by targeting most of the defects associated with the pathogenesis of T2DM [16].

Panel recommendations

- GLP-1 RAs have a multitargeted mode of action and are considered effective in promoting insulin secretion and inhibiting glucagon secretion versus other antidiabetic drugs.
- GLP-1 acts on various body tissues to maintain normal glucose metabolism and manage body weight without the risk of hypoglycemia. This treatment could be considered for Indian patients with T2DM who often have several comorbidities.
- GLP-1 RA could be primarily considered in patients planning to reduce weight, those with a high CV risk, or those with an underlying CVD.
- The role of GLP-1 RA as a novel therapeutic option for managing T2DM needs to be further emphasized among the medical fraternity, considering the limited awareness regarding the role and biological action of GLP-1 RA among the HCPs in India.

Why choose a GLP-1 RA?

This section describes the biological actions of GLP-1 RA and reasons to consider it as a potent therapeutic option for managing patients with T2DM. It briefly highlights the key characteristics of GLP-1 RAs.

The effects of GLP-1 RAs on insulin and glucagon secretion being glucose dependent, there is a considerably low risk of documented hypoglycemia when utilizing these drugs accompanied with a rapid reduction in HbA1c [20].

GLP-1 RAs improve β-cell glucose sensitivity, and effects can be observed within 8 h postinjection of GLP-1 RA (liraglutide) [23]; this effect can be maintained for 3 months (semaglutide) [24], and can persist for 3 years (exenatide) [25]. The pharmacokinetic properties of GLP-1 RAs indicate that short-acting GLP-1 RAs lead to intermittent exposure with highs and lows and have an insignificant drug concentration in between [26]. Compared with short-acting GLP-1 RAs, which essentially reduce postprandial glucose by delaying gastric emptying, long-acting GLP-1 RAs often result in constant medication exposure and maintain relative concentrations over 24 h and/or over a week, even if the interval between parenteral therapy is a day or a week [27]. This action of long-acting GLP-1 RAs is primarily due to an enhanced ability to decrease fasting glucose, improve compliance [26, 27], and reduce weight (LEAD-6, DURATION-6, HARMONY-7, AWARD-6, and LIRA-LIXI studies) [28–32] compared with short-acting GLP-1 RAs [28, 33, 34].

The benefits of GLP-1 RAs extend to a variety of nonglycemic clinical effects [19] (Fig. 2) To date, the available GLP-1 RAs (*short-acting*: exenatide twice daily [b.i.d.], lixisenatide o.d.; *intermediate-acting*: liraglutide o.d.; *long-acting*: exenatide extended-release q.w., semaglutide q.w., dulaglutide q.w., albiglutide q.w., all s.c. injections, and the first oral preparation, oral semaglutide, o.d.) have been examined in RCTs and cardiovascular outcomes trials (CVOTs). The key characteristics and general features of the GLP-1 RAs are shown in Table 1. These GLP-1 RAs demonstrate specific action, distinguishing characteristics, and variable properties, thereby allowing individualized therapy for patients with T2DM, especially in India where the T2DM patient population is diverse and varied. The South Asian Task Force has defined the rationale for selecting patients with T2DM for GLP-1 RA therapy, which considers whether GLP-1 RA should be used as a monotherapy, dual/triple therapy, or in combination with oral antidiabetic drugs (OADs) with or without insulin [11]. Their recommendation could be helpful for Indian patients while initiating treatment with GLP-1 RAs. Nevertheless, there is a lack of consensus on us-

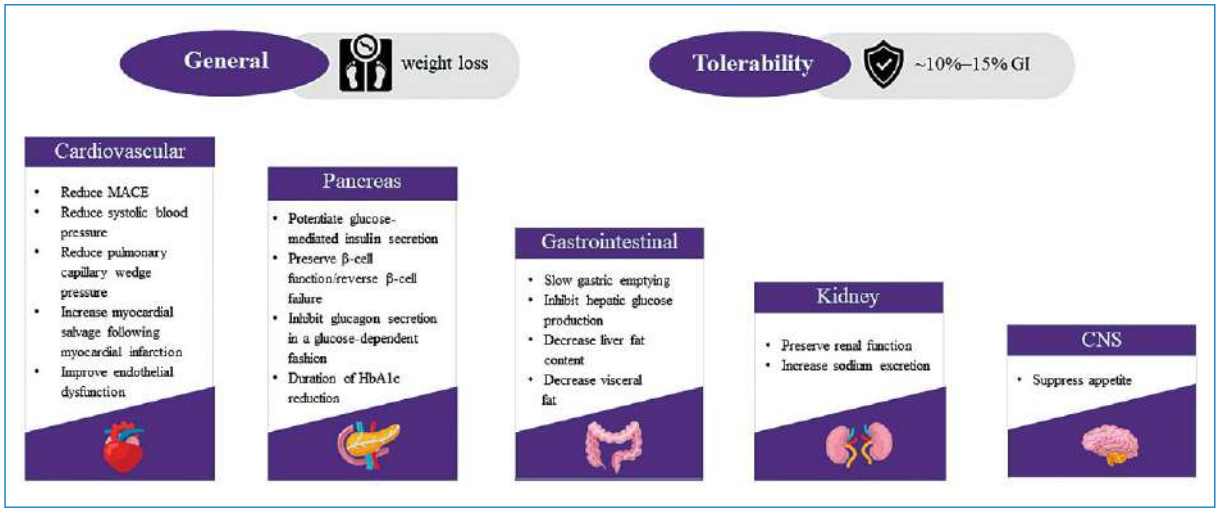

Figure 2. Nonglycemic Actions of GLP-1 RAs
β-cell — beta-cell; CNS — central nervous system; GI — gastrointestinal; GLP-1 RA — glucagon-like peptide-1 receptor agonist; HbA1c — glycated hemoglobin; MACE — major adverse cardiovascular events

ing GLP-1 RAs among HCPs in India, which primarily considers affordability an essential factor when recommending GLP-1 RAs [35].

Individual GLP-1 RAs are available as injections and prefilled pen devices for single or multiple uses. Concerning technical requirements, variability is observed across injection devices. The ease of using such injections and pen devices forms one of the primary criteria for achieving tighter treatment adherence [32]. Over 23% of cases with diabetes and uncontrolled HbA1c, blood pressure, or lipid levels have been linked with poor medication adherence approaches [36], which is primarily driven by patient medication preferences due to the convenience of usage. The future options of therapy include exploring noninvasive and convenient techniques via the oral route of peptides for improved patient compliance, early treatment commencement, addressing challenges with s.c. administration, and achieving better patient outcomes. The breakthrough in the GLP-1 RA drug class is the development of the "first in its class" oral semaglutide that offers increased patient medication compliance. With evolving diabetes technology, a variety of websites, software programs, and applications are available to assist health care professionals and patients in incorporating diabetes technology into their diabetes management schedules. Education and counseling from healthcare providers are critical for diabetics who are not on the HbA1c target.

Panel recommendations

- GLP-1 RAs unravel multiple pathophysiological defects related to T2DM, which could be helpful in the Indian population with a high risk of various comorbidities associated with T2DM.
- Long-acting GLP-1 RAs, which are highly effective in controlling HbA1c compared with short-acting GLP-1 RAs, should be a part of the treatment recommendation plan for managing patients with T2DM from India.
- Better compliance and medication adherence are essential for successful treatment outcomes. Patients should be educated regarding the ease of usage of the GLP-1 RAs, and this dialogue should continue throughout the treatment process. A multifaceted approach is required to manage such patients in India.
- Noninvasive and novel treatment options should be considered to improve adherence to medication among the population. Physicians and HCPs should educate patients regarding the benefits of such treatments.

GLP-1 RAs as the favored antidiabetic medication

This section briefly describes the CV and cardioprotective benefits offered by GLP-1 RAs in patients with T2DM. It showcases why this drug class should be considered the mainstay of treatment for T2DM.

The advanced treatment strategy for T2DM focuses on medications that may achieve tighter glycemic control without the risk of hypoglycemia, reduce weight, have a broader impact on CV risk reduction, renal benefits, decrease blood pressure, correct diabetic dyslipidemia, and reduce the time to MACEs. This shift in treatment strategy beyond glucose control will likely result in

Table 1. Overview of the Key Features, General Characteristics, Dosing, and Duration of the GLP-1 RAs Approved Globally for the Treatment of Patients with T2DM

Agent	FDA approval	Trade name	Approved dosage (μg or mg)	Dosing frequency	Half-life	Time to peak	Administration timing	Method of administration
Short-acting								
Exenatide b.i.d.	2005	Byetta	5–10 μg	b.i.d.	~2.4 h	~2.1 h	60 min before morning and evening meals	Subcutaneous, rotating injection site (thighs, abdomen, or upper arms)
Lixisenatide	2010	Adlyxin	10–20 μg	q.d.	~3 h	~1.5–2.5 h	60 min before first meal of the day	Subcutaneous, rotating injection site (thighs, abdomen, or upper arms)
Intermediate-acting								
Liraglutide	2010	Victoza	0.6–1.8 mg	q.d.	~12.6 h	~8–12 h	At any time of the day	Subcutaneous (thighs, abdomen or upper arms)
Long-acting								
Exenatide extended release q.w.	2012	Bydureon	2 mg	q.w.	~2 weeks	~ 2, 6 and 7 weeks	Per week, the same day at any time of the day	Subcutaneous (thighs, abdomen, or upper arms)
Dulaglutide	2014	Trulicity	0.75–14.5 mg	q.w.	~5 days	~48 h	Once weekly at any time of the day	Subcutaneous (thighs, abdomen, or upper arms)
Semaglutide	2017	Ozempic	0.25, 0.5, and 1 mg	q.w.	~1 week	~1–3 days	Per week, the same day at any time of the day	Subcutaneous, under the skin, rotating injection site (thighs, abdomen, or upper arms)
Orally administered								
Oral semaglutide	2019	Rybelsus	3, 7, and 14 mg	q.d.	~1 week	~1 h	30 min before the first beverage of the day and must be separated from all other medication and taken with up to 4oz of water.	Oral

b.i.d — twice daily; FDA — Food and Drug Administration; GLP-1 RA — glucagon-like peptide-1 receptor agonist; h — hour; T2DM — type 2 diabetes mellitus; q.d. — once daily; q.w. — once weekly

Table 2. Comparisons Across Different Antidiabetic Medications

Antidiabetic drugs	Physiological action	Efficacy (HbA1c reduction)	Risk of hypoglycemia	Body weight	Cardiovascular outcomes
SU	Increased insulin release	High	Moderate	Induces weight gain	Neutral
TZD	Increased insulin sensitivity	High	Low	Induces weight gain	Neutral
AGI	Delayed sugar absorption in the gut	Low	Low	Neutral effect	No benefit
DPP-4i	Increased insulin release Reduced glucagon secretion	Intermediate	Low	Neutral effect	Neutral
SGLT2i	Reduced renal glucose uptake	Intermediate	Low	Induces weight loss	Positive
GLP-1 RA	Increased insulin release Reduced glucagon secretion Slows gastric emptying Increased satiety	High	Low	Induces weight loss	Positive
Insulin	Increased glucose disposal Reduced hepatic glucose production	Highest	High	Induces weight gain	Neutral

AGI — alpha glucosidase inhibitor; DPP-4i — dipeptidyl peptidase-4 inhibitors; GLP-1 RA — glucagon-like peptide-1 receptor agonist; HbA1c — glycated hemoglobin; SGLT2i — sodium–glucose cotransporter-2 inhibitors; SU — sulfonylureas; TZD — thiazolidinedione

a sustained benefit to the T2DM management process [14, 37]. Thus, the vasculo-gluco-centric approach is an innovative way forward with new-age antidiabetic drugs.

When comparing the licensed antidiabetic drugs, GLP-1 RAs demonstrate significant or equivalent benefits over other antidiabetic medications (Tab. 2). The multifactorial benefits with GLP-1 RAs are briefly summarized below.

Glycemic control

GLP-1 RAs offer superior glycemic benefits in managing T2DM by reducing HbA1c levels. On the basis of the data from RCTs and CVOTs, both long- and short-acting GLP-1 RAs demonstrate benefits across the profiles of patients with T2DM, keeping in mind differences in study design, biological effects, duration of action, and their effects on fasting and postprandial blood glucose levels (Tab. 3). Long-acting GLP-1 RAs demonstrate significant reductions in fasting plasma glucose by stimulating glucose-dependent insulin secretion, and short-acting agents show substantial decreases in postprandial glucose mainly due to slow gastric emptying [26]. Briefly, significant but variable HbA1c reductions were observed across multiple GLP-1 RA dosages either as monotherapy or in combination with other OADs. These differences observed between long- and short-acting GLP-1 RAs are due to their variable half-lives and mechanisms of action [26]. The proportions of patients with T2DM presenting hypoglycemic cases across various RCTs and CVOTs with GLP-1 RAs are shown in Table 4. It was observed that when combined with sulfonylureas (SU), a higher incidence of hypoglycemia was noted with several GLP-1 RAs.

Weight control

Besides blood glucose levels, GLP-1 RAs are also characterized by bodyweight reduction. Losing 5% of body fat is clinically significant in patients with obesity and improves obesity-related complications, including impaired glucose metabolism [38]. Established evidence suggests a strong link between increased bodyweight and impaired secretion and action of incretins; individuals with obesity and T2DM have demonstrated reduced incretin effects [39, 40]. The weight loss benefit observed with GLP-1 RAs is primarily due to decreased appetite, reduced body fat, and improved endothelial function [41]. The details of GLP-1 RAs' benefits on bodyweight reduction are shown in Table 3. Compared with the glucose-lowering effects, there is no significant difference in body weight loss between short- and long-acting GLP-1 RAs. In a randomized crossover study in patients with obesity and T2DM, liraglutide resulted in reduced central nervous system activation, suggesting their role in weight loss induction but not its maintenance [42]. Moreover, in patients with obesity and prediabetes or those with T2DM, a decrease in visceral fat was observed using GLP-1 RAs [43, 44]. A meta-analysis of eight RCTs demonstrated that using GLP-1 RAs reduced body mass index (BMI), SBP, triglyceride levels, and waist circumference in over-

Table 3. Effect of Various GLP-1 RAs on Glycemic Control and Body Weight Reduction

Across RCTs				
GLP-1 RAs	**Evidence**	**HbA1c [%]**	**FPG [mg/dL]**	**Body weight [kg]**
Lixisenatide q.d.	Rosenstock et al. 2013	0.80	−23.4	−2.96
Exenatide b.i.d.		0.95	−26.82	−3.98
Dulaglutide q.w. 1.5 mg	Wysham et al. 2014	−1.51	−42.84	−1.30
		−0.99	−23.94	−1.07
Exenatide b.i.d.	Buse et al. 2009	−1.12	−28.98	−10.8
Liraglutide q.d.		−0.79		−3.24
				−2.87
Exenatide b.i.d.	Buse et al. 2013	−1.48	−38.16	−3.57
Liraglutide q.d.		−1.28	−31.68	−2.68
Exenatide q.w.				
Lixisenatide q.d.	Nauck et al. 2016 a	−1.2	−30.6	−3.7
Liraglutide q.d.		−1.8	−52.2	−4.3
Liraglutide q.d.	Dungan et al. 2014	−1.36	−34.2	−3.61
Dulaglutide q.w.		−1.42	−34.74	−2.90
Exenatide q.w.	Buse et al. 2013	−1.9	−41.4	−3.7
Exenatide b.i.d.		−1.5	−25.2	−3.6
Liraglutide q.d. 1.8 mg	Nauck et al. 2016 b	−1.3	−39.6	−2.6
Semaglutide s.c. q.w. 1.6 mg		−1.7	−46.8	−4.8
Exenatide ER q.w. 2 mg	Ahmann et al. 2018	−0.9	−36.0	−1.9
Semaglutide s.c. q.w. 1 mg		−1.5	−50.4	−5.6
Dulaglutide q.w. 1.5 mg	Pratley et al. 2018	−1.4	−39.6	−3.0
Semaglutide s.c. 1 mg		−1.8	−50.4	−6.5
Semaglutide s.c. q.w.	Davies et al. 2017	−1.9	−55.98	−6.9
Semaglutide PO q.d. 40 mg		−1.9	−50.94	−6.4
Liraglutide q.d.	Pratley et al. 2019	−1.1	−33.66	−3.1
Semaglutide PO q.d.		−1.2	−36.0	−4.4

Across CVOTs		
GLP-1 RAs	**ΔHbA1c[a] (%)**	**Body weight (kg)**
Lixisenatide (ELIXA)	−0.3	−0.7
Exenatide ER (EXSCEL)	−0.53	−1.3
Liraglutide (LEADER)	−0.4	−2.3
Dulaglutide (REWIND)	−0.61	−1.5
Semaglutide s.c. (SUSTAIN-6)	−0.7, −1.1[b]	−2.9, −4.3[b]
Oral Semaglutide (PIONEER-6)	−0.7	−3.4

[a]ΔHbA1c reflects change from placebo arm across trial and is not a measure of glycemic efficacy; [b]0.5 and 1.0 mg dose, respectively. b.i.d. — twice daily; CVOT — cardiovascular outcome trial; FPG — fasting plasma glucose; GLP-1 RA — glucagon-like peptide-1 receptor agonists; HbA1c — glycated hemoglobin; PO — by mouth; q.d. — once daily; q.w. — once weekly; RCTs — randomized clinical trials; s.c. — subcutaneous

weight or obese individuals [45]. Although GLP-1 RAs play a significant role in managing weight in individuals with T2DM, approval for obesity treatment has only been granted to liraglutide (3.0 mg) by the FDA and EMA and semaglutide (2.4 mg) s.c. injection by the FDA. A rapidly emerging and effective GLP-1 RA that promotes weight loss is oral semaglutide, which has demonstrated a significant weight loss in patients versus placebo.

Liver health

GLP-1 RAs have a positive impact on hepatic health, especially for the treatment of nonalcoholic steatohepatitis (NASH) [46]. Over two-thirds of patients with diabetes present with nonalcoholic fatty liver disease (NAFLD), which is the global cause of chronic liver disease with a prevalence of 90% in morbidly obese patients [47]. A meta-analysis of 946 patients with NAFLD

Table 4. The Proportion of T2DM Patients with Hypoglycemic Cases using GLP-1 RAs

Across RCTs			
GLP-1 RAs	**Evidence**	**SU**	**Proportion of patients with hypoglycemic cases (%)**
Lixisenatide q.d.	Rosenstock et al. 2013	No	2.5
Exenatide b.i.d.			7.9
Dulaglutide q.w. 1.5 mg	Wysham et al.	No	10.4
Exenatide b.i.d.			15.9
Liraglutide q.d.	Buse et al.	Yes	26
Exenatide b.i.d.			34
Liraglutide q.d.	Buse et al.	Yes	12
Exenatide q.w.			15
Lixisenatide q.d.	Nauck et al. 2016 a	No	2.5
Liraglutide q.d.			1.5
Liraglutide q.d.	Dungan et al.	No	6
Dulaglutide q.w.			9
Exenatide q.w.	Drucker et al.	Yes	14.5
Exenatide b.i.d.			15.4
Liraglutide q.d. 1.8 mg	Nauck et al. 2016 b	No	3.01
Semaglutide s.c. q.w. 1.6 mg			3.01
Exenatide ER q.w. 2 mg	Ahmann et al. 2018	No	8.1
Semaglutide s.c. q.w. 1 mg			8.2
Dulaglutide q.w. 1.5 mg	Pratley et al. 2018	No	2
Semaglutide s.c. 1 mg			2
Semaglutide s.c. q.w.	Davies et al. 2017	No	5.79*
Semaglutide oral q.d. 40 mg fast escalation group			1.40*
Liraglutide q.d.	Pratley et al.	No	2
Semaglutide oral q.d.			1

Across CVOTs	
GLP-1 RAs (Trials)	**Occurrence of severe hypoglycemia in agent vs. placebo (%)**
Lixisenatide (ELIXA)	% Not significant vs. placebo
Exenatide ER (EXSCEL)	3.4 vs. 3.0
Liraglutide (LEADER)	2.4 vs. 3.3
Dulaglutide (REWIND)	1.3 vs. 1.5
Semaglutide s.c. (SUSTAIN-6)	1.4 vs. 0.8
Oral Semaglutide (PIONEER-6)	22.4 vs. 21.2

*Severe or blood glucose-confirmed hypoglycemic episodes were defined as severe by ADA classification# or blood glucose-confirmed with a plasma glucose value of < 56 mg/dL (< 3.1 mmol/L) with/without symptoms consistent with hypoglycemia. # ADA-classified "severe" hypoglycemia is an episode requiring the assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions.
ADA — American Diabetes Association; b.i.d. — twice daily; CVOT — cardiovascular outcome trial; FPG — fasting plasma glucose; GLP-1 RA — glucagon-like peptide-1 receptor agonists; HbA1c — glycated hemoglobin; T2DM — type 2 diabetes mellitus; q.d. — once daily; q.w. — once weekly; RCTs — randomized clinical trials; s.c. — subcutaneous; SU — sulfonylureas

demonstrated that GLP-1 RAs reduced BMI, steatosis, and alanine transferase levels [48]. Drugs such as dulaglutide, liraglutide, exenatide, lixisenatide, and semaglutide have been investigated to manage NAFLD [46, 49]. Liraglutide and exenatide have demonstrated considerable liver function test and histological improvements, resulting in reduced hepatic and visceral fat accumulation [26]. Of these GLP-1 RAs, semaglutide is considered the most promising for treating NAFLD due to its role in preventing CV events [49]. Although favorable outcomes were observed, further long-term studies with robust evidence are needed to prove the effectiveness of GLP-1 RAs for NASH/NAFLD treatment and whether it may have a potential for reducing hepatic fibrosis.

Table 5. Effect of GLP-1 RAs Across Lipid Profiles (Blood Pressure, Cholesterol, and Triglycerides)

Across RCTs				
GLP-1 RAs	**Triglyceride (mg/dL)**	**HDL (mg/dL)**	**LDL (mg/dL)**	**SBP (mmHg)**
Exenatide b.i.d.	−3.6	0.18	0.36	−3.8
Lixisenatide	Not reported	Not reported	Not reported	0.2
Liraglutide	−1.8	0.36	1.44	−3.5
Exenatide o.w.	−5.04	0.36	−0.9	−2.5
Dulaglutide o.w.	−3.24	0.36	−3.42	−1.5
Semaglutide o.w.	−12.6	0.18	1.44	–8
Across CVOTs				
GLP-1 RAs (Trials)	**Systolic blood pressure difference vs. placebo (mmHg)**			
Lixisenatide (ELIXA)	−0.8			
Exenatide ER (EXSCEL)	−1.6			
Liraglutide (LEADER)	−1.2			
Dulaglutide (REWIND)	−1.7			
Semaglutide s.c. (SUSTAIN-6)	−1.3, −2.6[a]			
Oral Semaglutide (PIONEER-6)	2.6			

[a]0.5 and 1.0 mg dose, respectively
b.i.d. — twice daily; CVOT — cardiovascular outcome trial; GLP-1 RA — glucagon-like peptide-1 receptor agonists; HbA1c — glycated hemoglobin; HDL — high-density lipoprotein; LDL — low-density lipoprotein; o.w. — once weekly; RCTs — randomized clinical trials; SBP — systolic blood pressure

Lipid profile

GLP-1 RAs have reportedly improved lipid profiles across various RCTs and CVOTs (Tab. 5). Lowered low-density lipoprotein cholesterol (LDL-C) and triglycerides levels have also been observed [10]. From a clinical viewpoint, a slight improvement in the lipid profile of T2DM patients can have a significant impact. A meta-analysis showed reductions in LDL-C, total cholesterol, and triglyceride levels but not high-density lipoprotein cholesterol with GLP-1 RA treatment. However, the mechanisms of these changes remain vague and needs further exploration.

Blood pressure reduction

GLP-1 RAs also reduce SBP and diastolic blood pressure (DBP). The use of GLP-1 RAs has shown to decrease SBP by 2–5 mmHg, but this effect is inconsistently demonstrated with DBP. BP reductions have also been observed in patients with T2DM and hypertension independent of weight loss. A systematic review and network meta-analysis of 60 trials showed that GLP-1 RA treatment resulted in a modest reduction in SBP and DBP compared with placebo, insulin, and SU, with a minor increase in heart rate [50].

CV benefits

Postprandial endothelial function improved with exenatide b.i.d [51]. Improved CV health was observed when using GLP-1 RA, with a reduction in dyslipidemia and arterial hypertension risk factors. Blood glucose control, body weight reduction, and improvement of BP and lipid profiles enhance the beneficial response of GLP-1 RAs on CV outcomes. Favorable effects were observed on cardiac function and coronary ischemia, thereby delaying or preventing atherosclerosis, and also improving renal function (Fig. 3) [52].

Following guidance from regulatory bodies (FDA and EMA), several CVOTs have been conducted to examine the safety and tolerability of GLP-1 RAs, which include ELIXA (lixisenatide) [53], LEADER (liraglutide) [54], SUSTAIN (injectable semaglutide) [55] EXSCEL (exenatide ER) [56], HARMONY (albiglutide) [57], REWIND (dulaglutide) [58], and PIONEER 6 (oral semaglutide) [59]. A systematic review and meta-analysis synthesizing evidence from CVOTs with a total of 56,004 participants did not identify an increased risk of HF in such patients (reducing all-cause mortality by 12% and hospital admission for HF by 9%) [60]. However, in some instances, inconsistent effects were observed regarding the risk of hospitalization for congestive HF. Currently, European and American guidelines state GLP-1 RA may be considered in patients with T2DM and HF if SGLT-2i not tolerated or contraindicated. [13, 14]. Globally, CVOTs have not demonstrated an increased risk of MACEs using s.c. GLP-1 RAs. The data for the changes in the time to MACE, such as the first nonfatal acute MI, nonfatal stroke, cardiovascular death, all-cause mortality, or hospitalization for congestive HF, comparing GLP-1 RAs and placebo have been described previously [21]. Lixisenatide had no effects on MACEs,

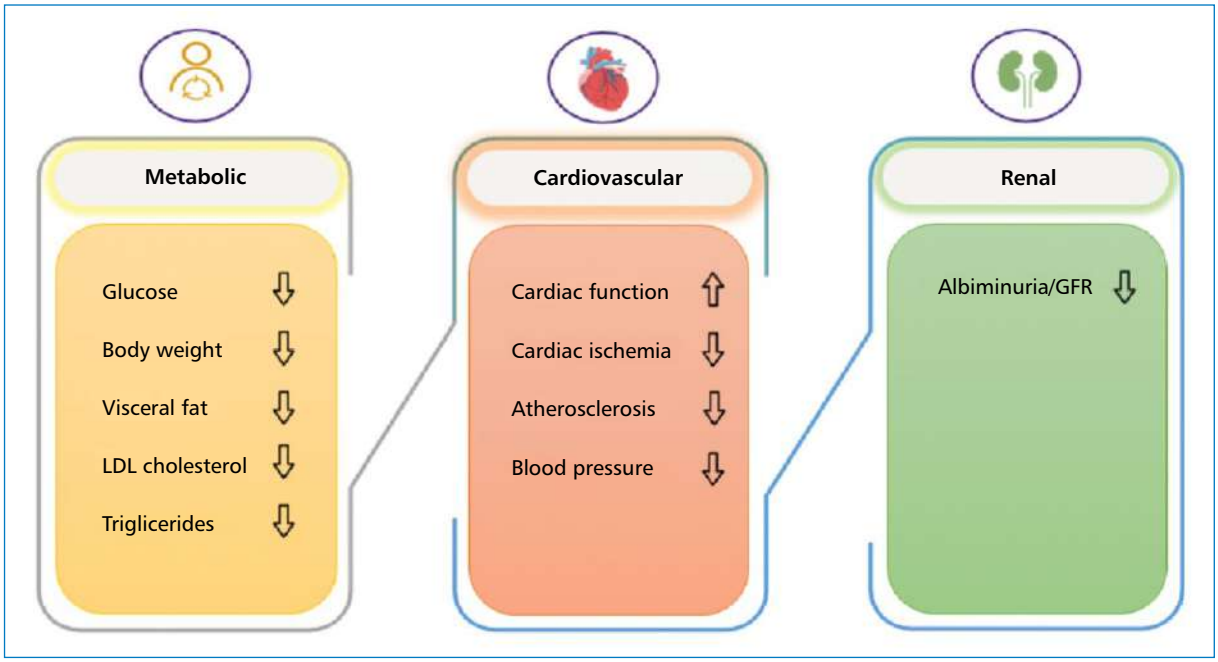

Figure 3. The Potential Mechanisms of the Cardiovascular Benefits of GLP-1 RAs
GLP-1 RA — glucagon-like peptide-1 receptor agonist; GFR — glomerular filtration rate; LDL — low-density lipoprotein

all-cause mortality, and hospitalization for HF (ELIXA trial). Other GLP-1 RAs showed either a 12–26% reduction or some reducing trend in MACEs [53–59]. Three GLP-1 RAs (liraglutide, dulaglutide, and semaglutide) have proven benefits in reducing the risk of MACEs in high-risk CVD patients or those with established CVD [61]. Meanwhile, lixisenatide and exenatide demonstrated a neutral effect on the CV system. A predictive model in a meta-analysis of GP-1 RA CVOTs showed a favorable number needed to treat with liraglutide and semaglutide (except for lixisenatide, which had a negative number needed to treat or number needed to harm; Fig. 4) [62]. In a meta-analysis, a random-effects model estimated the overall hazard ratios for MACE and its components, such as death from any causes, HF-related hospital admissions, and crucial safety outcomes (severe hypoglycemia, pancreatitis, and pancreatic cancer), and showed beneficial effects with GLP-1 RAs on CV outcomes [60]. Moreover, the CV benefits of GLP-1 RAs make them a preferred treatment for patients with pre-existing ASCVD [63]. Recently, oral semaglutide formulation has been introduced in the market and is used extensively in managing patients with T2DM as it has a low risk of hypoglycemia and enhanced CV benefits. Taken together, the currently approved GLP-1 RAs offer an effective treatment option for obese patients with T2DM at a high risk or with an underlying CVD. However, future long-term studies are needed to add to the growing evidence.

Renal health

A meta-analysis to estimate the overall hazard ratios for kidney and key safety outcomes (severe hypoglycemia, pancreatitis, and pancreatic cancer) showed that GLP-1 RAs reduced the overall composite kidney outcomes (new-onset macroalbuminuria progression, estimated glomerular filtration rate decline [or increase in creatinine], end-stage kidney disease progression, or death due to kidney causes) by 17% mainly due to a reduction in urinary albumin excretion [60]. However, for some GLP-1 RAs, caution is needed while using them in patients with renal impairment. In patients with mild renal impairment, as per the European labeling, dose adjustment for GLP-1 RAs is not needed, but some cannot be used or are not recommended in patients with severe renal impairment and end-stage disease [12], with exceptions such as dulaglutide, liraglutide, and semaglutide, which can be used in severe renal impairment but not end-stage renal disease. In the PIONEER 5 trial, oral semaglutide demonstrated effectiveness in T2DM patients with moderate renal impairment, thereby offering a new treatment option [64]. Moreover, oral semaglutide can be used at all stages of CKD as per the FDA label.

Special populations

The use of GLP-1 RAs has been described in adolescents, the elderly, pregnant and lactating women, and those with polycystic ovary syndrome by the South Asian Task Force [11].

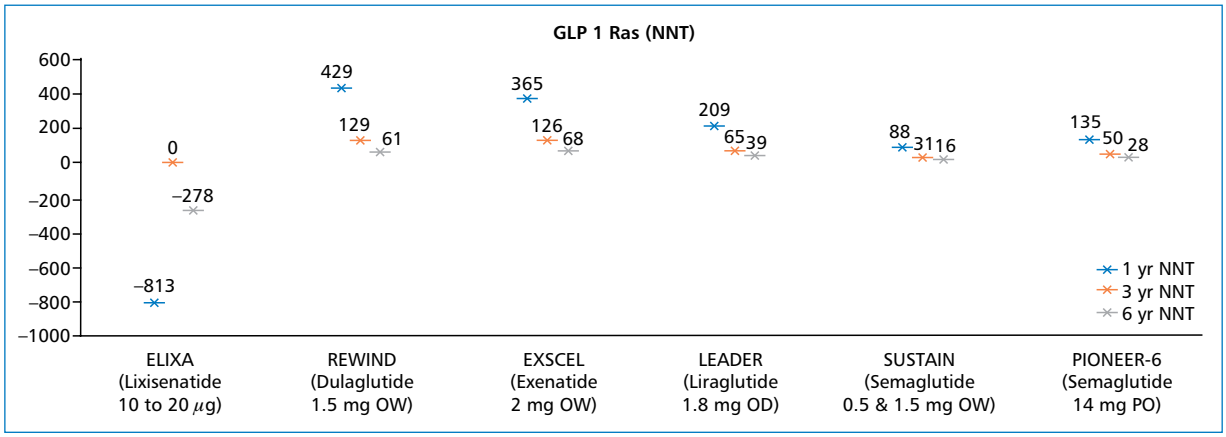

Figure 4. Numbers Needed to Treat for GLP-1 RAs
GLP-1 RA — glucagon-like peptide-1 receptor agonist; NNT — numbers needed to treat; OD — once daily; OW — once weekly; PO — by mouth

Safety and tolerability

The most common adverse events with GLP-1 RAs are gastrointestinal, that is, primarily nausea, vomiting, and diarrhea [7]. In addition, they are associated with an increased heart rate, typically by 2–3 beats per minute [11], although the clinical relevance of such effects is uncertain [10]. It has been suggested that increases in heart rate may imply a need for caution in HF patients with cardiac arrhythmias. The doses, indications, dose modifications, contraindications, and adverse effects of GLP-1 RAs with demonstrated CV benefits are summarized in Table 6. GLP-1 RAs seem to improve cardiovascular outcomes in patients with T2D compared with oral glucose-lowering drugs but with increased frequency of gastrointestinal events [9]. Nevertheless, all such events are typically mild to moderate and occur only during the first week of treatment [8]. Overall, the diverse outcomes and effects observed across GLP-1 RAs highlight the need for individualized care with these drugs classes.

Panel recommendations

- It is crucial to select an antidiabetic drug with established efficacy to address multiple pathophysiological defects.
- GLP-1 RAs are a popular choice for broader T2DM patient management due to their established safety and efficacy profile, especially in patients with underlying CVD.
- Currently, CVOTs have not shown an increased risk of CV events with GLP-1 RAs such as liraglutide, dulaglutide, and s.c. semaglutide, they were either neutral or showed benefit.
- Guidelines recommend GLP-1 RAs in high-risk or established ASCVD patients. Consider discussing GLP-1 RA use with the clinician responsible for glycemic control alone or a patient–clinician discussion.
- GLP-1 and its impact on the kidney may promote rapid natriuresis and may modulate renal hemodynamics and phosphorylation of proteins involved in sodium handling.
- Aside from glycemic control, weight reduction, and SBP reduction, GLP-1 RAs may possibly have direct renal benefits, making it an ideal choice in managing T2DM.

Therapeutic inertia and treatment adherence with GLP-1 Ras

This section emphasizes the need for GLP-1 RA treatment intensification and the challenges related to medication adherence and overcoming those challenges.

T2DM treatment involves multiple parameters due to the complexity of managing the disease, which involve medications and comorbidities, patient lifestyle, profile, duration of the disease, site of action, pharmacological approaches, and adherence or persistence to medication. Globally, medication adherence has been challenging for patients with several chronic diseases [65]. Similarly, adherence to s.c. GLP-1 RAs is reportedly suboptimal [66, 67]. This is a primary concern, especially when it is evident that strict adherence to GLP-1 RAs may result in significant glycemic control [66, 68]. Factors that may affect medication adherence include, but are not limited to, frequency of administration, side effects, efficacy, device type, and affordability [69]. Thus, adherence to treatment is causally linked with improved glycemic control and vice versa.

Clinical inertia affects medication adherence. An inverse correlation is observed between adherence to

Table 6. Doses, Indications, Dose Modifications, Contraindications, Cautions, and Adverse Effects of GLP-1 RAs with Demonstrated CV Benefits

	Dulaglutide	Exenatide QW	Liraglutide	Lixisenatide	Semaglutide SC	Semaglutide PO
Recommended initiation doses for CV benefit	0.75 mg s.c. daily	2 mg s.c. once weekly	0.6 mg s.c. daily	10 μg s.c. daily	0.25 mg s.c. once weekly	3 mg orally daily
Indications	• Improve blood plasma glucose, SBP, and lipid profile in adults with T2D • Reduce MACEs for people with T2D with and without established CV disease	• Improve blood plasma glucose, SBP, and lipid profile in adults with T2D • Reduce the risk of MI, CVD events, or CV death in adults with T2D and CV disease	• Improve blood plasma glucose, SBP, and lipid profile in adults with T2D • Reduce the risk of MI, stroke, or CV death in adults with T2D and CV disease	• Improve blood plasma glucose, SBP, and lipid profile in adults with T2D • Neutral effects on CV risk in adults with T2D (neither increasing nor decreasing incidence)	• Improve blood plasma glucose, SBP, and lipid profile in adults with T2D	• Improve blood plasma glucose, SBP, and lipid profile in adults with T2D
Dose modifications	• Up-titrate slowly to reduce nausea and vomiting • Discontinue if pancreatitis is suspected and do not restart if pancreatitis is confirmed • No dose adjustment is necessary with renal or hepatic impairment; data in end-stage renal disease are limited	• Up-titrate slowly to reduce nausea and vomiting • Discontinue if pancreatitis is suspected and do not restart if pancreatitis is confirmed • Not recommended with eGFR < 45	• Up-titrate slowly to reduce nausea and vomiting • Discontinue if pancreatitis is suspected and do not restart if pancreatitis is confirmed • No dose adjustment is necessary with renal or hepatic impairment	• Up-titrate slowly to reduce nausea and vomiting • Discontinue if pancreatitis is suspected and do not restart if pancreatitis is confirmed • Not recommended with eGFR < 15	• Up-titrate slowly to reduce nausea and vomiting • Discontinue if pancreatitis is suspected and do not restart if pancreatitis is confirmed • No dose adjustment is necessary with renal or hepatic impairment	• Up-titrate slowly to reduce nausea and vomiting • Discontinue if pancreatitis is suspected and do not restart if pancreatitis is confirmed • No dose adjustment is necessary with renal or hepatic impairment
Contraindications	• Severe prior hypersensitivity to dulaglutide or any component of the formulation • History of or family history of medullary thyroid carcinoma; patients with multiple endocrine neoplasia syndrome type 2	• Severe prior hypersensitivity to exenatide or any component of the formulation • History of or family history of medullary thyroid carcinoma; patients with multiple endocrine neoplasia syndrome type 2; history of drug-induced immune-mediated thrombocytopenia • End-stage renal disease or severe renal impairment (CrCl < 30 mL/min) including dialysis patients	• Severe prior hypersensitivity to liraglutide or any component of the formulation • History of or family history of medullary thyroid carcinoma; patients with multiple endocrine neoplasia syndrome type 2	• Hypersensitivity or anaphylaxis to lixisenatide or any product components • End-stage renal disease or severe renal impairment (CrCl < 15 mL/min) including dialysis patients	• Severe prior hypersensitivity to semaglutide any component of the formulation • History of or family history of medullary thyroid carcinoma; patients with multiple endocrine neoplasia syndrome type 2	• Severe prior hypersensitivity to oral semaglutide or any component of the formulation • History of or family history of medullary thyroid carcinoma; patients with multiple endocrine neoplasia syndrome type 2

Table 6. Doses, Indications, Dose Modifications, Contraindications, Cautions, and Adverse Effects of GLP-1 RAs with Demonstrated CV Benefits

	Dulaglutide	Exenatide QW	Liraglutide	Lixisenatide	Semaglutide SC	Semaglutide PO
Caution	• Use caution in patients with thyroid c-cell tumors, pancreatitis, hypoglycemia, impaired renal function, GI disease, hypersensitivity, macrovascular outcomes	• Use caution in patients with acute pancreatitis, hypoglycemia, acute kidney injury or impaired renal function, GI disease, immunogenicity, hypersensitivity, injection-site reactions, CV outcomes	• Use caution in patients with thyroid c-cell tumors, pancreatitis, hypoglycemia, impaired renal function, hypersensitivity, acute gall bladder disease. Liraglutide pen should not be shared	• Use caution in patients with pancreatitis, hypoglycemia with concomitant use of sulfonylurea or basal insulin, acute kidney injury, anaphylaxis, severe hypersensitivity, immunogenicity, and macrovascular outcomes. Lixisenatide pen should not be shared	• Use caution in patients with pancreatitis, diabetic retinopathy complications, hypoglycemia with concomitant use of sulfonylurea or basal insulin, acute kidney injury, anaphylaxis, and severe hypersensitivity immunogenicity, macrovascular outcomes. Semaglutide pen should not be shared	• Use with caution in patients with acute pancreatitis, diabetic retinopathy complications, hypoglycemia, acute kidney injury, hypersensitivity reactions
Adverse effects to monitor	The most common adverse reactions reported in ≥ 5% of patients treated with dulaglutide are nausea, diarrhea, vomiting, abdominal pain, and decreased appetite	Most common (≥ 5%) and occurring more frequently than the comparator in clinical trials: nausea, diarrhea, headache, vomiting, constipation, injection site pruritus, injection-site nodule, and dyspepsia	The most common adverse reactions reported in ≥ 5% of patients treated with liraglutide are: nausea, diarrhea, vomiting, abdominal pain, dyspepsia, constipation, and decreased appetite Immunogenicity-related events, including urticaria, were more common among liraglutide-treated patients (0.8%) than among comparator-treated patients (0.4%) in clinical trials	The most common adverse reactions (≥ 5%) of patients treated with lixisenatide are nausea, vomiting, headache, diarrhea, dizziness, and hypoglycemia	The most common adverse reactions reported in ≥ 5% of patients treated with semaglutide are nausea, vomiting, diarrhea, abdominal pain, and constipation	The most common adverse reactions reported in ≥ 5% of patients treated with oral semaglutide are: nausea, abdominal pain, diarrhea, decreased appetite, vomiting, and constipation

CrCl — creatinine clearance; CV — cardiovascular; CVA — cerebrovascular accident; CVD — cardiovascular disease; eGFR — estimated glomerular filtration rate; GI — gastrointestinal; GLP-1 RA — glucagon-like peptide receptor agonist; MACEs — major adverse cardiovascular events; MI — myocardial infarction; PO — by mouth; SBP — systolic blood pressure; s.c. — subcutaneous; T2D — type 2 diabetes; q.w. — once-weekly

medication and clinical inertia, and higher compliance is associated with appropriate treatment intensification [70]. Regarding treatment strategies for improved management of patients with T2DM and for reaching recommended HbA1c targets, international guidelines call for intensification of antidiabetic medications, which seem to vary based on the patient's preferences, characteristics, comorbidities, and hypoglycemia risk [7]. Nevertheless, a significant proportion of the T2DM population fails to accomplish their recommended targets, thereby adding to the glycemic burden. This delay in treatment initiation and intensification, known as treatment inertia or clinical inertia, poses a significant risk of diseases and comorbidities associated with T2DM. The terms treatment and clinical inertia are often used interchangeably. There is a growing consensus on improving compliance with T2DM treatment and increasing medication adherence with timely/early initiation of treatment to minimize risks associated with T2DM. [71] Data from the United Kingdom Clinical Practice Research Datalink showed that in patients with HbA1c $\geq$ 7%, a year's delay in receiving treatment intensification was associated with significantly increased risk of MI, HF, composite CV events, and stroke by 67%, 64%, 62%, and 51%, respectively [72].

There is a need for overcoming inertia by education and awareness, optimizing care and treatment for such patients, and leveraging available tools and technologies. Barriers to improved and early treatment access are primarily based on physicians' lack of novel drug awareness, perception of the drug, ease of handling a drug, and preference for using a drug for several years, making it easier for them to predict outcomes [73]. In an analysis of the Scottish Care Information Diabetes registry, which included observational data from 248,400 patients with diabetes, the use of GLP-1 RAs and SGLT2is was low, irrespective of the patient's history of CVD [74]. Furthermore, lesser exposure and limited knowledge of T2DM associated with CVD and renal disease may lead to unawareness of the cardiorenal benefits of SGLT2is and GLP-1 RAs among the primary-care physicians [75] compared to a specialist. Nevertheless, clinical inertia for glycemic control is noted even among specialists [76], which calls for a coordinated action plan to improve outcomes. A group of physicians has drafted a clinical manifesto to overcome clinical inertia by rethinking treatment algorithms to reduce CV events and hospitalizations due to HF and to delay the progression of renal disease in patients with T2DM (Fig. 5) [73]. The expected economic and societal benefits of overcoming clinical inertia [77] include reducing the costs of disease-related complications, enabling effective treatment in primary care, avoiding the use of insufficiently effective OADs, achieving better quality of life for such patients, and increasing event-free life years. To overcome the clinical inertia barrier, allowing personalization of treatment and reducing the treatment burden using oral medications earlier in the treatment schedule could be a preferred option by both patients and physicians.

Panel recommendations

- Poor glycemic control can lead to severe complications; a comprehensive approach is suggested. Initiating treatment closer to disease diagnosis coupled with education and awareness among patients regarding disease management could lead to higher adherence to medication with greater acceptability.
- Clinical inertia and nonadherence to medications pose significant obstacles from reaching appropriate glycemic targets. Thus, there is a need to overcome inertia.
- Early and efficient treatment intensification is recommended to improve glycemic control and achieve persistence. A patient–physician dialogue is recommended to achieve the desired outcomes. There is a need to rethink treatment algorithms to achieve better glycemic control.
- Newer routes of administration of GLP-1 RAs, such as oral GLP-1 RAs, for the treatment of T2DM could improve adherence and acceptance among patients and physicians. Oral therapy should be considered a part of the treatment algorithm and recommendation guidelines.

Cost-effectiveness and affordability of GLP-1 RAs

This section summarizes the cost-effectiveness of the current GLP-1 RAs and considerations for its wider use based on affordability.

The cost of antidiabetic drugs may play a crucial barrier that prevents its access to vulnerable populations. Challenging reimbursement processes in countries may also lead to nonadherence [78]. These barriers may prevent HCPs from prescribing drugs that are perceived expensive compared with others that may be more accessible, thereby preventing patients from accessing appropriate drugs.

Reimbursement laws within each country, challenges with acknowledgment, and awareness of the novel antidiabetic drugs such as GLP-1 RAs could further alienate such novel treatment options as a part of the standard of care by the respective authorities' reimbursement plan. The South Asian Task Force has already identified the cost of GLP-1 RAs as a significant

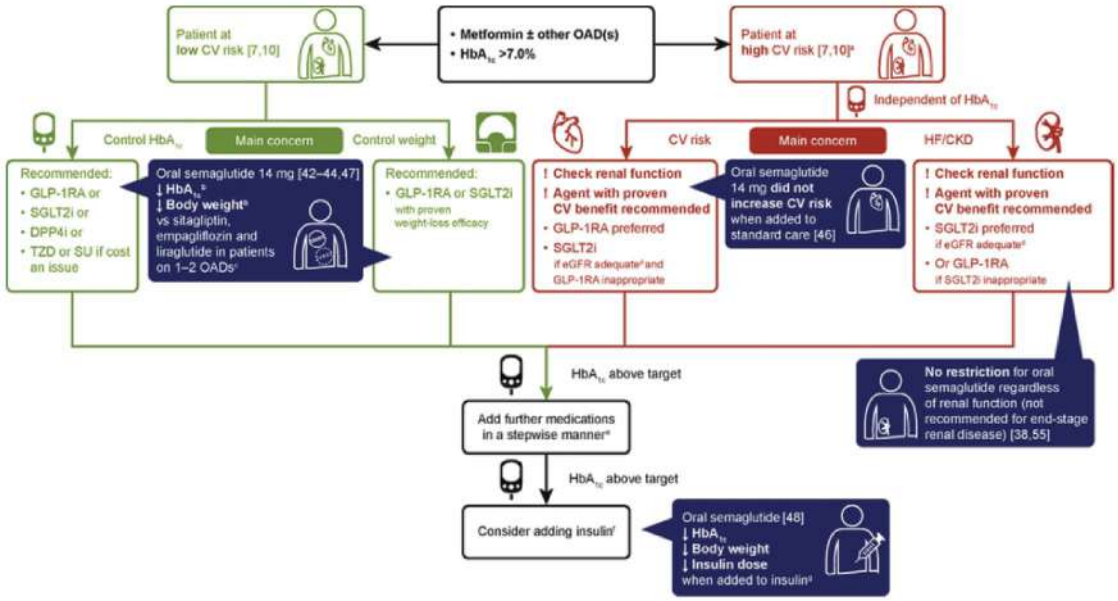

Figure 5. Potential Place of Oral Semaglutide in International Treatment Recommendations for People with T2DM
The figure is adapted from a publication by *Seidu S et al. Will oral semaglutide be a game-changer in the management of type 2 diabetes in primary care? Primary Care Diabetes 2021; 15:59-68* under the CC BY-NC-ND license http://creativecommons.org/licenses/by-nc-nd/4.0/ without making any changes.
[a]With established CV disease, CKD, or risk factors; [b]At the end of treatment in patients who remained on treatment and did not use rescue medication in PIONEER 2–4; [c]Metformin alone in PIONEER 2, metformin ± SU in PIONEER 3, metformin ± SGLT2i in PIONEER 4, and 1–2 of metformin, SU, TZD or SGLT2i in PIONEER 7; [d]Guidance varies by drug and region; [e]GLP-1 RAs and DPP4i are not recommended to be used in combination; [f]Consider basal insulin with lower risk of hypoglycemia; [g]Basal, bolus, and premix insulin.
CKD — chronic kidney disease; CV — cardiovascular; DPP-4i — dipeptidyl peptidase-4 inhibitor; eGFR — estimated glomerular filtration rate; GLP-1 RA — glucagon-like peptide-1 receptor agonist; HbA1c — glycated hemoglobin; HF — heart failure; OAD — oral antidiabetes drug; SGLT2i — sodium–glucose transporter-2 inhibitor; SU — sulfonylurea; T2D — type 2 diabetes; TZD — thiazolidinediones

barrier in the region, including India, which does not have government support for reimbursement due to lack of such policies. Hence, patients have to pay out of pocket [79]. By contrast, GLP-1 RAs are cost-effective when keeping the long-term benefits in mind. A French study on GLP-1 RA cost-effectiveness estimated the expected lifetime direct medical costs and outcomes from the perspective of the French National Health Service. The study found that dulaglutide 1.5 mg reduced the expected costs and increased the expected quality-adjusted life-years (QALYs) compared with exenatide q.w. Further health benefits offered by the drug may result in payers' expense savings [80]. Huetson et al. offered an improved perspective for the long-term cost-effectiveness of GLP-1 RAs by showcasing benefits in QALYs and reduced lifetime healthcare costs [81].

A systematic literature review of cost-effectiveness analysis compared semaglutide q.w. with other GLP-1 RAs. Overall, semaglutide effectively brought patients to each endpoint resulting in higher cost-of-control for dulaglutide and other GLP-1 RAs over a year. Semaglutide resulted in more QALYs gained and, which suggested a dominant or highly cost-effective treatment unlike dulaglutide and other GLP-1 RAs [82]. A UK-based analysis evaluated the long-term cost-effectiveness of semaglutide 1 mg q.w. versus liraglutide 1.2 mg o.d. from a UK healthcare payer perspective. Semaglutide demonstrated increased discounted life expectancy (0.21 years) and discounted quality-adjusted life expectancy (0.30 quality-adjusted life-years). Owing to decreased diabetes-related complications, particularly CVD, clinical benefits were accomplished at lower costs, with lifetime cost savings observed with semaglutide versus liraglutide [83]. Another UK-based cost analysis study demonstrated that semaglutide 1 mg q.w. offered a premium cost of control compared with exenatide extended-release 2 mg, dulaglutide 1.5 mg, and liraglutide 1.2 mg in achieving clinically relevant, single, and composite endpoints, thereby offering a good value for money [84]. Meanwhile, a Swedish cost-effectiveness analysis study showed that semaglutide 1 mg q.w. was cost-effective for treating T2DM in inadequately controlled patients on metformin or basal insulin, addressing the need of many current Swed-

ish clinicians, patients, and payers [85]. The budget impact of a treatment pathway was evaluated using oral semaglutide 14 mg daily versus oral sitagliptin 100 mg daily among patients unable to achieve their HbA1c target regardless of treatment with metformin. After over 5 years, patients on sitagliptin 100 mg who received oral semaglutide showed a substantial budget impact increase over those whose blood glucose level was uncontrolled with metformin [86].

Panel recommendations

- Patient preferences for daily oral medication versus daily or weekly s.c. injections may provide a directive toward the choice of drugs.
- Oral GLP-1 RAs may be more cost-effective in the long term when used in appropriate situations compared with other antidiabetic drugs and should be considered by physicians in the current setting.
- Cost-effectiveness may significantly affect its acceptance in the Asian population, and there is a need for physicians and governments to collaborate and find an effective solution.

Diabetes guideline recommendations — more uniform perspectives needed

Although there are some differences, there are also many similarities between the guidelines. However, the absence of a globally accepted and uniform policy for managing T2DM, emphasizes the need for a collaborative approach among HCPs and primary-care physicians to arrive at a universally accepted guideline for T2DM.

Currently, global guidelines for the management of T2DM are not uniform, with a scope of improvement between the involved organizations/parties. This discordance often leads to varied geographical practices that could lead to mixed outcomes. The guidelines are also variable based on the physician's clinical practicing style and preferences.

The ADA's current clinical practice recommendations emphasize that GLP-1 RAs are preferred over insulin. In patients with a high risk of or established ASCVD, HF, or CKD, SGLT2s or GLP-1 RAs are preferred over metformin independent of HbA1c [7]. On the basis of the research findings from CVOTs in 2019, the ADA-EASD briefly updated their 2018 recommendations on the management of hyperglycemia. It was recommended that in high-risk individuals with T2DM, the decision to treat with a GLP-1 RA or SGLT2i to reduce MACEs, HF, CV death, or CKD progression should be considered independently of baseline HbA1c or individualized HbA1c targets [13]. The ADA and EASD consensus report highlighted the strategy that focused on T2DM patients with established ASCVD, HF, or progressive CKD, implying a transition from current algorithms primarily based on glycemic control to a more comprehensive CV protection strategy, including HF and renal protection. [13] The 2019 ESC guidelines on diabetes, prediabetes, and CVD developed in collaboration with the EASD, which were updated briefly from the 2013 ESC guidelines, recommended liraglutide, semaglutide, or dulaglutide for T2DM and CVD patients or those with high/very high CV risk to reduce CV events (Class 1a) [14].

In India, apart from the ICMR 2018 guidelines [15] for T2DM (which follows the ADA guidelines), there is no uniform or recent recommendation for managing T2DM patients. Furthermore, frequent updates of the guidelines via emerging evidence could confuse primary-care physicians and HCPs who may not be abreast with such frequently changing practices and recommendations. Hence, there is a need for increased collaboration and dialogue between diabetologists, endocrinologists, specialists, and primary-care physicians to arrive at globally and uniformly accepted guidelines for T2DM, especially in India.

Panel recommendations

- GLP-1 RAs have been suggested in patients with ASCVD or at a high risk for CVD, irrespective of HbA1c (ADA/EASD).
- ESC has recommended using GLP-1 RAs as first-line therapy, even before metformin, in patients with CVD and high/very high CV risk.
- GLP-1 RAs have been advocated as the first-line therapy in patients with HbA1c $\geq$ 7.5% as per American Association of Clinical Endocrinologist guidelines.
- There is a need for guidelines to uniformly manage patients with T2DM in India.

Repositioning GLP-1 RAs in the Indian healthcare system

This section briefly reiterates why we should reposition GLP-1 RAs in the Indian context and how this could benefit the T2DM population.

Unlike other countries, the Indian healthcare system has the flexibility for the patient to approach a physician at any tier, from primary to tertiary. This offers the opportunity of bringing the best medication early in the therapy, mitigating or slowing down the complications associated with T2DM, and making way for shared decision-making. This approach could benefit both patients and HCPs who can work together toward better management practices.

Table 7. Overview of the PIONEER 1–10 Clinical Trials on Orally Administered Semaglutide

Name	Comparator	Study design	Key Outcomes	Conclusions
PIONEER 1	Placebo	26-week, randomized, double-blind, placebo-controlled, parallel-group, phase 3a trial	• Significant HbA1c reduction for all doses between 0.6% and 1.1% • Greater weight reduction with 14 mg dose (3.4 vs. 1.8 kg)	• Oral semaglutide monotherapy provided superior and clinically relevant improvements in HbA1c (all doses) and body weight loss (14 mg dose) to that of placebo
PIONEER 2	Empagliflozin 25 mg	52-week, randomized, open-labeled, active comparator, parallel-group trial, phase 3a trial	• Signification reduction in HbA1c at week 26 (1.4% vs. 0.9%) and week 52 (1.3% vs. 0.8%) • Significant weight reduction at week 52 (4.7 vs. 3.8 kg)	• Oral semaglutide showed a significant reduction in HbA1c but not in body weight at week 26. A significant reduction in both HbA1c and body weight were observed at week 52 with that of empagliflozin
PIONEER 3	Sitagliptin 100 mg	26-week, randomized, double-blind, double-dummy, parallel-group, phase 3a trial	• Significantly improved HbA1c reduction and body weight with oral semaglutide 7 mg (0.2% HbA1c and −1.6 kg weight) and 14 mg (0.5% HbA1c and −2.5 kg weight) vs. sitagliptin 100 mg (0.8% HbA1c and −0.6 kg weight)	• Oral semaglutide (7 mg and 14 mg/day) demonstrated significantly greater reduction in HbA1c vs. sitagliptin
PIONEER 4	Liraglutide 1.8 mg	52-week, randomized, double-blind, double-dummy, phase 3a trial	• Semaglutide and liraglutide showed average HbA1c reductions (1.2% and 1.1%) similar to each other and better than that of placebo • Semaglutide provided significantly greater weight loss than liraglutide (4.4 vs. 3.1 kg)	• Oral semaglutide showed noninferiority to subcutaneously administered liraglutide and superiority to placebo in reducing HbA1c and was significantly superior in reducing body weight vs. both liraglutide and placebo
PIONEER 5	Placebo	26-week, randomized, double-blind, phase 3a trial aiming to investigate the efficacy and safety of orally administered semaglutide in patients with type 2 diabetes and moderate renal impairment	• Oral semaglutide (dose-escalated to 14 mg/day) was linked with an avg. HbA1c reduction, 1.0% vs. 0.2% with placebo • Significant weight reduction of 3.4 vs. 0.9 kg	• Oral semaglutide was safe and effective in patients with diabetes with moderate renal impairment
PIONEER 6	Placebo	26 weeks, CVOT, event-driven, randomized, double-blind, placebo-controlled, phase 3a trial including patients at high CV risk, the median time in the trial was 15.9 months	• Oral semaglutide was associated with a reduction compared with placebo in both HbA1c (−1.0% vs. −0.3%, respectively) and body weight (−4.2 vs. −0.8 kg, respectively)	• The noninferior cardiovascular risk profile of oral semaglutide to that of placebo observed
PIONEER 7	Sitagliptin 100 mg	52-week, multicenter, randomized, open-label, phase 3a trial	• Oral semaglutide provided a significant reduction in HbA1c of 1.3% vs. 0.8% with sitagliptin • Significant weight reduction of 2.6 vs. 0.7 kg with sitagliptin	• Oral semaglutide with flexible dose adjustment, based on efficacy and tolerability, provided significant glycemic control and weight loss vs. sitagliptin

Table 7. Overview of the PIONEER 1–10 Clinical Trials on Orally Administered Semaglutide

Name	Comparator	Study design	Key Outcomes	Conclusions
PIONEER 8	Placebo	52-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 trial	• Oral semaglutide, 3, 7, and 14 mg/day doses, achieved average HbA1c reductions of 0.6%, 1.0%, and 1.4%, respectively, vs. 0% for placebo • Avg. body weight reductions were 1.3, 3.0, and 4.1 vs. 0.4 kg	• The superiority of oral semaglutide to placebo in reducing HbA1c and body weight when added to insulin with or without metformin
PIONEER 9	Liraglutide 0.9 mg	Multicenter, 52-week, randomized, controlled, phase 2/3a trial	• HbA1c reductions at week 26 ranged from 1.1% to 1.7% (all significant) with 3, 7, and 14 mg/day oral semaglutide vs. placebo (−0.1%) and liraglutide (−1.4%) • Weight reduction was −2.8 kg with oral semaglutide 14 mg vs. 0.4 kg with 0.9 mg of liraglutide	• Oral semaglutide provides significant HbA1c reductions as compared to placebo in a dose-dependent manner in Japanese patients with type 2 diabetes
PIONEER 10	Dulaglutide 0.75 mg	52-week, open-label, randomized, active-controlled, phase 3a trial	• Oral semaglutide (14 mg dose) produced significant HbA1c reduction of 1.7% vs. dulaglutide (−1.4%) at a dose of 0.75 mg • Estimated treatment difference of −2.6 kg for orally administered semaglutide 14 mg vs. dulaglutide 0.75 mg (1.0 kg)	• Significant reduction in HbA1c (14 mg dose) and body weight (7 mg and 14 mg doses) by oral semaglutide to that of dulaglutide 0·75 mg seen

CV — cardiovascular; CVOT — cardiovascular outcomes; HbA1c — glycated hemoglobin

Oral semaglutide as the first-line therapy for T2DM: relevance from the Asian Indian patient perspective

This section outlines the novel and first of its kind oral GLP-1 RA that offers several benefits over other antidiabetic drugs and how this could be integrated with the current treatment algorithm for managing patients with T2DM.

Barriers to s.c. GLP-1 RA therapy in patients with T2DM include the perceived difficulty of use and fear of its method of administration. As described previously, this perception often affects medication compliance and adherence. Oral GLP-1 RAs have been a novel addition to the growing class of antidiabetic treatment options in T2DM. The most recently approved oral GLP-1 RA, semaglutide, has shown glycemic and CV benefits without weight gain and enhances adherence in patients with T2DM, making them an attractive option for primary-care physicians. Oral semaglutide has been approved for use by the FDA, EMA, Health Canada, Australia, Switzerland, and Japan to improve glycemic control in adults with T2DM as an adjunct to diet and exercise. It is available as a 3 mg initiation dose and 7/14 mg maintenance dose. The absorption enhancer sodium N-(8-[hydroxybenzoyl] amino) caprylate increases GLP-1 RAs' absorption in the stomach by protecting its degradation [87].

The risk–benefit profile of oral semaglutide has been observed in the Phase III PIONEER trials (PIONEER 1–10) that evaluated the efficacy, safety, and tolerability of oral semaglutide o.d. in 9,543 patients with T2DM, of whom 5,707 received oral semaglutide (Tab. 7) [59, 64, 88–95]. The trials have established the efficacy and safety of oral semaglutide in patients with T2DM. From a cost-effectiveness perspective, oral semaglutide is possibly more cost-effective than most GLP-1 RAs in the US market [96]. For the UK market, oral semaglutide 14 mg was more cost-effective compared

with sitagliptin 100 mg and empagliflozin 25 mg and superior as compared to liraglutide 1.8 mg daily dose for T2DM. The cost-effectiveness ratio per QALY was reported as GBP 11,006 versus empagliflozin and GBP 4,930 versus sitagliptin [97]. Using a microsimulation model based primarily on the UK Prospective Diabetes Study Outcomes Model 2 equations, the lifetime cost-effectiveness of oral semaglutide added to the current antihyperglycemic treatment for T2DM in the US showed that oral semaglutide was more cost-effective compared with liraglutide and had incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY versus sitagliptin and background therapy alone. However, these thresholds were not met versus empagliflozin [98]. On the basis of the PIONEER clinical trials 2, 3, and 4, the long-term cost-effectiveness of novel oral semaglutide versus empagliflozin, sitagliptin, and injectable liraglutide showed that oral semaglutide 14 mg was considered more cost-effective compared with empagliflozin 25 mg and sitagliptin 100 mg and superior as compared with liraglutide 1.8 mg for the treatment of T2DM in the Netherlands [99]. Overall, other real-world studies are needed to further elucidate the potential cost-effectiveness of oral semaglutide from a cost–benefit perspective, especially in developing countries, including India.

On the basis of the established drug's benefits, GLP-1 RA could emerge as the first-line therapy for T2DM associated with obesity and ASCVD [12]. From an acceptability perspective, as part of the international treatment recommendation guidelines for the management of T2DM, a practical algorithm has been developed for primary-care physicians who are considering prescribing oral semaglutide aligned with global recommendations (Fig. 6) [100]. Oral medication, on the other hand, has few drawbacks. Oral semaglutide must be taken on an empty stomach with only 4 ounces of water and no food, drink, or medication for at least 30 minutes afterward. The pills cannot be broken or crushed in any way. If not taken correctly, the absorption will be poor, and the benefits will be lost. It's critical to provide instruction and counseling on how to take this drug, and it's not always possible for people to take it and then wait 30 minutes before taking any other medications.

Panel recommendations

- Oral semaglutide provides an attractive option for Indian physicians, subject to overall awareness and acceptance of the drug, its use, and its benefits in T2DM patients.
- The affordability of oral semaglutide, in alignment with global findings, will be critical in its usage. The physician's perspective, increased patient awareness, and patient preference will play a key role in its use.
- Because patients on oral medications are known to have better adherence and persistence than those on injectable therapies, oral semaglutide may bridge this unmet need related to medication adherence in India by allowing patients to benefit from its multitargeted mode of action.

Conclusions/Overall recommendations

Considering the rapid research advances and progress in managing patients with T2DM, there has been a shift in its treatment strategy and approach from a predominantly gluco-centric approach to a vasculo-gluco-centric one. The following recommendations are considered pertinent based on the GLP-1 RA profiles and evidence to support the effective management of patients with T2DM.

- Recent diabetes guidelines and recommendations have moved toward a more individualized and CV risk-focused approach for managing patients with T2DM.
- ADA/EASD, ACC/AHA, and ESC recommend GLP-1 RAs or SGLT2is for patients with a high CV risk or established ASCVD, CKD, or HF independent of baseline HbA1c.
- There is a shift in focus from initiating treatment with metformin to the use of GLP-1 RAs and SGLT2is. Guidelines recommend GLP-1 RAs with proven CV benefits if ASCVD predominates, whereas ESC recommends GLP-1 RAs as first-line therapy in drug-naïve patients.
- GLP-1 RAs are the ideal cardio-metabolic drugs addressing multiple facets of the disease.
- The current opinion and alignment among HCPs, primary-care physicians, and experts are to bring up GLP-1 RAs as a treatment option early during patient conversations.
- When should GLP-1 RAs with proven CVD benefit be initiated in T2DM patients with a high CV risk or established ASCVD, CKD, or HF?
  - **Independently of HbA1c:**
    - Patients with a high CV risk or established ASCVD, CKD, or HF, especially, if ASCVD predominates;
    - Upon diagnosis of clinical ASCVD;
    - Upon diagnosis of clinical ASCVD or having high risk for CV in a patient with T2DM;
    - Upon discharge after admission for an ASCVD or diabetes-related clinical event.
- In T2DM patients without increased risk for clinical ASCVD, CKD or HF, when should GLP-1 RAs be initiated?

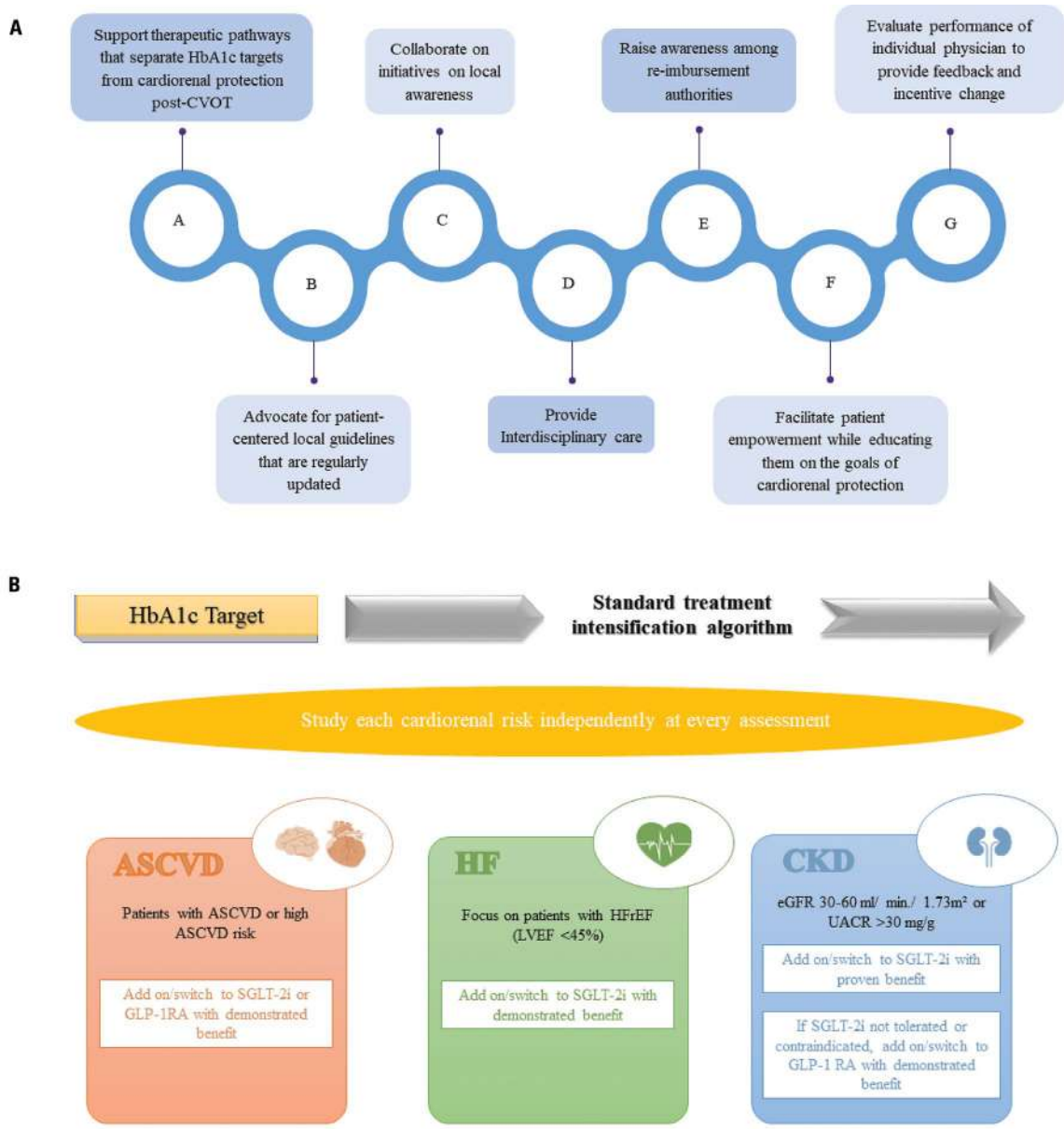

Figure 6. The Clinical Inertia Crisis: (A) Change Manifesto and (B) Rethinking Treatment Algorithm
Adapted from *Schernthaner G, Shehadeh N, Ametov AS, et al. Worldwide inertia to the use of cardiorenal protective glucose-lowering drugs (SGLT2i and GLP-1 RA) in high-risk patients with type 2 diabetes. Cardiovasc Diabetol. 2020;19:185*. The figure was adapted from the primary source article under the Creative Commons Attribution 4.0 International License http://creativecommons.org/licenses/by/4.0/.
ASCVD — atherosclerotic cardiovascular disease; CKD — chronic kidney disease; CVOT — cardiovascular outcomes trial; eGFR — estimated glomerular filtration rate; HbA1c — glycated hemoglobin; HF — heart failure; HfrEF — heart failure with reduced ejection fraction; GLP-1 RA — glucagon-like peptide-1 receptor agonist; LVEF — left ventricular ejection fraction; SGLT2i — sodium–glucose cotransporter-2 inhibitors; UACR — urine albumin-to-creatinine ratio

- When HbA1c is above the individualized HbA1c target and:
  - An urgent need gain or promote weight loss;
  - Intensifying to injectable therapy or strengthening basal insulin therapy.
  - Oral semaglutide offers a practical option for managing patients with T2DM in the primary care setting by allowing for treatment intensification and an individualized approach to treatment. The current opinion suggests including oral semaglutide as a part of international treatment recommendation guidelines for better understanding and adaptability among patients and HCPs.

- Dialogues between patients and physicians will play a significant role in including GLP-1 RAs early in the treatment paradigm and closer to disease diagnosis, resulting in the effective management of patients with T2DM.

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Conflict of interest

None declared.

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