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Research Article

Advances and Future Directions in GLP-1 Receptor Agonist Therapy for Type 2 Diabetes: Efficacy, Safety and Cardiometabolic Benefits

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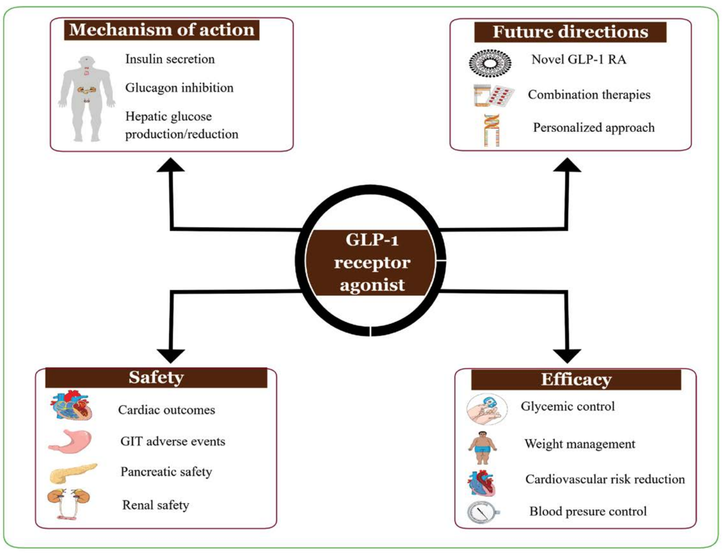
Abstract

The present review thoroughly evaluates the long-term safety, efficacy and cardiovascular outcomes of glucagon-like peptide-1 receptor agonists in the management of type 2 diabetes mellitus. The study was performed in major biomedical databases including PubMed, Embase and the Cochrane Library. The search strategy combined keywords terms related to GLP-1 receptor agonists, type 2 diabetes, safety, efficacy, cardiovascular outcomes and clinical trials. A comprehensive review of clinical trials, meta-analyses and safety reports demonstrates that GLP-1 receptor agonists (RAs) produce significant reductions in glycated hemoglobin (HbA1c) levels, ranging from 0.8% to 1.5%, along with substantial weight loss of 2–6 kg. In addition to controlling blood sugar, research shows that GLP-1 RAs can protect the kidneys and improve heart health. Also, it consistently lower major adverse cardiovascular events and cause mortality in high-risk patients. However, combination regimens incorporating insulin, sulfonylureas or SGLT2 inhibitors significantly improve glycemic control and weight outcomes without a notable rise in adverse events. Even though cardiovascular outcome trials are different from each other, the overall evidence supports the use of GLP-1 RAs as a key part of modern T2DM treatment. Subsequent investigations to emphasize long-term renal safety, biomarker driven individualized therapy and the preparation of novel formulations stratagies to enhance clinical outcomes and recommended customized patient care.

Graphical Abstract



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Keywords: GLP-1 receptor agonists, type 2 diabetes mellitus, cardiovascular outcomes, weight loss, clinical trials of GLP-1, combination therapy

Introduction

Diabetes is a chronic disease synonymous with significant clinical, humanistic and economic consequences that impact individuals worldwide [1]. The management of type 2 diabetes entails the utilization of approved antidiabetic agents that strive to strike a delicate balance between efficacy, safety and the capacity to attain desired glycosylated hemoglobin (HbA1c) targets when tailored to suit the needs of each patient [2]. An in-depth comprehension of the mechanisms of action, regulations, available clinical attributes/licensure and impacts of these agents on distinct subgroups of patients facing the jeopardy of specific adverse effects is paramount [3]. While the regulation of blood sugar levels is crucial, determinants such as body mass index (BMI) and the potential for hypoglycemia further complicate the pathophysiology and overall wellbeing of individuals living with T2DM [4,5]. Currently,the mainstream approach to antidiabetic therapy gravitates towards the amalgamation of different agents, as recommended by authorities in the realms of diabetes and cardiovascular diseases, steering the focus towards a holistic treatment approach [6].

Type 2 diabetes epitomizes a progressive ailment that is initially addressed through dietary modifications, physical activity and oral hypoglycemic drugs [7]. Emerging data on lipid-lowering medications underscore the gradual evolution of the disease, underscoring the necessity for supplementary measures when primary interventions prove ineffective. Despite this relentless progression, which triggers an upsurge in the consumption of antidiabetic drugs, the management of T2DM remains a primary therapeutic intervention lasting up to 8-12 years [8,9]. Nevertheless, the pharmacotherapies employed in diabetic management can precipitate weight gain and hypoglycemia, complicating the therapeutic paradigms [10]. Several oral hypoglycemic agents target the pancreas, where insulin synthesis and release are impaired, accentuating the likelihood of these untoward effects [11]. Consequently, long-acting insulin regimens are instigated to assuage the symptoms correlated with these side effects in T2DM, offering relief and palliation to afflicted individuals [12].

Managing the diverse array of symptoms and complications associated with diabetes mandates a multi-faceted and tailored therapeutic approach, encompassing regular monitoring, lifestyle modifications and pharmacological interventions to ensure comprehensive care of the affected individuals [13, 14]. This patient-centered care approach extends beyond the mere control of blood sugar levels, focusing on enhancing patient outcomes, quality of life and reducing the burden of diabetes-related complications [15]. The intricate interplay between various treatment modalities, ranging from oral antidiabetic agents to injectable insulin therapies and emerging non-pharmacological strategies, necessitates a comprehensive understanding of the disease trajectory and individual patient profiles to optimize therapeutic outcomes and patient well-being [16, 17]. Additionally, diabetes management such as continuous glucose monitoring systems and personalized medicine approaches, offer promising avenues for tailoring treatment plans to the unique needs and preferences of each patient, fostering greater treatment adherence and efficacy while mitigating the risk of adverse events [18, 19]. By embracing a holistic and patient-centric approach to diabetes care, healthcare providers can empower individuals living with diabetes to actively participate in their treatment journey, leading to improved health outcomes, enhanced quality of life and greater overall satisfaction with their care [20, 21]. A comprehensive literature search was conducted across various databases such as PubMed, Scopus, Web of Science, Science Direct, Wiley Online Library and Google Scholar to identify studies on the long-term safety and efficacy of GLP-1 receptor agonists. The investigation included examining publications, dissertations and published floras, clinical trial results, meta-analyses and official safety reports. However, GLP-1 receptor agonists (GLP-1 RAs) are recommended as the first line injectable therapy for type 2 diabetes due to better clinical outcomes, cardiovascular safety and glucose lowering efficacy. This review discusses clinical efficacy, safety, molecular developments, mechanistic effects and conflicting evidence in the GLP-1 RA class [22-26].

Therapeutic Strategies of GLP-1 Receptor Agonists in Diabetes Management

GLP-1 is an incretin hormone that stimulates insulin secretion and suppresses glucagon in a glucose-dependent manner. The enzyme dipeptidyl peptidase-4 (DPP-4) rapidly degrades active GLP-1 and GIP, limiting its duration of action [27, 28,29]. GLP-1 receptor agonists (GLP-1 RAs) are synthetic peptide analogues that are engineered to resist DPP-4 degradation, providing pharmacologic GLP-1 activity with greater potency, superior HbA1c reduction and weight loss, but with more gastrointestinal side-effects [30, 31] comparisons illustrated in **Fig. 1**. Thus, both drug classes act on the same incretin pathway DPP-4 inhibitors enhance the body's own GLP-1, whereas GLP-1 RAs replace it with a longer-acting analogue. Clinical head-to-head trials consistently show that GLP-1 RAs achieve better glycaemic control and weight loss than DPP-4 inhibitors, while both maintain a low incidence of hypoglycaemia [32, 33]. The most efficient strategies for increasing the effectiveness of GLP-1 receptor agonists are outlined in (**Table 1**). Furthermore, patients naturally lose sensitivity to certain antihyperglycemic medications, including GLP1-RAs and DPP-4 inhibitors. However, when prescribed the GLPRA, patients continuously take the medication, adhere to the therapeutic regimen and demonstrate a clear improvement in their cardiovascular status [34, 35, 36].

Abdu A, et al., Int J Appl Biol Pharm 2026
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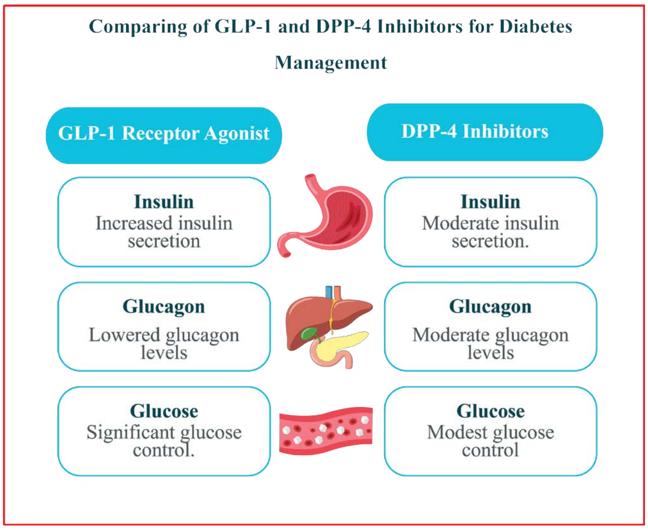

Figure 1: Comparing GLP-1 and DPP-4 inhibitors for diabetes management

Table 1: Strategies to improve efficiency of GLP-1 receptor agonists

Strategies	Improve efficiency	References
Preventing the degradation of DPP-4	Modification of the Ala8 position to protect from DPP-4 degradation for exenatide, lixisenatide, semaglutide, dulaglutide and albiglutide can enhance their stability and bioavailability. The effects of these modifications on the overall therapeutic efficacy of these drugs are crucial.	[22]
Binding to albumin	Albumin fusion technology enhances GLP-1RA drug stability and half-life, improving patient adherence and reducing dosing frequency, with promising results in preclinical and clinical studies.	[23]
Acylation with fatty acids	GLP-1 combines with fatty acids, it increases the time it takes to diffuse, slows down the kidneys' clearance and makes it possible to encapsulate the drug in nanoparticles or microparticles for controlled release and to put the drug into implants for continuous delivery.	[24]
Polyethylene glycol (PEG)	Polyethylene glycol (PEG) increases the water solubility, prolongs the half-life and reduces kidney clearance of GLP-1RA medications. This enhances their pharmacokinetics and stability and enables regulated medication release for sustained therapeutic benefits.	[25]
Fc fusion	Combining GLP-1 and IgG increases the molecular weight and prevents lysosomal degradation of the molecules. This makes drugs more stable and improves their pharmacokinetics, like dulaglutide. This allows controlled drug release for long-lasting therapeutic effects.	[26]
Sustained-release formulations	Bydureon, a sustained-release drug, uses biodegradable microspheres for improved patient adherence, convenience and treatment outcomes, reducing injection frequency and minimizing adverse reactions.	[22]
Oral formulation	Semaglutide from Rybelsus is a non-covalent linkage with a fatty acid derivative that can be taken by mouth. It is easier for patients to take and it keeps the drug stable longer, making it a convenient and comfortable treatment option.	[27]

GLP1-RAs are a group of medicines that have several pharmacodynamics effects that lead to better outcomes in the heart and kidneys [37, 38]. They have been established as the second-line therapy option for patients with type 2 diabetes mellitus and there have been several large-scale trials that demonstrated their clinical efficiency, reduction in glycated hemoglobin, weight and blood pressure and cardiovascular and renal protection [39, 40]. People also use GLP1-RAs to manage type 1 diabetes mellitus and obesity [41]. At present, the routinely used GLP1RA is found within four main groups, according to their half-lives and periods of action [42, 43], as short-acting formulations (Exenatide and Lixisenatide), intermediate-acting formulations (Lixisenatide), long-acting formulations (Liraglutide, Semaglutide, Albiglutide, Exenatide LAR, Dulaglutide and once-weekly Exenatide). Patients with severe renal impairment, advanced heart failure, inflammatory bowel disease, diabetic gastropathy, or a significant diabetic foot infection should not use GLP1-RAs. The most common adverse events associated with the use of the GLP1-RAs include weight loss, nausea, vomiting and diarrhea [44, 45, 46].

Impaired Incretin Action of GLP-1 in Type 2 Diabetes

The action of GLP-1 on secretion is an incretin, that is, it stimulates insulin secretion by glucose and other nutrients when they are absorbed from the gut and enter the circulation through natural portal circulation, to act later in the systemic way. As early as 1985, in a milestone study, it was shown that this action is attenuated among patients with diabetes and in more pronounced ways in patients with type 2 diabetes [47, 48]. After this first study, numerous further studies have confirmed the reduced incretin action in patients with type 2 diabetes. Today, the idea has been widely confirmed that in patients with type 2 diabetes, insulin secretion as a whole is

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reduced, as is the exaggerated counter-regulation of glucagon counter-regulation to post-prandial hyperglycemia, critically contributing to persisting hyperglycemia in the post-prandial phase of these patients [49, 50, 51].

The gastrointestinal peptide GLP-1 was originally discovered as a product of the glucagon precursor (Gcg), which was shown to undergo transcription in the lower part of the small intestine, in the so-called distal L-cells located from the distal jejunum to the distal ileum, up to their opening into the colon [52,53,54]. Starting from the first clone Gcg-expressing rodent cells, it was observed that with respect to glucagon, in addition to possessing a liberation stimulus glucose and other monosaccharides and a liberation inhibitor stimulus (somatostatin), GLP-1 has the same inhibitory effect on glucagon liberation as somatostatin [55,56]. Among the rediscovered physiological effects of the incretin hormone, the most important are the stimulation of insulin biosynthesis, the insulin-liberative activity, the inhibition of glucagon biosynthesis and liberation and the reduction of hepatic numeral liberation, which usually contribute to the post-prandial hyperglycemia [57, 58, 59]. Today, GLP-1 is known for numerous effects, among which it shows, at least in the long term, a trophic effect on the β cells, as the receptor for the GLP-1 hormone is expressed only in the insulin-storing insulin-secreting cells [60, 61]. The mechanism of action outlined in GLP-1RA is depicted in (**Fig. 2**).

Gastrointestinal and Multifaceted Metabolic Actions of GLP-1 Receptor Agonists

There are different effects on gastric emptying, as GLP-1 decreases the activity of the gastric motor and glucose uptake in peripheral organs, with the liver being the most important site of action [62, 63]. The ability to increase insulin secretion in response to glucose, suppress inappropriate glucagon secretion from the pancreas, reduce postprandial levels of glucagon, slow the rate of absorption of glucose into the circulation and reduce the rate of burial of glucose in the periphery are lost in patients with diabetes [64, 65]. Upon GLP-1 administration, these defects are partially restored. The relative contributions of glucose lowering and reduced postprandial glucagon levels are still subject to debate [66, 67]. While some studies emphasize the importance of glucagon for postprandial glucose increments, others have demonstrated the role of postprandial suppression of pancreatic insulin in glucose uptake in the periphery, mainly in patients with T2DM [68].

For example, dulaglutide and exenatide have been studied in patients with type 2 diabetes mellitus (T2DM) with different degrees of renal impairment. Both agents were effective in lowering HbA1c and weight. Both agents show similar efficacy in decreasing HbA1c with different eGFR (renal function evaluation using estimated glomerular filtration rate) [69, 70, 71]. The therapeutic effect of GLP-1 RA is likely achieved through a combination of mechanisms, including stimulation of glucose-dependent insulin secretion, suppression of glucagon secretion and reduction of food intake and weight. The primary effect in response to meal consumption is glucose-dependent insulin secretion by the beta cells, whereas the majority of its anorexigenic effect occurs via the brain, particularly the hypothalamus [72].

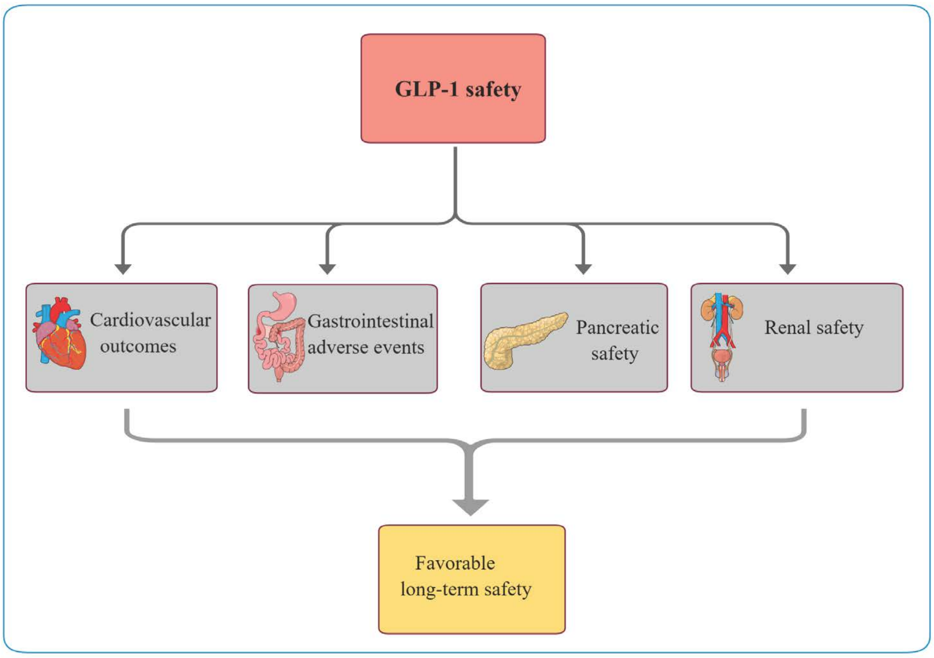

Figure 2: Mechanism action of GLP-1RA on DM

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Safety profile Adverse Events of GLP-1 Receptor Agonists

Clinical trials of dulaglutide showed that hypoglycemia was reported more frequently in people treated with the combination therapy of dulaglutide and insulin when compared with dulaglutide monotherapy [73, 74, 75]. The combination of dulaglutide and sulfonylurea therapy may also be associated with an increased risk of hypoglycemia because of the sulfonylurea therapy [76, 77]. Continuous long-term follow-up studies displayed a conclusion of an increased risk of pancreatic cancer, making dulaglutide have an altogether short-term benefit and overall limited safety. Another adverse event based on dulaglutide treatment is a potential increased risk of infections, especially GIT and skin-related infections [78, 79, 80]. Supplementation with lorcaserin could give a safety benefit in patients who are not highly likely to achieve pre-specified rather than those who are at high risk for major cardiac events in the same liraglutide trial with overall cardiovascular benefit [81, 82]. Additionally, anti-drug antibody formation associated with GLP-1 receptor agonists is generally drug-specific and that convincing evidence for clinically relevant cross-reactivity between different GLP-1 RAs is lacking [83].

Moreover, exenatide and lixisenatide demonstrated an overall favorable safety profile, with mostly transient, mild-to-moderate GI tolerability adverse effects. However, an increase in heart rate has been reported, potentially due to sympathomimetic activity, requiring caution with patients who have pre-existing tachyarrhythmias and other comorbidities [84, 85]. Liraglutide is generally well tolerated, but GI-related symptoms, particularly nausea, are frequent and can lead to discontinuation of the treatment [86]. Empagliflozin, known to cause genitourinary and metabolic adverse events, was also used with semaglutide as a supplementary enteral therapy. A unique adverse event of semaglutide is the increase in retinopathy complications, similar to other GLP-1 agonists [87, 88, 89].

Long-Term Safety of Glp-1 Receptor Agonists

Liraglutide-associated cholecystitis, a rare gastrointestinal side event caused by gallbladder motility and filling inhibition, demands special monitoring during long-term treatment [90, 91]. GLP-1's role in the development and treatment of gastrointestinal problems has been positively assessed and continuing investigations should clarify the underlying sarcopenia and frailty owing to gastrointestinal side effects. GLP-1 RAs have not been clearly linked to pancreatitis and pancreatic cancer, despite nonspecific research [92]. GLP-1 RAs have a good safety record despite long-term study outcomes that caused infrequent but severe hypoglycemia, problematic hypotension, alcohol withdrawal symptoms and voiding problems [93]. Although promising, these medicines' significance in treating a wider range of disorders will be clarified by ongoing studies. Long-term safety of GLP-1 receptor antagonists is shown in (**Fig. 3**). In addition, studies found that the latest GLP-1 RAs safety gains were maintained over time, giving physicians additional confidence in prescribing them to patients with long-term or early diabetes problems [94]. A prospective cardiovascular outcome showed semaglutide's noninferiority to standard diabetes treatment [95, 96]. Considering these medicines

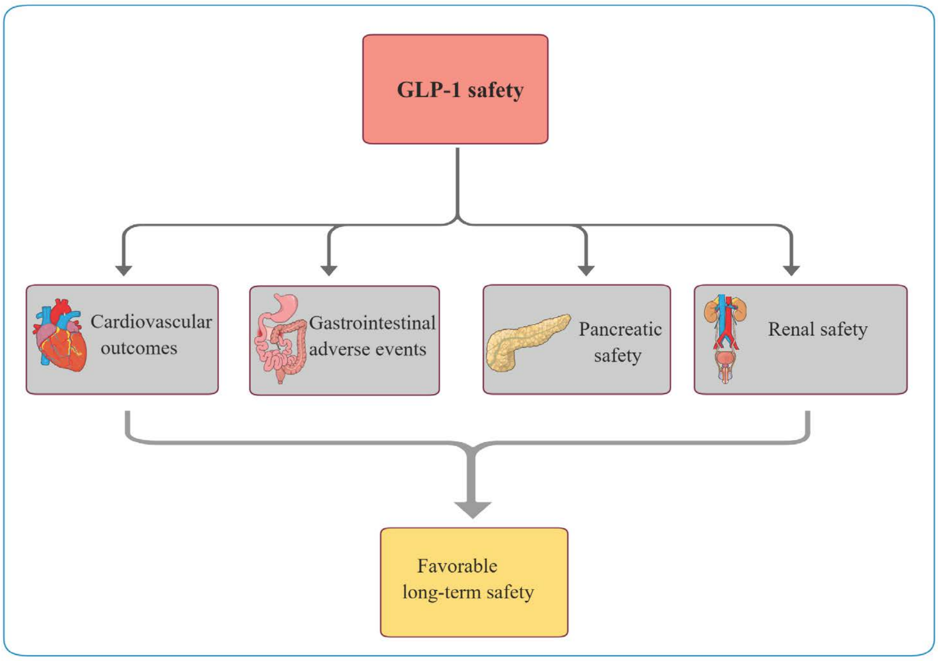

Figure 3: Long-term safety of GLP-1 receptor agonists

Abdu A, et al., Int J Appl Biol Pharm 2026
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distinct effects in weight loss and insulin resistance, lifestyle and cardiovascular outcomes may improve. The GLP-1 RA outlines the benefits and risks of diabetes treatment medications (**Table 2**).

Cardiovascular Safety and Outcomes of GLP-1 Receptor Agonists

The cardiovascular effects of GLP-1 are well documented and GLP-1 receptor agonists exert large-scale cardiovascular actions [97, 98]. It found that GLP-1RAs do not increase major adverse cardiovascular events (MACE) compared with conventional therapy or placebo, demonstrating their safety and identified a class-wide reduction in MACE across many patients [99, 100]. Clinical ambiguity regarding which GLP-1R agonists were compared across studies remains the main issue [101]. The meta-analysis showed that reductions in heart-failure hospitalizations contributed most to the MACE benefit. Although failing cardiomyocytes up-regulate GLP-1 receptors, long-term data on heart failure in humans are scarce. Multiple GLP-1RA trials with composite outcomes of MACE and stroke are ongoing [102-104].

Regulatory agencies are concerned about how glucose-lowering influences macrovascular outcomes when developing new antidiabetic drugs [105, 106]. The FDA's 2008 Guidance for Industry recommended that the upper bound of the two-sided 95 % confidence interval for the risk ratio of major adverse cardiac events [107-109]. Pioglitazone was the first glucose-lowering agent to reduce MACE in the PROactive and ADVANCE trials [110, 111]. Conversely, the rosiglitazone RECORD study showed a significant increase in myocardial infarction, emphasizing the need to mitigate cardiovascular risk. Consequently, GLP-1RAs are being investigated in rigorous phase III trials to assess their potential cardiovascular benefits [112-114].

GI adverse events: Incidence & Mechanisms of GLP-1RAs

Class-related treatment During commercialisation, GLP-1RA have caused emergent gastrointestinal problems [115]. Liraglutides caused the most nausea, emesis and bloating in a vector-related emergent gastrointestinal symptom assessment [116,117]. These side effects are dose-related and more severe at the start of treatment, according to studies. Early endoscopic biopsies showed dose- and time-dependent increases in bog dull and van RCC cell neuroendocrine binding after basalprepidilintide injection [118,119]. Patients receiving liraglutide have a higher incidence of diarrhoea, gastroparesis, pollinopia, nausea, severe nausea, postprandial

Table 2: GLP-1 RA detailed overview of the potential benefits and risks of diabetes management agents

Aspects	Potential benefits	Potential risks	References
Glucose control	Enhanced glucose regulation, lower HbA1c values, decrease in postprandial glucose, decelerated stomach emptying	Hypoglycemia particularly when taking additional diabetes drugs, stooling , queasiness, a diarrheal illness, pain in the abdomen elevated levels of lipase and amylase	[220]
Weight management	Weight loss, achieving a reduction in body fat	Nausea/loss of appetite, risk of hypoglycemia when taking other weight-loss drugs together	[221]
Cardiovascular safety	Potential for cardiovascular risk reduction, improved endothelial function	A higher heart rate, some people with pre-existing heart conditions may be at risk for heart failure	[222]
	Some agents are associated with cardiovascular safety	Limited long-term cardiovascular safety outcome data, potential for QT interval prolongation	
Renal benefits	Potential renal protection	Acute kidney injury, changes in renal function	[223]
Gastrointestinal adverse events	Identification of liraglutide association with higher incidence of symptoms	Highest incidence of nausea, emesis and bloating reported with liraglutides	[116, 117]
Pancreatic outcomes	Generally low risk of hypoglycemia, there is no evidence of an increased risk of pancreatic events.	There is no evidence of an increased risk of pancreatic cancer, increased amylase and lipase levels	[224]
Other outcomes			
Convenience	Once-weekly dosing options less frequent administration	Injection-site reactions can occur after receiving an injection, allergic reactions, injection site nodules are a common side effect.	[225]
		Lipodystrophy	
Compliance	Simplified treatment regimen, positive impact on patient adherence	Cost considerations, limited long-term safety data, emotional barriers to self-injection	[226]
Overall Safety Profile	Generally well-tolerated, low risk of hypoglycemia	Risk of allergic reactions, limited data on long-term safety and efficacy, interactions with other medications	[227]

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Abdu A, et al., Int J Appl Biol Pharm 2026
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nausea and vomiting than those taking other generals 1 neurones [120,121]. The study also suggests that a specific TCF7L2 gene polymorphism is associated with nausea and may be higher in patients with gastrointestinal symptoms, suggesting that personal genetic factors may be involved in treatment-related gastrointestinal symptoms [122,12].

GLP-1RA medications cause gastrointestinal side effects in 30% of patients, which are usually minor and temporary but can be life-threatening [124,125]. Their severity and frequency vary by GLP-1RA. The gastrointestinal program is initiated by contact with the gastrointestinal lumen mucosa and the treatment-related delay of gastric emptying, intestinal motility and gastric and pancreatic enzyme secretions are proposed physiopathological mechanisms. They are typically moderate and temporary but can become serious [126,46]. The most common reason for therapy cessation is adverse effects. The mucosal breach following this class may involve autoimmune and non-autoimmune processes. Histological study of endoscopic samples from acute pancreatitis patients shows an increase in mast cells with activation-like morphology [127].

Pancreatic Safety of GLP-1 Receptor Agonists

Multiple pharmacovigilance analyses have evaluated pancreatitis reports linked to FDA-approved type 2 diabetes agents. Compared with SGLT2 inhibitors, DPP-4 inhibitors, metformin, insulin and sulfonylureas, the incretin-based drugs saxagliptin, exenatide and sitagliptin generate a higher number of adverse-event (AE) reports for pancreatitis [128-130]. Post-marketing surveillance prompted the FDA in 2014 to highlight a potential pancreatitis signal for GLP-1RAs; however, subsequent reviews of experimental and clinical data found no clear increase in pancreatitis severity and an uncertain association with pancreatic cancer [131-134]. In a large meta-analysis, GLP-1RAs were associated with a statistically significant risk ratio for pancreatitis across five agents. Head-to-head network analyses similarly identified exenatide and tirzepatide as agents with relatively higher pancreatitis signals. Real-world evidence from a retrospective cohort matched patients found no significant difference in acute pancreatitis rates between GLP-1RA users and oral antidiabetic comparators. Nevertheless, exenatide treatment in patients with prior pancreatitis was linked to a 28-day increase in gastrointestinal and upper-abdominal AEs [135]. Because diabetes itself, gallstones, hypertriglyceridaemia and alcohol use also precipitate pancreatitis, clinicians must differentiate drug-related risk from underlying disease. Only a minority of primary-care patients on GLP-1RAs undergo confirmatory imaging after elevated amylase or lipase, underscoring the need for providers to advise drug discontinuation and prompt diagnostic evaluation when pancreatic enzymes rise or pancreatitis symptoms emerge [136-138].

Renal Safety of GLP-1 Receptor Agonists

Clinical trial meta-analyses have demonstrated that both short-acting and long-acting GLP-1 receptor agonists confer reno-protective effects, reducing the composite kidney outcome by approximately 18 % compared with placebo and lowering the incidence of kidney failure [139,140]. In patients with advanced chronic kidney disease or end-stage kidney disease, pooled data from five trials and three cohort studies showed significant reductions in cardiothoracic ratio, pro-BNP, mean blood glucose and body weight, indicating improved renal haemodynamics and reduced volume overload [141]. A cardiovascular outcome trials further reported that GLP-1 receptor agonists consistently decrease albuminuria, reflecting attenuation of glomerular hyperfiltration and oxidative stress [142]. These benefits are thought to arise from multiple mechanisms: weight loss and modest blood-pressure reductions, direct anti-inflammatory actions and activation of GLP-1 receptors expressed in the renal microvasculature that improve glomerular microcirculation and reduce oxidative injury. Although preclinical studies dominate the mechanistic literature, the emerging clinical evidence supports a favorable renal safety profile for GLP-1 receptor agonists across a spectrum of kidney disease stages [143,144].

Efficacy and Safety of GLP-1 Receptor Agonists

GLP-1 receptor agonists lower glucose primarily by enhancing glucose-dependent insulin secretion and delaying gastric emptying, rather than by inducing glycosuria. Consequently, even at higher exenatide doses, severe hypoglycemia is rare, making GLP-1 RA-based therapy safer than many other glucose-lowering agents [145,146]. In contrast, hypoglycemic episodes with insulin or sulfonylureas can lead to loss of consciousness, lactic acidosis and adverse neurocognitive outcomes [147,148]. When titrated to an individualized optimal dose, GLP-1 RAs do not increase pancreatic enzyme levels and fasting or post-prandial hypoglycemia remains unchanged [149]. Real-world data have confirmed the long-term safety and superior metabolic benefits of GLP-1 RAs across multiple diabetes domains, reinforcing their central role in contemporary diabetes care [150,151]. **Figure 4** illustrates the simultaneous effects of GLP-1 RAs on pancreatic function, glycemic control, renal protection and weight loss. Current guidelines from the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) endorse targeting an HbA1c < 7 % for most patients; however, emphasis is shifting toward outcomes that reduce cardiovascular morbidity and mortality [152,153]. Comprehensive analyses of long-term randomized trials demonstrate that GLP-1 RA therapy consistently outperforms comparators in cardiovascular endpoints, including angina, heart failure and myocardial infarction, while maintaining a favorable safety profile [154,155].

Glycemic control

Treatment adjustments using GLP-1 RAs have been useful in treating T2DM. Patient demands, including efficacy,

Abdu A, et al., Int J Appl Biol Pharm 2026
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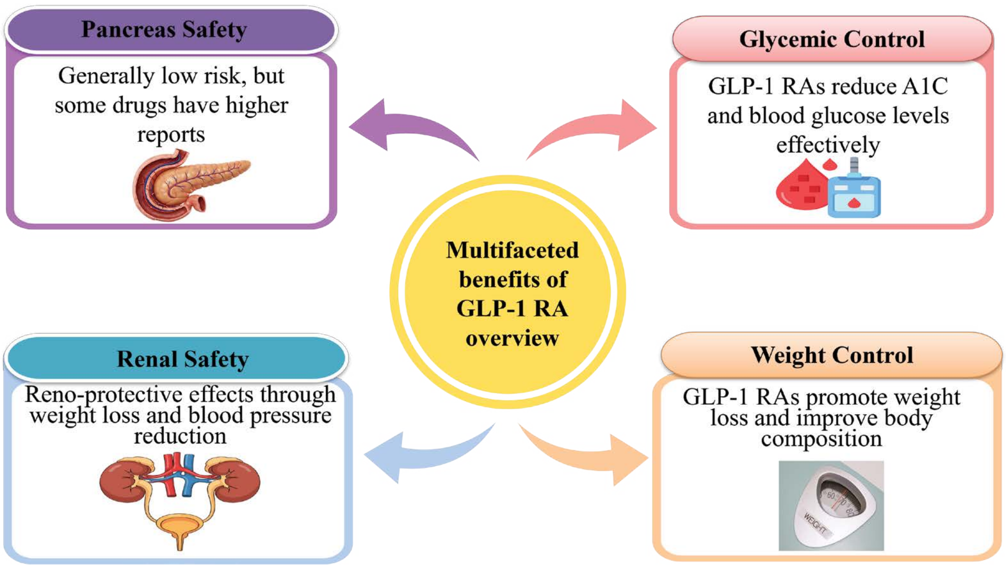

Figure 4: Multifaceted benefits of GLP-1 receptor agonists

hypoglycemia and glycaemic control, must be considered when choosing glucose-lowering medications and using A1C objectives to evaluate their efficacy [93,156]. Therapies that target numerous pathways to reduce glucose in T2DM address many causes that raise glucose. GLP-1 RAs can provide glycaemic control through many mechanisms, making them acceptable for individuals at varying phases of T2DM except those with T1DM or pancreatitis [7]. Other glucose-lowering medications rarely help obese patients like exenatide [157]. The other benefits of long-term usage of individual medicines beyond glucose management need more study.

GLP-1 RAs reduce A1C in T2DM patients, their greatest proven efficacy. A1C reductions from GLP-1 RAs depend on patient factors [156,100]. A1C reductions were modest for individuals with higher baseline A1Cs of 59 mmol/mol or higher versus 53 mmol/mol and ranged from 2.2 to 5.1 among agents in a GLP-1 RA trial compared to placebo in T2DM patients [158,159]. Semaglutide reduced the most at 26 weeks. Individual agent long-term effects are explored next. An important element in A1C readings is blood glucose. At 26 weeks, GLP-1 RA patients had significantly decreased fasting and 2-h postprandial blood glucose [160, 161, 162].

Weight control

GLP-1RA may improve cardiovascular health by changing body composition [163,164]. Increased lean tissue and decreased fat mass improve diabetic dyslipidaemia and insulin resistance by reducing free fatty acids on non-esterified fatty acids. Pancreatic health is another obesity-related overlook [165,166]. Weight loss can enhance islet β-cell activity in some circumstances. Preclinical models suggest that endocrine progenitor cells directly affect β-cell regeneration, resulting in increased islet and β-cell bulk. Fat accumulation in the abdomen can increase islet inflammation, resulting in the release of IL-6 and TNF-α. GLP-1RA reduces IL-6 and TNF-α levels, making it an anti-inflammatory medication. Reduced islet inflammation may further reduce T2D [167,168,169].

Weight gain often hinders dose-dependent glycaemic control with GLP-1RA. Treatment of T2D with obesogenic drugs can cause insulin resistance, worsening β-cell failure. Appetite suppression, calorie reduction and weight loss are metabolic benefits. Several gut, brain, lipid and pancreatic pathways are involved in weight management [170,171,172]. An intracellular domain on vagal neurone receptors interacts with signal-regulatory protein-binding protein-1C (SRBC-1C), activating the anorexigenic pro-opiomelanocortin (POMC) and cation channel (hyperpolarising) neuropeptide (HCN) pathways. Orexigenic neurones such agouti-related peptide and neuropeptide Y are suppressed. Diet-induced obesity is reduced by peripheral GLP-1RA receptors' catabolic actions, partly mediated by the CNS, but not with body fat reduction [173,174].

Cardiovascular Safety and Risk Reduction of GLP-1

A prespecified secondary-population subgroup analysis of REWIND participants without established cardiovascular disease (CVD) examined long-term cardiovascular (CV) safety and efficacy of dulaglutide, confirming its favorable profile in type 2 diabetes mellitus (T2DM) patients [175]. Although retrospective cohort studies have described baseline characteristics of T2DM cohorts, prospective randomized investigations remain essential. In the SUSTAIN-6 trial, semaglutide significantly reduced the hazard of major adverse cardiovascular events (MACE) compared with placebo [176]. Across multiple high-quality randomized controlled trials, GLP-1 receptor agonists (GLP-1RAs) consistently demonstrated cardiovascular safety, with a non-significant

Abdu A, et al., Int J Appl Biol Pharm 2026
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trend toward MACE risk reduction and in some analyses, a modest but meaningful decrease in MACE incidence [177]. The FDA's reanalysis of liraglutide data further corroborated a substantial reduction in CVD events among T2DM patients [184, 185]. Conversely, the LEADER and EXSCEL trials reported no significant difference in composite MACE outcomes between GLP-1RA treatment and placebo, although subgroup analyses suggested relative risk reduction in major CVD events [188, 189]. These findings underscore the potential of GLP-1RAs to lower CVD risk in T2DM, while also highlighting variability among agents and the need for further prospective evidence to delineate class-wide effects as given in (**Fig. 5**).

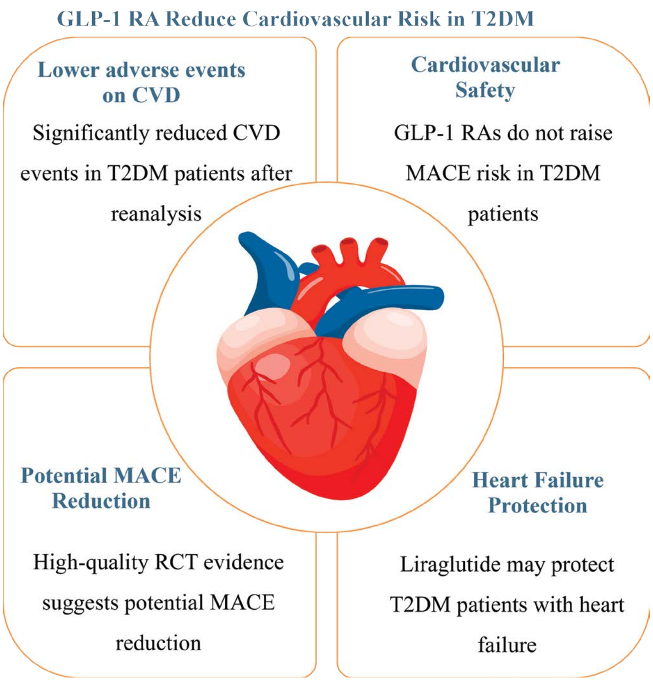

Figure 5: The impact of GLP-1 receptor agonists on cardiovascular health

Blood-Pressure Control of GLP-1RA

Resistant hypertension is defined as a systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg that persists despite an optimized three-drug regimen that includes a diuretic and it is associated with an increased risk of cardiovascular events [190]. In the Succeed study, three months of dulaglutide therapy lowered office SBP and DBP by 8 mmHg and 6 mmHg, respectively, in 66.5 % of patients without resistant hypertension (baseline < 140/90 mmHg). Among the 33.5 % of participants classified as resistant hypertensive (baseline ≥ 140/90 mmHg), reductions of 4.9 mmHg (SBP) and 5.1 mmHg (DBP) were observed [191,192]. These findings should be interpreted cautiously because the resistant-hypertensive subgroup was small, heterogeneous and included a patient intolerant to antihypertensive therapy as well as others with markedly elevated morning cortisol levels [193].

Clinical trials consistently report that GLP-1 receptor agonists produce modest SBP reductions of 2–4 mmHg [195]. Blood pressure has often been a secondary, not primary, endpoint in these studies, so the antihypertensive effect may be under-recognized compared with weight-loss benefits. The glucose-independent actions of GLP-1RAs likely contribute to this effect: obesity and insulin resistance promote hyperinsulinemia, sodium retention, reduced secretion of vasodilators (e.g., atrial and brain natriuretic peptides) and increased production of vasoconstrictors such as endothelin-1. By attenuating these pathways, GLP-1RAs can modestly lower blood pressure, offering an additional therapeutic target for managing hypertension, especially in patients with resistant disease [196,197].

Clinical Trials Involving GLP-1 Receptor Agonists

Recent clinical trials are rigorously investigating the effects of GLP-1 receptor agonists (GLP-1RA) across a range of metabolic conditions, especially diabetes and obesity. These studies explore diverse aspects, from pharmacogenetics in specific populations to comparative effectiveness against other diabetes medications. Interventions include GLP-1RA drugs like semaglutide and dulaglutide, both as monotherapies and in combination regimens, with outcome measures spanning glycemic control, cardiovascular and kidney health, liver fibrosis and quality of life. Sponsors include leading academic institutions and hospitals, with study phases ranging from pilot to late-stage Phase 4 trials. The collective aim is to refine treatment strategies, optimize individual response and broaden the understanding of GLP-1RA's role in managing diabetes, obesity and related diseases **Table 3** provides a summary of key clinical trials and their results.

Strategic Medication Sequencing in Type 2 Diabetes

There is a clear opportunity in T2DM disease management for focusing on the correct sequence of medications to obtain or maintain good glycemic control while reducing hypoglycemia events as well as overall cardiovascular disease risk. Alternative strategies can include incorporating first-line pharmacotherapy with agents that address insulin resistance and other concomitant cardiovascular risk factors in patients with prediabetes [198,199,200]. Furthermore, given the comprehensiveness and heterogeneous background of patients recruited in CVOT studies, the off-target effects of these medications in other groups of patients experiencing different forms of cardiovascular risk and associated events remain poorly understood [201,202]. Such knowledge can be achieved through the establishment of prospective comprehensive databases that include people with diabetes

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Abdu A, et al., Int J Appl Biol Pharm 2026
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Table 3: Ongoing clinical trials of GLP-1 receptor agonists study overview and outcomes

NCT Number	Study Title	Brief Summary	Conditions	Interventions	Outcome Measures	Sponsor	Phases	Completion Date
NCT05119179	Pharmacogenetics of the Response to GLP-1 in Mexican-Americans with Prediabetes	Researchers utilize transcriptomic and genomic data to investigate the effects of GLP-1 on individuals of Mexican-American descent who have prediabetes.	PreDiabetes	DRUG: Semaglutide	Genomic impact on beta cell responsivity, insulin sensitivity, disposition index and more	University of Texas Health Science Centre, Houston	PHASE4	Jul-26
NCT03648554	Researching an Effect of GLP-1 Agonist on Liver Steatosis (REALIST)	Investigates Dulaglutide's effect on liver histology improvement in type 2 diabetes and NASH patients.	Diabetes Mellitus, Type 2, NASH	DRUG: Dulaglutide (TRULICITY®) 1.5 mg	Fibrosis, lipid parameters, glycemic control, body composition and quality of life after 52 weeks	Central Hospital, Nancy, France	PHASE4	3/30/2024
NCT05297045	A Study of Oral GLP1RA RGT001-075 in Adults with Type 2 Diabetes	Evaluates the effectiveness of a daily oral RGT001-075 GLP1 receptor agonist in adult patients with type 2 diabetes mellitus.	Type 2 diabetes mellitus is a chronic condition characterized by high blood sugar levels.	DRUG: RGT001-075	Changes in HbA1c, fasting plasma glucose, body weight, BMI, waist circumference, blood lipids and percentages of patients achieving HbA1c <6.0%	Regor Pharmaceuticals Inc.	PHASE2	5/30/2023
NCT06138821	ESG vs. GLP-1RA vs. ESG + GLP-1RA in Patients With Obesity, NAFLD and Advanced Fibrosis: A Randomized Controlled Trial	Compares endoscopic bariatric and metabolic therapies for obesity patients, including suturing devices and semaglutide.	Obesity, NAFLD, liver fibrosis, etc.	DEVICE: ESG, DRUG: GLP1-RA	Compares liver fibrosis, Fibroscan score, %TBWL, weight measurements, quality of life and eating behaviours at baseline, 3, 6, 9 and 12 months.	Pichamol Jirapinyo, MD, MPH	PHASE4	2025-12
NCT05390892	Prevention of Cardiovascular and Diabetic Kidney Disease in Type 2 Diabetes	Randomized clinical trial comparing SGLT2i, GLP-1RA, or combination in type 2 diabetes patients.	Type 2 diabetes, ASCVD	DRUG: SGLT2 inhibitor, GLP-1 receptor agonist, combination drug	Tracks cardiovascular, kidney and death events over an average of 3 years.	Brigham and Women's Hospital	PHASE4	4/30/2028
NCT06142006	A Pilot Study to Test the Diabetes Staging System (DSS) in Patient-Aligned Care Teams (PACT) Teams	Examines the feasibility and acceptability of DSS in PACT teams for increasing SGLT2i and GLP-1 use in veteran patients with type 2 diabetes.	Type 2 diabetes	OTHER: Diabetes Staging System (DSS)	Examines SGLT2i and/or GLP-1 agonists' use, weight, blood pressure, HbA1C and glomerular filtration rate at baseline and 6 months after DSS EHR template implementation.	Durham VA Medical Centre	NA	09-01-2025

Abdu A, et al., Int J Appl Biol Pharm 2026
DOI:10.26502/ijabpt.202144

NCT03878706	The Cardiovascular Effect of GLP-1 Agonists, SGLT2 Inhibitors and Their Combination	Studies type 2 diabetes patients with high cardiovascular risk under different treatments.	Diabetes Mellitus, Type 2	Not specified	Examines heart health markers and biomarkers, including global longitudinal strain, arterial stiffness, pulse wave velocity and more.	University of Athens	NA	6/30/2024
NCT05161429	BESTMED: Observational Evaluation of Second Line Therapy Medications in Diabetes	Researchers conducted an observational study to determine the optimal balance of risks and benefits among diabetes medications.	Type 2 diabetes	DRUG: DPP-4, GLP-1 receptor agonist, basal insulin, SLGT2, SU	Identifies major adverse cardiac events, adverse outcomes, severe clinical outcomes and non-cardiovascular outcomes in patients with cardiovascular diseases.	Brigham and Women's Hospital	NA	6/30/2024
NCT05214573	Second-line Therapies for Patients with Type 2 Diabetes and Moderate Cardiovascular Disease Risk	Compares the effectiveness of four drug classes in adults with type 2 diabetes at moderate risk of cardiovascular disease.	Type 2 diabetes, cardiac disease	DRUG: GLP-1 receptor agonist, SGLT2 inhibitor, DPP-4 inhibitor, sulfonylurea	Provides data on non-fatal MI, stroke, mortality and various complications from 2014 to 2021.	Mayo Clinic	NA	2025-04
NCT05305794	Effect of Weekly GLP1 Agonist Treatment in "Double Diabetes"	Investigates the use of semaglutide to reduce insulin resistance in type 1 diabetic patients with a family history of type 2 diabetes.	Double Diabetes	DRUG: Insulin and semaglutide treatment	Measures the percentage of time spent within the glycemic target range and change from baseline at Day 180.	Centre Hospitalier Universitaire Dijon	PHASE3	2024-08
NCT05569772	Semaglutide for the Treatment of Glucose Intolerance in Women with Prior Gestational Diabetes	It aims to reduce type 2 diabetes risk in women with prior gestational diabetes and early postpartum glucose intolerance.	Glucose Intolerance After Gestational Diabetes	DRUG: Semaglutide Pen Injector	Evaluates type 2 diabetes development, symptoms and rescue therapy need over 160 weeks	Universitaire Ziekenhuizen, KU Leuven	PHASE3	2028-12
NCT03363464	Comparative Effectiveness of Empagliflozin in the US	Investigates the transferability of Empagliflozin's outcomes to a broader population under real-world conditions.	Diabetes Mellitus, Type 2	DRUG: Empagliflozin, DPP-4 inhibitor, GLP-1 receptor agonist	Examines the duration of major adverse cardiovascular events and various complications.	Boehringer Ingelheim	NA	12/31/2024
NCT06132477	Impact of GLP-1 Agonists Following Bariatric	Randomized trial examining the effects of continuing or discontinuing GLP1-RA therapy in patients undergoing bariatric surgery.	Morbid obesity, metabolic syndrome, diabetes mellitus, etc.	DRUG: GLP-1 receptor agonist	Investigates the effect of GLP1-RA on weight loss, metabolic determinants, psychological eating behaviour and adverse side effects.	University of Missouri-Columbia	NA	2024-07

Abdu A, et al., Int J Appl Biol Pharm 2026
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NCT05071898	Pharmacogenetics of Response to GLP1R Agonists	Assesses pharmacodynamic responses to a GLP1R agonist in overweight or obese volunteers from the Old Order Amish population.	Obesity and Diabetes Type 2	DRUG: Semaglutide Pen Injector [Ozempic]	Measures insulin secretion, plasma insulin levels, glucose disappearance rate and weight loss after 6 weeks of semaglutide therapy.	University of Maryland, Baltimore	PHASE1	12/31/2027

or prediabetes experiencing various cardiovascular events or comorbidities, administered various antihyperglycemic drug classes and have had different glucose-lowering effects [203]. With the information placed in appropriate conversational axes, the database can be queried to provide potential answers to some of the major clinical questions around cardiovascular safety as well as long- and short-term benefits of using anti-hyperglycemic drugs [204].

Given that T2DM is a progressive disease that evolves from insulin resistance to compromised insulin secretion by the β-cell, a major milestone in its management would be directing attention toward interventions aimed at delaying or preventing the onset of dysglycemia, rather than at simply treating the hyperglycemia that occurs in established disease [205,206]. Many studies reported the use of GLP-1RA as the first injectable antihyperglycemic medication, when the use of two different oral agents has failed to achieve the glycemic target in the early phase of T2DM before the initiation of insulin therapy [207]. The liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results, as well as other recent CVOT studies, has shown that the use of GLP-1RA superimposed on several classes of oral agents significantly reduces the occurrence of the primary MACE endpoint and is associated with reduced all-cause mortality [208]. However, because of their heterogeneity, the results of CVOT studies could not be used to support putting one specific medication before the others.

Novel GLP-1 receptor agonists

Novel GLP-1 receptor agonists have emerged as a distinct therapeutic class that combines prolonged efficacy with an overall favourable safety profile. Early proof-of-concept data came from phase 2 randomised trials and subsequent phase 3 programmes have confirmed robust glycaemic control, weight reduction and importantly, cardiovascular (CV) benefit across a range of agents, including semaglutide, tirzepatide and dulaglutide. Large CV outcome trials have shown 20 –24 % reductions in major adverse CV events and kidney-failure outcomes for semaglutide, while post-hoc analyses suggest tirzepatide may further lower cardiorenal risk compared with dulaglutide. These findings have prompted the inclusion of GLP-1RAs in guideline-directed care for type 2 diabetes (T2DM) patients at high ASCVD or CKD risk [209].

Formulation advances such as once-daily oral small-molecule agonists (orforglipron, danuglipron) and dual GIP/GLP-1 agents (tirzepatide) aim to improve patient adherence and expand therapeutic options. Phase 4 (post-marketing) studies now focus on long-term CV and renal safety signals, registering outcomes in clinical-trial databases to monitor real-world effectiveness and rare adverse events. Collectively, the evolving pharmacologic designs and expanding outcome data support the positioning of novel GLP-1RAs as a cornerstone of contemporary diabetes and obesity management, offering cardiovascular and renal protection without appreciable hypoglycaemia risk [210,211] shown in (**Fig. 6**).

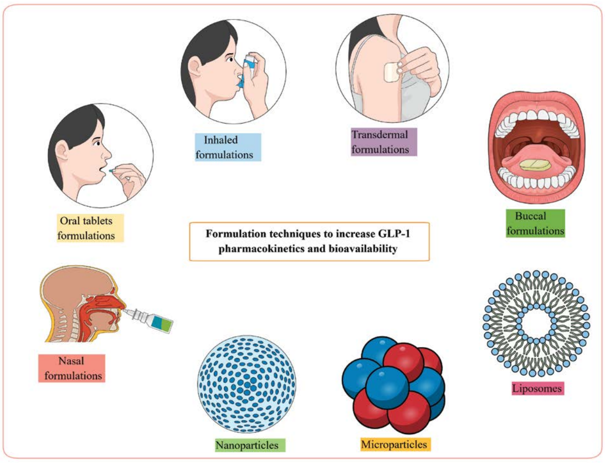

Figure 6: Formulation design for improving GLP-1 receptor for therapeutic purposes

Combination therapies

Exenatide once-weekly, in one of the first trials investigating the efficacy of the investigational drug in combination with oral antihyperglycemic agents, reported that the addition of exenatide once-weekly to pre-existing OAD regimens provided significant improvements in A1C, fasting plasma glucose (FPG) and in postprandial glucose excursions after 28 weeks of treatment. By week 28, patients receiving exenatide once weekly and glimepiride and metformin achieved significant median reductions from baseline body weight (2 kg and 4 kg, respectively). In addition, hypoglycemia rates were higher in exenatide once weekly +

glimepiride and in exenatide once weekly and TZD compared to exenatide QW as well as metformin [212,213,214].

There is growing evidence to support combination therapy of GLP-1 RAs either with insulin or other oral hypoglycemic agents for patients with type 2 diabetes. In the LEAD-5 trial, the addition of liraglutide to a sulfonylurea ± metformin provided improved glycemic control and less hypoglycemia than adding glimepiride to the placebo [215,216]. In the LIRA-ADD2BASAL trial, the addition of glargine to liraglutide + metformin + pioglitazone combination therapy led to further reductions in A1C, fasting plasma glucose (FPG) and 7-point self-monitored plasma-glucose (SMPG) profiles without additional weight increases [217,218,219]. A separate trial, the LEAD-6 study, reported that liraglutide as an add-on to pre-existing metformin/rosiglitazone combination therapy significantly improved glycemic control, reductions in body weight and fewer hypoglycemia episodes compared to exenatide after 26 weeks of treatment [220].

Personalized medicine approaches

To appropriate the large body of genetic information and develop personalized medication approaches, numerous measurement-based precision DPP-4 or GLP-1RA strategies are required to predict treatment response; the implementation of these biomarker and targeted therapy strategies remains a significant obstacle. Personalized diabetes medication, based on accurate and definitive patient phenotyping, improves glycemic control, increases β cell mass and function and increases weight loss rates, is essential for clinical practice [221]. To date, although multiple precision diabetes medication trials have been performed, including a genetic targeting DPP-4 trial, no biomarker-based clinical trials of GLP-1RA have been identified. Such large, expensive, multiyear health technology assessment-specific trials require a multidisciplinary diabetes medication biomarker consortium to advance medication therapy by addressing the significant gaps in knowledge unwritten by current medication delivery practices [222-224].

Apoptosis is increased in the pancreatic tissue of patients with recent-onset T1D, affecting both beta and non-endocrine islet cells. It is also believed to contribute significantly to reductions in beta cell mass in T2D. A remaining pool of beta cells following autoimmune destruction in individuals at risk for T1D is believed to serve as a source of antigens capable of local activation of the immune system. In T2D, increased circulating concentrations of proinflammatory cytokines, increased free fatty acid concentrations, endoplasmic reticulum stress and insulin resistance lead to beta cell dysfunction. By limiting beta cell stress and apoptosis, GLP-1RA may preserve beta cell mass. Salivary dipeptidyl peptidase 4 (DPP-4) activities supports the emergence of diabetes-associated autoantibodies in young children. Strategies that enhance incretin action and reduce GLP-1 degradation may prove to be useful in diabetes prevention [225-228].

Conclusion

GLP-1 receptor agonists improve glycemic control, weight loss and cardiovascular protection in diabetic mellitus (DM). Current evidence, including CVOT data, shows that these medicines reduce major adverse cardiovascular events (MACE) and improve patient outcomes. Present results suggest that GLP-1 receptor agonists may help T2DM patients with hyperglycemia, cardiovascular and renal concerns. The variety of CVOT outcomes suggests that more study is needed to determine the best treatment hierarchy for these drugs. Their long-term safety in varied patient populations must be assessed. The evidence suggests personalized therapeutic strategies based on patient-specific risk factors and treatment responses. Novel formulations and insulin/oral hypoglycemic agent combinations are important research areas. To better understand GLP-1 receptor agonists' involvement in T2DM therapy, large-scale studies and biomarker-based techniques should be prioritized. These methods will improve patient outcomes by personalizing treatment.

Abbreviations:

BMI :Body Mass Index; *T2DM*: Type 2 Diabetes Mellitus; *GLP-1* : Glucagon-like Peptide 1; *GIP* : Gastric Inhibitory Polypeptide; *DPP-4* : Dipeptidyl Peptidase 4; *GLP1-RAs* : Glucagon-like peptide-1 Receptor Agonists; *FDA* :Food and Drug Administration**;** *EASD* : The European Association for the Study of Diabetes; *ADA* : American Diabetes Association; *NEFA* : Non-esterified Fatty Acids; *IL-6* : Interleukin-6; *TNF-α* : Tumor Necrosis Factor Alpha; *SRBC-1C* :Signal-Regulatory Protein-Binding Protein-1C; *POMC* : Proopiomelanocortin; *CNS* : Central Nervous System; *CVD* : Cardiovascular Disease; *MACE* : Major Adverse Cardiovascular Events; *RCTs*: Randomized Controlled Clinical Trials; *HR* : Heart Rate; *SBP* : Systolic Blood Pressure; *DBP* : Diastolic Blood Pressure**;** *CVOT* : Cardiovascular Outcome Trial; *FPG* : Fasting Plasma Glucose; *OAD* : Obstructive Airway Disease; *SMPG* : Self-Monitored Plasma Glucose.

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Abdu A, et al., Int J Appl Biol Pharm 2026
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Conflict of interest

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Clinical trials

Not applicable

Ethical approval statement and consent to publish

Not applicable

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