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...
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 post-prandial 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...
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 m². Both exenatide and lixisenatide are contraindicated in patients with eGFR < 30 mL/min/1.73 m². 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].

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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

| Country   | Total adult populationa | Diabetes casesa | Ratioa,b | Undiagnosed diabetes casesa | Diabetes national prevalencea (%) | Diabetes age-adjusted comparative prevalencea (%) | Diabetes-related deatha | 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
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
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].

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...
insulinotropic mechanism of action in pancreatic \(\beta\)-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 \(\beta\)-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].

Intermediate-Acting GLP-1 RAs

The intermediate-acting GLP-1 RA 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 (~ 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
| Function     | Parameters | Dulaglutide QW [42] | Exenatide BID [43] | Exenatide QW [44] | Liraglutide QD [45, 46] | Lixisenatide QD [47] | Semaglutide QW [48–51] |
|--------------|------------|---------------------|--------------------|-------------------|------------------------|----------------------|------------------------|
| Absorption   | $C_{\text{max}}$ | 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 and proteolytic degradation | 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 |
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.

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 \( \leq 7.5\% \). 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<sup>a</sup> 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

<sup>a</sup> QTc: in electrocardiography, the duration of the QT interval adjusted for the patient’s heart rate
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

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

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
| Association/country | Top recommendations on the use of GLP-1 RAs | 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<sup>b</sup> |
|                     | 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<sup>c</sup>, 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 |
| Association/country | Top recommendations on the use of GLP-1 RAs | 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 |
| Association/country | Top recommendations on the use of GLP-1 RAs<sup>a</sup> | 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 | |
| Association/country                      | Top recommendations on the use of GLP-1 RAs\textsuperscript{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<sup>a</sup> | 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. |                   |

<sup>a</sup> Refer to cited guidelines for detailed information

<sup>b</sup> Individualised goals: A1c ≤ 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

<sup>c</sup> Typical osmotic or catabolic symptoms of diabetes mellitus

**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
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...
| 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 | 12–30 weeks, 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 |
| 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 |
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. 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)** |

**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) |
| Study details | Aim | Highlights of GLP-1 RA therapy |
|--------------|-----|-------------------------------|
| Exenatide QW | 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 |
| Kayaniyil et al. [87]. Network meta-analysis and systematic review of 14 RCTs [N = 161]. Duration 24 ± 6 weeks | | |
| 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<sup>c</sup> 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<sup>d</sup> were met in 16.9% to 47.0% of patients |
| Lixisenatide | 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 \((-0.52\%; 95\% \text{ CI } -0.64\text{ to } -0.39\) and 2-h PPBG. \((-4.58 \text{ mmol/L}; 95\% \text{ CI } 5.88 \text{ to } 3.28\), respectively\) |
| 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 \((\text{WMD } -0.93\%, 95\% \text{ CI } -1.24\text{ to } -0.62, P < 0.001\), FBG \((\text{WMD } -1.15 \text{ mmol/L}, 95\% \text{ CI } -1.67\text{ to } -0.63, P < 0.001\) and mean SMPG \((\text{WMD } -1.19 \text{ mmol/L}, 95\% \text{ CI } -1.68\text{ to } -0.70, P < 0.001\))\). Higher risk of GI disorders \((\text{RR } 1.98; 95\% \text{ CI } 1.49–2.62; P < 0.001)\) |
| Multiple GLP-1 analogues Kim et al. [94]. Systematic review and meta-analysis with 15 trials \(n = 5090, (2703 \text{ in treatment groups and } 2387 \text{ in control groups})\). 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 \(-1.48\text{ to } -0.85\) 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 \([\text{RR } 5.7(3.8, 8.7)]\) than non-Asian-dominant studies \([\text{RR } 2.8(2.4, 3.3)]\), respectively |
Table 12 continued

| Study details | Aim | Highlights of GLP-1 RA therapy |
|---------------|-----|-------------------------------|
| Esposito et al. [95]. Meta-analysis of 25 RCTs \( [N = 9771; \text{GLP-1 RA treated, 5083; placebo or comparator treated, 4688}] \). 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. 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 \( [N = 812 \text{ received study drug}] \). Duration \( \sim 6 \text{ months} \) | 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 |

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
| 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 \(\geq 3\) years | To evaluate the effects of exenatide therapy on glycaemic control, body weight, cardiometabolic markers and safety | Progressive reduction in body weight \((-5.3 \pm 0.4\) 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 \(-4.7 \pm 0.3\) 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 \((6.46 \pm 0.8\) kg; \(P < 0.001\)) |
| Study details | Aim | Highlights |
|---------------|-----|-----------|
| **Exenatide QW**<br>Grimm et al. [88]. Post hoc analysis of integrated data from DURATION trials (6 randomised, comparator-controlled) \(N = 1379\). Duration 24–30 weeks<br>Jabbour et al. [105]. Post hoc analysis, DURATION-8 study \(N = 574\). Duration 28 weeks | To evaluate the efficacy, safety and tolerability of EQW in patients with T2DM<br>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 | 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<br>Reduction in weight: EQW plus dapagliflozin group: \((- 3.55 \pm 0.29\) kg); Significant vs. EQW group \((- 1.56 \pm 0.29\) kg; \(P < 0.001\)) vs. dapagliflozin \((- 2.22 \pm 0.28\) kg; \(P < 0.001\)) |
| **Liraglutide**<br>Blonde and Russell-Jones [106]. Overview of LEAD (1–5) trials \(N > 4000\). Duration 26–52 weeks<br>Davies et al. [107]. Randomised, double-blind, placebo-controlled, parallel-group trial. SCALE Diabetes RCT \(N = 846\). Duration 56 weeks<br>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 safety and efficacy of liraglutide with or without OAD drug therapy in patients with T2DM<br>To evaluate the efficacy and safety of liraglutide versus placebo for weight management in overweight or obese adults with T2DM<br>To evaluate the effectiveness and tolerability of liraglutide for 2 years in patients with and without previous BS and T2DM with obesity | Liraglutide vs. comparators: Significantly greater weight reduction (1–3.24 kg). Greater weight loss in subjects with high BMIs<br>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 \(\geq 5\)% 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)<br>Significant weight reduction: BS group: \(\Delta\) weight \(- 3.4\) kg<br>Non-BS group: \(\Delta\) weight \(- 3.8\) kg; \((P < 0.05)\) |
| **Lixisenatide**<br>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) |
| Study details | Aim | Highlights |
|---------------|-----|-----------|
| **Semaglutide** | 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 (≥ 5% and ≥ 10%) with semaglutide versus comparators across all BMI subgroups (P < 0.05) |
| Ahren et al. [109]. Post hoc analysis of SUSTAIN (1–5) trials \(N = 3899\). Duration 30 or 56 weeks | | |
| **GLP-1 RAs: Exenatide BID, albiglutide, dulaglutide, liraglutide and lixisenatide** | 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) |
| 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 | | Weight reduction with liraglutide was similar to exenatide BID but greater than that observed with EQW, albiglutide and dulaglutide |
| Madsbad [96]. Review including 9 phase 3 head-to-head trials and 1 large phase 2 study \(N = 812\). Duration ~ 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** | 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 |
| Bhandari et al. [113]. Prospective study \(N = 90\). Duration 12 months | | |
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 \((- 12.5 \text{ kg})\) and waist circumference \((- 13 \text{ cm})\); \(P < 0.0001\). BMI was reduced to \(< 35 \text{ kg/m}^2\) in about 20% of patients |
| Sun et al. [114]. Systematic review and network meta-analysis of 17 RCTs \([N = 4365]\). Duration \(\geq 8\) weeks | To assess the effect of GLP-1 RAs on waist circumference for T2DM patients | Significant waist circumference reduction vs. placebo: \(- 5.24 \text{ cm (liraglutide 1.8 mg QD)}\) (95% CI \(- 7.68, - 2.93\)), \(- 4.73 \text{ cm (liraglutide 1.2 mg QD)}\) (95% CI \(- 6.68, - 2.65\)), \(- 1.34 \text{ cm (exenatide 10 \mu g BID)}\) (95% CI \(- 2.00, - 0.75\)). Significantly decreased waist circumference by \(- 1.73 \text{ cm (liraglutide 1.8 mg vs. sitagliptin)}\) (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
| Study details | Aim | Highlights |
|---------------|-----|------------|
| 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 | GLP-1 RAs 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 $-0.11$] |
| Sun et al. [116]. Systematic review and network meta-analyses of 35 RCTs [$N = 14,340$]. Duration $\geq 8$ weeks | To assess the effect of GLP-1 RAs on lipid profiles in patients with T2DM | |

*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
| Reference/study          | Study design                                                                 | Duration | Change in SBP (mmHg)                                                                 | Change in DBP (mmHg)                                                                 |
|--------------------------|------------------------------------------------------------------------------|----------|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| Dulaglutide              |                                                                              |          | 
| Giorgino et al. [118].   | Randomised open-label comparator (double blind to dulaglutide dose),         | 78 weeks | \(-0.70 \pm 0.85\) (1.5 mg), \(-0.59 \pm 0.85\) (0.75 mg) (on treatment with       | \(-0.44 \pm 0.52\) (1.5 mg), \(-0.36 \pm 0.52\) (0.75 mg) (on treatment with       |
| AWARD-2                  | parallel-arm study                                                          |          | dulaglutide)                                                                          | dulaglutide)                                                                          |
| Umpierrez et al. [119].  | Randomised, parallel-arm, double-blind, double-dummy, non-inferiority study | 52 weeks | \(-0.1 \pm 0.88\) (1.5 mg), \(-2.7 \pm 0.88\) (0.75 mg)                              | \(-0.3 \pm 0.60\) (1.5 mg), \(-1.4 \pm 0.59\) (0.75 mg)                              |
| AWARD-3                  |                                                                              |          |                                                                                      |                                                                                      |
| Skrivanek et al. [120].  | Randomised, multicentre, double-blind, parallel-arm study                   | 26 weeks | NA                                                                                    |                                                                                      |
| AWARD-5                  |                                                                              |          |                                                                                      |                                                                                      |
| Dungan et al. [71].      | Phase 3, randomised, open-label, parallel-group study                       | 26 weeks | \(-3.36 \pm 0.7\) (1.5 mg)                                                           | \(-0.22 \pm 0.4\) (1.5 mg)                                                          |
| AWARD-6                  |                                                                              |          |                                                                                      |                                                                                      |
| Ferdinand et al. [121]   | Randomised, double-blind, placebo-controlled study                         | 26 weeks | \(-2.5 \pm 0.6\) (1.5 mg), \(-1.6 \pm 0.6\) (0.75 mg)                               | \(0.3 \pm 0.4\) (1.5 mg), \(-0.1 \pm 0.4\) (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-treated vs. placebo \(-5.91\) (95% CI \(-7.53\) to \(-4.28\), \(P < 0.00001\)). |
|                          |                                                                              |          | Exenatide 2 mg/week vs. insulin glargine \(-3.46\) (95% CI \(-3.63\) to \(-3.29\), \(P < 0.00001\)). | Exenatide-treated vs. sitagliptin \(-0.99\) (95% CI \(-1.12\) to \(-0.87\), \(P < 0.00001\)). |
|                          |                                                                              |          | 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 \(-2.33\), \(P < 0.00001\)). | |
| Reference/study | Study design | Duration | Change in SBP (mmHg) | Change in DBP (mmHg) |
|-----------------|--------------|----------|----------------------|---------------------|
| Exenatide BID   |              |          |                      |                     |
| Baretic et al.  | 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.  | 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, 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 | 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) |
| 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) |
| 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 (12 mg), − 2.9 ± 0.7 (18 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 |
| 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, \(I^2 = 30\%\)) |
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 (QW) | LEADER | ELIXA | SUSTAIN-6 | HARMONY |
|-------------|------------------------------|-------------|--------|-------|-----------|---------|
|             |                              | [139, 140]  | [139, 140] | [139, 140] | [139, 140] | [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/m²) |                             | 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 m² (%) |                             | 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 |

△ Adis
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 m². Both exenatide and lixisenatide are contraindicated in patients with eGFR < 30 mL/min/1.73 m². 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 16 continued**

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

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

| Study details | Aim | Highlights |
|---------------|-----|-----------|
| Dulaglutide | 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 | 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) | 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

△ Adis
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 m² [SE 0.7]; \( P = 0.005 \) vs. insulin glargine), dulaglutide 0.75 mg (LSM 33.8 mL/min/1.73 m² [0.7]; \( P = 0.009 \) vs. insulin glargine) (for insulin glargine 31.3 mL/min/1.73 m² [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 \( \mu \)g) in patients with RI | Well tolerated in mild and moderate RI groups. Therapeutic doses (5 and 10 \( \mu \)g) 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 m² (HR 0.69 [0.57–0.85]) than those with an eGFR > 60 mL/min/1.73 m² (HR 0.94 [0.83–1.07]). Doubling of serum creatinine concentration to an eGFR ≤ 45 mL/min/1.73 m² 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 \( n = 140 \) 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 \( n = 24 \) and control subjects \( n = 23 \). 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 \(-2.4 \pm 0.8 \text{ kg}, \ P = 0.22 \) (ESRD group) and \(2.9 \pm 1.0 \text{ kg}, \ P = 0.03 \) (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 \((+0.1 \text{ mL/min/1.73 m}^2)\) [95% CI \(-9\) to \(9\)] and ERPF \((-17 \text{ mL/min/1.73 m}^2\) \([-61\) 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 \([\text{normal renal function } (\text{lixisenatide } n = 2094, \text{placebo } n = 1150); \text{renal impairment } (\text{mild: lixisenatide } n = 637, \text{placebo } n = 414; \text{moderate: lixisenatide } n = 122, \text{placebo } n = 68)]\). 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 \((P = 0.003 \text{ for both})\). |
| 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 \(\leq 45 \text{ mL/min/1.73 m}^2\), ESRD or renal death were unaffected; however, the event rate was too low \((<1\%)\) to sufficiently explore these outcomes. |
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 \[194\].

**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                          | 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. |
| Seko et al. [171]. Retrospective study [N = 15]. Duration 12 weeks |                                                                      |                                                                            |
| Exenatide BID                         | 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. 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) |
| Klonoff et al. [101]. Open-ended, open-label clinical trial [N = 217 subjects; n = 116, baseline]. Duration 3 years |                                                                      |                                                                            |
| 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 QW                          | 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. |
| Bergenstal et al. [173]. Analysis [N = 675]. Duration 52 weeks |                                                                      |                                                                            |
| Liraglutide                           | 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 |
| Armstrong et al. [174]. A multicentre, double-blind, randomised, placebo-controlled phase II study; LEAN trial [N = 23]. Duration 48 weeks |                                                                      |                                                                            |
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 (hyperinsulinemia) 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...
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. 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 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<sup>a</sup> | 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<sup>b</sup> 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 \( \mu \)g 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

<sup>a</sup> Including metformin, sitagliptin, exenatide BID and insulin glargine

<sup>b</sup> Glimepiride, rosiglitazone, insulin glargine, sitagliptin and exenatide
glycaemic control in women with PCOS [211, 212].
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)** | 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. |
| Boustani et al. [195]. Pooled analysis from 6 phase 3 clinical studies ([≥ 65 years, n = 958; < 65 years, n = 4213]). Duration 26 weeks | | |
| **Exenatide BID (10 µg)** | 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. |
| Pencek et al. [196]. Post hoc analysis from 16 RCTs ([≥ 65 years, n = 454; < 65 years, n = 1613]). Duration 12–30 weeks | | |
| **Exenatide QW (2 mg)** | 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. |
| Loughlin et al. [153]. Observational, real-world study [EQW (n = 2075), BI (n = 73,610)]. Duration 3 years | | |
| 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)** | 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. |
| Gilbert et al. [198]. Post hoc analysis of randomised, placebo-controlled, double-blind, CV outcomes LEADER trial [N = 9340]. Duration 3.5–5 years | | |
| 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. |
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

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### Table 23 continued

| Study details | Aim | Highlights |
|---------------|-----|-----------|
| Lixisenatide (20 µg) | 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 |
| 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 | | |
| Semaglutide (0.5 or 1.0 mg) | 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 |
| 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 | | |

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

| Study details | Aim | Highlights |
|---------------|-----|-----------|
| 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] |
| 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

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

| Study details | Aim | Highlights |
|---------------|-----|-----------|
| 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-1 RAs: 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
| Patients with special populations | 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 studied | Not studied | No dose adjustment is 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 | Not studied/other antidiabetic medications to be considered |
| H/O pancreatitis                 | Not studied/other antidiabetic medications to be considered | Not studied/other antidiabetic medications to be considered | Not studied | – | 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.
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...
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 29 Comparison of injection pens and delivery patterns of GLP-1 RAs

| Parameters GLP-1 RA | Delivery devices                                                                 | Time to steady state<br><br><sup>a</sup> | Administration frequency<br><br><sup>b</sup> | Need to attach needle to pen | Need to prime pen?<br><br><sup>c</sup> | 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)<br><br><sup>c</sup> | 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

<sup>a</sup> Approximate values
<br><br><sup>b</sup> All GLP-1 receptor agonists administered subcutaneously
<br><br><sup>c</sup> Also available as a treatment-initiation pack containing both doses of multi-dose prefilled pens

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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 | Refrigerator | Unopened | 16 units | 2 units | 1–2 days: resume every with next |
|                                   | 5 pack | Room temp | Unopened | 21 days | 3–4 days, scheduled max 50 dose; > 3 days: units/day | 16 units |

- **Initial dose:** 16 units
- **Titration:** 2 units
- **Missed dose:** 1–2 days: resume every with next
- **Clinical evidence highlights: 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]
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 ($P \leq 0.05$), well-being ($P \leq 0.05$) and reduced hospital anxiety and depression scale scores ($P \leq 0.05$) compared to the insulin-treated group. Results from multivariate analysis showed a cumulative significant effect ($P \leq 0.05$) 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 general perceived health improved more with liraglutide (1.8 mg) than with glimepiride [219].

A 52-week randomised, double-blind controlled trial of 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].

Table 30 continued

| Fixed-dose basal insulin/GLP-1 RA | Product information | Dosing and administration | Clinical evidence highlights |
|-----------------------------------|---------------------|---------------------------|-----------------------------|
| iGlarLixi: Insulin glargine/lixisenatide (Soliqua<sup>®</sup>) | 3-mL pens 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
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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