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Cardiovascular Effects Of GLP-1 Receptor Agonists In Type 2 Diabetes: Mechanisms And Outcome Data Review

Preeti Maurya[1]*, Shruti Shukla[2], Siddharth Kesharwani[3], Kumari Abha[4]

Department of Pharmacology[1,2], Department of Pharmaceutics[3,4]
Shambhunath Institute of Pharmacy, Jhalwa, Prayagraj, Uttar Pradesh, 211012

ABSTRACT

Patients diagnosed with type 2 diabetes (T2DM) face a significant risk of developing cardiovascular disease due to the profound impact of hyperglycemia and associated metabolic changes on vascular health. This underscores the urgent need for therapeutic advancements targeting not only glycemic control but also other metabolic risk factors to mitigate cardiovascular complications such as cardiovascular death, myocardial infarction, stroke, unstable angina, and heart failure (collectively termed major adverse cardiovascular events).

In recent years, the introduction of glucagon-like peptide-1 receptor agonists (GLP-1RAs) has revolutionized T2DM treatment. GLP-1RAs exert their beneficial effects through various mechanisms, including appetite regulation, glucose-dependent insulin secretion, and inhibition of glucagon release. Importantly, these drugs have shown additional benefits extending to cardiovascular outcomes. Large-scale clinical trials have confirmed the cardiovascular efficacy of GLP-1RAs in patients with T2DM at high risk of cardiovascular disease, demonstrating promising results.

However, while these findings are promising, several crucial aspects remain to be fully understood, such as the specific mechanisms underlying the cardioprotective effects of GLP-1RAs. Interpretation of trial data requires careful consideration due to variability across studies in terms of how cardiovascular risk or disease is defined, patient characteristics, standard care protocols, and event rates.

This review aims to comprehensively outline the clinical profiles of GLP-1RAs, drawing on evidence from both mechanistic studies and randomized controlled trials. It also seeks to explore potential reasons behind the observed improvements in cardiovascular outcomes in these trials. By synthesizing this information, clinicians can make informed decisions regarding the most appropriate treatment strategies for reducing cardiovascular risk in patients with T2DM.

Keywords: Cardiovascular outcomes, Diabetes, GLP-1 receptor agonist, Obesity

INTRODUCTION

The prevalence of type 2 diabetes (T2DM) has been on the rise, with approximately 425 million adults aged 20-79 affected worldwide, a number projected to reach 629 million by 2045 if current trends persist [1-4]. Contributing factors include genetic predisposition, aging, and obesity [5]. T2DM primarily stems from insulin resistance, pancreatic beta cell dysfunction, and abnormal glucagon secretion [6,7]. It is recognized as a systemic disease involving dysfunction across multiple organs and tissues leading to hyperglycemia [8,9].

Diabetes is associated with both microvascular (e.g., nephropathy, retinopathy, neuropathy) and macrovascular complications, predominantly atherosclerosis [10-14]. Disturbances in glucose levels due to insulin resistance or impaired insulin secretion associated with obesity lead to endothelial and smooth muscle dysfunction [15-18]. Alarmingly, many patients already have vascular complications at the time of T2DM diagnosis. Comorbidities like obesity, hypertension, and dyslipidemia further increase cardiovascular disease (CVD) risk in T2DM beyond traditional factors [19,21]. Consequently, the risk of cardiovascular death and non-fatal atherothrombotic events in T2DM rivals or exceeds that of individuals with a history of myocardial infarction [22].

Over the past two decades, improvements in glucose, blood pressure, and cholesterol management have reduced cardiovascular risks and mortality in T2DM patients [28-32]. Nevertheless, macrovascular disease remains the leading cause of death in this population [33-38], necessitating new diabetes treatments that offer cardiovascular benefits.

The strong correlation between T2DM and obesity underscores an impaired communication between the brain and peripheral organs. The "incretin effect" refers to the enhanced insulin secretion in response to oral glucose compared to intravenous glucose at similar levels. This effect is mediated by gut hormones like glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), which stimulate insulin release from pancreatic beta cells. Incretins also regulate glucose levels, gut function, lipid metabolism, immune response, appetite, and body weight[39]. Reduced GLP-1 action in T2DM led to the development of incretin-based therapies such as GLP-1 receptor agonists (GLP-1RAs) and dipeptidyl peptidase-4 (DPP-4) inhibitors. DPP-4 inhibitors prevent GLP-1 and GIP degradation, thereby enhancing their insulinotropic effects [43-54]

The effectiveness of bariatric surgery and GLP-1RAs in managing T2DM underscores the gut's crucial role in maintaining hormonal and neural balance in diabetes treatment [54].

This review examines the clinical impact of GLP-1 receptor agonists (GLP-1RAs) on cardiovascular outcomes, specifically cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke, hospitalization for unstable angina, and heart failure (collectively termed major adverse cardiovascular events, MACE). We focus on recent large-scale trials involving patients with type 2 diabetes mellitus (T2DM) who are at high risk for cardiovascular disease (CVD). A comprehensive analysis of the cardiovascular data from these trials is provided, followed by a critical assessment of the observed improvements in cardiovascular outcomes. Potential reasons underlying these favorable cardiovascular effects are also discussed.[55]

GLP-1RAs have emerged as significant therapeutic agents in T2DM due to their multifaceted benefits beyond glycemic control, including weight management and cardiovascular risk reduction. Recent trials have systematically evaluated these benefits in T2DM patients with established cardiovascular risk factors, yielding promising results regarding MACE reduction. However, interpreting these outcomes requires careful consideration of trial methodologies, patient demographics, and baseline characteristics to understand the full clinical implications.

By synthesizing evidence from these trials, this review aims to elucidate the mechanisms through which GLP-1RAs exert their cardiovascular effects, providing clinicians with valuable insights into their potential role in managing cardiovascular risk in T2DM patients.[57]

GLP-1, its receptor agonists and derived metabolites

GLP-1, derived from the glucagon gene, is a 30-amino acid peptide synthesized in the L-cells of the small intestine. Following food ingestion, active GLP-1 is swiftly released into circulation, where it binds to specific G-protein coupled receptors. The GLP-1 receptor (GLP-1R), composed of 463 amino acids with eight hydrophobic domains, exhibits high conservation of its N-terminal extracellular hydrophobic domain across various tissues such as the hypothalamus, lung, pancreatic islets, stomach, kidney, intestine, and heart.[58]

Activation of GLP-1R initiates a rapid rise in cyclic adenosine monophosphate (cAMP) and intracellular calcium levels, leading to glucose-dependent insulin secretion. However, the metabolic activity of GLP-1 is short-lived due to rapid degradation by dipeptidyl peptidase-4 (DPP-4), resulting in a half-life of merely 1-2 minutes. Modifications in the N-terminus and specific C-terminal positions influence receptor binding and resistance to DPP-4 degradation, thereby extending its duration of action.

GLP-1 circulates in several forms, with GLP-1[7-36]amide as the major biologically active variant. This form undergoes rapid cleavage by DPP-4 between positions 8 and 9, producing GLP-1[9-36]amide, which lacks affinity for GLP-1R. Previously considered metabolically inactive, GLP-1[9-36]amide and other metabolites like GLP-1[28-36]amide and GLP-1[32-36]amide are now recognized for their biological activities independent of GLP-1R. These metabolites exhibit beneficial effects such as cardioprotection, modulation of oxidative stress in vascular tissues, preservation of beta cell function, and inhibition of gluconeogenesis and oxidative stress in hepatocytes.[59]

Recent findings suggest that these GLP-1 metabolites contribute to the pleiotropic effects of GLP-1 beyond their role in glucose metabolism, indicating potential therapeutic benefits in treating cardiovascular and metabolic disorders.

GLP-1[7-36]amide and its metabolites exert direct effects on cardiomyocyte viability, enhancing cardiac function and promoting vasodilation. Notably, there is growing interest in understanding the differences in cardiovascular effects among these metabolites. For instance, GLP-1[7-36]amide primarily exerts cardiovascular effects through a pathway dependent on the GLP-1 receptor (GLP-1R), whereas GLP-1[9-36]amide acts via a pathway independent of GLP-1R. This diversity suggests that targeting either GLP-1R activation or GLP-1 degradation may lead to distinct cardiovascular outcomes.

GLP-1 therapies are primarily approached through two methods: DPP-4-resistant GLP-1 agonists (GLP-1RAs) and DPP-4 inhibitors, both designed to prolong the activity of circulating GLP-1[7-36]amide. GLP-1RAs are classified based on their structural resemblance to native GLP-1 and their pharmacokinetic properties. Some GLP-1RAs are structurally akin to native GLP-1 with modifications to resist degradation by DPP-4, while others, like exendin-4 analogs, mimic a naturally occurring peptide from the saliva of the lizard Heloderma suspectum, possessing GLP-1R activation properties and inherent DPP-4 resistance.

GLP-1RAs are valuable in treating type 2 diabetes mellitus (T2DM), particularly in patients aiming for weight loss or reduced hypoglycemia risk. They effectively target both fasting and postprandial glucose levels by increasing insulin secretion and reducing glucagon release, particularly in response to elevated glucose levels after meals. Unlike intravenous administration of GLP-1, GLP-1RAs do not lower glucose levels below fasting levels, thereby minimizing the risk of hypoglycemia. Additionally, GLP-1RAs decrease hepatic glucose production, enhance insulin sensitivity, delay gastric emptying, potentially promoting satiety, and reducing overall caloric intake. They also stimulate beta cell proliferation, inhibit apoptosis, and increase insulin biosynthesis.[60,61]

Common adverse effects associated with GLP-1RAs include nausea, vomiting, and diarrhea. Table 1 provides a comparative summary of the fundamental characteristics of various GLP-1RAs, highlighting their differences in tolerability, efficacy in weight reduction and glycated hemoglobin (HbA1c) management, as well as immunogenicity.[62]

Exenatide

Exenatide, developed as a recombinant synthetic version of the peptide exendin-4, became the first GLP-1 receptor agonist (GLP-1RA) approved by the US Food and Drug Administration (FDA) for treating type 2 diabetes mellitus (T2DM) in 2005. Initially, exenatide was administered twice daily at doses of 5 mcg for the first month, followed by 5 mcg or 10 mcg. A later formulation was introduced as an extended-release injection of 2 mg once weekly, which demonstrated superior reduction in HbA1c levels and better glucose control.

Exendin-4, upon peripheral administration, crosses the blood-brain barrier more effectively than native GLP-1. This property allows exenatide to suppress food intake through pathways involving both vagal-dependent and vagal-independent mechanisms, directly activating GLP-1 receptors (GLP-1R) in the central nervous system.

Exenatide is primarily eliminated from the body via the kidneys, where it undergoes renal filtration and enzymatic degradation in the tubules. This pharmacokinetic profile contributes to its once-weekly dosing regimen, offering convenience and improved adherence compared to more frequent injections.

Overall, exenatide represents a significant advancement in T2DM treatment, providing effective glycemic control with the added benefit of weight loss, primarily through its action on GLP-1 receptors in both peripheral tissues and the central nervous system.[68,69]

Lixisenatide

Lixisenatide features an exendin-4 backbone, which contributes to its extended half-life. Approximately 55% of lixisenatide is bound to plasma proteins. It is administered as a daily injection of 10 mcg, with a dose adjustment to 20 mcg after two weeks. Clinical trials have shown that lixisenatide can reduce HbA1c levels from baseline by 0.7% to 0.94%, accompanied by a weight loss ranging from 0.2 to 2.8 kg. This drug primarily impacts postprandial glycemia by delaying gastric emptying. When used alone, lixisenatide is effective in lowering HbA1c as well as fasting and postprandial blood glucose levels. Animal studies have demonstrated that lixisenatide can cross the blood-brain barrier following peripheral administration. Its elimination is believed to occur through renal filtration, tubular reabsorption, and metabolic breakdown, although there is no available information on the nature and potential effects of its metabolites.[67]

Liraglutide

Liraglutide is a long-acting GLP-1 analogue created through recombinant DNA technology, with 97% amino acid similarity to natural human GLP-1. The peptide backbone of liraglutide includes a fatty-acyl group, which extends its half-life by making it resistant to DPP-4 and enabling non-covalent binding to serum albumin. Treatment typically starts with a dose of 0.6 mg per day for one week, with weekly increases up to a maximum of 1.8 mg per day. Liraglutide effectively lowers both fasting and postprandial blood glucose levels, as well as HbA1c, while posing a low risk of hypoglycemia and weight gain. Its notable weight loss benefits in individuals with and without type 2 diabetes mellitus make it a preferred option. Unlike GLP-1 receptor agonists derived from exendin-4, liraglutide is not cleared by the kidneys, making it less affected by reduced glomerular filtration rate (GFR). Additionally, liraglutide can cross the blood-brain barrier and exhibits anti-apoptotic, anti-inflammatory, antioxidant, and neuroprotective properties, which could be beneficial for treating neurodegenerative diseases. The metabolite GLP-1 [9–36] amide, produced when

liraglutide is cleaved by DPP-4, is involved in the anti-inflammatory effects seen after intracerebral hemorrhage.[70-75]

Table 1 Characteristics of GLP-1RAs

Drug	Structure/Homology to Human GLP-1	DPP-4 Cleavage	Half-life	Recommendations in Renal Impairment	Antibodies
Exenatide	Substitution of alanine in position 2 by resistant glycine; 53% homology	Resistant	2-4 hours (12 hours for sustained release)	Not recommended in patients with GFR < 30 mL/min; sustained release exenatide licensed in mild-to-moderate renal impairment (GFR > 50 mL/min)	Anti-drug antibodies more common and higher titres with exenatide once weekly; 56-60% of patients developed antibodies with no apparent effect on efficacy or safety
Lixisenatide	Exendin-4 elongated with a residue of 6 resistant lysines at the C-terminus; 50% homology	Resistant	2-3 hours	Not recommended in patients with GFR < 30 mL/min	Low incidence of anti-drug antibodies
Liraglutide	One amino acid substitution (Lys34 Arg); addition of C-16 acyl group (palmitoyl) attached to Lys26 via a glutamate linker; 97% homology	Resistant	10-12 hours	No restrictions or dose adjustments required	Low incidence of anti-drug antibodies
Albiglutide	Composed of a GLP-1 (7-36) dimer fused to recombinant human albumin; 95% homology	Resistant	5 days	No restrictions or dose adjustments required	Low incidence of anti-drug antibodies
Dulaglutide	Two DPP-4 resistant GLP-1 molecules covalently bound to a modified immunoglobulin 4 Fc fragment; 90% homology	Resistant	5 days	No restrictions or dose adjustments required	Low incidence of anti-drug antibodies
Taspoglutide	Alpha-aminoisobutyric acid substitution at positions 8 and 35 of GLP-1 (7-36)NH2; 93% homology	Resistant	165 hours	Renal impairment alters pharmacokinetics; increased risk of gastrointestinal adverse events	Incidence of anti-drug antibodies as high as 49%
Semaglutide	Acyl group with a steric diacid at Lys26; large synthetic spacer; modified by alpha-amino butyric acid at position	Resistant	1 week	No restrictions or dose adjustments required	Low incidence of anti-drug antibodies

	8; 94% homology				

Albiglutide

Albiglutide is a long-acting GLP-1 receptor agonist (GLP-1RA) designed by attaching a GLP-1 dimer to recombinant human albumin. A key modification in albiglutide is the substitution of alanine with glycine, which prevents the peptide from being degraded by DPP-4, resulting in an extended half-life and enabling weekly administration. Albiglutide shares 97% amino acid sequence homology with endogenous GLP-1. It enhances glucose-dependent insulin secretion and delays gastric emptying. The starting dose for albiglutide is 30 mg administered once a week. Being a large biochemical molecule, albiglutide does not cross the blood-brain barrier, which may contribute to its lower incidence of nausea compared to other GLP-1RAs. Despite its advantages, albiglutide was voluntarily withdrawn from the market by its manufacturer due to commercial reasons.[75]

Dulaglutide

Dulaglutide is a long-acting GLP-1 receptor agonist (GLP-1RA) characterized by two identical GLP-1 analogue peptide chains attached to an immunoglobulin G4 heavy chain, which reduces renal clearance. It is about 90% similar to native human GLP-1. This modification gives dulaglutide a prolonged half-life, improved solubility, and lower immunogenicity. The recommended starting dose is 0.75 mg administered subcutaneously once a week, with the option to increase to 1.5 mg weekly.

In a randomized, placebo-controlled, double-blind trial involving 262 obese patients with diabetes, dulaglutide led to a reduction in HbA1c of approximately 1.28% to 1.52% and a weight loss ranging from 1.40 to 2.51 kg. Due to its larger molecular size, dulaglutide may have limited ability to cross the blood-brain barrier. While its cardiovascular benefits are still being explored, initial findings suggest that dulaglutide does not increase the risk of major cardiovascular events in patients with type 2 diabetes mellitus.[76]

Taspoglutide

Taspoglutide is a long-acting GLP-1 receptor agonist (GLP-1RA) with potency comparable to native GLP-1 and complete resistance to DPP-4 degradation. It was the first GLP-1RA designed for once-weekly administration. Taspoglutide, administered at doses of 10 or 20 mg once weekly, has been shown to effectively control glycemia and promote weight loss, with HbA1c reductions estimated at around 1.1%.

In the T-emerge 2 study, taspoglutide demonstrated a higher incidence of gastrointestinal side effects and hypersensitivity reactions compared to exenatide. These adverse effects constrained its clinical use and further research. Consequently, the manufacturer halted late-stage clinical trials of taspoglutide in 2010[77]

Semaglutide

Semaglutide is a GLP-1 receptor agonist (GLP-1RA) administered once weekly. Its extended half-life is achieved through fatty acid acylation, which enhances its binding affinity to albumin and reduces renal filtration. The FDA has approved semaglutide for treating type 2 diabetes mellitus (T2DM) in doses of 0.5 mg and 1.0 mg. Additionally, an oral formulation of semaglutide has been explored with promising results.

Semaglutide is known for its strong metabolic control and effectiveness in reducing body weight, while maintaining a safety profile typical of GLP-1RAs. Clinical trials have shown that semaglutide lowers HbA1c by 1.5% to 1.8%, outperforming other active comparators, and is associated with a weight loss of 4.5 kg to 6.4 kg.[78]

GLP-1 receptor stimulation: diabetes treatment and cardiovascular benefits

GLP-1 receptor agonists (GLP-1RAs) are used for glycemic control in type 2 diabetes mellitus (T2DM). These medications are well-tolerated and administered via subcutaneous injection. They replicate the effects of natural GLP-1 by stimulating insulin release and inhibiting glucagon secretion in a glucose-dependent manner. Additionally, GLP-1RAs influence gastrointestinal motility and help normalize both fasting and postprandial insulin levels. Many patients experience weight loss over several months, typically between 1 and 4 kg, due to increased satiety and reduced caloric intake, which results from their effects on the brain's reward and satiety centers.

Key benefits of GLP-1RAs include their potential for weight loss and a relatively low risk of hypoglycemia compared to other antihyperglycemic agents. While GLP-1RAs may cause slight increases in heart rate, they are also associated with improvements in cardiovascular outcomes. Evidence from animal and human studies suggests that stimulating GLP-1 receptors has positive effects on various organ systems, including the cardiovascular system. GLP-1 stimulation provides cytoprotection, particularly in cardiomyocytes, and has been shown to enhance nitric oxide (NO) production, glucose uptake, and coronary blood flow in isolated rodent hearts. Additionally, vasorelaxation has been observed in various rat vessels, which may offer benefits during acute cardiac ischemia.[79-82]

GLP-1 receptor agonists (GLP-1RAs) may offer long-term benefits for the progression of atherosclerosis. For instance, liraglutide has been shown to inhibit the progression of early, low-burden atherosclerotic disease in the apolipoprotein E-deficient (ApoE−/−) mouse model. Rizzo and colleagues reported that liraglutide significantly improved metabolic parameters, such as triglycerides, and reduced carotid intima-media thickness after 18 months in patients with type 2 diabetes mellitus (T2DM) and metabolic syndrome. However, in overweight patients with stable coronary artery disease and T2DM, liraglutide increased heart rate and decreased heart rate variability, despite significant weight loss and improvements in metabolic parameters. Conversely, a smaller, short-term study found that liraglutide did not enhance left ventricular systolic function or exercise capacity in T2DM patients with stable coronary disease.

In models of heart failure, GLP-1R stimulation has demonstrated improvements in cardiac function. For example, 12 weeks of albiglutide therapy enhanced oxygen consumption in heart failure patients, while exenatide improved cardiac function in individuals with T2DM.[83]

Research into the neuroprotective and neurotrophic effects of GLP-1RAs is also ongoing. In animal models of stroke, with or without T2DM, exenatide has been shown to reduce brain damage and improve functional outcomes. It has also been observed to lessen neuroinflammation and mitigate warfarin-associated hemorrhagic transformation after cerebral ischemia in mice. Additionally, liraglutide administered intraperitoneally 2.5 hours post-stroke in rat models has been reported to induce neuroprotection through upregulation of vascular endothelial growth factor (VEGF) and anti-oxidative effects. Despite these promising results, the precise mechanisms by which GLP-1RAs affect the brain are not fully understood, and further animal studies are necessary.

Large-scale clinical trials are needed to definitively establish whether GLP-1RAs have significant impacts on cardiovascular outcomes and risk in T2DM patients. This review examines the findings from major clinical trials involving exenatide, liraglutide, semaglutide, and lixisenatide, focusing on exploratory cardiovascular outcomes such as cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and hospitalizations for unstable angina or heart failure, which are collectively assessed as major adverse cardiovascular events (MACE).[84,85]

Reasons for improved cardiovascular outcomes

GLP-1 receptor agonists (GLP-1RAs) exert effects across various organ systems, including those not directly involved in glucose regulation, such as the cardiovascular system. These medications have shown potential in improving cardiovascular risk factors that go beyond mere weight loss, reductions in HbA1c, or the incidence of severe hypoglycemia. This additional benefit is notable because while intensive glycemic control is effective at preventing microvascular complications like retinopathy, neuropathy, and nephropathy, macrovascular complications are more influenced by the management of traditional cardiovascular risk factors.[86]

The precise mechanisms connecting hyperglycemia to accelerated atherosclerosis remain partially understood, but they are believed to involve vascular inflammation, endothelial dysfunction, and oxidative stress. However, hyperglycemia alone seems to contribute only marginally to cardiovascular risk, as intensive glycemic control has only a modest effect on reducing non-fatal myocardial infarction by approximately 17% relative risk reduction. Therefore, optimal diabetes management should address multiple cardiovascular risk factors to improve both macrovascular and microvascular outcomes, in addition to glycemic control.

GLP-1RAs might influence cardiovascular outcomes through their impact on various risk factors such as blood pressure, dyslipidemia, platelet reactivity, endothelial function, and insulin sensitivity, alongside their potential direct cardioprotective effects.

Clinical trials have demonstrated that GLP-1RAs can lower blood pressure, with exenatide and liraglutide reducing mean blood pressure by 1–5 mmHg compared to placebo or other active treatments. These effects appear early in the treatment course, indicating that mechanisms other than weight loss might be involved.[87]

Postprandial dyslipidemia, which is associated with a higher risk of cardiovascular disease, is more pronounced in individuals with T2DM. This condition is characterized by elevated and prolonged levels of postprandial triglycerides, which are linked to early atherosclerosis independently of traditional risk factors. GLP-1RAs may help mitigate postprandial dyslipidemia by reducing intestinal lipid absorption and enhancing hepatic fatty acid oxidation. Both exenatide and liraglutide have been shown to effectively lower postprandial dyslipidemia, with this effect becoming apparent soon after treatment initiation. In a randomized, placebo-controlled, crossover study involving subjects with impaired glucose tolerance or recent-onset T2DM, a single subcutaneous dose of exenatide significantly reduced postprandial increases in proatherogenic lipids and lipoproteins.

The ability of GLP-1RAs to impact postprandial dyslipidemia may contribute to their role in reducing macrovascular risk, in addition to their effects on body weight, blood pressure, and glycemic control. Understanding the specific contributions of these effects is crucial for both academic research and clinical practice, highlighting the broad range of risk factors that GLP-1RAs can influence.

In patients with Type 2 Diabetes Mellitus (T2DM), disturbances in platelet aggregation can arise from reduced nitric oxide (NO) bioavailability, endothelial insulin resistance, and the presence of the NO signaling pathway within platelets, which contributes to heightened platelet activity. Under conditions of oxidative stress, this increased platelet activity significantly impacts the risk of atherothrombotic events. Research involving cultured human megakaryocytes has shown that exenatide can increase cyclic AMP levels and inhibit platelet aggregation triggered by thrombin, adenosine diphosphate, or collagen. These findings suggest that GLP-1 receptor agonists (GLP-1RAs) may help reduce platelet aggregation and thrombosis by activating endothelial NO synthase and enhancing NO production. However, estimating the exact contribution of this antiplatelet effect to the reduction in major adverse cardiovascular events (MACE) is challenging, especially since many participants in clinical trials were already on antiplatelet therapy. This effect might be particularly relevant for individuals in primary prevention settings, such as those in the LEADER trial, where 20% of participants were in this category.[88,89]

Severe hypoglycemia in T2DM patients is a strong predictor of macrovascular events and mortality. Hypoglycemia can cause cellular glucose deprivation or activate the sympathoadrenal response, leading to arrhythmias, inflammation, endothelial dysfunction, and a prothrombotic state. Insulin resistance further increases cardiovascular risk through mechanisms such as fatty acid efflux, inflammation, endothelial dysfunction, and atherogenic dyslipidemia. GLP-1RAs improve glucose control primarily by enhancing glucose-stimulated insulin secretion and insulin sensitivity, which reduces the risk of hypoglycemia. Additionally, GLP-1 stimulates insulin secretion, insulin gene transcription, and beta-cell proliferation.

GLP-1RAs may also improve cardiovascular outcomes through their effects on endothelial dysfunction, a condition that can precede the diagnosis of T2DM and is characterized by reduced NO bioavailability and broader functional impairments, including thrombogenicity and inflammation. Early research showed that GLP-1 infusion could ameliorate endothelial dysfunction in T2DM patients with coronary artery disease, as assessed by flow-mediated dilation (FMD). Exenatide, for instance, promotes NO production in endothelial cells through GLP-1 receptor activation and AMP-activated protein kinase (AMPK) stimulation, leading to vasorelaxation even in the presence of high blood glucose or lipid levels. In vivo studies have also demonstrated that liraglutide improves endothelial function in mice by increasing endothelial NO synthase expression and reducing ICAM-1 (intercellular adhesion molecule-1) production, which is dependent on GLP-1R activation. Liraglutide also decreases PAI-1 (plasminogen activator inhibitor type-1) and VCAM (vascular cell adhesion molecule) expression in human vascular endothelial cells in vitro.[90]

However, clinical studies examining the impact of GLP-1RAs on endothelial function have yielded mixed results. In one study with 20 T2DM patients, exenatide improved brachial artery function after 4 months, as measured by FMD, compared to glimepiride. Conversely, in a study with 11 obese T2DM patients, neither exenatide nor liraglutide improved vascular function parameters after 6 months, despite significant improvements in body composition and glycemic control. The variability in these results highlights the challenges in assessing the impact of GLP-1RAs on endothelial function, particularly given the limitations and statistical power of these studies. The value of FMD as a surrogate outcome and the mechanistic insights provided by these studies should be considered when evaluating the relevance of these findings.

In the context of ischemia-reperfusion (IR) injury, exenatide has demonstrated protective effects against IR-induced endothelial dysfunction, as measured by flow-mediated dilation (FMD), through the activation of adenosine triphosphate-sensitive potassium channels in a human IR injury model. Additionally, administering exenatide during reperfusion in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI) has been shown to enhance myocardial salvage, indicating a cardioprotective effect. Liraglutide has produced similar outcomes. In a study involving 92 STEMI patients treated with primary PCI, a brief course of liraglutide was linked to modest improvements in left ventricular ejection fraction and favorable changes in markers of inflammation and endothelial function.[91]

These protective effects are partly mediated through the GLP-1 receptor and involve the AMPK/phosphoinositide 3-kinase (PI3K)-protein kinase B (Akt) signaling pathway. Observations of endothelial and myocardial protection from IR injury with exendin-4, GLP-1, and various GLP-1RAs support this mechanism. However, myocardial protection against IR injury has also been noted in GLP-1 receptor knockout animal models, suggesting that other pathways and metabolites might contribute to these effects. Furthermore, GLP-1 [9–36] amide and exendin-4 exhibited myocardial protection, which was only partially diminished by GLP-1R blockade.[92]

Emerging evidence indicates that GLP-1 degradation products might act through novel receptors distinct from the traditional GLP-1 receptor or through passive cellular transport mechanisms. For example, GLP-1 [9–36] amide might directly interact with the CD36/fatty acid translocator. Additionally, the small metabolite GLP-1 [28–36] amide, due to its amphipathic structure, can traverse cell membranes and interact with intracellular organelles such as mitochondria. This interaction is facilitated by the peptide's C-terminal domain binding to mitochondrial targeting sequences or proteins, particularly the tryptophan residue at position 31.[93]

The mitochondrial response triggered by GLP-1 [28–36] amide supports anti-apoptotic and antioxidant activities, along with modifications in fatty acid oxidation and energy expenditure. The observed myocardial protection provided by GLP-1RAs, even in tissues lacking classical GLP-1 receptors, suggests that distinct receptors and potentially novel metabolites of these agonists may play significant roles in their beneficial clinical effects.[94]

Heterogeneity and impact of cardiovascular safety studies

In 2008, the FDA introduced new guidelines for the development of diabetes medications, focusing on the need to evaluate cardiovascular safety for new antidiabetic drugs. These guidelines require that all new antidiabetic medications demonstrate no excessive cardiovascular risk through long-term cardiovascular outcome trials (CVOTs). The guidelines specify that CVOTs should involve high-risk patient populations, including those with existing cardiovascular disease, multiple risk factors, and renal impairment. Additionally, trials must provide at least two years of cardiovascular safety data.

Since the issuance of these guidelines, results from five major randomized trials have been reported, evaluating cardiovascular outcomes for various GLP-1 receptor agonists (GLP-1RAs). These trials include:

- **EXSCEL (EXenatide Study of Cardiovascular Event Lowering)** for exenatide
- **ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome)** for lixisenatide
- **LEADER** for liraglutide
- **SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes)** for semaglutide
- **HARMONY Outcomes (Albiglutide and Cardiovascular Outcomes in Patients with T2DM and Cardiovascular Disease)** for albiglutide
- **REWIND (Researching Cardiovascular Events with a Weekly Incretin in Diabetes)** for dulaglutide

These trials were designed to evaluate non-inferiority or detect differences between the GLP-1RAs and placebo concerning cardiovascular outcomes in patients with type 2 diabetes mellitus who were at high risk for cardiovascular events or had established cardiovascular disease. This approach contrasts with earlier studies, which often included patients at lower cardiovascular risk and were typically part of pooled analyses and meta-analyses of incretin therapies.[95-99]

Table 2 provides a summary of the key findings from these trials.

EXSCEL

Prior to the completion of the EXSCEL trial, exploratory findings from a large, uncontrolled study involving 39,275 patients indicated that exenatide administered twice daily was associated with a significantly lower rate of cardiovascular events and hospitalizations compared to other glucose-lowering treatments. However, the subsequent results from the randomized, placebo-controlled EXSCEL trial did not confirm these preliminary findings.

The EXSCEL trial, which enrolled the largest and most diverse patient population among GLP-1RA cardiovascular outcome trials, assessed the effects of weekly exenatide 2 mg against a placebo in individuals with type 2 diabetes mellitus (T2DM) and elevated cardiovascular risk. This trial was distinctive for including patients with varying levels of cardiovascular risk, including 26.9% who had no prior cardiovascular events. Although the exenatide group experienced fewer cardiovascular events, indicating cardiovascular safety, there was no significant cardiovascular benefit compared to the placebo group. Additionally, the trial found no significant differences between exenatide and placebo in terms of severe hypoglycemia, pancreatitis, pancreatic cancer, or medullary thyroid cancer.[99-102]

Table 2 Characteristics of GLP-1RA trials

Trial	GLP-1RA	N	Inclusion Criteria	Study Design	Primary Outcome	Results	Additional Findings
EXSCEL	Exenatide	14,752	Type 2 Diabetes Mellitus (T2DM) with prior cardiovascular events or risk factors	Phase 3/4, multicenter, randomized, double-blind, placebo-controlled, non-inferiority, superiority (hierarchical analysis)	3-point MACE: cardiovascular death, non-fatal MI, non-fatal stroke	Exenatide group: 11.4% Placebo group: 12.2% HR 0.91; 95% CI 0.83-1.00 P<0.001 for non-inferiority, P=0.06 for superiority	No significant differences in secondary endpoints; similar rates of cardiovascular events in both groups
ELIXA	Lixisenatide	6,068	T2DM with acute coronary syndrome within 180 days prior to randomization	Multicenter, randomized, double-blind, placebo-controlled, non-inferiority, superiority	4-point MACE: cardiovascular death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina	Lixisenatide group: 13.4% Placebo group: 13.2% HR 1.02; 95% CI 0.89-1.17 P<0.001 for non-inferiority, P=0.81 for superiority	No significant impact on cardiovascular events; similar rates between treatment and placebo groups
LEADER	Liraglutide	9,340	T2DM with established CVD or CKD, or high cardiovascular risk	Multicenter, double-blind, placebo-controlled, non-inferiority, superiority (hierarchical analysis)	3-point MACE: cardiovascular death, non-fatal MI, non-fatal stroke	Liraglutide group: 13.0% Placebo group: 14.9% HR 0.87; 95% CI 0.78-0.97 P<0.001 for non-inferiority, P=0.01 for superiority	Reduction in all-cause mortality (8.2% vs. 9.6% in placebo; HR 0.85, 95% CI 0.74-0.97; P=0.02) Reduction in cardiovascular death
SUSTAIN-6	Semaglutide	3,297	T2DM with established CVD or CKD, or	Multicenter, double-blind, placebo-	3-point MACE: cardiovascular death, non-fatal	Semaglutide group: 6.6% Placebo group: 8.9% HR	Significant reduction in non-fatal stroke (1.6% vs. 2.7%; HR 0.61, 95% CI

			high cardiovascular risk	controlled; non-inferiority; superiority analysis not pre-specified	MI, non-fatal stroke	0.74; 95% CI 0.58-0.95 P<0.001 for non-inferiority, P=0.02 for superiority	0.38-0.99; P=0.04)
HARMONY	Albiglutide	9,463	T2DM with established CVD or high cardiovascular risk	Multicenter, randomized, double-blind, placebo-controlled; non-inferiority, superiority testing pre-specified	3-point MACE: cardiovascular death, non-fatal MI, non-fatal stroke	Albiglutide group: 7.1% Placebo group: 9.0% HR 0.78; 95% CI 0.68-0.90 P<0.001 for non-inferiority, P=0.0006 for superiority	Demonstrated significant cardiovascular benefit compared to placebo
REWIND	Dulaglutide	9,901	T2DM with established CVD or high cardiovascular risk	Multicenter, randomized, double-blind, placebo-controlled; non-inferiority, superiority testing pre-specified	3-point MACE: cardiovascular death, non-fatal MI, non-fatal stroke	Preliminary results showed positive outcomes; HR 0.78; 95% CI 0.66-0.93; P=0.007	Significant reduction in major cardiovascular events compared to placebo

ELIXA

The ELIXA trial was designed to compare the effects of lixisenatide, starting at 10 mcg for 2 weeks and increased to a maximum of 20 mcg, against a placebo over a median follow-up period of 25 months. The study aimed to evaluate both the non-inferiority and superiority of lixisenatide regarding cardiovascular outcomes. It was the first randomized, double-blind trial to assess cardiovascular outcomes for a GLP-1 receptor agonist (GLP-1RA). The trial specifically included patients with a history of acute coronary events.

The primary endpoint was the time to the first major adverse cardiovascular event (MACE), which was a composite of four cardiovascular outcomes. The results showed comparable rates of the primary composite endpoint between the lixisenatide and placebo groups. No significant differences were observed between the groups for individual components of the primary outcome. Additionally, there were no notable differences in hospitalizations for heart failure, even when including hospitalizations for coronary revascularization.[102]

Lixisenatide did not lead to a higher incidence of serious adverse events or severe hypoglycemia and provided a modest benefit in weight management.

LEADER

The LEADER trial evaluated the impact of liraglutide on cardiovascular outcomes in patients with type 2 diabetes mellitus (T2DM) who were also receiving standard care. Participants were randomly assigned to receive either liraglutide at a dose of 1.8 mg daily (or the highest tolerated dose) or a placebo. The median follow-up duration was 3.8 years. The study included approximately 80% of patients with established cardiovascular disease (CVD) or chronic kidney disease (CKD) and 20% with cardiovascular risk factors but no established CVD.

The primary endpoint of the trial was the time to first occurrence of a major adverse cardiovascular event (MACE), which was a composite of three cardiovascular outcomes. Results indicated that liraglutide treatment led to a reduction in both all-cause mortality and 3-point MACE. Specifically, patients on liraglutide had a lower overall risk of death from cardiovascular causes. However, the rates of non-fatal myocardial infarction (MI) and non-fatal stroke did not differ significantly between the liraglutide and placebo groups. In patients with established CVD, the primary endpoint rates were 14% in the liraglutide group compared to 16.7% in the placebo group, translating to an absolute risk reduction of 2.7% and a number needed to treat (NNT) of 37. There were no significant differences between the groups regarding heart failure hospitalizations.[103]

Additionally, the liraglutide group showed a lower incidence of renal or retinal microvascular events compared to the placebo group, driven primarily by a reduced rate of nephropathy events. The rate of nephropathy was 1.5 events per 100 patient-years in the liraglutide group versus 1.9 events per 100 patient-years in the placebo group, with a hazard ratio (HR) of 0.78 (95% confidence interval [CI] 0.67–0.92; P=0.003).

Kaplan–Meier curves for 3-point MACE, cardiovascular mortality, and all-cause mortality began to show separation around 12–18 months after randomization. This delay suggests that part of liraglutide's effect on cardiovascular events may be attributed to its anti-atherosclerotic properties. Compared to traditional diabetes studies focused on achieving near-normoglycemia, the cardiovascular benefits of GLP-1 receptor agonists were observed relatively early.

In comparison, the UKPDS (United Kingdom Prospective Diabetes Study) and the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study revealed that intensive glucose-lowering therapy was associated with reduced microvascular complications but did not show significant long-term reductions in macrovascular events. The ADVANCE (Action in Diabetes and Vascular Disease) study found reduced microvascular complications with intensive therapy but no change in macrovascular event rates after 5 years. Similarly, the VADT (Veterans Affairs Diabetes Trial) showed no significant reduction in major cardiovascular events with intensive glucose control, although fewer major cardiovascular events were noted in the intensive control group during post-trial follow-up.

The beneficial effects of liraglutide on cardiovascular outcomes and mortality appear to be independent of its association with a lower incidence of severe hypoglycemia, as observed in a post-hoc analysis of the LEADER study.[104]

SUSTAIN-6

The SUSTAIN-6 trial was a randomized, placebo-controlled study designed to evaluate the cardiovascular safety of semaglutide compared to a placebo in patients with type 2 diabetes mellitus (T2DM). At the start of the study, 83% of participants had pre-existing cardiovascular disease (CVD). Over two years, patients

received weekly subcutaneous injections of semaglutide at doses of 0.5 or 1.0 mg. The trial found that semaglutide significantly reduced cardiovascular risk. Although the study was not intended to demonstrate superiority, the semaglutide group experienced significantly fewer cardiovascular events compared to the placebo group. The reduction in major adverse cardiovascular events (MACE) was primarily attributed to a lower incidence of non-fatal strokes in the semaglutide group compared to the placebo group, with no significant differences in cardiovascular deaths or non-fatal myocardial infarctions. Additionally, the incidence of new or worsening nephropathy was lower in the semaglutide group (3.8%) compared to the placebo group (6.1%), with a hazard ratio of 0.64 (95% CI, 0.46–0.88; P=0.005). However, the semaglutide group did see a higher rate of retinopathy complications (3.0%) compared to the placebo group (1.8%), with a hazard ratio of 1.76 (95% CI, 1.11–2.78; P=0.02). Subgroup analyses indicated that retinopathy complications were more common in patients who experienced a rapid reduction in HbA1c, regardless of the treatment received.[105-109]

HARMONY

The HARMONY study represents the most recent large cardiovascular outcome trial (CVOT) involving albiglutide. It included 9,463 participants, who were randomized to receive either albiglutide, administered subcutaneously once a week, or a placebo, over a median duration of 1.6 years. Participants were required to be 40 years or older with type 2 diabetes mellitus (T2DM) and had pre-existing coronary, cerebrovascular, or peripheral arterial disease. Individuals with severe chronic kidney disease (CKD) were excluded.

The study found that albiglutide reduced the risk of major adverse cardiovascular events (MACE) by 22% (95% CI 10–32%) compared to placebo when added to standard care in patients with T2DM and cardiovascular disease. Specifically, the hazard ratios were 0.93 (95% CI 0.73–1.19) for cardiovascular death, 0.75 (95% CI 0.61–0.90) for myocardial infarction, and 0.86 (95% CI 0.66–1.14) for stroke. The tolerability and safety of albiglutide were deemed acceptable. Despite the relatively short follow-up period, the study contributes further evidence supporting the potential cardiovascular benefits of GLP-1 receptor agonists in T2DM patients.

Forest plots in Figures 1 and 2 illustrate the cardiovascular outcomes associated with exendin-4, GLP-1-based therapies, and non-GLP-1 therapies. Combined results from the LEADER, SUSTAIN-6, and HARMONY studies demonstrate a significant reduction in MACE, myocardial infarction, and cardiovascular death with GLP-1-based therapies compared to exendin-4 and non-GLP-1 therapies. Although heterogeneity among trials was not significant for most endpoints, cardiovascular death showed a marked decrease only with GLP-1-based therapies. This finding aligns with the stronger effects of GLP-1-based treatments on MACE and myocardial infarction, although differences might also be attributed to variations in the studied populations.[108]

REWIND

The REWIND trial aimed to assess the impact of adding once-weekly dulaglutide to the standard care regimen on the incidence of cardiovascular events in patients with type 2 diabetes mellitus (T2DM). The study enrolled patients with an HbA1c $\leq$ 9.5% who were already on up to two classes of antidiabetic medications. Participants were 50 years or older if they had a history of cardiovascular disease, or 60 years or older if they had at least two other cardiovascular risk factors. Exclusion criteria included an estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73 m², gastric emptying abnormalities, anterior pancreatitis, liver disease, or medullary thyroid carcinoma.[109]

The primary cardiovascular endpoint of the REWIND trial was a composite of major adverse cardiovascular events (MACE), including cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. Secondary endpoints included each component of the primary endpoint, as well as retinal or renal disease, hospitalization for unstable angina, heart failure requiring hospitalization, and all-cause mortality. Safety

outcomes monitored were acute pancreatitis, severe gastrointestinal pain, pancreatic, thyroid, or other cancers, and severe hypoglycemia.

The study has concluded, and preliminary results indicate that dulaglutide significantly reduced the primary composite endpoint. Full details of the results are expected to be published later this year.[110]

Critical overview of the RCTs

Despite the variations in study design, patient cohorts, and degrees of background cardiovascular disease (CVD) across different trials, there are notable similarities among the LEADER, SUSTAIN-6, and HARMONY studies. All three trials reported positive cardiovascular outcomes. Differences in cardiovascular benefits were observed within the first 12 months, indicating that these effects are likely not due to variations in glucose-lowering efficacy. The variability in cardiovascular outcomes might be attributed to differences in study design, patient populations, treatment durations, and the pharmacokinetic and pharmacodynamic properties of the drugs, or their structural similarity to human GLP-1.

In these large-scale trials of GLP-1 receptor agonists (GLP-1RAs), a reduced incidence of stroke was specifically noted with semaglutide in the SUSTAIN-6 study, although stroke was part of the major adverse cardiovascular events (MACE) composite in all these trials.

The ELIXA study, which involved lixisenatide, had a shorter duration and included patients who had recently experienced acute coronary syndrome (ACS) (within 180 days). The short-acting nature of lixisenatide meant that patients were not exposed to the medication for most of the day. The patients in ELIXA had a significant cardiovascular risk due to their recent ACS events, which is a notable factor since acute coronary syndrome heightens cardiovascular risk through increased monocyte homing and systemic inflammation, thus leading to a higher incidence of recurrent events in the first year. Additionally, the persistent thrombotic tendency after an ACS could potentially obscure non-ischemic benefits of GLP-1RAs, reducing the clarity of their impact.[111]

The EXSCEL trial, which included a diverse patient population with T2DM, did not achieve statistical significance for its primary endpoint (P=0.06). Although there was a 14% reduction in total mortality, this was not deemed significant due to hierarchical criteria requiring primary outcomes to be significant before considering secondary endpoints. Post hoc analyses, while useful, must be interpreted cautiously. Notably, the primary outcome approached significance with approximately a 10% relative risk reduction when excluding 30% of patients who were undergoing primary prevention. In the LEADER trial, significant differences between patients with primary and secondary prevention also suggested that patient-specific factors rather than drug-related mechanisms may influence outcomes.

Heart failure has primarily been evaluated as a secondary safety outcome in large clinical trials involving patients with type 2 diabetes (T2DM). Unlike findings from numerous animal studies, human trials have not shown significant concerns regarding heart failure. Overall, these studies have not demonstrated an increased risk of hospitalization due to heart failure, indicating a neutral effect of the treatments.

The FIGHT trial, a smaller study involving 300 patients with heart failure and reduced ejection fraction (≤40%), assessed the impact of liraglutide compared to placebo. The study found that liraglutide did not significantly affect the primary combined endpoint of mortality or hospitalization rates.[112]

Several ongoing studies aim to explore the effects of GLP-1 receptor agonists on cardiac function more thoroughly. For instance, the Efects of Liraglutide in Young Adults with Type 2 Diabetes (LYDIA) trial is examining how liraglutide influences cardiac structure and function in younger, obese patients (ages 18–40) with T2DM, specifically focusing on cardiac diastolic function.

Table 3. Here is a tabular representation of the effect of GLP-1 and non-GLP-1-based therapies on Major Adverse Cardiovascular Events (MACE), including relative risk (RR) and the associated confidence intervals (CI):

Category	Trial	Events, Treatment	Events, Control	% Weight	RR (95% CI)
Exendin-4-based trials	ELIXA	406/3440	399/3433	10.58	1.02 (0.89, 1.16)
	EXSCEL	839/8195	905/8301	23.81	0.94 (0.86, 1.03)
	Subtotal	**1245/11635**	**1304/11734**	**34.39**	**0.96 (0.89, 1.04)**
GLP-1 analog trials	LEADER	608/5276	694/5366	18.22	0.89 (0.80, 0.99)
	SUSTAIN 6	108/1756	146/1795	3.82	0.76 (0.59, 0.96)
	HARMONY	338/5069	428/5160	11.23	0.80 (0.70, 0.92)
	Subtotal	**1054/12101**	**1268/12321**	**33.28**	**0.85 (0.78, 0.91)**
Non-GLP-1-based therapies	ACCORD	352/5480	371/5494	9.81	0.95 (0.83, 1.10)
	ADVANCE	557/6128	590/6159	15.59	0.95 (0.85, 1.06)
	VADT	235/1134	264/1156	6.92	0.91 (0.78, 1.06)
	Subtotal	**1144/12742**	**1225/12809**	**32.32**	**0.94 (0.87, 1.01)**
Overall		**3443/36478**	**3797/36864**	**100.00**	**0.92 (0.88, 0.96)**

- **Active better** indicates that the treatment group has a lower risk relative to the control.
- **Placebo better** indicates that the control group has a lower risk relative to the treatment group.

Table 4. Here is a tabular representation of the effect of GLP-1 and non-GLP-1-based therapies on incident myocardial infarction (MI), including relative risk (RR) and the associated confidence intervals (CI):

Category	Trial	Events, Treatment	Events, Control	% Weight	RR (95% CI)
Exendin-4-based trials	ELIXA	270/3304	261/3295	14.05	1.03 (0.88, 1.21)
	EXSCEL	466/7822	480/7876	25.72	0.98 (0.86, 1.11)
	Subtotal	**736/11126**	**741/11171**	**39.77**	**1.00 (0.90, 1.10)**
GLP-1 analog trials	LEADER	292/4960	339/5011	18.13	0.87 (0.75, 1.01)
	SUSTAIN 6	47/1695	64/1713	3.42	0.74 (0.51, 1.07)
	HARMONY	181/4912	240/4972	12.82	0.76 (0.63, 0.92)
	Subtotal	**520/11567**	**643/11696**	**34.38**	**0.82 (0.73,**

					0.91)
Non-GLP-1-based therapies	ACCORD	205/5333	248/5371	13.29	0.83 (0.69, 1.00)
	ADVANCE	153/5724	156/5725	8.39	0.98 (0.79, 1.22)
	VADT	64/963	78/970	4.18	0.83 (0.60, 1.14)
	Subtotal	**422/12020**	**482/12066**	**25.85**	**0.88 (0.77, 1.00)**
Overall		**1678/34713**	**1866/34933**	**100.00**	**0.90 (0.85, 0.96)**

- **Active better** indicates that the treatment group has a lower risk of incident MI compared to the control.
- **Placebo better** indicates that the control group has a lower risk of incident MI compared to the treatment group.

Table 5. Here's a tabular representation of the effect of GLP-1 and non-GLP-1-based therapies on cardiovascular (CV) deaths, including relative risk (RR) and the associated confidence intervals (CI):

Category	Trial	Events, Treatment	Events, Control	% Weight	RR (95% CI)
Exendin-4-based trials	ELIXA	156/3190	158/3192	11.26	0.99 (0.80, 1.23)
	EXSCEL	340/7696	383/7779	27.16	0.90 (0.78, 1.03)
	Subtotal	**496/10886**	**541/10971**	**38.42**	**0.92 (0.82, 1.04)**
GLP-1 analog trials	LEADER	219/4887	278/4950	19.69	0.80 (0.67, 0.95)
	SUSTAIN 6	44/1692	46/1695	3.28	0.96 (0.64, 1.44)
	HARMONY	122/4853	130/4862	9.26	0.94 (0.74, 1.20)
	Subtotal	**385/11432**	**454/11507**	**32.23**	**0.86 (0.75, 0.98)**
Non-GLP-1-based therapies	ACCORD	135/5263	253/5824	6.73	1.42 (1.10, 1.85)
	ADVANCE	94/5217	289/5858	20.54	0.88 (0.75, 1.04)
	VADT	38/937	29/921	2.09	1.29 (0.80, 2.07)
	Subtotal	**426/12024**	**412/11996**	**29.36**	**1.03 (0.91, 1.18)**
Overall		**1307/34342**	**1407/34474**	**100.00**	**0.93 (0.87, 1.01)**

- **Active better** indicates that the treatment group has a lower risk of CV deaths compared to the control.
- **Placebo better** indicates that the control group has a lower risk of CV deaths compared to the treatment group.

CONCLUSION AND FUTURE PERSPECTIVES

The use of GLP-1 receptor agonists (GLP-1RAs) has become well-established for managing both early and advanced stages of type 2 diabetes mellitus (T2DM). However, ongoing research is focused on several key areas, including enhancing treatment adherence through the development of oral and inhaled formulations. A current trial (NCT02692716) is exploring the cardiovascular safety of oral semaglutide in T2DM patients. Other notable research areas include the use of osmotic pump systems, the integration of GLP-1RAs with basal insulin therapy, and the potential application of GLP-1RAs for treating type 1 diabetes.

Sodium-glucose co-transporter 2 inhibitors (SGLT2i), similar to GLP-1RAs, have also been shown to reduce cardiovascular mortality and hospitalizations for heart failure in high-risk T2DM patients. A recent network meta-analysis revealed that the difference in cardiovascular mortality reduction between SGLT2i and GLP-1RAs was not statistically significant. However, this type of meta-analysis is subject to biases related to clinical severity and differences in complementary treatments, especially within placebo groups. For instance, the incidence of major adverse cardiovascular events (MACE) in the placebo groups of SGLT2i studies is higher compared to those in GLP-1RA studies, leading to substantial heterogeneity that is not easily statistically scalable.

The combination of GLP-1RAs and SGLT2i holds promise for future treatment strategies, as this combined therapy could potentially offer additive cardiovascular benefits for T2DM patients. Additionally, the development of new peptide hormones that stimulate insulin secretion and regulate appetite is an exciting area of research. This includes dual agonists that target both GLP-1 and peptide YY receptors, as well as the co-administration of glucagon and GLP-1, which could offer new therapeutic avenues.

Emerging evidence suggests that GLP-1 receptor agonists (GLP-1RAs) offer promising cardiovascular benefits for patients with type 2 diabetes mellitus (T2DM) who are at high risk for cardiovascular disease (CVD), particularly with drugs like liraglutide and semaglutide. However, variations in the definition of cardiovascular risk, baseline characteristics, trial durations, standard care practices, and event rates across different studies make it challenging to compare cardiovascular outcomes directly. Additionally, differences in the diseases and their severity among trial participants further complicate comparisons.

GLP-1RAs are known for their beneficial effects across multiple organ systems, potentially offering cardiovascular advantages. Despite the encouraging results, large-scale trials are still needed to specifically confirm the efficacy of GLP-1RAs in improving stroke outcomes. Moreover, it is crucial to assess whether these treatments can also reduce damage and enhance functional recovery after a stroke. To address this, exenatide is currently being investigated in studies involving hyperglycemic patients with suspected stroke and those receiving thrombolytic therapy for stroke.

GLP-1RAs have significantly changed diabetes management strategies. While current data are promising, further research is needed to fully understand the mechanisms through which these drugs may provide cardiovascular benefits. The structural differences among various GLP-1RAs could lead to distinct clinical profiles, which should be taken into account when choosing a GLP-1RA for individual patients. This patient-centered approach could offer particular advantages for those with high cardiovascular risk, especially concerning safety considerations.

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