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REVIEW

Consensus Recommendations on GLP-1 RA Use in the Management of Type 2 Diabetes Mellitus: South Asian Task Force

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ABSTRACT

The advent of incretin mimetics such as glucagon-like peptide-1 receptor agonists (GLP-1 RAs) has enriched the armamentarium for diabetes management owing to their glycaemic as well as extra-glycaemic benefits. The approval status and availability of this class of drugs vary widely across the globe. Being a relatively newer class of drug with numerous benefits, several national and international guidelines are working towards addressing clinical questions pertaining to the optimal use of GLP-1 RAs for the management of diabetes. Although the newer class of drugs are associated with significant benefits such as patient-centric approach, these drugs demand the providers to be vigilant and knowledgeable about the medication. The South Asian population is at higher risk of type 2 diabetes mellitus (T2DM) because of their genetic predisposition and lifestyle changes. Hence, prevention and management of T2DM and its associated complications in this population are of paramount importance. The current report aims to present an overview of

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current knowledge on GLP-1 RAs based on pragmatic review of the available clinical evidence. In addition, this report is a consensus of expert endocrinologists representing South Asian countries including India, Pakistan, Bangladesh, Nepal, Sri Lanka, Afghanistan and the Maldives on essential recommendations related to the use of GLP-1 RAs in a real-world scenario.

Keywords: Calorie restriction mimetics; Calorie restriction facilitators; Consensus; GLP-1 RA; Incretin-based therapies; Type 2 diabetes mellitus

EXECUTIVE SUMMARY

The current report is an overview of current knowledge on glucagon-like peptide-1 receptor agonists (GLP-1 RAs) based on pragmatic review of the available clinical evidence on use of GLP-1 RAs in the management of type 2 diabetes mellitus (T2DM). This report is also a consensus of an expert panel of endocrinologists representing South Asian countries on essential recommendations related to the use of GLP-1 RAs which may aid in rational, smart and safe prescription of GLP-1 RAs in a real-world scenario.

The current report discusses the mechanism of action, classification, pharmacokinetic and pharmacodynamic properties of various GLP-1 RAs. Further, an overview of the prescribing information and recommendations on GLP-1 RA use in T2DM management from diabetic associations across the world is presented.

Clinical evidence (based on the literature) on GLP-1 RAs licensed in South Asia or under regulatory approval in one or more South Asian countries is presented and based on prescription pattern and the geography of the reported patient group. In an evidence-based approach, the key points contributing to this consensus with respect to the clinical impact and benefits of GLP-1 RAs and their use in special populations are as follows:

Clinical impact of GLP-1 RAs:

- GLP-1 RAs improve glucose homeostasis by enhancing glucose-dependent insulin secretion, by suppressing inappropriately elevated glucagon levels, both in fasting and postprandial states (Grade A; Evidence Level [EL] 1).
- GLP-1 RAs are associated with weight loss benefits which might be due to suppressed appetite, reduced body fat or improved endothelial function (Grade A; EL 1).
- GLP-1 RAs are known to have a beneficial effect on lipid profile and blood pressure (BP). In addition, GLP-1 RAs have demonstrated cardioprotective effects in patients with T2DM (Grade A; EL 1).
- GLP-1 RAs are known to have both direct and indirect renoprotective effects and are also associated with hepatic health benefits (Grade A; EL 1).

GLP-1 RA use in complicated diabetes:

- There is no clear evidence regarding the use of GLP-1 RA in acute myocardial infarction, although the use of these agents is encouraged in patients with asymptomatic and

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stable coronary artery disease (CAD). The use of GLP-1 analogues in such cases could be a pragmatic approach based on prescribing information, available clinical evidence and clinical sense of physicians (Grade D; EL 4)

- Exenatide and lixisenatide are predominantly cleared by the kidney. Exenatide dosage is not recommended to be increased in patients with an estimated glomerular filtration rate (eGFR) of 30–60 mL/min/1.73 m^2. Both exenatide and lixisenatide are contraindicated in patients with eGFR < 30 mL/min/1.73 m^2. Although clearance of liraglutide and dulaglutide is predominantly hepatic, administration of these drugs in patients with renal impairment needs to be considered with caution because of gastrointestinal side effects (Grade D; EL 4).
- There is limited information available on the safety and efficacy of GLP-1 RAs in patients with hepatic impairment. The prescribing information advises cautious use in this patient population (Grade D; EL 4).

GLP-1 RA use in special situations:

- GLP-1 RAs are known to have low risk of hypoglycaemia and offer least glycaemic variability which is suitable for the elderly population (Grade B; EL 2).
- GLP-1 RAs do not require dose adjustments during fasting including the period of Ramadan; however, dose adjustments for concomitant medications such as insulin may be required (Grade D; EL 4).
- GLP-1 RAs have expanded the treatment option for polycystic ovary syndrome owing to their ability to influence both body weight and glycaemic control (Grade A; EL 1).
- There is limited data on the use GLP-1 RAs in pregnant and lactating women (Grade D; EL 4).

Based on the experience, judgement and consensus of the expert panel of endocrinologists, essential information on GLP-1 RA therapy for healthcare practitioners in the form of checklists has been presented. The checklists include patient selection and rationale for GLP-1 RA therapy initiation, factors influencing selection of appropriate GLP-1 RA, selection of appropriate GLP-1 RA and monitoring checklist specific for GLP-1 RA-based therapy. Cost implications, barriers to GLP-1 RA therapy and measures to mitigate the barriers have also been discussed.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is the most common type of diabetes, accounting for approximately 90% of all cases worldwide. The global prevalence of diabetes was estimated to be 8.8% (as of 2017) and is foreseen to rise to 9.9% by 2045 [1]. Among the ethnic groups, people of South Asian ancestry are four times more susceptible to T2DM compared to Europeans owing to their genetic predisposition [2]. In addition, lifestyle changes including those associated with urbanisation and migration play a major role in the rapid rise of diabetes in South Asia [3]. Notably, India and Pakistan are listed among the top 10 countries worldwide for the number of adults (age group 20–79 years) with diabetes [1]. The prevalence of diabetes and the mortality and expenditure associated with it in South Asia (as of 2017) are presented by country in Table 1.

Obesity is identified as a major risk factor leading to diabetes, hypertension, dyslipidaemia, coronary heart disease and many types of cancers [5]. The mean prevalence of obesity in South Asia rose to 28.85% in 2013 from 23.62% in 1990, drawing attention to the seriousness of this growing public health issue [6]. The thin-fat Indian concept or Asian Indian phenotype is characterised by less generalised obesity measured by body mass index (BMI) and greater central obesity associated with waist circumference and waist–hip ratio [7–9]. Higher prevalence of central obesity among South Asians is also considered to be an important risk factor for T2DM, metabolic syndrome (MetS) and cardiovascular disease (CVD) [10, 11]. Nutritional transition, urbanisation, physical inactivity, socio-economic factors, cultural factors and genetics are currently the determinants of obesity and dyslipidaemia in South Asians [10].

Table 1 Prevalence, mortality and expenditure associated with diabetes burden in South Asian countries. Adapted from IDF Diabetes Atlas, 8th Edition [4]

Country	Total adult population[a]	Diabetes cases[a]	Ratio[a,b]	Undiagnosed diabetes cases[a]	Diabetes national prevalence[a] (%)	Diabetes age-adjusted comparative prevalence[a] (%)	Diabetes-related death[a]	Cost per person with diabetes (USD)
Afghanistan	17,150,814	1,054,460	1:16	733,870	6.1	9.2	20,960	114.67
Bangladesh	108,274,040	7,349,526	1:15	4,115,734	6.8	8.3	108,530	50.94
India	892,039,240	74,047,266	1:12	42,847,334	8.3	9.8	1,123,804	120.07
Maldives	254,702	18,996	1:13	10,319	7.5	8.9	128	1939.74
Nepal	18,141,114	679,207	1:27	549,934	3.7	7.1	13,431	74.18
Pakistan	116,776,556	7,656,317	1:15	4,706,338	6.6	8.0	89,285	63.23
Sri Lanka	14,922,252	1,248,310	1:12	446,645	8.4	10.3	17,747	189.63

[a] Age group 18–99 years
[b] Total number of diabetes cases: total adult population

The term diabesity, first coined in 1970, has been used to describe the strong association between diabetes and obesity when they co-exist in an individual [12, 13]. At least 80–90% of T2DM patients are reported to be obese [14, 15]. Diabesity is expected to be one of the biggest epidemics in human history. Intriguingly, there are no guidelines from associations worldwide for the optimal management of diabesity to date [12, 16].

The therapeutic armamentarium for management of T2DM ranges from the conventional oral antidiabetic (OAD) medications and insulin therapy along with lifestyle modifications to the newer class of drugs including glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose co-transporter-2 (SGLT2) inhibitors. SGLT2 inhibitors are a class of OADs that function by reducing renal tubular glucose reabsorption, thereby reducing blood glucose without stimulating insulin release [17].

GLP-1 RAs are a class of injectable drugs used for the management of T2DM. Currently, few drugs in this class are approved globally, and the rest are at various stages of approval. GLP-1 RAs aid in glycaemic control through multiple mechanisms. In a glucose-dependent mechanism, GLP-1 RAs stimulate insulin secretion and suppress inappropriately elevated glucagon levels. These drugs are known to delay gastric emptying and promote satiety and are associated with a reduced risk of hypoglycaemia [18–21]. Accordingly, GLP-1 RAs can be considered as calorie restriction mimetics or calorie restriction facilitators. Furthermore, these drugs aid in modest weight loss unlike the weight gain typically observed with some of the antidiabetic medications and are being explored for their potential to address all components of MetS including obesity, hypertension, dyslipidaemia, polycystic ovary syndrome (PCOS) and fatty liver [22–24].

Diabetes associations across the globe have been formulating and updating guidelines on GLP-1 RAs in T2DM management to optimise and provide targeted treatment for the effective use of this class of agents. As there remains a gap in guidance towards GLP-1 RA therapy in the South Asian region, this report attempts to address any issues or specific guidance to real-world healthcare practitioners (HCPs) in order to manage T2DM using GLP-1 RAs in this geography.

The objective of this report is to develop a consensus for the use of GLP-1 RAs in the management of T2DM in the South Asian population based on a pragmatic review of clinical evidence and insights from experts representing

India, Pakistan, Bangladesh, Nepal, Sri Lanka, Afghanistan and the Maldives. In addition, this report provides an objective snapshot of consensus practices for HCPs among the participating countries regarding the characteristics of ideal GLP-1 RA candidates, timing of therapy initiation, parameters to be monitored during therapy, use in special populations, cost implications, management of adverse events (AEs) and strategies to combat multidimensional barriers to support adherence to GLP-1 RA therapy.

Current Approval Status of GLP-1 RAs in South Asia

The approval status of GLP-1 RAs in the participating South Asian countries is presented in Table 2. Other GLP-1 RAs, namely albiglutide QW, exenatide QW and semaglutide QW, approved by the US Food and Drug Association (USFDA), are currently not available in the South Asian market and are in approval stages in South Asia. However, none of the GLP-1 RAs have been listed in the national list of essential medicines in any of the South Asian countries to date.

METHODOLOGY

This report is based on a review of published guidelines and clinical evidence from meta-analyses, systematic reviews, randomised controlled trials, prospective and retrospective studies, and real-world data on GLP-1 RA use in the management of T2DM. Conference abstracts were not included for this report. The consensus was developed in accordance with the American Association of Clinical Endocrinologists' protocol [25]. Recommendations were based on clinical importance coupled with four intuitive levels of evidence as presented in Table 3. In case of little or no evidence, the panel relied on logical empiricism, judgement and consensus to make the recommendations. The panellists of the consensus were endocrinologists representing South Asian countries including India, Pakistan, Bangladesh, Nepal, Sri Lanka, Afghanistan and the Maldives. This report was developed following a preliminary consensus meeting held in New Delhi, India on 2 June 2018, followed by another meeting held in Colombo, Sri Lanka, on 1 September 2018. These meetings were sponsored by Eli Lilly, India, and were organized under the auspices of the steering committee. The sponsor had no formal voting during the consensus, and had no influence on the development of consensus statements or this manuscript.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

RATIONALE

The incretin system or incretin hormones principally include glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which are released by the gut endocrine cells in response to meal intake [26].

Table 2 Current approval status of GLP-1 RAs in South Asia

GLP-1 RA	Approval in participating countries						
	Afghanistan	Bangladesh	India	Maldives	Nepal	Pakistan	Sri Lanka
Dulaglutide (QW)		✔	✔			✔	
Exenatide (BID)			✔			✔	
Liraglutide (QD)		✔	✔		✔	✔	✔
Lixisenatide (QD)			✔				

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

Table 3 Evidence and recommendation grading according to the American Association of Clinical Endocrinologists' guidelines

Evidence level	Semantic descriptor (reference methodology)	Grades	Recommendation
1	Meta-analyses of RCTs, RCTs	A	Strong
2	Meta-analyses of non-randomised prospective or case-controlled trials, non-RCT, prospective cohort study, retrospective case-control study	B	Intermediate
3	Cross-sectional study, surveillance study (registries, surveys, epidemiologic study, retrospective chart review, mathematical modelling of database), consecutive case series, single case reports	C	Weak
4	No evidence (theory, opinion, consensus, review or preclinical study)	D	No evidence

RCTs randomised controlled trials

GLP-1 lowers blood glucose through stimulation of insulin secretion (and production) and suppression of glucagon secretion in a glucose-dependent manner [22]. GLP-1 is a pluripotent incretin hormone in humans which exerts multiple physiological actions, and the main targets of GLP-1 and its actions are depicted in Fig. 1 [27].

The incretin hormones may be responsible for up to 70% of postprandial insulin secretion. Their effects are progressively amplified from the beginning of a meal in response to increase in plasma glucose concentrations. The incretin effect is severely reduced or absent in patients with T2DM. Impaired incretin effect in T2DM could be due to impaired incretin hormone secretion (incretin hormone deficiency) and/or defective insulinotropic action of the incretin hormones (incretin hormone resistance). Despite controversies in the literature, the data indicate the impaired incretin effect in patients with T2DM to be associated with defective insulin secretory effects of GIP and GLP-1 as opposed to defective secretion of the incretin hormones [28]. In the case of GLP-1, their secretion in patients with T2DM is impaired; however, the insulinotropic and glucagon-suppressive actions are preserved. This forms the rationale for incretin-based therapy in T2DM [26].

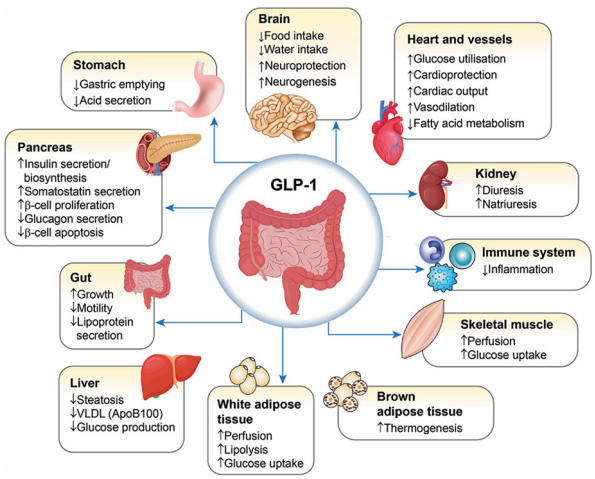

Fig. 1 GLP-1 target organs and its action. *GLP-1* glucagon-like peptide-1, *VLDL* very low density lipoprotein

Interestingly, the point of action of GLP-1 RAs extends beyond β-cells, and these agents effectively act on the cells of the islets of Langerhans as a whole to bring in equilibrium in both pre-diabetic and diabetic conditions as illustrated in an islet-centric fulcrum (Fig. 2).

Exogenous GLP-1 administration may restore blood glucose regulation to near normal levels in patients with T2DM whose incretin effect is reduced [26]. GLP-1 RAs or incretin mimetics are agonists of the GLP-1 receptors. GLP-1 RAs possess pleiotropic effects similar to endogenous GLP-1 [29, 30].

MECHANISM OF ACTION OF GLP-1

GLP-1 elicits protracted glucose-lowering in a glucose-dependent manner owing to its

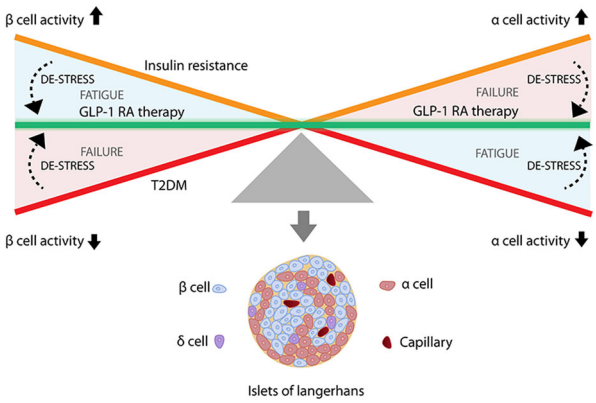

Fig. 2 Islet-centric fulcrum for GLP-1 RA-based therapy. *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *T2DM* type 2 diabetes mellitus

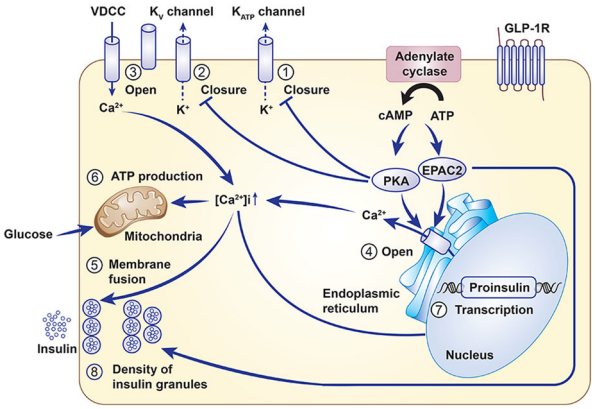

Fig. 3 Molecular mechanisms underlying insulinotropic effects of GLP-1. Binding of GLP-1 to GLP-1 receptors leads to the activation of adenylate cyclase and elevation of intracellular cAMP levels. Increased cAMP levels subsequently activate PKA and the cAMP-regulated guanine nucleotide exchange factor II (cAMP-GEFII, also known as Epac2). Activation of PKA leads to the closure of K_{ATP} channels, thereby facilitating membrane depolarisation (1). PKA activation also leads to the inhibition of delayed rectifying K^+ (K_v) channels, which is a negative regulator of insulin secretion in pancreatic β-cells, thus resulting in prolongation of action potentials (2). Depolarisation results in the opening of voltage-gated Ca^{2+} channels, leading to an increase in intracellular Ca^{2+} concentrations (3). Increased intracellular Ca^{2+} concentrations mobilise Ca^{2+} from intracellular stores through PKA- and Epac2-dependent mechanisms (4). The increased Ca^{2+} concentration leads to the events as follows: insulin-containing granules fuse with the plasma membrane and insulin is secreted from β-cells (5); Ca^{2+}-induced Ca^{2+} mobilisation from intracellular stores stimulates ATP synthesis in mitochondria which further enhances membrane depolarisation through K_{ATP} channel closure (6); Transcription of the proinsulin gene is promoted (7); Activation of EPAC2 also increases the density of insulin-containing granules near the plasma membrane to potentiate insulin secretion from β-cells (8). *cAMP* cyclic adenosine monophosphate, *GLP-1* glucagon-like peptide-1, *PKA* protein kinase A

insulinotropic mechanism of action in pancreatic β-cells. In contrast, its non-insulinotropic action is marked by extra-pancreatic effects which might be beneficial for the prevention and treatment of diabetes-related complications and comorbidities presented independently of glycaemic control.

Insulinotropic Mechanism of Action

The insulinotropic activity of GLP-1 is (at least) partly exerted through interaction with the GLP-1 receptors located on the cell membrane of the β-cells. Figure 3 depicts the molecular mechanisms underlying the insulinotropic effects of GLP-1 along with a brief summary of the mechanism of action [31, 32].

Non-Insulinotropic Actions of GLP-1

Suppression of glucagon expression by GLP-1 is considered to be clinically important as GLP-1 loses its inhibitory effect on glucagon secretion at hypoglycaemic levels. However, there is uncertainty around the mechanism whereby this occurs [33, 34]. GLP-1 inhibits meal-induced acid secretions, gastric emptying, gastrointestinal (GI) motility and pancreatic secretions. The effects of GLP-1 on gastric functions are mediated through vagal pathways [31, 35].

GLP-1 influences feeding behaviour and body weight both through direct (by entering the brain via the systemic circulation and by crossing the blood–brain barrier) and indirect pathways (via neural afferents) which are largely mediated by the central nervous system. Evidence from preclinical data demonstrates that central GLP-1 induces satiety by affecting

both homeostatic and reward-associated food intake, and such effects seem to be mediated by the GLP-1 receptor [36].

GLP-1 aids in β-cell proliferation and survival. An increase in β-cell mass and decrease in apoptotic β-cells were demonstrated in several animal studies [37, 38]

CLASSIFICATION OF GLP-1 RAS

On the basis of the duration of action, GLP-1 RAs can be classified as short-acting, intermediate-acting, long-acting and continuous-acting GLP-1 RAs (Table 4). The differences between short-acting and long-acting GLP-1 RAs in terms of their effectiveness on several physiological parameters are presented in Table 5 [39].

Short-Acting GLP-1 RAs

Short-acting GLP-1 RAs provide short-lived GLP-1 receptor activation. Although resistant to dipeptidyl peptidase-4 (DPP4), GLP-1 RAs have a plasma half-life of about 2–4 h and are eliminated through the renal system. Short-acting GLP-1 RAs primarily lower postprandial blood glucose (PPBG) levels through delayed gastric emptying because of which the rate of glucose entry into the duodenum and subsequently into the circulation is delayed [22, 39].

Table 4 Classification of GLP-1 RAs

Classification	Compound	Half-life
Short-acting	Exenatide	< 12 h
	Lixisenatide	
Intermediate-acting	Liraglutide	12–24 h
Long-acting	Exenatide LAR	> 24 h to 1 month
	Albiglutide	
	Semaglutide	
Continuous-acting	ITCA 650[a]	> 1 month

GLP-1 RA glucagon-like peptide-1 receptor agonist, *LAR* long-acting release

[a] ITCA 650 is an investigational drug

Intermediate-Acting GLP-1 RAs

The intermediate-acting GLP-1 RAs liraglutide is an acylated GLP-1 RA that exhibits a prolonged half-life of 13 h. Liraglutide is endogenously metabolised in a similar manner to large proteins without a specific organ as a major route of elimination [40].

Long-Acting GLP-1 RAs

Long-acting GLP-1 RAs keep activating the GLP-1 receptors continuously at the recommended doses. Long-acting GLP-1 RAs lower blood glucose primarily by stimulating insulin secretion and reducing glucagon levels. Greater reductions in plasma glycated haemoglobin (HbA1c) are observed with long-acting GLP-1 RAs compared to short-acting GLP-1 RAs due to their consistently high plasma levels. The reduction in body weight with long-acting GLP-1 RAs is comparable to those with short-acting GLP-1 RAs [39].

Continuous-Acting GLP-1 RA (Implantable GLP-1 RAs)

A miniature implantable GLP-1 RA, ITCA 650, is hereby classified as a continuous-acting GLP-1 RA. ITCA-650, with an osmotic pump system, delivers zero-order continuous subcutaneous exenatide at a precise, pre-set rate for up to 12 months. Although an invasive therapy, ITCA 650 is advantageous in terms of injection frequency and effort needed from the patient. However, uncertainty about the usefulness of the therapy during illness, fasting or sudden change in the renal/hepatic parameters is considered one of the limitations [41].

PHARMACOKINETICS AND PHARMACODYNAMICS OF GLP-1 RAS

The GLP-1 RAs are administered weekly to twice daily according to the formulation. The pharmacokinetics and pharmacodynamics of this

Table 5 Comparison between short-acting and long-acting GLP-1 RAs

Parameters	Short-acting GLP-1 RAs	Long-acting GLP-1 RAs
Effects		
Fasting blood glucose levels	Modest reduction	Strong reduction
Postprandial hyperglycaemia	Strong reduction	Modest reduction
Fasting insulin secretion	Modest stimulation	Strong stimulation
Postprandial insulin secretion	Reduction	Modest stimulation
Glucagon secretion	Reduction	Reduction
Gastric emptying rate	Deceleration	No effect
Blood pressure	Reduction	Reduction
Heart rate	No effect or small increase (0–2 bpm)	Moderate increase (2–5 bpm)
Body weight reduction	1–5 kg	2–5 kg
Occurrence of nausea	20–50%, attenuates slowly (weeks to many months)	20–40%, attenuates quickly ($\sim$ 4–8 weeks)

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

class of drugs are presented in Tables 6 and 7, respectively.

OVERVIEW OF PRESCRIBING INFORMATION/PACKAGE INSERT OF GLP-1 RAs IN SOUTH ASIA

An overview of the prescribing information/package insert of GLP-1 RAs pertaining to all GLP-1 RAs approved in South Asia as well as the ones to be launched in the near future is provided in Table 8 with a brief summary as follows.

GLP-1 RAs including dulaglutide, exenatide BID, liraglutide, lixisenatide and semaglutide are indicated in adults with T2DM as an adjunct to diet and exercise to improve glycaemic control. Dulaglutide is even recommended as monotherapy in India. In addition to glycaemic control, liraglutide has been indicated in adults with established CVD to reduce the risk of major adverse cardiovascular events. GLP-1 RAs are contraindicated in patients with prior hypersensitivity to the respective drug or any product components, personal or family history of medullary thyroid carcinoma (MTC) or in patients with multiple endocrine neoplasia syndrome type 2 (MEN2). These GLP-1 RAs are not to be used in the treatment of type 1 diabetes mellitus or diabetes ketoacidosis. In case of suspected pancreatitis, GLP-1 RAs are to be discontinued and should not be restarted if pancreatitis is confirmed.

A detailed description on the use of GLP-1 RA in special populations and AEs common for GLP-1 RAs is given in the following sections.

OVERVIEW OF GLP-1 RA RECOMMENDATIONS FOR T2DM MANAGEMENT FROM DIABETIC ASSOCIATIONS ACROSS THE WORLD

Diabetes, a chronic and complex condition, demands continuous and individualised care with a multipronged approach. Diabetes management is comprehensive and extends beyond glycaemic control in T2DM patients, often taking into consideration other comorbidities associated with the condition [55, 56].

Guidelines for the management of diabetes intend to provide evidence-based

Table 6 Pharmacokinetics of GLP-1 RAs

Function	Parameters	Dulaglutide QW [42]	Exenatide BID [43]	Exenatide QW [44]	Liraglutide QD [45, 46]	Lixisenatide QD [47]	Semaglutide QW [48–51]
Absorption	C_{max}	114 ng/mL	211 pg/mL (10 μg)	137.3 pg/mL	35 ng/mL (0.6 mg)	56.7 pg/mL (10 μg)	10.9 nmol/L (0.5 mg)
	AUC	14,000 ng h/mL	1036 pg h/mL (10 μg)	405.6 pg h/mL	960 ng h/mL (0.6 mg)	175 pg h/mL (5 μg), 365 pg h/mL (10 μg), 503 pg h/mL (20 μg)	3123.4 nmol h/L (0.5 mg)
	Steady state	Within 2 and 4 weeks	NA	9–10 weeks	4 days	NA	4–5 weeks
Distribution	Volume of distribution	For 0.75 mg, 19.2 L. For 1.5 mg, 17.4 L	28.3 L	28.3 L	13 L, after SC administration (0.6 mg), 0.07 L/kg (after IV) (0.6 mg)	90–140 L	12.5 L
Metabolism	Metabolic pathway	General protein catabolism pathway	Glomerular filtration and proteolytic degradation	Glomerular filtration with proteolytic degradation	No specific organ as a major route of elimination. Excreted as related metabolites in urine or faeces (6% and 5%, respectively)	Presumed to be eliminated through glomerular filtration, tubular reabsorption and metabolic degradation resulting in smaller peptides reintroduced in protein metabolism	Proteolytic cleavage of the peptide backbone and sequential beta-oxidation of fatty acid side chain

Table 6 continued

Function	Parameters	Dulaglutide QW [42]	Exenatide BID [43]	Exenatide QW [44]	Liraglutide QD [45, 46]	Lixisenatide QD [47]	Semaglutide QW [48–51]
Elimination	Clearance	For 0.75 mg, 0.111 L/h. For 1.5 mg, 0.107 L/h	9.1 L/h	9.1 L/h	20–67 L/h	35 L/h	0.05 L/h
	Elimination half-life	5 days	2.4 h	Median half-life, 2 weeks (2 mg)	13 h	1.5–4.5 h	1 week

AUC area under the curve, C_{max} maximum concentration achieved before the administration of second dose, *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *NA* not available, *SC* subcutaneous

recommendations to physicians across the world for diagnosis, management and follow-up [57]. Consequently, guidelines provide a comprehensive picture and awareness to the practitioner to confront the situation effectively.

A study conducted in the USA reported that a periodic evaluation of HbA1c and lipid profile as recommended by the guidelines had resulted in a significant decrease in the rates of hospitalisation due to vascular, renal and other diabetes-related complications [58].

Table 9 summarises the key points on the recommendation of GLP-1 RAs in T2DM management from selected diabetic associations across the world.

The usefulness of GLP-1 analogues in glycaemic control with low risk of hypoglycaemia and body weight reduction has been taken into consideration in all the guidelines listed in Table 9.

All the guidelines listed in Table 9 recommend GLP-1 RAs as a part of dual or triple therapy in combination with OAD drugs with or without insulin in accordance with the respective algorithm [55, 59, 60, 62–64].

In the consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE), GLP-1 RA is recommended as monotherapy in individuals with HbA1c $< 7.5\%$. In addition, GLP-1 RA is recommended in pre-diabetic patients if glycaemia is not normalised with medications such as metformin and acarbose [59]. AACE/ACE guidelines strive for stringent HbA1c targets ($\leq 6.5\%$) compared to American Diabetes Association–European Association for the Study of Diabetes (ADA/EASD) guidelines which aim for an HbA1c target of 7% [68].

It is important to note that both ADA/EASD and AACE/ACE guidelines endorse the overall cardiovascular and pancreatic safety of incretin therapies [68].

Associations like International Diabetes Federation, Research Society for the Study of Diabetes in India and Pakistan Endocrine Society take the aspect of affordability into consideration while recommending GLP-1 RAs [62, 69].

From a South Asian perspective, countries including Bangladesh do not mention GLP-1

Table 7 Pharmacodynamics of GLP-1 RAs

GLP-1 RA	Effect on insulin secretion	Effect on glucagon secretion	Effect on GI motility	Electrophysiological effect
Dulaglutide QW [42]	Increase in 1st and 2nd phase insulin secretion	Reduces fasting glucagon concentration by 1.71 and 2.05 pmol/L	Causes a delay in gastric emptying (the delay is largest with the first dose and diminishes with subsequent doses)	Does not prolong QTc[a] interval (at supra-therapeutic doses of 4 mg and 7 mg)
Exenatide BID [43]	Increase in 1st and 2nd phase insulin secretion	Moderates glucagon secretions and lowers serum concentrations during periods of hyperglycaemia	Delays gastric emptying	Not associated with clinically meaningful prolongation of QTc interval
Exenatide QW [52]	1st and 2nd phase insulin secretion enhancement	Moderates glucagon secretion and lowers glucagon concentration during periods of hyperglycaemia	Slows gastric emptying	Not associated with prolongation of QTc
Liraglutide QD [45, 52]	1st and 2nd phase of insulin secretion enhancement	Lowers glucagon secretion. Does not impair normal glucagon response to low glucose concentrations	Delays gastric emptying	Does not produce QTc interval (up to 1.8 mg)
Lixisenatide QD [47, 53]	Resensitisation of 1st phase insulin secretion and increase in 2nd phase insulin secretion	Glucagon secretion is suppressed	Slows gastric emptying	There was no mean increase in QTc even at supra-therapeutic doses
Semaglutide QW [48]	Increase in 1st and 2nd phase insulin secretion	Lowers fasting and postprandial glucagon concentrations	Delays early postprandial gastric emptying	Does not prolong QTc interval to any clinically relevant extent (1.5 times the recommended dose)

GI gastrointestinal, *GLP-1 RA* glucagon-like peptide-1 receptor agonist

[a] QTc: in electrocardiography, the duration of the QT interval adjusted for the patient's heart rate

Table 8 Overview of the prescribing information/package insert of GLP-1 RAs in South Asia

Indications [42–45, 47, 48, 54]	Contraindications/limitations [42–45, 47, 48, 54]	Warnings and precautions [42–45, 47, 48, 54]
As an adjunct to diet and exercise in adults with T2DM. Recommended as monotherapy in a few countries (e.g. dulaglutide in India). Indicated in adults (liraglutide) with established CVD to reduce the risk of major adverse CV events	Personal or family history of MTC or in patients with MEN2. Prior serious hypersensitivity. Not to be used in T1DM or diabetic ketoacidosis. Lack of data in patients with pancreatitis	Risk of MTC. Pancreatitis—to be discontinued promptly. Hypoglycaemia— reduction of doses of concomitant medications. Renal impairment—patients reporting severe GI adverse events. Hypersensitivity. Not recommended in patients with severe GI diseases

CV cardiovascular, *CVD* cardiovascular disease, *GI* gastrointestinal, *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *MEN2* multiple endocrine neoplasia type 2, *MTC* medullary thyroid carcinoma, *T1DM* type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus

RAs in region-specific guidelines, which limits the prescription of GLP-1 RAs by HCPs in those countries.

CLINICAL EVIDENCE ON GLP-1 RAs LICENSED IN SOUTH ASIA

Efficacy and Safety of GLP-1 RAs (Clinical Trial and Real-World Evidence)

As the proposed consensus on GLP-1 RAs is based on a pragmatic review of clinical evidence and insights from experts across South Asia, pragmatic review relies on detailed and thorough analysis of clinical evidence to draw inferences. The clinical trial programme of GLP-1 RAs licensed or under regulatory approval in one or more South Asian countries is presented in Table 10. The available evidence on the efficacy with respect to glycaemic control and change in body weight and safety (nausea and vomiting) from the studies included in the respective clinical trial programme of the GLP-1 RAs along with a few others including real-world studies is presented according to the prescription pattern (monotherapy or in combination with other oral antidiabetic medications and/or insulin) and further classified on the basis of the geography of the reported patient groups as global, global including South Asia and/or South Asia specific in Supplementary Information. The evidence derived from meta-analyses, systematic reviews and pooled analyses is, however, discussed across multiple sections on clinical impact and special populations. Clinical evidence comparing the efficacy of GLP-1 RAs head-to-head and with other classes of antidiabetic agents such as SGLT2 inhibitors (SGLT2i) is exclusively covered in this section.

Several head-to-head comparative trials and retrospective studies involving GLP-1 RAs have been conducted and a few pivotal studies with key inferences are presented in Table 11.

GLP-1 RAs: CLINICAL IMPACT AND BENEFITS

GLP-1 RAs are known for their glycaemic control as well as extra-glycaemic benefits which are elaborated below.

Glycaemia

GLP-1 RAs improve glucose homeostasis by enhancing glucose-dependent insulin secretion by suppressing inappropriately elevated glucagon levels, both in fasting and postprandial states, and by delaying gastric emptying [22]. This cumulatively helps in the reduction of HbA1c levels in patients with T2DM. Changes in HbA1c levels due to GLP-1 RA administration

Table 9 Overview of recommendations from diabetes associations across the world for the use of GLP-1 RAs in T2DM management

Association/country	Top recommendations on the use of GLP-1 RAs[a]	Comments (if any)
AACE/ACE [59]	Pre-diabetes	The observational window to achieve glycaemic goal in each stage, i.e. mono-, dual and triple therapy, during progression of disease is 3 months. If the goals are unmet, the therapy should be escalated to next phase and/or insulin should be added or intensified as required[b]
	To be considered with caution along with lifestyle therapy if glycaemia is not normalised with low-risk medications such as metformin and acarbose	
	HbA1c < 7.5%	
	Recommended as monotherapy for patients with recent-onset T2DM or mild hyperglycaemia along with lifestyle therapy	
	HbA1c > 7.5%	
	Recommended in dual therapy along with metformin or another first-line agent along with lifestyle therapy	
	Recommended in triple therapy along with metformin or other first-line agent and second-line agent along with lifestyle therapy	
	HbA1c > 9%	
	For patients without symptoms[c], GLP-1 RA is recommended in dual therapy or triple therapy	
	For patients with symptoms, insulin with or without other agents is recommended along with lifestyle therapy	
ADA/EASD [60]	In dual therapy along with metformin	–
	In triple therapy along with metformin and SU, TZD or insulin	
	In combination injectable therapy with metformin and basal insulin	

Table 9 continued

Association/country	Top recommendations on the use of GLP-1 RAs[a]	Comments (if any)
Non-insulin antidiabetic pharmacotherapy in patients with established CVD: a position paper of the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy [61]	A few SGLT2i (empagliflozin and canagliflozin) and GLP-1 RAs (liraglutide and semaglutide) reduced CV events in adequately powered studies with contemporary concomitant CV treatment in patients with established CVD (mainly stable CHD with the exclusion of recent ACS) and hence may be considered as the preferred treatment choice When the aforementioned preferred treatments (with selected SGLT2i and GLP-1 RA) are not sufficient to achieve therapeutic goals or are contraindicated, agents such as thiazolidinedione-pioglitazone, GLP1 RA-exenatide and dipeptidyl peptidase inhibitors which have established neutral or potentially beneficial effects on CV events in adequately powered, contemporary trials may be preferred	Antidiabetic pharmacotherapy should be chosen on the basis of beneficial effects on CV events in phase 3 and post-marketing trials and as per EMA; improvement of glycaemic control and reduction of CV morbidity and mortality should be major goals in the treatment of T2DM
IDF [62]	In dual therapy if weight loss is a priority and if the drug is affordable In triple therapy instead of basal insulin along with 2 glucose-lowering drugs if weight loss has been insufficient	Patients should not remain longer than 3 to 6 months with HbA1c above target before adding a second glucose-lowering drug

Table 9 continued

Association/country	Top recommendations on the use of GLP-1 RAs[a]	Comments (if any)
NICE [63]	In combination with metformin and SU if triple therapy with metformin and 2 other OADs is not effective, not tolerated or contraindicated	–
	Continued only if the person with T2DM has had a beneficial metabolic response (a reduction of at least 1% in HbA1c and a weight loss of at least 3% of initial body weight in 6 months)	
	In combination with insulin, only with specialist care advice and ongoing support from a consultant-led multidisciplinary team	
RSSDI [64]	As an add-on to metformin in obese T2DM patients in addition to lifestyle changes	
	As second-line or third-line option for the management of uncontrolled hyperglycaemia	
	As second-line therapy in overweight/obese patients with metformin inadequacy and as first-line therapy in patients with metformin intolerance	
	As an add-on to insulin therapy if glycaemic goals are unmet with reasonably high doses of insulin or if unacceptable weight gain or hypoglycaemia occurs	
	GLP-1 RAs with proven CV benefit, e.g. liraglutide, should be considered to reduce the risk of major adverse CV events	
DEAN [65]	As a third-line agent to metformin (+ lifestyle modification) and SU/DPP4 inhibitor/α-glucosidase inhibitor if glycaemic target is not achieved in 2 months	

Table 9 continued

Association/country	Top recommendations on the use of GLP-1 RAs[a]	Comments (if any)
Pakistan Endocrine Society [66]	For initial fasting plasma glucose of 200–300 mg/dL GLP-1 RA is added as a third drug to metformin and OADs like SU, DPP4i and pioglitazone if glycaemic target is not achieved at 6 months with OADs (metformin, SU, DPP4i and pioglitazone) and lifestyle modifications GLP-1 RA is considered as an add-on to insulin regimen if glycaemic target is not achieved at 9 months For initial fasting plasma glucose of > 300 mg/dL GLP-1 RA is considered as a part of triple therapy with metformin and other OADs like SU/DPP4i/pioglitazone or basal insulin if glycaemic target is not achieved at 3 months GLP-1 RA is considered as an add-on to insulin regimen if glycaemic target is not achieved at 9 months	

Table 9 continued

Association/country	Top recommendations on the use of GLP-1 RAs[a]	Comments (if any)
Endocrine Society of Sri Lanka [67]	As a first-line medication if metformin is not tolerated or contraindicated As a second-line agent to lifestyle modification ± metformin if glycaemic target is not achieved in 3 months and as a third agent to lifestyle modification ± metformin and oral antidiabetics if glycaemic target is not achieved in 6 months	

AACE American Association of Clinical Endocrinologists, *ACE* American College of Endocrinology; *ACS* acute coronary syndrome, *ADA* American Diabetes Association, *CHD* coronary heart disease, *CV* cardiovascular, *CVD* cardiovascular disease, *DEAN* Diabetes and Endocrinology Association of Nepal, *DPP4i* dipeptidyl peptidase-4 inhibitor, *EASD* European Association for the Study of Diabetes, *EMA* European Medicines Agency, *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *HbA1c* glycated haemoglobin, *IDF* International Diabetes Federation, *NICE* National Institute for Health and Care Excellence, *OAD* oral antidiabetic drug, *RSSD* Research Society for the Study of Diabetes in India, *SGLT2i* sodium-glucose co-transporter-2 inhibitors, *SU* sulfonylurea, *TZD* thiazolidinediones, *T2DM* type 2 diabetes mellitus

[a] Refer to cited guidelines for detailed information

[b] Individualised goals: A1c $\leq$ 6.5% for patients without concurrent serious illness and at low hypoglycaemic risk; A1c $>$ 6.5% for patients with concurrent serious illness and at risk of hypoglycaemia progression

[c] Typical osmotic or catabolic symptoms of diabetes mellitus

Table 10 GLP-1 RAs clinical trial programme

Dulaglutide QW	Exenatide QW	Liraglutide QD	Lixisenatide QD	Semaglutide QW
Key clinical trials for GLP-1RAs (phase 3)				
AWARD-1	AMIGO trials	LEAD-1	GETGOAL-MONO	SUSTAIN-1
AWARD-2	DURATION-1[b]	LEAD-2	GETGOAL-MONO	SUSTAIN-2
AWARD-3	DURATION-2	LEAD-3	Japan	SUSTAIN-3
AWARD-4	DURATION-3	LEAD-4	GETGOAL-M	SUSTAIN-4
AWARD-5	DURATION-4	LEAD-5	GETGOAL-M-Asia	SUSTAIN-5
AWARD-6	DURATION-5[b]	LEAD-6	GETGOAL-X	SUSTAIN-7
AWARD-7	DURATION-6		GETGOAL-F1	SUSTAIN-8[a]
AWARD-8	DURATION-7		GETGOAL-S	SUSTAIN-9[a]
AWARD-9	DURATION-8		GETGOAL-P	
AWARD-10			GETGOAL-L	
AWARD-11[a]			GETGOAL-L-Asia	
			GETGOAL-Duo-1	
Cardiovascular outcome trials for GLP-1 RAs				
REWIND[a]	EXSCEL[c]	LEADER	ELIXA	SUSTAIN-6

AMIGO AC2993 diabetes management for improving glucose outcomes (exenatide, 10 μg BID), *AWARD* assessment of weekly administration of LY2189265 in diabetes (dulaglutide, 0.75 mg or 1.5 mg QW), *DURATION* diabetes therapy utilization: researching changes in A1C, weight and other factors through intervention with exenatide QW (extended-release exenatide, 2 mg, once weekly), *ELIXA* evaluation of lixisenatide in acute coronary syndrome (lixisenatide, maximum dose 20 μg per day), *EXSCEL* exenatide study of cardiovascular event lowering trial (exenatide QW, 2 mg), *GETGOAL* GLP-1 agonist AVE0010 in patients with type 2 diabetes mellitus for glycaemic control and safety evaluation (lixisenatide, 20 μg once daily), *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *LEAD* liraglutide effect and action in diabetes (liraglutide 1.2 mg or 1.8 mg daily), *LEADER* liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results (liraglutide, 1.8 mg QD), *REWIND* researching cardiovascular events with a weekly incretin in diabetes (dulaglutide, 0.75 mg or 1.5 mg QW), *SUSTAIN-6* trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes (semaglutide, 0.5 mg or 1.0 mg QW)

[a] Ongoing

[b] Includes for exenatide BID

[c] Conducted for exenatide QW

from various clinical trials are presented in Supplementary Information. Table 12 presents exclusive evidence from key meta-analyses, systematic reviews and pooled studies discussing the impact of GLP-1 RAs on glycaemia.

Body Weight and Composition

GLP-1 RA decreases gastrointestinal motility and hence increases the time for nutrient absorption. It promotes satiety and resting metabolic rate and lowers plasma concentrations of free fatty acids [97]. It is hypothesised that the weight loss benefits associated with GLP-1 RAs are likely to be due to suppressed appetite, reduced body fat and improved endothelial function [98]. Changes in body weight due to GLP-1 RA administration from various clinical trials are presented in Supplementary Information. Table 13 presents the effect of GLP-1 RAs on body weight and waist

Table 11 Head-to-head comparison of GLP-1 RAs

Study	GLP-1 RAs compared	Number of patients	Duration	Key inferences
Odawara et al. [70]. Phase 3, randomised controlled trial	Dulaglutide vs. liraglutide	Dula = 281, Lira = 141	52 weeks	Dulaglutide demonstrated better glycaemic control compared to liraglutide
Dungan et al. [71]. Phase 3, randomised, open-label parallel-group study (AWARD-6)	Dulaglutide vs. liraglutide	Dula = 299, Lira = 300	26 weeks	Dulaglutide proven non-inferior to liraglutide for least-squares mean reduction in HbA1c. Safety and tolerability profile were similar to that of liraglutide
Ghosal and Sinha [72]. Retrospective real-world observational case note study	Liraglutide vs. dulaglutide	Dula = 30, Lira = 30	13 weeks	Addition of GLP-1 RAs to metformin and SGLT2i had meaningful impact on all metabolic parameters. Larger proportion of patients achieved HbA1c < 7% with liraglutide compared to dulaglutide
Drucker et al. [73]. Randomised, non-inferiority study	Exenatide QW vs. exenatide BID	EQW = 148, ExBID = 145	30 weeks	Significantly a greater improvement in glycaemic control was demonstrated with EQW compared to ExBID. The body weight reduction was similar between the 2 groups
Blevins et al. [74]. Randomised, open-label study	Exenatide QW vs. exenatide BID	EQW = 129, ExBID = 123	24 weeks	EQW demonstrated superior glycaemic control with less nausea compared with ExBID
Sheu et al. [75]. Retrospective post hoc analysis	Exenatide BID vs. exenatide QW	ExBID: Asian, *n* = 787; White, *n* = 2223; EQW: Asian, *n* = 511; White, *n* = 1104	ExBID: 12–30 weeks, EQW: 24–30 weeks	Asian patients exhibited significantly greater reductions in HbA1c and PPBG than white patients with ExBID
Ji et al. [76]. Randomised, comparator-controlled, open-label study	Exenatide QW vs. exenatide BID	EQW = 340, ExBID = 338	26 weeks	EQW was superior to ExBID in HbA1c reduction. Weight loss was greater with ExBID

Table 11 continued

Study	GLP-1 RAs compared	Number of patients	Duration	Key inferences
Buse et al. [77]. Randomised, parallel-group, multinational, open-label trial (LEAD-6)	Liraglutide vs. exenatide BID	Lira = 233, ExBID = 231	26 weeks	Significantly greater improvement in glycaemic control was observed with liraglutide compared to ExBID
Buse et al. [78]. Open-label, randomised, parallel-group study (DURATION-6)	Exenatide QW vs. liraglutide QD	EQW = 461, Lira = 450	26 weeks	A greater reduction in HbA1c was observed with liraglutide compared to EQW
Feher et al. [79]. Real-world, observational study	Liraglutide QD vs. lixisenatide QD	Lira = 579, Lixi = 213	12 months	Treatment with liraglutide demonstrated better glycaemic control compared to lixisenatide
Nauck et al. [80]. Randomised, parallel-group, open-label trial	Liraglutide QD vs. lixisenatide QD	Lira = 202, Lixi = 202	26 weeks	Liraglutide demonstrated to be more effective in improving glycaemic control compared to lixisenatide
Stryker et al. [81]. Real-world observational study	Exenatide QW vs. liraglutide QD	EQW = 75, Lira = 75	12 months	More subjects in the EQW arm achieved an HbA1c $< 7\%$ compared to liraglutide arm; however, the baseline HbA1c was lower for the EQW arm (7.9%) compared to liraglutide arm (8.4%)
McAdam-Marx et al. [82]. Retrospective cohort study	Exenatide QW vs. liraglutide QD	EQW = 808, Lira = 4333	1 year	HbA1c and weight reductions were similar in EQW- and liraglutide-treated patients
Rosenstock et al. [83]. Randomised, open-label, active-controlled study	Lixisenatide vs. exenatide BID	Lixi = 318, ExBID = 316	24 weeks	Lixisenatide demonstrated to be non-inferior in HbA1c reduction compared to ExBID. Slightly lower mean weight loss, lower incidence of hypoglycaemia and better gastrointestinal tolerability were demonstrated with lixisenatide compared with ExBID

Table 11 continued

Study	GLP-1 RAs compared	Number of patients	Duration	Key inferences
Ahmann et al. [84]. Phase 3a, open-label, parallel-group randomised controlled trial	Semaglutide QW vs. exenatide QW	Sema = 404, EQW = 405	56 weeks	Semaglutide was superior to EQW in improving glycaemic control and reducing body weight

Refer to Supplementary Information for changes in HbA1c and body weight and information on adverse events
AWARD assessment of weekly administration of LY2189265 in diabetes (dulaglutide, 0.75 mg or 1.5 mg QW), *Dula* dulaglutide, *ExBID* exenatide BID, *EQW* exenatide QW, *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *HbA1c* glycated haemoglobin, *Lira* liraglutide, *Lixi* lixisenatide, *PPBG* postprandial blood glucose, *Sema* semaglutide, *SGLT2i* sodium-glucose co-transporter-2 inhibitor

circumference from meta-analyses, systematic reviews and pooled studies. In addition, studies comparing the treatment with GLP-1 RA, SGLT2i and bariatric surgery are also presented in Table 13.

Cardiovascular Health

GLP-1 RAs have been reported to be beneficial for cardiovascular health in patients with T2DM as these drugs aid in controlling cardiovascular (CV) risk factors such as hyperglycaemia, dyslipidaemia, weight gain and arterial hypertension (Tables 14, 15). Evidence also suggests that these drugs may have beneficial effects on endothelial function, coronary ischaemia and heart failure [117]. Several cardiovascular outcome trials (CVOTs) have been conducted or are being conducted to elucidate CV safety of GLP-1 RAs in patients. The key results from CVOTs for various GLP-1 RAs are presented in Table 16. In addition, key systematic reviews and meta-analyses involving CVOTs and other studies discussing CV outcomes with the use of GLP-1 RA are presented in Table 17.

CV protection has been demonstrated with liraglutide (The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results trial; LEADER), semaglutide (Semaglutide in Subjects with Type 2 Diabetes; SUSTAIN-6) and albiglutide (HARMONY). The effect was neutral with exenatide LAR (Exenatide Study of Cardiovascular Event Lowering Trial; EXSCEL) and lixisenatide (Evaluation of LIXisenatide in Acute coronary syndrome; ELIXA) [146]. The result of Researching cardiovascular Events with a Weekly INcretin in Diabetes (REWIND) trial, which is reported to be the longest among the CVOT trials, is due to be published in the near future and may bring about new dimensions to CV health in patients with T2DM [147, 148].

Renal Health

GLP-1 RAs have both direct and indirect renoprotective effects. GLP-1 RAs directly exert their renoprotective effects by reducing the markers involved in renal hypoxia and those involved in the activation of the renin–angiotensin system. They also aid in preventing glomerular atherosclerosis. Indirect renoprotective effects include improved glucose control, BP and weight loss. Although available evidence supports reduction of albuminuria in patients treated with GLP-1 RAs, clear evidence for its effects on renal outcomes is still lacking. This is primarily because very few patients with advanced renal disease receive GLP-1 RA as a result of its poor tolerability in this patient subset [149].

A more detailed discussion on the effects of each GLP-1 RA on renal health is presented with clinical evidence in Table 18.

Hepatic Health

GLP-1 RAs may play a role in protecting both lean and fatty livers from ischaemic injury by

Table 12 GLP-1 RAs: clinical impact and benefits on glycaemia

Study details	Aim	Highlights of GLP-1 RA therapy
Dulaglutide		
Zhang et al. [85]. Meta-analysis and systematic review of 12 RCTs with a range of study durations. Duration 12–104 weeks	To assess the clinical efficacy and safety of dulaglutide in patients with T2DM	As monotherapy: Significant reduction in HbA1c and FBG (WMD − 0.68%; 95% CI − 0.95 to − 0.40) (WMD − 0.90 mmol/L; 95% CI − 1.28 to − 0.52), respectively[a]. 17.4% more patients had HbA1c < 7% with dulaglutide. As add-on intervention with OAM and insulin: Dulaglutide lowered HbA1c (WMD − 0.51%; 95% CI − 0.68 to − 0.35)[b]
Exenatide BID		
Best et al. [86]. Systematic review and meta-analysis, including 15 retrospective or prospective observational studies of ≥ 100 patients per treatment group from n = 381,218 (overall) and n = 392,759 (treated with exenatide). Duration ∼ 3 years, 9 months	To assess the effectiveness of exenatide BID in clinical practice for T2DM patients	Significant reduction in HbA1c (− 0.4 to − 0.9%) and FBG (− 10 mg/dL). Statistically significant dosage reductions up to 22% in metformin, 66% in TZD or TZD combination therapy, 75% in SU and prandial insulin
Sheu et al. [75]. Retrospective post hoc analysis for exenatide BID 12 weeks and EQ [n = 4625]. Duration 24 weeks	To evaluate the efficacy and safety of exenatide BID 10 µg (12–30 weeks) and EQW 2 mg (24–30 weeks) in Asian versus white patients with T2DM	HbA1c, FBG, and PPBG were significantly reduced from baseline ($P < 0.0001$) for both groups. For exenatide BID, HbA1c and PPBG (for all meals) reductions were greater in Asians ($P < 0.0001$ vs. whites). For EQW, post-breakfast and post-lunch excursions were significantly greater in Asians ($P = 0.0009$ and $P = 0.0189$ vs. whites, respectively)

Table 12 continued

Study details	Aim	Highlights of GLP-1 RA therapy
Exenatide QW		
Kayaniyil et al. [87]. Network meta-analysis and systematic review of 14 RCTs [*N* = 161]. Duration 24 ± 6 weeks	To estimate the relative efficacy and tolerability of EQW versus other GLP-1 RAs for the treatment of adults with T2DM inadequately controlled on metformin	Significant HbA1c reduction relative to lixisenatide (20 μg) QD
Grimm et al. [88]. Post hoc analysis of integrated data from DURATION trials (6 randomised, comparator-controlled trials) [*N* = 1379]. Duration 24–30 weeks	To evaluate the efficacy, safety and tolerability of EQW in patients with T2DM	Significant reductions in HbA1c and FBG (− 1.4% [95% CI − 1.5 to − 1.4%] (−36 mg/dL [95% CI − 38.4 to − 33.8 mg/dL]), respectively. Significant improvements in glycaemic control and body weight. Minimal hypoglycaemia risk and good tolerability
Liraglutide		
Raskin and Mora [89]. Review of phase 3 trial including 6 randomised LEAD trials [*N* = 4456]. Duration 26–52 weeks	To assess the efficacy and safety of liraglutide in terms of glycaemic control	HbA1c reduction by 1.5% from baseline, which was significantly greater than the comparators[c] FBG and PPBG decreased from baseline (up to − 43.2 mg/dL and − 48.6 mg/dL respectively) with liraglutide (1.8 mg)
Ostawal et al. [90]. Systematic review conducted according to the NICE guidance [*N* = 7413]. Duration 3 years	To assess the real-world clinical effectiveness of liraglutide in T2DM treatment	Significant HbA1c reductions (− 0.9% to − 2.26%). One-third patients achieved HbA1c of < 7.0%. NICE composite endpoints[d] were met in 16.9% to 47.0% of patients
Lixisenatide		
Anderson et al. [91] Prospective, multinational, randomised, controlled. Duration 12–26 weeks	To evaluate the efficacy and safety profile of lixisenatide 20 μg once daily across the spectrum of patients with T2DM, including patients not treated with antidiabetic agents and those failing on oral agents, and as an adjunct to basal insulin therapy	Effectively reduced HbA1c (range − 0.7% to − 1.0%) and PPBG (range – 3.1 to − 7.96 mmol/L) across various patient types. Main efficacy feature: Ability to decrease 2-h PPBG immediately post injection

Table 12 continued

Study details	Aim	Highlights of GLP-1 RA therapy
Schmidt et al. [92]. Systematic review and meta-analysis including 14 studies (placebo and active comparators) [N = 6156]. Duration 4–76 weeks	To assess the efficacy and safety of lixisenatide for treating T2DM	Significant reduction in HbA1c (– 0.52%; 95% CI – 0.64 to – 0.39) and 2-h PPBG. (– 4.58 mmol/L; 95% CI – 5.88 to – 3.28), respectively[e] Significantly fewer symptomatic hypoglycaemic events[f]. More effective 2-h PPBG reduction with a better AE profile[g]. Improved HbA1c levels and moderately reduced body weight[e]
Semaglutide		
Shi et al. [93]. Systematic review and meta-analysis of 9 phase 3 RCTs [N = 9773]. Duration 30–104 weeks	To evaluate the clinical efficacy and safety of once-weekly semaglutide in patients with T2DM	Significant reduction in HbA1c (WMD – 0.93%, 95% CI – 1.24 to – 0.62, $P < 0.001$), FBG (WMD – 1.15 mmol/L, 95% CI – 1.67 to – 0.63, $P < 0.001$) and mean SMPG (WMD – 1.19 mmol/L, 95% CI – 1.68 to – 0.70, $P < 0.001$)[a]. Higher risk of GI disorders (RR 1.98; 95% CI 1.49–2.62; $P < 0.001$)[h]
Multiple GLP-1 analogues		
Kim et al. [94]. Systematic review and meta-analysis with 15 trials [n = 5090, (2703 in treatment groups and 2387 in control groups)]. Duration $\geq$ 12 weeks	To compare the HbA1c-lowering efficacy of GLP-1 RAs between Asian and non-Asian populations with T2DM	HbA1c reduction was reported to be 1.16% (95% CI – 1.48, – 0.85) versus – 0.83% (95% CI – 0.97, – 0.70) for Asian versus non-Asian-dominant studies, respectively. RR for target HbA1c of $\leq$ 7.0% was more inclined towards Asian-dominant studies [RR 5.7 (3.8, 8.7)] than non-Asian-dominant studies (RR 2.8 [2.4, 3.3]), respectively

Table 12 continued

Study details	Aim	Highlights of GLP-1 RA therapy
Esposito et al. [95]. Meta-analysis of 25 RCTs [*N* = 9771; GLP-1 RA treated, 5083; placebo or comparator treated, 4688). Duration 12–52 weeks	To assess the efficacy of exenatide (BID and long-acting release LAR) and liraglutide in achieving HbA1c target of < 7% in people with T2DM	Statistically significant HbA1c reduction was observed; HbA1c < 7% was achieved in 46% on exenatide, 47% on liraglutide and 63% on exenatide LAR. Higher HbA1c reduction and HbA1c goal attainment for exenatide LAR and liraglutide[i]. More hypoglycaemia cases with exenatide BID, liraglutide and concomitant use of SU
Madsbad [96]. Review including 9 phase 3 head-to-head trials and 1 large phase 2 study [*N* = 812 received study drug]. Duration ~ 6 months	To compare the efficacy and safety of 7 GLP-1 RAs in a head-to-head comparison	Notable reductions in HbA1c levels. Liraglutide led to greater HbA1c levels reduction[j]

AE adverse events, *DURATION* diabetes therapy utilization: researching changes in A1c, weight and other factors through intervention with exenatide QW (extended-release exenatide, 2 mg, once weekly), *EQW* exenatide QW, *FBG* fasting blood glucose, *GI* gastrointestinal, *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *HbA1c* glycated haemoglobin (type A1c), *LAR* long-acting release, *LEAD* liraglutide effect and action in diabetes, *NICE* National Institute for Health and Care Excellence, *OAM* oral antihyperglycaemic medication, *PPBG* postprandial blood glucose, *RCTs* randomised controlled trials, *RR* relative risk, *TZD* thiazolidinediones, *T2DM* type 2 diabetes mellitus, *WMD* weighted mean difference

[a] Compared to control (placebo, metformin and liraglutide)

[b] Compared to control (placebo, sitagliptin, exenatide, liraglutide and glargine)

[c] Sitagliptin (− 0.9%), glimepiride (− 0.5%), rosiglitazone − 0.4%), insulin glargine (− 1.1%) and exenatide (− 0.8%)

[d] HbA1c reduction > 1% and weight reduction ≥ 3%

[e] Compared to placebo

[f] Compared to other incretin mimetics

[g] Compared to exenatide and liraglutide

[h] Compared to other therapies

[i] Compared to comparator drugs

[j] Compared to exenatide formulations and albiglutide

Table 13 GLP-1 RAs: clinical impact and benefits on body weight and composition

Study details	Aim	Highlights
Dulaglutide		
Umpierrez et al. [99]. Pooled analysis of 6 head-to-head WARD RCTs [N = 5171; dulaglutide 1.5 mg, n = 1718; dulaglutide 0.75 mg, n = 1417]. Duration 26–104 weeks	To evaluate the relationship between changes in body weight and HbA1c levels	At 26 weeks, patients with weight loss: 57–88% (1.5 mg), 43–84% (0.75 mg). Patients with weight loss and HbA1c reductions: 55–83% (1.5 mg), 41–79% (0.75 mg)
Yajima et al. [100]. Prospective study [N = 21; dulaglutide, n = 11; teneligliptin, n = 10]. Duration 11 months with follow-up of 6 months	To evaluate the effect of dulaglutide QW on body composition in T2DM patients undergoing HD	Teneligliptin group: No change. FM (15.7 kg to 14.1 kg, P = 0.63) SMM (18.6 kg to 18.9 kg, P = 0.16). Dulaglutide group: Significant decrease in FM (21.9 kg to 18.9 kg, P = 0.037) and SMM (21.0 kg to 20.2 kg, P = 0.011)
Exenatide BID		
Best et al. [86]. Systematic review of 15 retrospective or prospective observational studies [$N \geq 100$]. Duration 12 months	To assess the effectiveness of exenatide BID in clinical practice	Significant reduction in body weight: − 2 to − 11 kg
Klonoff et al. [101]. Study of 3 open-ended, open-label, uncontrolled trials [N = 217]. Duration ≥ 3 years	To evaluate the effects of exenatide therapy on glycaemic control, body weight, cardiometabolic markers and safety	Progressive reduction in body weight (− 5.3 ± 0.4 kg; $P < 0.0001$)
Buse et al. [102]. Interim analysis of pooled data from open-label, uncontrolled extension of 3 double-blind, placebo-controlled trials [N = 974]. Duration 2 years	To assess the metabolic effects of exenatide treatment on diabetes, obesity and hepatic biomarkers	Progressive reduction in body weight (mean reduction − 4.7 ± 0.3 kg; $P < 0.001$)
Iglesias et al. [103]. Uncontrolled, prospective study. Duration 3–6 months	To evaluate weight and metabolic effects of exenatide in patients with T2DM and obese patients waiting for BS	Significant reduction in body weight (− 12.5 kg) and waist circumference (– 13 cm); $P < 0.0001$. BMI reduction to < 35 kg/m^2 in about 20% of patients
Viswanathan et al. [104]. Retrospective study [N = 52]. Duration 4 months with follow-up period of 26 weeks	To evaluate the effect of exenatide BID on clinical parameters in obese patients with T2DM in whom hyperglycaemia was inadequately controlled	At 26 weeks follow-up, patients on regular exenatide dosing had body weight reduction (6.46 ± 0.8 kg; $P < 0.001$)

Table 13 continued

Study details	Aim	Highlights
Exenatide QW		
Grimm et al. [88]. Post hoc analysis of integrated data from DURATION trials (6 randomised, comparator-controlled) [N = 1379]. Duration 24–30 weeks	To evaluate the efficacy, safety and tolerability of EQW in patients with T2DM	Progressive reductions in body weight (LSM − 2.5 kg; 95% CI − 2.8 to − 2.3 kg). At endpoint, weight loss was evident in 76% of the population
Jabbour et al. [105]. Post hoc analysis, DURATION-8 study [N = 574]. Duration 28 weeks	To assess the effects of EQW plus dapagliflozin versus EQW, or dapagliflozin on body weight in patients with T2DM with inadequately controlled with metformin monotherapy	Reduction in weight: EQW plus dapagliflozin group: (− 3.55 ± 0.29 kg); Significant vs. EQW group (− 1.56 ± 0.29 kg; $P < 0.001$) vs. dapagliflozin (− 2.22 ± 0.28 kg; $P < 0.001$).
Liraglutide		
Blonde and Russell-Jones [106]. Overview of LEAD (1–5) trials [$N > 4000$]. Duration 26–52 weeks	To evaluate the safety and efficacy of liraglutide with or without OAD drug therapy in patients with T2DM	Liraglutide vs. comparators: Significantly greater weight reduction (1–3.24 kg). Greater weight loss in subjects with high BMIs
Davies et al. [107]. Randomised, double-blind, placebo-controlled, parallel-group trial. SCALE Diabetes RCT [N = 846]. Duration 56 weeks	To evaluate the efficacy and safety of liraglutide versus placebo for weight management in overweight or obese adults with T2DM	Weight loss: 6.0% (6.4 kg) (liraglutide 3.0 mg), 4.7% (5.0 kg) (liraglutide 1.8 mg), 2.0% (2.2 kg) (placebo). Weight loss of ≥ 5% and > 10%: 54.3% and 25.2% (liraglutide 3.0 mg), 40.4% and 15.9% (liraglutide 1.8 mg), 21.4% and 6.7% (placebo)
Gorgojo-Martinez et al. [108]. Retrospective study of 2 cohorts [N = 164, n = 15 with previous BS and n = 149 without BS]. Duration 2 years	To evaluate the effectiveness and tolerability of liraglutide for 2 years in patients with and without previous BS and T2DM with obesity	Significant weight reduction: BS group: Δ weight − 3.4 kg; Non-BS group: Δ weight − 3.8 kg; ($P < 0.05$)
Lixisenatide		
Anderson et al. [91] Pooled analysis of 11 phase 3 RCTs of the GetGoal programme	To evaluate the efficacy and safety profiles of lixisenatide in patients with T2DM	Effectively reduced body weight across a variety of patient types (reduction of − 0.2 to − 2.96 kg)

Table 13 continued

Study details	Aim	Highlights
Semaglutide		
Ahren et al. [109]. Post hoc analysis of SUSTAIN (1–5) trials [N = 3899]. Duration 30 or 56 weeks	To evaluate the consistency of semaglutide-induced weight loss across baseline BMI subgroups	Body weight decreased by 2.5–5.7 kg (0.5 mg) and 2.0–7.9 kg (1.0 mg), versus 3.7 kg with comparators. Significantly greater proportions of subjects achieved weight loss ($\geq$ 5% and $\geq$ 10%) with semaglutide versus comparators across all BMI subgroups ($P < 0.05$)
GLP-1 RAs: Exenatide BID, albiglutide, dulaglutide, liraglutide and lixisenatide		
Vilsboll et al. [110]. Meta-analysis including 21 trials [N = 6411 participants; GLP-1 RAs, n = 3395 and control groups, n = 3016]. Duration 20 weeks	To assess the effect of GLP-1 RAs versus placebo, no intervention or other antidiabetic interventions for weight loss in overweight patients with or without T2DM	GLP-1 RAs vs. control groups: Greater reduction in weight (WMD − 2.9 kg, 95% CI − 3.6 to − 2.2)
Madsbad [96]. Review including 9 phase 3 head-to-head trials and 1 large phase 2 study [N = 812]. Duration $\sim$ 6 months	To evaluate the relative clinical benefits of GLP-1 RAs	Weight reduction with liraglutide was similar to exenatide BID but greater than that observed with EQW, albiglutide and dulaglutide
Trujillo et al. [111]. Review of 8 head-to-head trials from phase 3 clinical trial programs. Duration 24–32 weeks	To evaluate the safety and efficacy of GLP-1 RA active comparators	Dulaglutide and exenatide BID: Similar weight loss. Liraglutide vs. dulaglutide: Greater weight loss with liraglutide
Robinson et al. [112]. Systematic review and meta-analysis of 32 RCTs. Duration 16 weeks–4.5 years with follow-up of 12 weeks	To analyse the effects of GLP-1 RAs exenatide (BID and QW) and liraglutide on body weight	At 12 weeks' follow-up, body weight decreased as follows: − 3.31 kg for GLP-1 RAs vs. active control (95% CI − 4.05 to − 2.57); − 1.22 kg for GLP-1 RAs vs. placebo (95% CI − 1.51 to − 0.93)
Comparative efficacy of bariatric surgery, incretin-based therapy (glucagon-like peptide-1 analogues) and SGLT2 inhibitors		
Bhandari et al. [113]. Prospective study [N = 90]. Duration 12 months	To assess the comparative efficacy of bariatric surgery, GLP-1 analogues and SGLT2 inhibitors in class 1 obese Indian patients with T2DM for a median duration of 3 years	Clinically important weight loss (loss of > 5% of usual body weight over 6 to 12 months) and a significant reduction in HbA1c occurred in patients treated with bariatric surgery and GLP-1 RAs; however, not in the case of patients treated with SGLT2i

Table 13 continued

Study details	Aim	Highlights
GLP-1 RAs: clinical impact on waist circumference		
Exenatide BID		
Iglesias et al. [103]. Uncontrolled, prospective study [N = 100]. Duration 6 months	To evaluate weight and metabolic effects of exenatide (after 3 and 6 months) in patients with T2DM and obese patients waiting for BS	Significantly reduced body weight (− 12.5 kg) and waist circumference (−13 cm); $P < 0.0001$. BMI was reduced to < 35 kg/m^2 in about 20% of patients
Sun et al. [114]. Systematic review and network meta-analysis of 17 RCTs [N = 4365]. Duration ≥ 8 weeks	To assess the effect of GLP-1 RAs on waist circumference for T2DM patients	Significant waist circumference reduction vs. placebo: − 5.24 cm (liraglutide 1.8 mg QD) (95% CI − 7.68, − 2.93), − 4.73 cm (liraglutide 1.2 mg QD) (95% CI − 6.68, − 2.65), − 1.34 cm (exenatide 10 μg BID) (95% CI − 2.00, − 0.75). Significantly decreased waist circumference by − 1.73 cm (liraglutide 1.8 mg vs. sitagliptin) (95% CI − 3.04, − 0.55). Decreased waist circumference: 98.36% (liraglutide 1.8 mg), 91.82% (liraglutide 1.2 mg)

AWARD assessment of weekly administration of LY2189265 in diabetes (dulaglutide, 0.75 mg or 1.5 mg QW), *BS* bariatric surgery, *BMI* body mass index, *DURATION* diabetes therapy utilization: researching changes in A1C, weight and other factors through intervention with exenatide QW (extended-release exenatide, 2 mg, once weekly), *EQW* exenatide QW, *FM* fat mass, *GETGOAL* GLP-1 agonist AVE0010 in patients with type 2 diabetes mellitus for glycaemic control and safety evaluation (lixisenatide, 20 μg once daily), *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *HbA1c* glycated haemoglobin, *HD* haemodialysis, *LEAD* liraglutide effect and action in diabetes (liraglutide 1.2 mg or 1.8 mg daily), *OAD* oral antidiabetics, *RCT* randomised controlled trial, *SCALE* satiety and clinical adiposity—liraglutide evidence in individuals with and without diabetes, *SGLT2* sodium-glucose co-transporter-2, *SMM* skeletal muscle mass, *SUSTAIN-6* trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes (semaglutide, 0.5 mg or 1.0 mg QW), *T2DM* type 2 diabetes mellitus, *WMD* weighted mean difference

Table 14 GLP-1 RAs: clinical impact and benefits on lipid profile

Study details	Aim	Highlights
Exenatide QW		
Grimm et al. [88]. Post hoc analysis of integrated data from 6 randomised, comparator-controlled trials of EQW (DURATION trials) [*N* = 1379]. Duration 24–30 week	To evaluate the efficacy, safety and tolerability of EQW in patients with T2DM	Significant reductions in fasting lipid levels (in mg/dL): total cholesterol, − 6.5 [95% CI − 8.2 to − 4.7]; LDL-C, − 3.9 [95% CI − 5.3 to − 2.5]; triglycerides, − 6% [95% CI − 8 to − 4]
Trautmann et al. [115]. Post hoc analysis of pooled data from 3 studies (DURATION 1–3 extension studies) [*N* = 329]. Duration 3 years	To evaluate efficacy and safety of EQW versus insulin glargine in patients with T2DM	At week 156, final LDL-C reductions (in mmol/L) − 0.13 ± 0.73 (range − 0.01 to − 0.15 mmol/L). Week 52 onwards, final HDL-C increase of 0.08 ± 0.20 mmol/L ($P < 0.05$). Final reductions in total cholesterol were as follows: − 0.11 ± 0.93 mmol/L (EQW), − 0.15 ± 0.86 mmol/L (insulin glargine). Final reductions in triglycerides were as follows: − 0.05 ± 1.79 mmol/L (EQW), − 0.14 ± 1.19 mmol/L (insulin glargine)
Sheu et al. [75]. Post hoc analysis of pooled data [*N* = 4625]. Duration 24–30 weeks	To evaluate the efficacy and safety of exenatide twice daily and EQW in Asian versus white patients with T2DM	Change across lipid outcomes were similar in Asian and white populations. Final reductions in triglycerides were as follows: − 0.12 mmol/L (Asian) (95% CI − 0.21 to 0.02; $P = 0.0206$ vs. baseline), – 0.18 mmol/L (White) (95% CI − 0.27 to − 0.08; $P = 0.0004$ vs. baseline)

Table 14 continued

Study details	Aim	Highlights
Liraglutide		
Multiple GLP-1 analogues		
Sun et al. [116]. Systematic review and network meta-analyses of 35 RCTs [*N* = 14,340]. Duration ≥ 8 weeks	To assess the effect of GLP-1 RAs on lipid profiles in patients with T2DM	GLP-1RAs decreased HDL-C versus thiazolidinediones with a range of − 0.06 mmol/L [95% CI − 0.11 to − 0.01] to − 0.13 mmol/L [95% CI − 0.17 to − 0.10] respectively. Significant LDL-C reduction for all GLP-1 RAs vs. placebo (− 0.08 to − 0.16 mmol/L), insulin (− 0.10 to − 0.19 mmol/L) and TZD (− 0.16 to − 0.24 mmol/L). Significant triglyceride level reduction with liraglutide 1.8 mg once daily as compared to placebo: − 0.30 mmol/L [95% CI − 0.49 to − 0.11]

DURATION diabetes therapy utilization: researching changes in A1C, weight and other factors through intervention with exenatide QW (extended-release exenatide, 2 mg, once weekly), *EQW* exenatide QW, *HDL-C* high density lipoprotein cholesterol, *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *LDL-C* low density lipoprotein cholesterol, *RCTs* randomised controlled trials, *T2DM* type 2 diabetes mellitus, *TZD* thiazolidinediones

Table 15 GLP-1 RAs: clinical impact and benefits on BP

Reference/ study	Study design	Duration	Change in SBP (mmHg)	Change in DBP (mmHg)
Dulaglutide				
Giorgino et al. [118]. AWARD-2	Randomised open-label comparator (double blind to dulaglutide dose), parallel-arm study	78 weeks	− 0.70 ± 0.85 (1.5 mg), − 0.59 ± 0.85 (0.75 mg) (on treatment with dulaglutide)	− 0.44 ± 0.52 (1.5 mg), − 0.36 ± 0.52 (0.75 mg) (on treatment with dulaglutide)
Umpierrez et al. [119]. AWARD-3	Randomised, parallel-arm, double-blind, double-dummy, non-inferiority study	52 weeks	− 0.1 ± 0.88 (1.5 mg), − 2.7 ± 0.88 (0.75 mg)	− 0.3 ± 0.60 (1.5 mg), − 1.4 ± 0.59 (0.75 mg)
Skrivanek et al. [120]. AWARD-5	Randomised, multicentre, double-blind, parallel-arm study	26 weeks	NA	− 0.02 (0.25 mg), − 0.26 (0.5 mg), − 0.65 (0.75 mg), − 0.92 (1.0 mg), − 0.99 (1.5 mg), − 0.78 (2.0 mg), − 0.57 (3.0 mg)
Dungan et al. [71]. AWARD-6	Phase 3, randomised, open-label, parallel-group study	26 weeks	− 3.36 ± 0.7 (1.5 mg)	− 0.22 ± 0.4 (1.5 mg)
Ferdinand et al. [121]	Randomised, double-blind, placebo-controlled study	26 weeks	− 2.5 ± 0.6 (1.5 mg), − 1.6 ± 0.6 (0.75 mg)	0.3 ± 0.4 (1.5 mg), − 0.1 ± 0.4 (0.75 mg)
Exenatide (2 mg/week or 5–10 μg/day) and liraglutide (1.2 mg or 1.8 mg/day)				
Wang et al. [122]	Meta-analyses of 16 crossover or parallel design, randomised controlled and extended open-label RCTs	> 12 weeks	Exenatide 2 mg/week vs. placebo − 5.24 (95% CI − 6.88 to − 3.59, $P < 0.00001$). Exenatide 2 mg/week vs. insulin glargine − 3.46 (95% CI − 3.63 to − 3.29, $P < 0.00001$). Liraglutide 1.2 mg vs. placebo − 5.60 (95% CI − 5.84 to − 5.36, $P < 0.00001$). Liraglutide 1.2 mg vs. glimepiride − 2.38 (95% CI − 4.75 to − 0.01, $P = 0.05$). Liraglutide 1.8 mg vs. placebo − 4.49 (95% CI − 4.73 to − 4.26, $P < 0.00001$) Liraglutide 1.8 mg vs. glimepiride − 2.62 (95% CI − 2.91 to − 2.33, $P < 0.00001$)	Exenatide-treated vs. placebo −5.91 (95% CI − 7.53 to − 4.28, $P < 0.00001$). Exenatide-treated vs. sitagliptin − 0.99 (95% CI − 1.12 to − 0.87, $P < 0.00001$)

Table 15 continued

Reference/ study	Study design	Duration	Change in SBP (mmHg)	Change in DBP (mmHg)
Exenatide BID				
Baretic et al. [123]	Open-label, intention-to-treat, phase 3 study	52 weeks	− 4.65 (5 and 10 μg) (with EBID treatment)	− 1.48 (5 and 10 μg) (with EBID treatment)
Sheu et al. [75]	Retrospective post hoc analysis	12–30 weeks	− 1.4 (Asian), − 1.2 (White)	− 3.3 (Asian), − 2.8 (White)
Moretto et al. [124]	Randomised, double-blind, placebo-controlled	24 weeks	− 3.7 ± 1.2 (both 5 and 10 μg)	−2.3 ± 0.7 (10 μg)
Ji et al. [76]	Randomised, comparator-controlled, open-label study	26 weeks	− 5.38 ± 0.86 (10 μg EBID group)	− 2.26 ± 0.55 (10 μg EBID group)
Rosenstock et al. [83]. GetGoal-X	Phase 3, randomised, parallel-group, open-label, multicentre, multinational, non-inferiority study	24 weeks	− 2.5 (10 μg exenatide group)	− 1.3 (10 μg exenatide group)
Best et al. [86]	Systematic review including 15 retrospective or prospective observational studies	12 months	Significant reductions: − 2 to − 11 (10 μg exenatide)	
Exenatide QW				
Grimm et al. [88]. Integrated DURATION trials	Randomised, comparator-controlled 6 trials, post hoc analysis	24–30 weeks	− 2.8 [− 3.5 to − 2.1] (on treatment with EQW)	− 0.8 [− 1.2 to − 0.4] (on treatment with EQW)
Exenatide BID and QW				
Sheu et al. [75]	Randomised, controlled, retrospective post hoc analysis	12–30 weeks (exenatide BID) 24–30 weeks (exenatide QW)	Exenatide BID − 3.3 (Asian), − 2.8 (White) (all $P < 0.001$ vs. baseline), EQW-treated − 4.3 (Asian), − 3.0 (White) (both $P < 0.0001$ vs. baseline)	Exenatide BID – 1.4 (Asian), – 1.2 (White). EQW-treated patients – 1.1 (Asian) ($P = 0.0052$ vs. baseline), – 0.6 (White) ($P = 0.0283$ vs. baseline)

Table 15 continued

Reference/ study	Study design	Duration	Change in SBP (mmHg)	Change in DBP (mmHg)
Exenatide (BID and QW) and liraglutide				
Robinson et al. [112]	Randomised comparator-controlled trials, systematic review and meta-analyses	12 weeks follow-up	GLP-1 agonists vs. placebo − 1.79 (− 2.94 to − 0.64). GLP-1 agonists vs. active control − 2.39 (− 3.35 to − 1.42)	GLP-1 agonists vs. placebo − 0.54 (− 1.15 to 0.07). GLP-1 agonists vs. active control − 0.50 (− 1.24 to 0.24)
Exenatide BID and QW, dulaglutide (0.75–1.5 mg), liraglutide (1.2–1.8 mg)				
Sun et al. [125]	Systematic review and network meta-analyses including 60 trials with 14 treatments	≥ 12 weeks	GLP-1RAs vs. placebo – 1.84 mmHg (95% CI − 3.48 to – 0.20). GLP-1RAs vs. insulin and sulfonylureas − 4.60 (95% CI − 7.18 to – 2.03)	Exenatide BID (10 μg) vs. placebo – 1.08 mmHg (95% CI − 1.78 to − 0.33)
Liraglutide				
Bailey et al. [126]. LIRA-SWITCH	Phase 4, randomised study	26 weeks	− 4.05 (1.8 mg liraglutide)	− 0.27 (1.8 mg liraglutide)
Ghosal et al. [72]	Retrospective real-world observational case note	13 weeks	− 10.23 (1.2 mg/day liraglutide)	NS
Kesavadev et al. [127]	Real-world, prospective study	24 weeks	NS	− 5.3 (when treated with liraglutide)
Wangnoo et al. [128]. LEAD-In	Prospective, observational study	26 weeks	− 10.7 (1.8 mg liraglutide)	− 5.0 (1.8 mg liraglutide)
Fonseca et al. [129]	Pooled analysis (6 phase 3 studies)	26 weeks	− 2.7 ± 0.8 (1.2 mg), − 2.9 ± 0.7 (1.8 mg)	NA
Ahmann et al. [130]	Randomised, placebo-controlled, double-blind, parallel-group	26 weeks	− 5.8 (liraglutide treated)	NA
Azar et al. [131]. LIRA-RAMADAN	Randomised, open-label, active-controlled, parallel-group study	33 weeks	− 3.45 (liraglutide treated)	NS

Table 15 continued

Reference/ study	Study design	Duration	Change in SBP (mmHg)	Change in DBP (mmHg)
Yang et al. [132]	Randomised, double-blind, double-dummy, 4-arm, active control, phase 3 study	16 weeks	Reduction > 3	A slight decrease in mean DBP
Lixisenatide				
Pfeffer et al. [133]. ELIXA trial	Multicentre, randomised, double-blind, placebo-controlled trial	25 months	− 0.8 (95% CI − 1.3 to − 0.3) ($P = 0.001$) (with lixisenatide)	
Tonneijck et al. [134]	Secondary analysis of a phase 4, single-centre, randomised, open-label, comparator-controlled, parallel-group intervention trial	4 weeks	Post breakfast: Lixisenatide vs. insulin glulisine + 5.2 ± 2.9 ($P = 0.087$)	Post breakfast: Lixisenatide vs. insulin glulisine +5.4 ± 1.4 ($P < 0.001$)
Rosenstock et al. [83]. GetGoal-X	Phase 3, randomised, parallel-group, open-label, multicentre, multinational, non-inferiority study	24 weeks	− 2.9 (20 μg)	− 1.8 (20 μg)
Lixisenatide 20 μg and liraglutide 1.2 and 1.8 mg				
Meier et al. [135]	Multicentre, randomised, open-label, 3-arm trial	8 weeks	Liraglutide 1.8 mg, − 2.5 ± 7.7. Liraglutide 1.2 mg, − 0.5 ± 7.1. Lixisenatide 20 μg, 0.4 ± 6.4	Liraglutide 1.8 mg, 1.6 ± 4.7. Liraglutide 1.2 mg, 2.4 ± 4.7. Lixisenatide 20 μg, 0.8 ± 4.1
Semaglutide QW				
Andreadis et al. [136]. SUSTAIN-6 trial	Systematic review and meta-analyses of 6 placebo-controlled and 7 active-controlled studies	12–56 weeks (104 weeks for SUSTAIN-6)	Semaglutide 0.5 mg vs. placebo − 1.31 (95% CI 0.07–2.56, $I^2 = 0\%$), Semaglutide 1 mg vs. placebo WMD − 3.05 (95% CI − 4.63 to − 1.47, $I^2 = 21\%$), Semaglutide 0.5 mg vs. other antidiabetic agents − 1.78 (95% CI 0.43–3.13, $I^2 = 44\%$), Semaglutide 1 mg vs. other antidiabetic agents − 3.17 (95% CI 2.31–4.03, $I^2 = 0\%$)	Semaglutide 1 mg vs. other antidiabetic agents − 0.85 (95% CI − 1.54 to − 0.16, $I^2 = 30\%$)

Table 15 continued

Reference/study	Study design	Duration	Change in SBP (mmHg)	Change in DBP (mmHg)
Ahren et al. [137]. SUSTAIN-2	Phase 3a, randomised, double-blind, double-dummy, active-controlled, parallel-group, multinational, multicentre study	56 weeks	− 5.1 (0.5 mg), − 5.6 (1 mg)	− 2.0 (0.5 mg), −1.9 (1 mg)
Pratley et al. [138]. SUSTAIN-7	Phase 3b randomised study	40 weeks	− 2.4 ± 0.76 (0.5 mg), − 4.9 ± 0.77 (1.0 mg)	− 0.6 ± 0.48 (0.5 mg), − 2.0 ± 0.49 (1.0 mg)

BP blood pressure, *DBP* diastolic blood pressure, *EBID* exenatide BID, *EQW* exenatide QW, *NA* not applicable, *NS* not significant, *SBP* systolic blood pressure, *RCTs* randomised controlled trials, *WMD* weighted mean difference

[a] Only significant values ($P < 0.05$) presented

inhibiting cell death and stimulating lipolysis [162, 163]. GLP-1 RAs can reduce hepatic steatosis and improve survival by enhancing the unfolded protein response by promoting macroautophagy. In addition, they improve insulin resistance and insulin sensitivity to prevent the progression of non-alcoholic fatty liver disease (NAFLD) [164–167]. The unique ability of GLP-1 RAs to promote weight loss, improve glycaemic control and potentially reverse hepatocyte injury, liver inflammation, and liver fibrosis makes them a novel and attractive therapeutic option for the treatment of non-alcoholic steatohepatitis (NASH) [168]. A literature review evaluating the safety and efficacy of medications for the treatment of NASH in patients with T2DM reported favourable outcomes associated with the use of GLP-1 RAs with respect to reducing transaminases and steatosis along with improvements in insulin sensitivity and weight loss [169]. Currently, there is limited clinical experience with GLP-1 RAs in patients with severe hepatic impairment [170]. The beneficial effects of GLP-1 RAs on hepatic health are presented with clinical evidence in Table 19.

Pancreatitis

GLP-1 RAs are recommended to be used with caution/not used in patients with a familial/personal history of pancreatitis depending on the respective prescribing information [178]. A few clinical studies and meta-analyses focussing on pancreatitis are presented in Table 20.

Cholelithiasis

GLP-1 RAs are known to pose a significantly increased risk of cholelithiasis [183]. The key clinical evidence on cholelithiasis associated with GLP-1 RAs is presented in Table 21.

GLP-1 RAS USE IN COMPLICATED DIABETES AND SPECIAL POPULATIONS

GLP-1 RA use in patients with cardiovascular complications, renal impairment and hepatic impairment along with their use in elderly,

Table 16 Baseline characteristics and key results of CVOTs for GLP-1 RAs

Trial **Drug tested**	**EXSCEL** **Exenatide (QW)** [139, 140]	**LEADER** **Liraglutide** [139, 140]	**ELIXA** **Lixisenatide** [139, 140]	**SUSTAIN-6** **Semaglutide** [139, 140]	**HARMONY** **Albiglutide** [141, 142]
Baseline characteristics					
Dose	Up to 2 mg weekly	Up to 1.8 mg/day	Up to 20 μg/day	0.5 or 1 mg weekly	30–50 mg/week
No. of patients	14,752	9340	6068	3297	9463
Mean age (years)	61	64.3	59.9	64.6	64.1
Women (%)	38	36	31	39	31
Mean BMI (kg/m^2)	32.7	32.5	30.1	32.8	32.3
Mean HbA1c (%)	8.1	8.7	7.7	8.7	8.7
Mean duration of diabetes (years)	13.1	12.8	9.2	13.9	13.8
Prior CVD (%)	73	81.3	100	83	NA[a]
Heart failure (%)	16	17	22.5	24	20.2
SBP (mmHg)	136	138	130	136	134.7
eGFR < 60 mL/min/1.73 m^2 (%)	21.3	24	22	28.5	10.6
Comparator	Placebo and standard of care	Placebo and standard of care	Placebo and standard of care	Placebo and standard of care	Placebo and standard of care
Median follow-up (years)	3.2	3.8	2.1	2.1	1.5
Results					
No. of primary events observed	1744	1302	844	254	338
Non-inferiority for MACE demonstrated?[b]	Yes	Yes	Yes	Yes	Yes
Superiority for MACE[b]	No difference	Superior (13% reduction)	No difference	Superior (26% reduction)[c]	Superior
CV death reduced?	No	Yes	No	No	No
All-cause mortality reduced?	Yes	Yes	No	No	No
Difference in HbA1c (% units)	0.27	0.4	1.0	0.53	0.63

Table 16 continued

Trial Drug tested	EXSCEL Exenatide (QW) [139, 140]	LEADER Liraglutide [139, 140]	ELIXA Lixisenatide [139, 140]	SUSTAIN-6 Semaglutide [139, 140]	HARMONY Albiglutide [141, 142]
Mean reduction in weight (kg)	0.7	2.3	4.3	1.27	0.83

Cited references to be visited for detailed information

BMI body mass index, *CV* cardiovascular, *CVD* cardiovascular disease, *CVOT* cardiovascular outcome trials, *eGFR* estimated glomerular filtration rate, *ELIXA* evaluation of lixisenatide in acute coronary syndrome (lixisenatide, maximum dose 20 μg per day), *EXSCEL* exenatide study of cardiovascular event lowering trial (exenatide QW, 2 mg), *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *HARMONY* trial to evaluate the effect of albiglutide on major cardiovascular events in patients with type 2 diabetes mellitus, *HbA1c* glycated haemoglobin, *LEADER* liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results (liraglutide, 1.8 mg QD), *MACE* major adverse cardiovascular events, *NA* not available, *SBP* systolic blood pressure, *SUSTAIN-6* trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes (semaglutide, 0.5 mg or 1.0 mg QW)

[a] Prior coronary artery disease, 70.5%; peripheral arterial disease, 25.0%; stroke, 17.7%; heart failure, 20.2%

[b] Compared to placebo and standard of care

[c] The comparison was not pre-specified and not to be used for regulatory purposes

pregnant and lactating women is discussed here along with relevant clinical evidence. Special situations including fasting have been discussed.

GLP-1 RAs Use in Complicated Diabetes

Patients with Cardiovascular Complications

Patients with T2DM are at a higher risk of developing CVD, which in turn is recognised to be the leading cause of death in patients with diabetes [184]. Although the use of these agents is encouraged in patients with asymptomatic and stable CAD, there is no clear evidence regarding their usage in acute myocardial infarction. Hence, factors to be considered before/during the use of GLP-1 analogues in such cases could be a pragmatic approach based on prescribing information, available clinical evidence and clinical sense of physicians [185]. The CV safety of GLP-1 RAs was presented in previous sections.

Patients with Renal Impairment

Exenatide and lixisenatide are predominantly cleared by the kidney. Exenatide dosage is not recommended to be increased in patients with an eGFR of 30–60 mL/min/1.73 m^2. Both exenatide and lixisenatide are contraindicated in patients with eGFR < 30 mL/min/1.73 m^2. Although clearance of liraglutide and dulaglutide is predominantly hepatic, administration of these drugs in patients with renal impairment needs to be considered with caution. This is largely because of the GI side effects and risk of associated volume depletion in case of chronic kidney disease (CKD) and brittle renal haemodynamics [149]. The renal safety of GLP-1 RAs has been discussed in previous sections.

Recommendations for the usage of GLP-1 RA in T2DM patients with renal impairment (as per the European label) are presented in Table 22.

Patients with Hepatic Impairment

Elimination of GLP-1 RAs does not occur mainly by hepatic metabolism. As discussed in the previous sections, exenatide is primarily eliminated by the kidneys, whereas liraglutide and dulaglutide are metabolised endogenously into their component amino acids by general protein catabolism pathways. No specific organ is presumed to be the major route of elimination for GLP-1 RAs. It is important to note that there is limited information available on the safety and efficacy of GLP-1 RAs in patients with

Table 17 Key studies reporting cardiovascular outcomes with GLP-1 RA therapy

Study details	Aim	Highlights
Dulaglutide		
Ferdinand et al. [143]. Meta-analysis of 9 randomised safety and efficacy trials [N = 6010; dulaglutide, 3885; comparator therapy active or placebo, 2125]	To evaluate the CV risk in patients with T2DM treated with dulaglutide	Patients who experienced primary 4-component MACE: 26 (0.67%) for dulaglutide vs. 25 (1.18%) for comparator (HR 0.57; adjusted 98.02% CI 0.30–1.10). No significant difference between the groups for 3-component MACE, 6-component MACE and all-cause mortality, (HR < 1.0 for all). Dulaglutide does not increase major CV events risk in T2DM patients
Exenatide BID		
Ratner et al. [144]. Pooled analysis of retrospectively examined data from RCTs (8 blinded, 4 open label); [Exenatide BID (n = 2316), pooled comparator (placebo, n = 971; or insulin, n = 658)]	To evaluate the CV safety of exenatide BID versus pooled comparator or insulin, in patients with T2DM	Exenatide use did not increase CV risk. Primary MACE RR 0.7, 95% CI 0.38–1.31 (calculated by the Mantel–Haenszel method as compared to pooled comparators)
Multiple GLP-1 analogues: lixisenatide (up to a maximum dose of 20 μg QD), liraglutide (1.8 mg QD), semaglutide (0.5 mg or 1.0 mg QW) and extended-release exenatide (2 mg QW)		
Bethel et al. [145]. Systematic review and meta-analysis of 4 CV outcome trials (EXSCEL, ELIXA, SUSTAIN-6, LEADER)	To examine the overall CV safety and efficacy for multiple GLP-1 analogues in adult patients (> 18 years) with T2DM	GLP-1 RA treatment group vs. placebo: Significant 10% RRR in the 3-point major adverse CV event primary outcome (HR 0.90, 95% CI 0.82–0.99; P = 0.33), 13% RRR in CV mortality (HR 0.87, 95% CI 0.79–0.96; P = 0.007), 12% RRR in all-cause mortality (HR 0.88, 95% CI 0.81–0.95; P = 0.002), with low-to-moderate degree of heterogeneity between trials

CV cardiovascular, *ELIXA* evaluation of lixisenatide in acute coronary syndrome (lixisenatide, maximum dose 20 μg per day), *EXSCEL* exenatide study of cardiovascular event lowering trial (exenatide QW, 2 mg), *LEADER* liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results (liraglutide, 1.8 mg QD), *MACE* major adverse cardiac events, *HR* hazards ratio, *RRR* relative risk reduction, *RCTs* randomised controlled trials, *SUSTAIN-6* trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes (semaglutide, 0.5 mg or 1.0 mg qW), *T2DM* type 2 diabetes mellitus

Table 18 GLP-1 RAs: clinical impact and benefits on renal health

Study details	Aim	Highlights
Dulaglutide		
Tuttle et al. [150]. Multicentre, open-label, randomised interventional study (AWARD-7) [Dulaglutide 1.5 mg, n = 193 and 0.75 mg, n = 190 versus insulin glargine, n = 194]. Duration 52 weeks	To investigate the efficacy and safety of dulaglutide (1.5 and 0.75 mg) vs. insulin glargine in T2DM patients and moderate-to-severe CKD (stage 3–4)	At 52 weeks, higher eGFR was reported with dulaglutide 1.5 mg (LSM 34.0 mL/min/1.73 m^2 [SE 0.7]; P = 0.005 vs. insulin glargine), dulaglutide 0.75 mg (LSM 33.8 mL/min/1.73 m^2 [0.7]; P = 0.009 vs. insulin glargine) (for insulin glargine 31.3 mL/min/1.73 m^2 [0.7]). UACR reduction with dulaglutide (1.5 mg and 0.75 mg) was not significantly different from insulin glargine. ESRD occurred in 38 participants: 4% (dulaglutide 1.5 mg), 7% (dulaglutide 0.75 mg), 8% (insulin glargine)
Tuttle et al. [151]. Pooled analysis of phase II and phase III studies of 9 clinical trials [N = 6005]. Duration 26 weeks	To evaluate the effects of dulaglutide on kidney function in patients with T2DM	No significant differences were observed for eGFR between dulaglutide group and comparators. Lower UACR values were observed for dulaglutide vs. placebo, active comparators and insulin glargine (at 26 weeks) and the values were dulaglutide vs. placebo 8.0 [4.4–20.4] vs. 8.0 [4.4–23.9] mg/g, P = 0.023; dulaglutide vs. active comparators 8.0 [4.4–21.2] vs. 8.9 [4.4–27.4] mg/g, P = 0.013; and dulaglutide vs. insulin glargine 8.9 [4.4–29.2] vs. 12.4 [5.3–50.5] mg/g, P = 0.029. Potential acute renal failure (in events/1000 patient-years): 3.4 (dulaglutide), 1.7 (active comparators), 7.0 (placebo). Dulaglutide treatment did not affect eGFR but demonstrated a slight decrease in albuminuria
Exenatide BID		
Linnebjerg et al. [152]. Open-label, observational study, 4 parallel study groups [N = 31]. Duration 30 weeks	To evaluate the PK, safety and tolerability of exenatide BID (5 or 10 μg) in patients with RI	Well tolerated in mild and moderate RI groups. Therapeutic doses (5 and 10 mg) are unsuitable in severe RI or ESRD

Table 18 continued

Study details	Aim	Highlights
Exenatide QW		
Loughlin et al. [153]. Observational, real-world study; [EQW (n = 2075), basal insulin (n = 73,610)]. Duration 3 years	To evaluate the effectiveness and tolerability of EQW compared with basal insulin among injectable-drug-naïve patients with T2DM who are elderly or have RI	In elderly patients (age ≥ 65 years), HbA1c levels changed as follows: − 0.50% (EQW), − 0.31% (BI initiators). Weight changed as follows: − 1.6 kg (EQW initiators), 0.2 kg (BI initiators). EQW initiators had a 1.45-fold increased risk of nausea and vomiting compared with BI initiators. In RI patients, HbA1c changed by − 0.58% (EQW), − 0.33% (BI initiators). Weight changed by − 1.9 kg (EQW initiators). No change (BI initiators). EQW initiators had a 1.28-fold increased risk of constipation and diarrhoea compared with BI initiators. The renal function, assessed according to eGFR, remained stable from baseline for both EQW and BI initiators, regardless of RI
Liraglutide		
Marso et al. [154]; Leon et al. [155]. LEADER [N = 9340]. Duration 3.8 years	To assess the long-term effects of liraglutide on cardiovascular outcomes and other clinically important events	In liraglutide-treated arm: 26% reduced macroalbuminuria (HR 0.74 [0.60–0.91]). 19% reduced urine ACR (CI 0.14%–0.24%). Gained significantly greater CV benefit who had an eGFR < 60 mL/min/1.73 m^2 (HR 0.69 [0.57–0.85]) than those with an eGFR > 60 mL/min/1.73 m^2 (HR 0.94 [0.83–1.07]). Doubling of serum creatinine concentration to an eGFR ≤ 45 mL/min/1.73 m^2 was unaffected. ESRD or renal death incidence was small

Table 18 continued

Study details	Aim	Highlights
Davies et al. [156]. Randomised, double-blind, placebo-controlled, parallel-group trial; LIRA-renal study [liraglutide (n = 140) or placebo (n = 139)]. Duration 26 weeks	To examine the efficacy and safety of liraglutide in patients with T2DM and moderate renal impairment	No changes in renal function (eGFR relative ratio to baseline − 1% [liraglutide], + 1% [placebo]; estimated treatment ratio [ETR] 0.98, P = 0.36). The most common AEs were of GI in nature: 35.7% (liraglutide), 17.5% (placebo), with no difference in hypoglycaemic episodes
Idorn et al. [157]. Investigator-initiated, placebo-controlled, double-blind, parallel-group, randomised trial [patients with T2DM and ESRD (n = 24) and control subjects with T2DM and normal kidney function (n = 23)]. Duration 12 weeks	To evaluate the parameters related to the safety and efficacy of liraglutide in patients with T2DM and dialysis-dependent ESRD	Liraglutide vs. control group: 49% increase in dose-corrected plasma trough concentration in ESRD group (95% CI 6–109, P = 0.02). Nausea and vomiting (initial and temporary) occurred more frequently in patients with ESRD ($P < 0.04$). In both liraglutide-treated groups significant improvement in glycaemic control ($P < 0.01$) and reduction in the dose of baseline insulin ($P < 0.04$). Body weight reduction was observed in − 2.4 ± 0.8 kg, P = 0.22 (ESRD group) and 2.9 ± 1.0 kg, P = 0.03 (control group)
Lixisenatide		
Pfeffer et al. [133]. CVOT, ELIXA. Duration 25 months	To assess the effects of lixisenatide in patients with T2DM who had had a recent acute coronary event	Median UACR increased to 24% (CI 19–30%) compared to placebo with an increase of 34% (CI 24–40%)

Table 18 continued

Study details	Aim	Highlights
Tonneijck et al. [158]. Phase 4, single-centre, randomised, open-label, comparator-controlled, parallel-group intervention trial [N = 35]. Duration 8 weeks	To evaluate whether lixisenatide when added to insulin glargine ameliorates postprandial glomerular hyperfiltration in overweight patients with T2DM compared with insulin glulisine	No effect on eGFR (+0.1 mL/min/1.73 m^2) [95% CI − 9 to 9] and ERPF (− 17 mL/min/1.73 m^2 [− 61 to 26]), other (intra-)renal haemodynamics or renal damage markers as compared to insulin glulisine. Increased fractional sodium excretion [+ 0.25% (0.09–0.41)] and urinary pH [+ 0.7 (0.3–1.2)]. Unchanged: Plasma renin, angiotensin II and aldosterone levels. Decreased HbA1c level in both groups. PPBG was lower. Prolonged treatment resulted in sustained natriuretic effect in contrast to reports on long-acting GLP-1 RAs
Hanefeld et al. [159]. Post hoc assessment of 9 lixisenatide trials in the GetGoal clinical trial programme [normal renal function (lixisenatide n = 2094, placebo n = 1150); renal impairment (mild: lixisenatide n = 637, placebo n = 414; moderate: lixisenatide n = 122, placebo n = 68)]. Duration 12–24 weeks	To assess the efficacy and safety of once-daily lixisenatide in patients with T2DM with normal-to-moderate renal impairment	Reduced HbA1c, PPBG and FBG in lixisenatide-treated patients vs. placebo. Mild renal impairment vs. normal kidney function: 14% higher incidence of GI, 10% higher incidence of nausea and vomiting (P = 0.003 for both)
Semaglutide		
Marso et al. [160]. CVOT, SUSTAIN-6 [N = 3297]. Duration 154 weeks	To assess the non-inferiority of semaglutide as compared with placebo in terms of cardiovascular safety in patients with T2DM	Treatment reduced the frequency of new or worsening nephropathy (HR 0.64 [0.46–0.88], P = 0.005). Doubling of serum creatinine concentration to an eGFR $\leq$ 45 mL/min/1.73 m^2, ESRD or renal death were unaffected; however, the event rate was too low (< 1%) to sufficiently explore these outcomes

Table 18 continued

Study details	Aim	Highlights
Marbury et al. [161]. Multicentre, single-dose, open-label, parallel-group study [N = 54]. Duration 21 days	To compare the PK and tolerability of semaglutide (0.5 mg) in T2DM patients with mild/moderate RI or ESRD versus those with normal renal function	Mean semaglutide exposure was 22% higher than subjects with normal renal function. No relationship between CL_{CR} and semaglutide exposure, or between CL_{CR} and semaglutide C_{max}. Haemodialysis did not affect the PK of semaglutide

ACR albumin-to-creatinine ratio, *AEs* adverse events, *AWARD* assessment of weekly administration of LY2189265 in diabetes (dulaglutide, 0.75 mg or 1.5 mg qw), *bi* basal insulin, C_{max} maximum plasma drug concentration, *CKD* chronic kidney disease, CL_{CR} creatinine clearance, *CVOT* cardiovascular outcome trials, *ELIXA* evaluation of lixisenatide in acute coronary syndrome (lixisenatide, maximum dose 20 μg per day), *eGFR* estimated glomerular filtration rate, *ERPF* effective renal plasma flow, *ESRD* end-stage renal disease, *EQW* exenatide QW, *FBG* fasting blood glucose, *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *GI* gastrointestinal, *LSM* least squares mean, *PK* pharmacokinetics, *PPBG* postprandial blood glucose, *RI* renal impairment, *SE* standard error, *SUSTAIN-6* trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes (semaglutide, 0.5 mg or 1.0 mg QW), *T2DM* type 2 diabetes mellitus, *UACR*, urine albumin-to-creatinine ratio

hepatic impairment. Prescribing information of the respective products advises cautious use in this patient population; however, there is no dosage adjustment recommended [192, 193]. The impact of GLP-1 RAs on hepatic health is presented in the clinical impact section.

GLP-1 RAs Use in Special Situations

Elderly

Characteristics that inform the choice of effective antidiabetic medications in the elderly include medications with relatively low risk of hypoglycaemia and glycaemic variability without overt GI side effects to prevent malnutrition and worsening frailty. It is important to reduce regimen complexity and avoid episodes of hypo- and hyperglycaemia. This should be specifically considered in patients with cognitive problems. Ageing is described as a progressive impairment in carbohydrate tolerance which may be related to disorderly insulin release, reduced insulin production, reduced GLP-1 secretion, increased adiposity, sarcopenia and physical inactivity. GLP-1 RAs are known to have low risk of hypoglycaemia and offer least glycaemic variability [194].

The key clinical evidence in elderly population for various GLP-1 RAs is presented in Table 23.

Paediatric and Adolescents

The uses of GLP-1 RAs are widely used in adults for glycaemic control and other benefits associated with the drug. Table 24 presented the key clinical evidence in paediatric and adolescent population.

Sleep Apnoea

The key clinical evidence on sleep apnoea for various GLP-1 RAs is presented in Table 25.

Fasting Conditions: Ramadan

GLP-1 RAs do not cause hypoglycaemia; hence, dose adjustments or modification is not required during fasting days. The dose of GLP-1 analogues, liraglutide, exenatide or lixisenatide, should be the same as pre-Ramadan dose even when used with insulin. However, dose adjustments are required for insulin, sulfonylureas or any other antidiabetics which can cause hypoglycaemia when administered concomitantly with GLP-1 RAs. Other oral hypoglycaemic agents do not require dose adjustments.

Table 19 GLP-1 RAs: clinical impact and benefits on hepatic health

Study details	Aim	Highlights
Dulaglutide		
Seko et al. [171]. Retrospective study [N = 15]. Duration 12 weeks	To evaluate the efficacy and safety of dulaglutide (0.75 mg) in Japanese NAFLD patients with T2DM	Significant decrease in transaminase activities: AST − 8.9 IU/L [baseline = 50.4 ± 6], P = 0.03; ALT − 11 IU/L [baseline = 52.1 ± 7.2], P = 0.003 was observed. Reduction in total body fat mass and liver stiffness was observed
Exenatide BID		
Klonoff et al. [101]. Open-ended, open-label clinical trial [N = 217 subjects; n = 116, baseline]. Duration 3 years	To evaluate the effects of exenatide BID on glycaemic control, body weight, cardiometabolic markers and safety	ALT reduction (− 10.4 ± 1.5 IU/L; $P < 0.0001$) was observed; normal ALT levels were achieved in 41% of the treated patients
Shao et al. [172]. Prospective RCT [N = 60]. Duration 12 weeks	To evaluate the advantages of exenatide treatment on obesity and NAFLD with elevated liver enzymes in T2DM patients	Exenatide vs. intensive insulin group: Significantly lower levels of ALT, AST and γGGT and correlated mean body weight change ($P < 0.001$). Significantly ($P < 0.01$) higher fatty liver reversal rate: 93.3% (exenatide), 66.7% (intensive insulin)
Exenatide QW		
Bergenstal et al. [173]. Analysis [N = 675]. Duration 52 weeks	To evaluate the potential effects of exenatide once weekly on glycaemic control and CV risk factors	Significant ALT reduction: − 4.3 (0.71) IU/L, with greater improvements in patients with elevated ALT levels at baseline
Liraglutide		
Armstrong et al. [174]. A multicentre, double-blind, randomised, placebo-controlled phase II study; LEAN trial [N = 23]. Duration 48 weeks	To assess the administration of liraglutide (1.8 mg) versus placebo in patients who were overweight with clinically proven NASH	Resolution of definite NASH: 9 (39%) in liraglutide group, 2 (9%) in placebo (RR 4.3 [95% CI 1.0–17.7]; P = 0.019). Fibrosis progression: 2 (9%) of 23 patients in liraglutide group, 8 (36%) of 22 patients in the placebo group (RR 0.2 [95% CI 0.1–1.0]; P = 0.04). Liraglutide administration led to histological resolution of non-alcoholic steatohepatitis

Table 19 continued

Study details	Aim	Highlights
Lixisenatide		
Gluud et al. [175]. Systematic review and meta-analysis of 15 RCTs. Duration 4–76 weeks	To evaluate the effects of lixisenatide on elevated liver transaminase levels in patients with T2DM	At 29 weeks, beneficial effect on normalisation of ALT among obese patients ($P = 0.01$) or overweight ($P = 0.004$), but not among normal weight patients ($P = 0.98$) was observed
Multiple GLP-1 RAs		
Carbone et al. [176]. Systematic review and meta-analysis (random-effects model) of 4 studies [$N = 136$]. Duration 16–56 weeks	To evaluate the efficacy of incretin-based therapies (GLP-1 RA and DPP4i) in treating NAFLD via a structured retrieval and pooled analysis of relevant studies	Post incretin-based therapies: Significant ALT reduction (MR 14.1 IU/L; 95% CI 8.3–19.8, $P < 0.0001$). Significant reduction ($P < 0.05$) in steatosis, inflammation and fibrosis in imaging and tissue data was demonstrated in 2 studies
Cuthbertson et al. [177]. Prospective study [$N = 25$]. Duration 6 months	To determine the impact of GLP-1 RA therapy on IHL levels in obese T2DM patients with hepatic steatosis, and evaluate the inter-relationship between changes in IHL with those in HbA1c, body weight, and volume of abdominal VAT and SAT	Treatment group associated with mean weight loss of 5.0 kg (95% CI 3.5–6.5), mean HbA1c reduction of 1.6% (95% CI 0.8–2.4), 42% relative reduction in IHL (95% CI 16.5–59.3). In individuals with highest pre-treatment levels, a greater IHL reduction was observed

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *CV* cardiovascular, *DPP-4*i dipeptidyl peptidase-4 inhibitor, *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *GGT* gamma-glutamyl transferase, *HbA1c* glycated haemoglobin, *IHL* intrahepatic lipid, *LEAN* liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis, *NAFLD* non-alcoholic fatty liver disease, *NASH* non-alcoholic steatohepatitis, *RCT* randomised controlled trial, *RR* relative risk, *SAT* subcutaneous adipose tissue, *T2DM* type 2 diabetes mellitus, *VAT* visceral adipose tissue

Table 26 presents the guidelines for the use of GLP-1 RAs during Ramadan.

Polycystic Ovary Syndrome

PCOS is one of the most common endocrine disorders that affect women of reproductive age [206]. PCOS is associated with high levels of androgen and insulin (hyperinsulinaemia) which contribute to the risk of developing disorders including obesity, high BP, high cholesterol, diabetes mellitus and CVD [207, 208]. Excess body weight is a key phenotype of PCOS wherein 60–70% of women with this condition are reported to be obese or overweight [206]. Another common feature associated with PCOS is insulin resistance [209].

Women with PCOS are 5–10 times more prone to the risk of developing T2DM, and the progression from impaired glucose tolerance to T2DM is faster in women with PCOS compared to women without PCOS (age and weight matched) [210].

Reduction in body weight has been demonstrated to improve hyperandrogenism, reproductive function and metabolic parameters such as hypertension, hyperlipidaemia and

Table 20 GLP-1 RAs: clinical impact and benefits in pancreatitis

Study details	Aim	Highlights
Storgaard et al. [179]. Systematic review and meta-analysis of 3 multicentre, double-blinded, placebo-controlled RCTs (ELIXA, LEADER, SUSTAIN-6) [GLP-1 RA treated, n = 9347; placebo treated, n = 9353]. Duration 24 months	To assess the risk of AP (predefined AE) in patients with T2DM with GLP-1 RA	GLP-1 RA was not associated with increased risk of AP (OR 0.745 [95% CI 0.47–1.17]).
Dulaglutide		
Nauck et al. [180]. Integrated assessment of 9 trials, 4 phase 2 trials (trials 1–4) and 5 phase 3 confirmatory trials (AWARD 1–5) [dulaglutide (n = 4006), placebo (n = 703), insulin glargine (n = 1541)]. Duration 104 weeks	To evaluate the risk of AP during treatment with dulaglutide, placebo and active comparators[a]	AP was confirmed in 7 patients distributed in all groups. Exposure-adjusted incidence rates (in patients/1000 patient-years) were as follows: dulaglutide group 0.85, placebo group 3.52 and sitagliptin group 4.71
Liraglutide		
Jensen et al. [181]. Post hoc review of pooled and patient-level data of phase 2 and 3 RCTs [N = 9016]. Duration 1 year	To report the incidence of AP and CP in T2DM trials of liraglutide vs. active comparator groups[b] vs. placebo	AP cases: 8 (liraglutide) and 1 (comparator group, glimepiride). AP and CP incidence reports were greater with liraglutide than comparators
Steinberg et al. [182]. Secondary analyses of pooled data of the phase 3a, 4 randomised, placebo-controlled trials from the SCALE clinical development programme [N = 5358]. Duration 32 weeks–3 years	To investigate the association between amylase/lipase activity levels and subsequent AP occurrence	Liraglutide resulted in dose-independent, reversible increase in amylase/lipase activity. Gallstones possibly contributed to 50% of AP cases

AE adverse event, *AP* acute pancreatitis, *AWARD* assessment of weekly administration of LY2189265 in diabetes (dulaglutide, 0.75 mg or 1.5 mg QW), *CP* chronic pancreatitis, *ELIXA* evaluation of lixisenatide in acute coronary syndrome (lixisenatide, maximum dose 20 μg per day), *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *LEADER* liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results (liraglutide, 1.8 mg QD), *OR* odds ratio, *RCTs* randomised controlled trial, *SCALE* satiety and clinical adiposity—liraglutide evidence in individuals with and without diabetes, *SUSTAIN-6* trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes (semaglutide, 0.5 mg or 1.0 mg QW), *T2DM* type 2 diabetes mellitus

[a] Including metformin, sitagliptin, exenatide BID and insulin glargine

[b] Glimepiride, rosiglitazone, insulin glargine, sitagliptin and exenatide

glycaemic control in women with PCOS [211, 212].

GLP-1 RAs have expanded the treatment option for PCOS owing to their ability to influence both body weight and glycaemic control. These agents are also associated with a modest decrease in BP and improvement in hyperlipidaemia [206]. The evidence on the use of GLP-1 RAs for the treatment of PCOS in women is currently available only for exenatide BID and liraglutide QD.

Table 21 GLP-1 RAs: clinical impact and benefits in cholelithiasis

GLP-1 RAs included in the study	Study details	Aim	Highlights
Exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide and semaglutide [183]	Systematic review and meta-analysis of randomised controlled trials [GLP-1 RA (n = 33,167), comparator arms (n = 26,683)]. Duration 41.7 weeks	To evaluate the effect of GLP-1 RA treatment on the incidence of pancreatitis, pancreatic cancer and cholelithiasis in patients with T2DM	Significant increase in cholelithiasis with GLP-1 RAs (OR 1.30 [95% CI 1.01–1.68], P = 0.041). No significant difference in incidence of pancreatitis and pancreatic cancer in both the arms

GLP-1 RA glucagon-like peptide-1 receptor agonist, *OR* odds ratio, *T2DM* type 2 diabetes mellitus

Table 22 Data on GLP-1 RA use in patients with CKD (based on European Union label)

Drug class and dosing		eGFR (mL/min/1.73 m^2) (associated stage)				
GLP-1 RAs	**Licensed dose**	**60–89 (stage 2)**	**45–59 (stage 3a)**	**30–44 (stage 3b)**	**15–29 (stage 4)**	**< 15 (stage 5)**
Dulaglutide QW [186]	0.75–1.5 mg SC injection QW	✔	✔	✔	✗	✗
Exenatide BID [187]	5–10 μg SC injection BID	✔	✔[a]	–	✗	✗
Exenatide QW [188]	2 mg SC injection QW	✔	✔[a]	✗	✗	✗
Liraglutide QD [189]	0.6–1.8 mg SC injection QD	✔	✔	✔	✗	✗
Lixisenatide QD [190]	10–20 μg SC injection QD	✔	✔[a,b]	–	✗	✗
Semaglutide QW [191]	0.25, 0.5 and 1 mg, SC injection QW	✔	✔[a]	✔[a]	✔[a]	✗

CKD chronic kidney disease, *eGFR* estimated glomerular filtration rate, *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *SC* subcutaneous, ✔ indicated and no dose adjustment required, – indication may be variable/consider dose reduction, frequent monitoring and relevant health status, ✗ contraindicated

[a] No dose adjustment required if eGFR is > 50 mL/min

[b] Contraindicated if eGFR < 50 mL/min

Pregnancy and Lactation

Animal studies have reported reproductive toxicity with all GLP-1 RAs and hence use of GLP-1 RAs is contraindicated during pregnancy. It is not recommended for use in breastfeeding women. Women of childbearing age are advised to use contraception during treatment [213]. GLP-1 RA use in special population according to the prescribing information/package insert is summarised in Table 27.

Table 23 GLP-1 RAs in a special population: the elderly

Study details	Aim	Highlights
Dulaglutide (1.5 and 0.75 mg)		
Boustani et al. [195]. Pooled analysis from 6 phase 3 clinical studies [≥ 65 years, n = 958; < 65 years, n = 4213]. Duration 26 weeks	To evaluate the efficacy and safety of dulaglutide in elderly patients with T2DM	Lower hypoglycaemia incidence if patients were not on concomitant SU or insulin therapy. Similar GI AEs incidence with both doses
Exenatide BID (10 μg)		
Pencek et al. [196]. Post hoc analysis from 16 RCTs (≥ 65 years, n = 454; < 65 years, n = 1613). Duration 12–30 weeks	To assess the efficacy and safety of exenatide BID in patients with T2DM	Improvements in HbA1c, FBG and lipid levels (except HDL-C) in both age groups. ≥ 65 years age group: Lower hypoglycaemia incidence (1.2%) if not on concomitant SU and fewer fall-related injuries
Exenatide QW (2 mg)		
Loughlin et al. [153]. Observational, real-world study [EQW (n = 2075), BI (n = 73,610)]. Duration 3 years	To evaluate the effectiveness and tolerability of EQW compared with BI among injectable-drug-naïve patients with T2DM who are elderly (age ≥ 65 years) or have RI	In elderly patients, HbA1c levels changed by − 0.50% (EQW initiators), and − 0.31% (BI initiators) from baseline to follow-up. Weight changed by − 1.6 kg (EQW initiators) and 0.2 kg (BI initiators). Stable renal function from baseline for both initiator groups. 1.45-fold increased risk of nausea and vomiting with EQW initiators than BI initiators
Pencek et al. [197]. Post hoc analysis of pooled data from 7 randomised, controlled, phase 3 trials [n = 1719) including age (< 65 or ≥ 65 years). Duration 24–30 weeks	To evaluate the efficacy and tolerability of EQW in patients with T2DM	Significant improvements in HbA1c, FBG and body weight, BP, lipids. Most common AEs: GI in nature
Liraglutide (up to 1.8 mg/day)		
Gilbert et al. [198]. Post hoc analysis of randomised, placebo-controlled, double-blind, CV outcomes LEADER trial [N = 9340]. Duration 3.5–5 years	To assess the risk of CV events and all-cause mortality in elderly patients with T2DM	Significant reduction in CV risk events and all-cause mortality ($P < 0.05$) as compared to placebo
Chitnis et al. [199]. Real-world retrospective cohort study [≥ 65 years (n = 517)]. Duration 6–12 months	To assess the clinical effectiveness of liraglutide in patients with T2DM	Significant and sustained reduction in HbA1c and weight ($P < 0.01$). No evidence of severe hypoglycaemia

Table 23 continued

Study details	Aim	Highlights
Lixisenatide (20 μg)		
Raccah et al. [200]. Pooled data from 6 placebo-controlled phase 3 trials from lixisenatide [elderly (≥ 65 years, *n* = 544) and very elderly (≥ 75 years, *n* = 79)]. Duration 12–24 months	To evaluate the efficacy and safety of lixisenatide QD in elderly and very elderly patients	Placebo-adjusted HbA1c reductions were comparable with the younger age groups (< 65 and < 75 years old). Maintained efficacy in patients with more severe β-cell dysfunction. Reported symptomatic hypoglycaemia in patients with insulin as concomitant medication
Semaglutide (0.5 or 1.0 mg)		
Warren et al. [201]. Pooled analysis of phase 3 SUSTAIN 1–5 trials (elderly ≥ 65 years, *n* = 854; non-elderly < 65 years, *n* = 3045). Duration 30–56 weeks	To assess the efficacy and safety of semaglutide vs. comparators in patients with T2DM	Consistent improvement in HbA1c and body weight across both age groups. > 85% of treated elderly patients achieved a less stringent target of HbA1c < 8%. Premature treatment discontinuations were higher in elderly versus non-elderly patients. No increased risk of hypoglycaemia was observed

AEs adverse events, *BI* basal insulin, *EQW* exenatide QW, *CV* cardiovascular, *FBG* fasting blood glucose, *GI* gastrointestinal, *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *HbA1c* glycated haemoglobin, *HDL-C* high-density lipoprotein cholesterol, *LEADER* liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results (liraglutide, 1.8 mg QD), *RCTs* randomised controlled trial, *RI* renal impairment, *SU* sulfonylurea, *SUSTAIN-6* trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes (semaglutide, 0.5 mg or 1.0 mg QW), *T2DM* type 2 diabetes mellitus

Checklists for GLP-1 RA Therapy Initiation

GLP-1 RA therapy initiation is largely influenced by clinical requisites of patients. The criteria for patient selection for GLP-1 RA-based therapy, ideal patient type, rationale for initiation of different kinds of GLP-1 RA-based therapy and factors affecting the selection of the appropriate GLP-1 RA are discussed below.

Patient Selection and Rationale for GLP-1 RA-Based Therapy Initiation

Checklists for patient selection and rationale for GLP-1 RA-based therapy initiation are listed in Fig. 4.

Factors Influencing the Selection of Appropriate GLP-1 Analogue

An array of GLP-1 analogues are available on the market, and a few others are at various stages of approval to be released in the near future. Given the range and unique pharmacological properties, a patient-centred approach is feasible with this class of drugs. The factors that influence the choice of GLP-1 RA could be largely classified into biomedical and psychosocial factors [214].

Biomedical Factors

Biomedical factors that dictate the choice of GLP-1 RAs consist of efficacy, safety and tolerability along with its versatility in combination with insulin [214]. The efficacy of GLP-1 RAs

Table 24 GLP-1 RAs in special populations: paediatric and adolescents

Study details	Aim	Highlights
Exenatide		
Censani et al. [202]. Case series [$N = 2$]. Duration 3–6 months	To report the effects of exenatide on metabolic risk and weight in adolescents with morbid obesity and T2DM	Exenatide treatment resulted in improvements in cardiometabolic risk factors[a]
Liraglutide		
Klein et al. [203]. Randomised, double-blind, placebo-controlled trial [$N = 21$]. Duration 5 weeks	To assess the safety, tolerability, PK/PD of liraglutide (monotherapy or combination therapy with metformin) in youth (10–17 years old) with T2DM	Liraglutide 1.8 mg: $t_{1/2} = 12$ h, clearance = 1.7 L/h. Liraglutide 1.8 mg resulted in greater decline in HbA1c level compared with placebo (– 0.86 vs. 0.04%, $P = 0.0007$), no severe hypoglycaemia but transient GI AEs during dose escalation. Liraglutide 1.8 mg was safe and well tolerated
Zhou et al. [204]. Prospective randomised controlled trial [$N = 42$]. Duration 3 months	To evaluate the clinical efficacy of GLP-1 RAs for reversal of normal blood glucose in children with pre-diabetes	GLP-1 analogues were better as compared to control group owing to significantly lower FBG and 2 h PPBG levels (post 1 month) ($P < 0.01$); statistically better controlled HbA1c, lipids and BMI (post 3 months); significantly decreased IR index ($P < 0.05$); statistically higher values of the β-cell islet function index ($P < 0.05$)

AEs adverse events, *BP* blood pressure, *BMI* body mass index, *FBG* fasting blood glucose, *GI* gastrointestinal, *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *HbA1c* glycated haemoglobin, *IR* insulin resistance, *PD* pharmacodynamics, *PK* pharmacokinetics, *PPBG* postprandial blood glucose, *T2DM* type 2 diabetes mellitus

[a] Triglyceride levels, BP, FBG, HbA1c

largely depends on their ability to exert a stronger effect on either fasting or postprandial glucose. Long-acting agents are known to act on fasting blood glucose to a larger extent, whereas short-acting agents are known to have a greater effect on PPBG. Therefore, the choice of the drug could depend on the time when the patient is experiencing glucose fluctuations. Interestingly, GLP-1 RAs such as dulaglutide, liraglutide and lixisenatide are reported to have exhibited clinically relevant fasting and postprandial glycaemic benefits [22, 214, 215].

The duration of action also determines the possible combination with insulin (short-acting insulin or basal) owing to their complementary pharmacology; theoretically, this combination influences both fasting and postprandial glucose [214].

The choice of GLP-1 RAs may also be influenced by the anticipated AEs including upper and/or lower GI AEs which may vary among GLP-1 analogues and autonomic functions such as GI motility [39, 178, 214, 216].

Other factors to be considered are the effect of GLP-1 RAs on cardiac and renal systems and other comorbidities of concern [214].

Table 25 GLP-1 RAs in a special population: sleep apnoea

Study details	Aim	Highlights
Liraglutide		
Blackman et al. [205]. SCALE Sleep Apnoea randomised, double-blind, placebo-controlled parallel-group trial [liraglutide, n = 180; placebo, n = 179]. Duration 32 weeks	To investigate whether liraglutide 3.0 mg reduces OSA severity versus placebo	Liraglutide 3.0 mg resulted in (when compared to placebo) greater AHI mean reduction (− 12.2 vs. − 6.1 events/h, estimated treatment difference − 6.1 events/h [95% CI − 11.0 to − 1.2]; P = 0.0150); greater mean reduction in weight (− 5.7% vs. − 1.6%, estimated treatment difference − 4.2% [95% CI − 5.2 to − 3.1%], $P < 0.0001$); greater reductions in HbA1c levels and SBP (both $P < 0.001$)

AHI apnoea–hypopnoea index, *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *HbA1c* glycated haemoglobin, *OSA* obstructive sleep apnoea, *SBP* systolic blood pressure, *SCALE* satiety and clinical adiposity–liraglutide evidence in individuals with and without diabetes

Table 26 Guidelines for the use of GLP-1 RAs during Ramadan

Situation in pre-Ramadan	Action during Ramadan
Single dose before breakfast. Exenatide may be used twice within 1 h before meal	Same dose to be taken before Iftar. Exenatide same as pre-Ramadan before Iftar/or Sahur

Guidelines are for GLP-1RAs: liraglutide 0.6/1.2/1.8 mg, lixisenatide 10/20 µg and exenatide 5/10 µg
GLP-1 RA glucagon-like peptide-1 receptor agonist

Patient-Related Factors

Psychosocial factors that affect the selection of GLP-1 RAs include the ability of the patient to self-inject, their meal patterns and adherence to the pre-specified time of injection, frequency of contact with healthcare providers, cost-effectiveness and so on [214].

For a person who can self-inject, all GLP-1 RAs are equally feasible for use. Certain GLP-1 RAs require manual dexterity as a few of them need needle attachment, reconstitution and priming prior to injection. Injection frequency, discussed in a forthcoming section, is another important factor. The injection frequencies among GLP-1 analogues vary from twice-daily to once-weekly administration owing to different pharmacological profiles [214].

Meal patterns may also influence the choice of GLP-1 analogues. Liraglutide is effective with all kinds of meal patterns adopted by patients. Exenatide BID may benefit patients who consume heavy breakfast and dinner, whereas those who take a light dinner may benefit from lixisenatide. Patients with irregular meal patterns and lifestyle who are at risk of hypoglycaemia may benefit from once-weekly drugs without major safety concerns [214].

Another important psychosocial aspect is the cost associated with GLP-1 analogues. Currently, none of the agents are available generically and therefore all GLP-1 analogues have a relatively high cost [178, 214].

A few GLP-1 analogues have, however, demonstrated treatment satisfaction versus a few comparators such as sulfonylureas, insulin and DPP4 inhibitors [217–219].

Table 27 Recommendations on GLP-1 RA use in special populations

Patients with [42–45, 190, 191]	Dulaglutide QW	Exenatide BID	Exenatide QW	Liraglutide QD	Lixisenatide QD	Semaglutide QW
Renal impairment						
Mild/moderate renal disease	No dose adjustment required	Caution should be taken when initiating or escalating dose	Caution should be taken when initiating a dose	No dose adjustments needed/to be used with caution in patients with dehydration	No dose adjustments needed	Renal function to be monitored in patients with renal impairment reporting severe GI symptoms
End-stage renal disease	No dose adjustment required/to be used with caution in patients with GI side effects	Not to be used	Not recommended		Not recommended	
Hepatic impairment	To be used with caution/dose adjustment not needed	Primarily cleared by kidney/ hepatic impairment does not affect blood concentration	Not studied	To be used with caution/dose adjustment not needed	Not studied	No dose adjustment is recommended
H/O pancreatitis	Not studied/other antidiabetic medications to be considered	Not studied/ other antidiabetic medications to be considered	Not studied/ other antidiabetic therapies to be considered	–	Not studied/ other antidiabetic medications to be considered	Not studied/other antidiabetic medications to be considered
Geriatric patients	Subject to sensitivity (≥ 65) 0.75 mg is recommended	Dose should be selected on the basis of renal function of the elderly patients	Caution should be taken when initiating	Subject to sensitivity (≥ 65 years)	Subject to individual sensitivity (≥ 65 years)	Subject to individual sensitivity

Table 27 continued

Patients with [42–45, 190, 191]	Dulaglutide QW	Exenatide BID	Exenatide QW	Liraglutide QD	Lixisenatide QD	Semaglutide QW
Pregnancy	Limited data/only if the potential benefit justifies the potential risk to the foetus. Physician should be informed	Physician should be informed	Only if the potential benefit justifies the potential risk to the foetus	Only if the potential benefit justifies the potential risk to the foetus/physician should be informed	Limited data. Physician should be informed	Limited data with semaglutide use in pregnant women
Lactation	No data on human milk/ developmental and health benefits of breastfeeding should be considered along with the mother's clinical need	Caution should be taken	–	No data on human milk. Developmental and health benefits of breastfeeding should be considered along with the mother's clinical need	–	No data on the presence of semaglutide in human milk, effects on the breastfed infant or effects on milk production
Women of childbearing age	Physician to be informed if planning to get pregnant	Physician to be informed if planning to get pregnant	–	Physician to be informed if planning to get pregnant	–	To be discontinued in women at least 2 months before a planned pregnancy because of the long washout period for semaglutide

– not specified, *GI* gastrointestinal tract, *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *H/O* history of

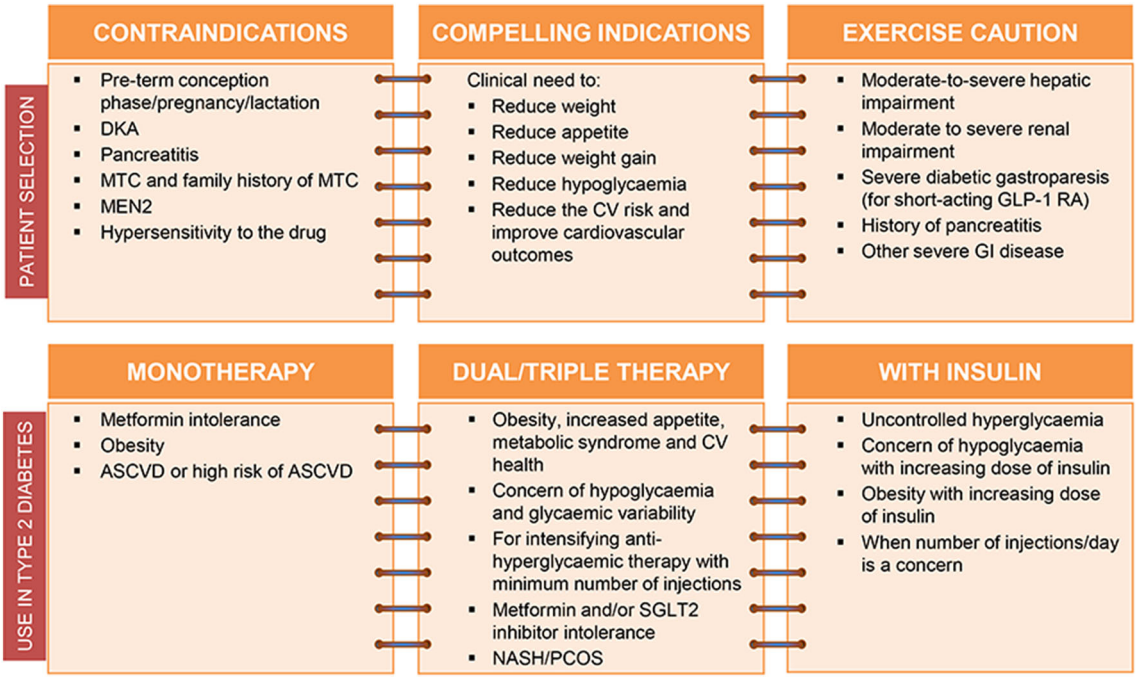

Fig. 4 Patient selection and rationale for GLP-1 RA therapy initiation. *ASCVD* atherosclerotic cardiovascular disease, *CV* cardiovascular, *DKA* diabetic ketoacidosis, *GI* gastrointestinal, *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *MEN2* multiple endocrine neoplasia, *MTC* medullary thyroid carcinoma, *NASH* non-alcoholic steatohepatitis, *PCOS* polycystic ovary syndrome, *SGLT2* sodium-glucose co-transporter-2

Table 28 Selection of appropriate GLP-1 RA

Parameters	GLP-1 RA		
	Short-acting	Intermediate-acting	Long-acting
Glycaemia			
FBG	+	++	+++
PPBG	+++	++	++
Weight	++	+++	+++
CVO	+	+++	+++
Injection burden	+++	++	+
Renal safety	+	++	++
GI intolerance	+++	++	+

The number of '+' signs indicates the weighting for consideration of the parameter for respective therapy
CVO cardiovascular outcomes, *FBG* fasting blood glucose, *GI* gastrointestinal, *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *PPBG* postprandial blood glucose

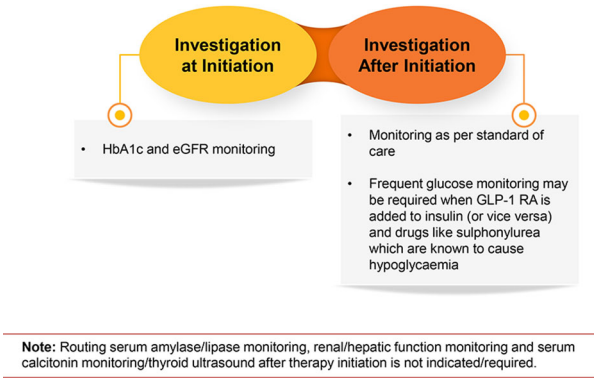

Fig. 5 Monitoring checklist for GLP-1 RA-based therapy. *eGFR* estimated glomerular filtration rate, *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *HbA1c* glycated haemoglobin

Selection of Appropriate GLP-1 Analogue

The efficacy and safety profiles vary among the GLP-1 RAs because of their varying pharmacokinetic profiles. Hence, GLP-1 RAs can be chosen on the basis of the clinical need of the patients. Table 28 illustrates the selection criteria based on the efficacy of GLP-1 RAs to act upon a clinical parameter.

Monitoring Checklist Specific for GLP-1 RA-Based Therapy

Proactive monitoring aids in improving therapeutic outcomes and preventing potential adverse drug effects. It provides essential information for the management of chronic conditions such as diabetes to both healthcare providers and patients. Figure 5 lists the recommended procedures, lab tests and physical assessments to be performed or reviewed before and after the initiation of GLP-1 RA therapy.

Injection Technique and Frequency

One of the main advantages of GLP-1 RAs with respect to mode of administration is the ready-to-use pens which improve adherence to therapy. Studies have reported favourable patient outcomes with pen delivery systems compared to vial or syringe systems [220, 221]. Table 29 compares the injection pens and delivery patterns of GLP-1 RAs.

Dulaglutide has a hidden, ready-attached needle which requires no priming; this may help patients with fear of needles [223]. Once-weekly doses reduce the injection burden on patients who are unwilling to self-inject, have aversion to needles and are unable to adhere to frequently administered therapy. This also helps patients who depend on caregivers for injections. Dulaglutide and semaglutide require once-weekly doses owing to their extended duration of action [223]. Such once-weekly injections can also be administered as directly observed therapy which encourages regular patient–provider contact.

Combinations of GLP-1 RA and Insulin

As discussed earlier, many guidelines across the world recommend GLP-1 RAs along with insulin. Given the versatility of GLP-1 RAs, the rationale behind combining basal insulin with GLP-1 RAs is the fact that combination optimises the prandial endogenous insulin response to control PPBG and reduces the insulin dose requirement [228]. Their complementary modes of action are known to improve glycaemic control in many patients with T2DM with no significant risk of hypoglycaemia and weight gain [229]. In addition, fixed-ratio combination has the advantage of a less complex treatment regimen, with only one injection per day.

The USFDA has currently approved two titratable, fixed-ratio combination therapies for the treatment of patients with T2DM [230]. Table 30 presents the fixed-ratio combination of insulin/GLP-1 RA currently available on the market along with the clinical evidence available on combination therapy.

Quality of Life: GLP-1 RA-Based Therapy

Quality of life associated with GLP-1 RA-based therapy is presented in an evidence-based manner as follows:

A study examined and compared patient perceptions of the injection devices used with liraglutide and dulaglutide. Patients with T2DM

Table 29 Comparison of injection pens and delivery patterns of GLP-1 RAs

Parameters GLP-1 RA	Delivery devices	Time to steady state[a]	Administration frequency[b]	Need to attach needle to pen	Need to prime pen?	Reconstitution requirement
Dulaglutide [222, 223]	Single-dose prefilled pen (0.75 mg, 1.5 mg)	2–4 weeks	Once weekly	No	No	No
Exenatide BID [223, 224]	Multi-dose prefilled pens (5 μg/dose, 10 μg/dose)	Not reported	Twice daily	Yes	Yes	No
Exenatide QW [223, 225]	Single-dose, dual-chamber pen containing powder (2 mg) and solvent for prolonged-release suspension and single-dose prefilled pen for prolonged-release suspension (2 mg)	6–7 weeks	Once weekly	Yes	No	Yes
Liraglutide [223, 226]	Multi-dose prefilled pen (device delivers 0.6, 1.2 or 1.8 mg/dose)	Not reported	Once daily	Yes	Yes	No
Lixisenatide [223, 227]	Multi-dose prefilled pens (10 μg/dose, 20 μg/dose)[c]	Not reported	Once daily	Yes	Yes	No
Semaglutide [50, 51]	Multi-dose prefilled pens (device delivers 0.25, 0.5 and 1 mg/dose)	4–5 weeks	Once weekly	Yes	Yes	No

All the above drugs should be refrigerated between 2 and 8 °C before their first use. Not to be kept in freezer and not be used if frozen. The devices should be protected from heat and sunlight

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

[a] Approximate values

[b] All GLP-1 receptor agonists administered subcutaneously

[c] Also available as a treatment-initiation pack containing both doses of multi-dose prefilled pens

across the USA (N = 404, mean age = 60.7 years, 54.0% female; 204 liraglutide; 200 dulaglutide) were recruited for the study. Patients who had experience with both the treatments completed the Diabetes Injection Device Preference Questionnaire (DID-PQ) to report preferences between the two devices. Analysis of covariance was used to compare Diabetes Injection Device Experience Questionnaire (DID-EQ) scores. Although the mean DID-EQ item scores for both treatments were high (ranging from 3.48 to 3.90 on a 4-point scale), it was demonstrated that dulaglutide had higher scores than liraglutide on DID-EQ global items, which assessed the ease of use (3.82 vs. 3.73, P = 0.040) and convenience (3.79 vs. 3.66, P = 0.004). Among the 58 patients who had used both devices, more patients reported a preference for the dulaglutide device than the liraglutide device on every item of the DID-PQ [237].

A study on the safe and effective use of dulaglutide single-dose pen in injection-naïve patients with T2DM reported that the majority of patients (> 96%) found the device easy to use. They were satisfied with the pen, and were willing to continue and recommend the pen to others. A significant reduction in the fear of self-injection from baseline to the end of the study was also reported [238].

Another prospective, observational study analysed the changes in health-related quality of life and emotional well-being in patients who

Table 30 Fixed-dose basal insulin/GLP-1 RA combination product information and clinical evidence on basal insulin/GLP-1 RA combination

Fixed-dose basal insulin/GLP-1 RA	Product information			Dosing and administration			Clinical evidence highlights
	Package	Storage	Expiration	Initial dose	Titration	Missed dose	
IDegLira: Insulin degludec/liraglutide (Xultophy®) [231]	3-mL pens, 5 pack	Unopened: Refrigerator Opened: Room temp	Unopened: Expiration date Room temp: 21 days	16 units	2 units every 3–4 days, max 50 units/day	1–2 days: resume with next scheduled dose; > 3 days: 16 units	DUAL-I, a phase 3, open-label, randomised, 26-week, treat-to-target trial reported IDegLira to be non-inferior to insulin degludec and superior to liraglutide. A significantly greater number of patients in the insulin degludec/liraglutide group achieved HbA1c < 7%, weight loss and lower insulin requirements [232] DUAL-II, a 26-week, randomised, double-blind trial (N = 413) reported that IDegLira was superior to IDeg, with significantly greater reduction in HbA1c (1.9% vs. 0.9%, $P < 0.0001$) without hypoglycaemia or weight gain [233] DUAL-V, a phase 3, multinational, multicentre, 26-week, randomised, open-label (N = 557), reported insulin degludec/liraglutide to be non-inferior compared to up-titration with glargine. Treatment with degludec/liraglutide compared with glargine showed a statistically superior HbA1c reduction (− 1.81% vs. − 1.13, $P < 0.001$), weight loss of 1.4 kg vs. 1.8 kg weight gain and fewer hypoglycaemic episodes [234]

Table 30 continued

Fixed-dose basal insulin/GLP-1 RA	Product information			Dosing and administration			Clinical evidence highlights
	Package	Storage	Expiration	Initial dose	Titration	Missed dose	
iGlarLixi: Insulin glargine/lixisenatide (Soliqua®) [235]	3-mL pens, 5 pack	Unopened: Refrigerator Opened: Room temp	Unopened: Expiration date Room temp: 14 days	<30 units basal insulin or on lixisenatide: 15 units 30–60 units basal insulin: 30 units	2–4 units weekly, max 60 units/day	Resume with next scheduled dose	LixiLan-O, a 30-week, randomised trial (N = 1170), reported iGlarLixi compared with insulin glargine and lixisenatide to be superior in HbA1c reductions (6.5% vs. 6.8% and 7.3%, respectively; both $P < 0.0001$) along with improvement in adverse effects (hypoglycaemia, weight gain, nausea and vomiting) [236]

GLP-1 RA glucagon-like peptide-1 receptor agonist, *HbA1c* glycated haemoglobin

had commenced GLP-1 analogue therapy (exenatide) in comparison with new insulin starters. At 6 months, the patient group treated with exenatide experienced significantly greater treatment satisfaction ($P < 0.05$), well-being ($P < 0.05$) and reduced hospital anxiety and depression scale scores ($P < 0.05$) compared to the insulin-treated group. Results from multivariate analysis showed a cumulative significant effect ($P < 0.05$) of exenatide analogue therapy on diabetes treatment satisfaction questionnaire and Well-Being Questionnaire 12 scores after controlling for the effect of BMI [218].

Treatment satisfaction and improvement in the quality of life influence adherence to medications. A series of randomised trials assessed once-weekly administration of dulaglutide as an add-on therapy in patients with T2DM. The study reported improvement in perceived hypoglycaemia and treatment satisfaction as assessed by Diabetes Treatment Satisfaction Questionnaire (DTSQ) status and change version compared to placebo and exenatide BID at 26 and 52 weeks [239].

A 52-week randomised, parallel-group, open-label trial compared the efficacy and safety of once-daily human GLP-1 analogue liraglutide (1.2 or 1.8 mg) with DPP4 inhibitor sitagliptin, added onto metformin in individuals with T2DM. DTSQ scores increased significantly ($P = 0.03$) more with liraglutide (1.8 mg) than with sitagliptin [217].

A 52-week randomised, double-blind controlled trial investigated the patient-reported outcomes which included psychological well-being and distress in addition to other factors following treatment with liraglutide (1.2 or 1.8 mg) or glimepiride monotherapies in patients with T2DM. Glycaemic control and weight reduction were significantly greater in patients treated with 1.2 or 1.8 mg liraglutide ($P < 0.0001$) compared to glimepiride which resulted in weight gain. Mental and emotional health, and general perceived health improved more with liraglutide (1.8 mg) than with glimepiride [219].

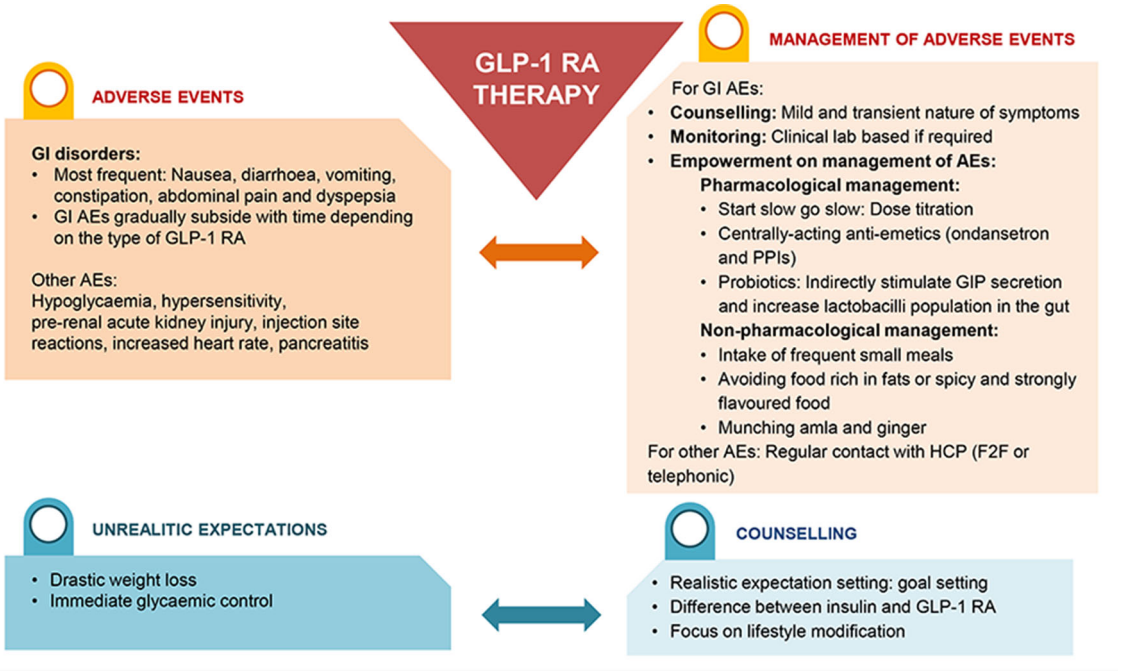

Fig. 6 Barriers to bridges in GLP-1 RA therapy. *AEs* adverse events, *F2F* face-to-face, *GI* gastrointestinal, *GIP* glucose-dependent insulinotropic polypeptide, *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *HCP* healthcare practitioner, *PPI* proton pump inhibitor

Cost Implications

Cost-effectiveness plays a major role from the South Asian perspective wherein out-of-pocket health expenditure is witnessed by patients without any aid from the government [240, 241]. Listing GLP-1 RAs in the national list of essential medicines may reduce financial burden and pave the way for insurance benefits.

Barriers to Bridges: GLP-1 RA Therapy

Adverse events associated with GLP-1 RAs are one of the major barriers for adherence to the therapy. The AEs most frequently associated with GLP-1 RAs are GI disorders, as evident from clinical trials and real-world studies [242–244]. The GI symptoms are reported to gradually subside with time and are dependent on the kind of GLP-1 RAs administered (short- or long-acting) [39]. GI AEs may not affect glycaemic control but may be associated with greater weight loss [245]. Among the GI symptoms, nausea and diarrhoea were reported to be the most common, followed by vomiting, constipation, abdominal pain and dyspepsia [246]. The incidence of nausea is reported to vary between 25% and 60%, and its occurrence in specific individuals seems to be dependent on factors such as meal size, frequency and BMI [39]. The other AEs include pre-renal acute injury, hypoglycaemia, injection site reactions, hypersensitivity, increase in heart rate and acute pancreatitis (proven in animal studies) [39, 178, 214, 216, 246, 247].

Counselling patients on mild and transient nature of symptoms, especially GI symptoms, may aid them to deal with unrealistic fears associated with AEs. Additionally, patient counselling about realistic expectations from the therapy may improve adherence to the therapy. The barriers associated with GLP-1 RA-based therapy and the ways to mitigate these barriers are presented in Fig. 6.

Directly observed therapy (DOT) is an approach that facilitates patients to self-inject in the presence of a diabetes educator. This

method is advantageous for both patient and the practitioner supporting the patient. It encourages regular patient–provider contact, which in turn facilitates early detection of AEs and complications and promotes more efficient lifestyle modifications [22].

CONCLUSIONS

GLP-1 RAs, recognised as calorie restriction mimetics or calorie restriction facilitators, are relatively a newer class of injectable drugs in the pharmacological armamentarium for the management of T2DM. With benefits extending beyond glucose control, GLP-1 RAs are associated with extra-glycaemic effects including positive effects on weight, BP, cholesterol levels and β-cell function. Fortuitously, increasing evidence from large clinical trials aimed at studying CV episodes has also demonstrated CV risk reduction with GLP-1 RAs. The REWIND trial is anticipated to resolve the long-standing question on whether this class of drug could be beneficial in patient populations without an established CVD as their usefulness in patients with established CVD had already been demonstrated with a wealth of evidence. As GLP-1 RA therapy initiation is largely influenced by clinical requisites of patients, it is imperative that a pragmatic review of current evidence be integrated and applied in the context of an individualised patient-centred approach. However, there are quite a few unanswered questions on GLP-1 RAs such as long-term durability of their glycaemic effect, recommendation in the current cascade of therapy for T2DM, long-term safety concerns and so on. It is anticipated that the ongoing trials, in an evidence-based manner, will continue to fill these gaps and bring new paradigm shifts in diabetes care.

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