Review

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Exploring the clinical effectiveness of glucagon-like peptide-1 receptor agonists in managing cardiovascular complications: an updated comprehensive review and future directives

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Abstract

The possible cardiovascular advantages of glucagon-like peptide-1 receptor agonists (GLP-1RAs), a class of drugs predominantly used to treat type 2 diabetes (T2D), have garnered increasing attention in recent years. Clinical trials have looked into the possibility that GLP-1RAs have extra cardioprotective benefits in addition to their ability to manage T2D, demonstrating significant major adverse cardiovascular events (MACE) reduction and a favorable safety profile. GLP-1 RAs improve cardiovascular outcomes, especially in those with existing cardiovascular disease. MACE has been steadily declining with this class of drugs, which results in a noticeable rise in cardiovascular outcome trials (CVOTs). GLP-1 RAs have a variety of impacts on the cardiovascular system beyond their function in glycemic control. They offer direct cardioprotection, vasodilation, promotion of salt excretion, reduction of weight, improved lipid profile, and anti-inflammatory qualities through a variety of mechanisms. Thus, this review focuses on GLP-1RAs, its mechanism of action, its clinical effectiveness in CVOTs, the mechanism behind its cardiovascular benefits, its potential role in heart failure, cardiovascular outcomes, its underutilization, and future directives. In conclusion, GLP-1 RAs shows potential in controlling T2D while also lowering cardiovascular risk, but warrants further study into long-term results and real-world data to optimize treatment regimens, ultimately increasing patient outcomes and lowering the burden of cardiovascular disease in T2D populations.

Keywords: cardiovascular complications, cardiovascular outcome trials, glucagon-like peptide-1 receptor agonists, heart failure, type 2 diabetes

Introduction

Cardiovascular complications dominate the landscape of type 2 diabetes (T2D) as the primary reason for both mortality and morbidity[1,2], and individuals with diabetes exhibit an approximately three-fold increase in mortality rate due to coronary artery disease compared to non-diabetic individuals[3]. For individuals 50 and older with diabetes, there is a considerable differential in life expectancy without cardiovascular disease: women face a 7.8-year decline, while men face a slightly larger decrease of 8.4 years[4]. When combined, diabetes and atherosclerotic cardiovascular disease (ASCVD) increase mortality and reduce life expectancy by 12–15 years[5]. Improvements in diabetes therapy options and the subsequent publication of cardiovascular

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outcomes trials (CVOTs) for newer antihyperglycemic drugs have led to modifications in treatment algorithms for people with T2D. According to current guidelines, physicians should prioritize lowering cardiovascular risk by using a cardiometabolic approach rather than a glucocentric one[6–10].

As part of the endeavor to assess cardiovascular health and the efficacy of various anti-diabetic medications, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have drawn a lot of interest, which has resulted in a noticeable rise in CVOTs during the last 10 years. Since major adverse cardiovascular events (MACE) have been steadily declining with this class of drugs, CVOTs have expressed a significant interest in them. This holds particularly true for non-fatal stroke rates, cardiovascular mortality, and non-fatal myocardial infarction (MI) incidence. Numerous pathways contribute to these favorable results for cardiovascular outcomes[11]. Additionally, it has been established that selective GLP-1 RA, dulaglutide, liraglutide, injectable, and oral semaglutide delay the progression of macroalbuminuria and are beneficial for atherosclerotic cardiovascular disease (ASCVD) in both primary[5] and secondary preventive groups[6]. Because of this, the American Diabetes Association (ADA) now suggests, without regard to baseline A1C, customized A1C target, or metformin usage, these particular GLP-1 RA as first-line treatment in those with T2D and ASCVD or those with symptoms of high cardiovascular risk. Unless there are contraindications, GLP-1 RAs should also be taken into consideration as the first injectable treatment for those with T2D, independent of cardiovascular risk[12]. This comprehensive review explores the clinical effectiveness of GLP-1RAs with an emphasis on cardiovascular outcomes, offering a thorough and current overview along with recommendations for future research.

HIGHLIGHTS

- Individuals with type 2 diabetes (T2D) face a three-fold higher risk of mortality from coronary artery disease compared to those without diabetes, resulting in significant reductions in life expectancy.
- In T2D patients, cardiovascular outcome trials (CVOTs) have shown that glucagon-like peptide 1 receptor agonists (GLP-1 RAs) reduce major adverse cardiovascular events (MACE), cardiovascular mortality, non-fatal myocardial infarction (MI), and non-fatal stroke rates.
- GLP-1 RAs exert antihyperglycemic effects by reducing food intake, delaying gastric emptying, inhibiting glucagon secretion, and enhancing glucose-dependent insulin release. They also have weight-reducing and hypoglycemia-lowering properties.
- GLP-1 RAs offer the potential for managing heart failure (HF) by various means, including direct heart protection, promotion of natriuresis and vasodilation, and control of weight and glucose levels.
- GLP1-RAs have been recommended by the American College of Cardiology (ACC), the European Society of Cardiology (ESC), and the American Diabetes Association (ADA) for use in treatment regimens aimed at reducing atherosclerotic cardiovascular disease (ASCVD) in high-risk patients with T2D.

Mechanism of action of glucagon-like peptide-1 receptor agonists

GLP-1RAs are synthetic analogs of the gut hormone GLP-1, which increases the pancreatic release of insulin, a process known as the incretin effect that decreases blood glucose levels. Unlike the natural hormone, these synthetic GLP-1RAs are resistant to degradation by the body enzyme dipeptidyl peptidase 4 (DPP-4), which prolongs the duration of activity. GLP-1 has also been shown to have limited activity in T2D patients. By promoting the growth of beta cells in the pancreas and enhancing satiety, GLP-1 RAs decrease appetite and the rate of gastric emptying. Additional studies show that GLP-1 RAs aid in the restoration of insulin secretory activity, which benefits diabetic patients by improving glycemic control and promoting weight reduction. While long-acting formulations impact both fasting and postprandial glucose levels, short-acting GLP-1RAs largely lower postprandial glucose concentration by delaying gastric emptying. Clinical evidence indicates that GLP-1 analogs may have additional beneficial effects on various body receptors, such as lowering blood pressure, enhancing myocardial and endothelial tissue function, assisting failing or ischemic heart tissue in recovering, promoting arterial vasodilatation, and bolstering natriuresis and diuresis[13].

Oral vs. injectable glucagon-like peptide-1 receptor agonists

In individuals with T2D inadequately managed on basal insulin, a network meta-analysis comparing once-daily oral semaglutide to injectable GLP-1 RAs consisted of seven trials. The results showed that, in contrast to most other GLP-1 RA therapies, the HbA1c levels fell quickly with once-daily oral semaglutide 14 mg, decreasing between – 0.42% and – 1.32%. The 0.5 or 1 mg injectable semaglutide administered once a week did not show any statistically significant difference from the 14 mg oral semaglutide administered once a day. Weight reductions with once-daily oral semaglutide 14 mg were significantly greater than those with exenatide 2 mg and lixisenatide 20 μg, varying by – 2.21 and – 2.39 kg, respectively. Once-daily oral semaglutide 14 mg was shown to be more effective in reducing weight than most other therapies, except for once-weekly injectable semaglutide 1 mg, even though the difference was not statistically significant. Comparable trends were seen by the composite endpoint and those with HbA1c levels of less than 6.5% and less than 7.0%. The incidence of nausea, vomiting, or diarrhea with oral semaglutide 14 mg once a day was similar to all other GLP-1 RA therapies. The results show that 14 mg of oral semaglutide added to basal insulin once daily can considerably decrease body weight and HbA1c, enabling the accomplishment of glycemic control throughout a 26 ± 4 week period. The oral semaglutide 14 mg has equivalent or higher effectiveness and a good tolerability profile when compared to the majority of injectable GLP-1 RAs[14].

Contraindications on glucagon-like peptide-1 receptor agonists use

A warning about GLP-1 receptor agonist contraindications is as follows:

- It is contraindicated to provide any GLP-1 RA to someone who has a known GLP-1 RA drug hypersensitivity[15,16].

- There is a higher chance of deadly hemorrhagic and necrotizing pancreatitis with any GLP-1 analog. Although post-marketing surveillance has identified this, the precise mechanism causing pancreatitis is unknown. If a patient has a history of pancreatitis or develops pancreatitis, GLP-1 RAs should be stopped[17].
- Patients with a family history of medullary thyroid cancer or those with type 2 multiple endocrine neoplasia are not candidates for semaglutide, dulaglutide, exenatide extended-release, liraglutide, or tirzepatide. Liraglutide was found to cause C-cell hyperplasia and raise calcitonin release in rats. For conclusive results on people, more research is needed[18,19].
- Patients with end-stage renal disease and a CrCl less than 30 ml/min should not use exenatide. Additionally, if a complete blood count panel confirms that exenatide is causing drug-induced thrombocytopenia, the medication should be stopped right away.
- GLP-1RAs should not be used in people who have a history of inflammatory bowel disease or gastroparesis. They should also be taken cautiously by women who are pregnant. Research on animals has demonstrated that at dosages greater than the maximum advised human dosage, teratogenicity, intrauterine mortality, and adverse effects on embryo-fetal development can occur. There is not enough evidence available on drug-associated risk for other GLP-1RAs. Consequently, these drugs ought to be administered only in cases when the mother's possible benefit outweighs the fetus's possible danger.
- Regarding compounded semaglutide formulations, the FDA issued a warning. Patients and medical professionals are being reminded by the FDA that compounded medications are not FDA-approved. The safety and efficacy of compounded drugs have not been assessed by the FDA. Semaglutide compounded with different salts has been associated with serious side effects. The FDA has been notified of three linked recent reports of patient injury resulting from adult users of semaglutide at dosages meant to produce weight reduction. Semaglutide is authorized for the treatment of diabetes. People got the drug from spas and compounding pharmacies. After taking a dosage that exceeded the prescribed amount by 10 times, two individuals had extreme stomach discomfort, nausea, and vomiting. One of them had an overdose that needed medical attention, but it was resolved with treatment. Patients were given syringes to self-administer without receiving the appropriate instruction on how to use them. Overdose might be lethal in this case since the compounded semaglutide lacks safety mechanisms. Dosing variations and confusion might be caused by using the incorrect syringes. Strict labeling, dispensing, and counseling procedures are necessary to reduce the risks. To prevent serious adverse effects and hospitalizations due to dosage mistakes, healthcare providers should promote its correct usage[20].
- The FDA has also issued a warning on semaglutide-related ileus. According to recent research, compared to bupropion-naltrexone, using GLP-1RAs for weight reduction carries a greater risk of pancreatitis, gastroparesis, and intestinal obstruction[21,22].

Evaluating cardiovascular outcome trials for glucagon-like peptide-1 receptor agonists

CVOTs have become essential in evaluating the cardiovascular effects of GLP-1 RAs[23]. The GLP-1 RA family of anti-diabetic medications has garnered significant interest because of its capacity to control blood sugar levels and its advantages for CVS[24]. Since regulatory agencies demand that anti-diabetic medications not increase the risk of developing cardiovascular disease, CVOTs have become a crucial part of the review process. The goal of these precisely constructed randomized, placebo-controlled studies is to look into the impact of anti-diabetic medicines on cardiovascular events, especially in poorly controlled glycemic control patients[23]. By connecting diabetes care with cardiovascular health, CVOT addresses the urgent need to lower cardiovascular events in this susceptible patient group.

The LEADER study, which showed that liraglutide improves cardiovascular outcomes in people with T2D and elevated cardiovascular risk, was a critical turning point. Participants in the trial were given a daily dosage of 1.8 mg of liraglutide and had a median age of 64 years, an A1C level of 8.7%, and an average duration of 12.8 years with diabetes. There were over 9340 people with T2D in total. Remarkably, 81% of participants had CVD at the time of registration. In contrast to trials like ELIXA and EXSCEL, the LEADER study boasted an extended average period of follow-up that was 3.8 years longer. The analysis demonstrated a notable decrease in the composite of MACE with liraglutide compared to placebo [HR: 0.87 (95% CI: 0.78–0.97)]. A significant fall in cardiovascular mortality, as shown by a [HR: 0.78 (95% CI: 0.66–0.93, $P = 0.007$)], was the primary cause of this decline. On the other hand, there was no discernible decline in non-fatal MI or stroke. Fascinatingly, there was no variation in the risk of MACE depending on heart failure (HF) state at baseline in the post hoc analysis, nor was there a significant difference in the incidence of hospitalization for HF among the therapy groups, as indicated by [HR: 0.87 (95% CI, 0.73–1.05, $P = 0.14$)]. Additionally, liraglutide use did not substantially increase the incidence of diabetic retinopathy[25–27].

Many pivotal trials, including SUSTAIN-6, REWIND, and Harmony, have confirmed the effectiveness of weekly injected GLP-1 RAs in improving cardiovascular health. For instance, semaglutide demonstrated a substantial 26% decrease in the incidence of MACE in patients with T2D, mostly as a result of a large 39% decline in non-fatal stroke occurrences as compared to the control group in the SUSTAIN-6 study. While in the REWIND trial, dulaglutide was also found to be superior to a placebo in terms of lowering the incidence of non-fatal strokes. Notably, there was no appreciable variation in the risks of non-fatal MI or cardiovascular death between individuals in the SUSTAIN-6 and REWIND trials who received GLP-1 RAs and those who received placebos. In contrast, the Harmony Outcomes trial identified ASCVD and specifically targeted T2D patients. Albiglutide, as opposed to a placebo, significantly decreased MACE in this high-risk population. Remarkably, in contrast to semaglutide, albiglutide significantly reduced the incidence of MI in SUSTAIN-6[28–30]. Since 4076 high-risk patients in the AMPLITUDE-O trial had at least one cardiovascular risk factor and pre-existing renal or cardiovascular illnesses, they were treated with efpeglenatide, a weekly injectable GLP-1 RA. According to the trial findings, a possible relationship between dosage and the incidence of MACE was seen in the

Table 1

Summary of cardiovascular outcome trials for glucagon-like peptide-1 receptor agonists

Study	GLP-1 RA	Participants	Duration of follow-up	Baseline HbA1c level (%)	Dosage	CV risk (%)	Main cardiovascular outcomes HR (95% CI)
LEADER	Liraglutide	9340	3.8 years	8.7	0.6 mg once daily for the first week, then 1.2 mg (1.8 mg if needed) once daily	81.3	Primary outcome 3-point MACE 0.87 (0.78–0.97)
SUSTAIN-6	Semaglutide	3297	2.1 years	8.7	0.25 mg once weekly for the first month, then 0.5 mg once weekly (can increase to 1 mg once weekly after a further 1 month)	58.8	Primary outcome 3-point MACE 0.74 (0.58–0.95)
REWIND	Dulaglutide	9901	5.4 years	7.3	0.75 mg once weekly as monotherapy; 1.5 mg once weekly as add-on therapy	31.4	Primary outcome 3-point MACE 088 (0.79–0.99)
HARMONY	Albiglutide	9463	1.6 years	8.7	30 mg, can increase to 50 mg	100	Primary outcome 3-point MACE 0.78 (0.68–0.90)
ELIXA	Lixisenatide	6068	2.1 years	7.7	10 µg once daily for the first 2 weeks, then 20 µg once daily	100	Primary outcome 3-point MACE 1.02 (0.89–1.17) Non-inferior to placebo
EXSCEL	Exenatide once weekly	14 752	3.2 years	8	2 mg once weekly	73.1	Primary outcome 3-point MACE 0.91 (0.83–1.00) Non-inferior to placebo
PIONEER-6	Oral Semaglutide	3183	1.3 years	8.2	3 mg once daily for 1 month, then 7 mg once daily for at least 1 month. If necessary, increase dose to 14 mg once daily.	84.6	Primary outcome 3-point MACE 0.79 (0.57–1.11) Non-inferior to placebo

CV, cardiovascular; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; MACE, major adverse cardiovascular event.

AMPLITUDE-O trial; the hazard ratio between the 6 mg per week dosage of efpeglenatide and placebo was 0.65 (95% CI: 0.5–0.86). The hazard ratio for the weekly dosage of 4 mg was 0.82 (95% CI: 0.63–1.06)[31]. With the exception of the REWID study, the majority of patients in the preceding studies had previous cardiovascular problems, confirming the efficacy of GLP-1 RAs in secondary prevention. Due to the limited proportion of patients with previous cardiovascular illness in the REWIND trial (31%), dulaglutide's effectiveness in preventive care was proven. In the ELIXA and EXSCEL trials, whether lixisenatide was given once daily or once weekly, respectively, there was no statistically significant reduction in MACE when compared to placebo. However, they were judged to be non-inferior to placebos in relation to the primary combined outcome of MACE. Although the MACE did not decrease in participants receiving lixisenatide compared to those receiving a placebo, the ELIXA trial emphasized the assessment of cardiovascular well-being associated with lixisenatide in this particular at-risk group as the trial focused on patients with recent cardiovascular events, specifically those who had acute coronary syndrome within 180 days prior to randomization[32,33]. Cardiovascular outcome trials for glucagon-like peptide-1 receptor agonists are summarized in Table 1.

The PIONEER 6 trial introduced an innovative oral form of GLP-1 RA. Even though the trial was published in 2019, it did not seem to be better at lowering MACE but provided insightful information about the oral administration and safety of GLP-1 RAs, increasing the range of available treatments for T2D patients[34]. The potential cardiovascular advantages of oral semaglutide in individuals with T2D, pre-existing ASCVD, and/or CKD are now being investigated by the Semaglutide Cardiovascular Outcomes (SOUL) study[35]. In comparison to a placebo and 0.9 mg liraglutide, the Japanese PIONEER 9 study demonstrated the subtle benefits of oral semaglutide by showing substantial decreases in both HbA1c levels and weight loss[36]. Comparably, a significant increase is indicated by raising the dulaglutide dosage from 1.5 mg in those with unsatisfactorily metformin-controlled T2D to either 3 mg or 4.5 mg, which led to improvements in HbA1c and weight reduction that were dose-dependent while also keeping the same safety profile in the AWARD-11 Randomized Control Trial[37]. While a number of CVOTs only addressed target dosages without exploring dose-dependent analyses, their collective contributions greatly improved our comprehension of the cardiovascular effects of GLP-1 RAs in T2D. These collective insights have improved therapeutic approaches, enabling medical professionals to customize care to each patient's unique requirements.

Exploring the mechanisms behind the cardiovascular benefits of glucagon-like peptide-1 receptor agonists

Multiple pathways can be attributed to the cardiovascular effects of GLP-1 RAs in CVOTs. To treat T2D as effectively as possible, it is essential to comprehend the processes behind these cardiovascular benefits. Glycemic management is essential for reducing cardiovascular risk in T2D patients, even though it is not usually thought of as a direct cardiovascular risk factor. The primary mechanism of action of GLP-1 RAs is to enhance glycemic control by increasing postprandial insulin production and

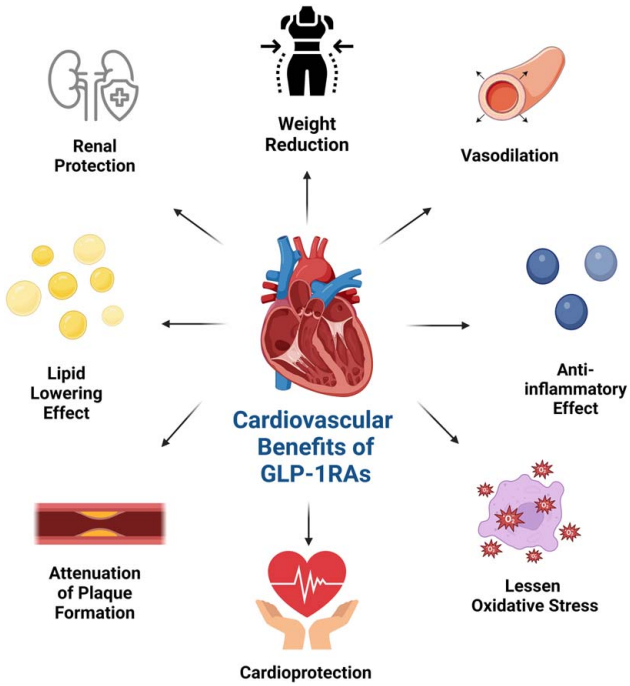

Figure 1. Cardiovascular benefits of glucagon-like peptide-1 receptor agonists (GLP-1 RAs).

inhibiting glucagon release[24]. A reduction in the risk of cardiovascular events has been linked to tight glucose control, as shown in seminal clinical trials like the United Kingdom Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCCT). By reducing blood vessel damage caused by hyperglycemia and promoting stable blood glucose levels through medication and lifestyle changes, diabetic individuals can lower their risk of cardiovascular disease (CVD)[38,39]. Recent data indicate that GLP-1 R is expressed in cardiomyocytes and vascular endothelial cells in addition to pancreatic islets[40,41]. GLP-1 RAs prevent cardiomyocyte apoptosis, lessen oxidative stress, and enhance myocardial glucose uptake and use[42]. All of these systems work together to avoid unfavorable cardiac remodeling and have cardioprotective effects on heart function.

Vasodilation is caused by the activation of GLP-1R via a number of mechanisms. It increases the synthesis of endothelial nitric oxide (NO), a powerful vasodilator that relaxes blood vessels and improves blood flow to the heart[43,44]. Furthermore, GLP-1 agonists may alter the renin-angiotensin-aldosterone system (RAAS), which would have an additional impact on blood pressure control and vascular tone[44]. GLP-1 agonists' vasodilatory actions minimize systemic vascular resistance, which lowers blood pressure as a result. Through the enhancement of natriuresis, GLP-1 RAs also reduce blood pressure[45]. GLP-1 RAs have been shown in several trials to systematically reduce hunger, increase feelings of fullness, delay the emptying of the stomach, and decrease food intake. Losing weight improves insulin sensitivity and lowers the incidence of cardiovascular illnesses, among other benefits[33,46,47]. Numerous advantages result from this weight loss, including decreased cardiovascular risk and improved insulin sensitivity. When comparing the LDL, total, and triglyceride levels of patients treated with GLP-1 RAs to controls, a meta-analysis of results from 35 clinical studies shows a slight decrease[48]. Beyond these benefits, GLP-1 RAs have anti-inflammatory qualities as well; in comparison to other anti-diabetic medications, they dramatically reduce inflammatory biomarkers[49]. Further supporting cardiovascular health, these anti-inflammatory and anti-atherogenic properties slow the development and progression of atherosclerotic lesions[50,51].

GLP-1 RAs have a variety of impacts on the cardiovascular system beyond their function in glycemic control. They offer direct cardioprotection, vasodilation, salt excretion promotion, weight reduction, improved lipid profiles, anti-inflammatory qualities, renal protection, attenuation of plaque formation, and neurohormone control through a variety of mechanisms. These thorough findings provide important treatment options for treating different T2D patient profiles by revealing the variety of pathways via which GLP-1 RAs reduce cardiovascular risk. Figure 1 outlines the cardiovascular benefits of glucagon-like peptide-1 receptor agonists.

Glucagon-like peptide-1 receptor agonists and heart failure

HF represents a significant worldwide health burden, characterized by its complexity and devastating nature[52]. GLP-1 RAs have attracted a lot of interest lately due to their possible advantages in the treatment of HF. Clinical studies, however, have not yet demonstrated that GLP-1 RAs are clearly beneficial for HF. Up until now, only two limited-scale clinical trials, namely the FIGHT and LIVE studies, have explored the effects of GLP-1 receptor agonists on HF, characterized by a lower ejection fraction. In both trials, both studies focused on liraglutide as the study drug. In the FIGHT trial, which comprised 300 individuals experiencing acute HF and an ejection fraction of less than 40%,

the groups that were given liraglutide therapy and those who were given a placebo did not differ significantly in terms of the primary endpoints[53]. While the LIVE trial investigated the effect of liraglutide on individuals with decreased LVEF (LVEF $\leq$45%) and chronic HF, individuals treated with liraglutide in this trial experienced a higher prevalence of acute coronary syndrome and arrhythmia compared to those receiving a placebo, with no discernible therapeutic benefit[54]. A second small trial evaluated the effectiveness of semaglutide in individuals with adiposity (BMI > 30 kg/m^2) and maintained LVEF (LVEF $\geq$ 45%). It was called the impact of a Once-Weekly Semaglutide of 2.4 mg on symptoms and function in Individuals with obesity-related HF and maintained ejection fraction (EF) (STEP-HFpEF). In this experiment, semaglutide exhibited superior outcomes compared to the placebo, demonstrating significant weight loss, alleviation of HF-related symptoms, and improvement in the 6-min walk distance. The STEP-HFpEF investigation holds significance as it established the efficacy of semaglutide in non-diabetic individuals with obesity and HFpEF. The "STEP-HFpEF DM" trial is presently undergoing research to investigate the effects of a 2.4 mg injectable semaglutide dose once a week on people with HFpEF, obesity, and T2D. This study aims to assess the efficacy of semaglutide treatment in this complex patient population[55,56].

There was no discernible difference observed between those receiving GLP-1 RAs and those getting a placebo in terms of the percentage of patients with a history of HF, which ranged from 9 to 24% across eight CVOTs. Study protocols did not provide a clear definition of HF; the EXSCEL trial was the only one to provide LVEF, and the functional class for HF was defined in four trials. The exclusion criteria among the LEADER, SUSTAIN-6, and ELIXA trials were NYHA class IV. Studies such as ELIXA, REWIND, LEADER, EXSCEL, and SUSTAIN-6 did not find any statistically significant variation in HF hospitalization rates within the groups treated with GLP-1 RAs and those receiving a placebo[25,28–34,57]. Therefore, the benefits of GLP-1 RAs in lowering the risk of HF were not demonstrated by the results. The Harmony Outcomes Study yielded indifferent results for albiglutide as well, despite the fact that hospitalization for HF was evaluated as a reinforcement with cardiovascular mortality as a secondary objective[29]. It was seen that neither oral semaglutide nor efpeglenatide demonstrated any advantage concerning the risk of HF hospitalization[31,34]. After analyzing a portion of HF patients from the EXSCEL study, it was shown that people without HF who took once-weekly exenatide had a lower chance of dying from all causes (HR: 0.79; 95% CI: 0.68–0.92). On the other hand, no appreciable benefit was seen for individuals who had HF at baseline (HR: 1.05; 95% CI: 0.85–1.29)[58]. A review of CVOTs revealed a positive effect of GLP-1 RAs on HF in patients diagnosed with T2D. With a study population exceeding 60 000 patients, this meta-analysis aimed to analyze the cardiovascular implications of GLP-1 RAs. The results of this investigation unveiled positive trends in HF outcomes, affirming the favorable influence of GLP-1 RAs on MACE among T2D patients. Moreover, the results indicated encouraging developments in reducing the occurrence of HF-related events[59]. GLP-1 RAs offer potential for managing HF by various means, including direct heart protection, promotion of natriuresis and vasodilation, and control of weight and glucose levels. While clinical trials have revealed their benefits, additional research is needed to investigate the optimal utilization of these medications among different cohorts of HF patients.

Glucagon-like peptide-1 receptor agonists and cardiovascular outcomes

Patients with T2D who have increased A1c values above 6.5% and are either at high risk of developing CVD or who have already developed it have been shown to benefit from GLP1-RA in terms of their cardiovascular health[25,28–31]. These findings were further supported by a 2019 meta-analysis, which demonstrated a 12% decrease in the incidence of MACE in T2D individuals using GLP1-RA [HR: 0.88 (95% CI: 0.82–0.94)][57]. Data from seven CVOTs were included in this analysis: LEADER (liraglutide)[25], ELIXA (lixisenatide)[32], PIONEER 6 (oral semaglutide)[34], REWIND (dulaglutide)[30], EXSCEL (exenatide)[33], SUSTAIN-6 (subcutaneous semaglutide)[28], and HARMONY OUTCOMES (albiglutide)[29].

Sattar and colleagues, in their 2021 revised meta-analysis, uncovered robust cardiovascular protection, amalgamating data from the seven previously mentioned studies alongside fresh insights from the AMPLITUDE-O trial (efpeglenatide)[31]. The 3-point MACE, comprising cardiovascular mortality, MI, and stroke, exhibited a decrease of 14% [HR: 0.86 (CI of 0.80–0.93)]. The pooled analysis of GLP1-RA trials also indicated advantages in secondary outcomes: a 13% drop in cardiovascular deaths [HR, 0.87 (0.80–0.94)], a 10% decrease in MI cases [HR, 0.90 (0.83–0.98)], a 17% decrease in stroke cases [HR, 0.83 (0.76–0.92)], an 11% decrease in hospitalizations for HF (HR, 0.89 with a 95% CI of 0.82–0.98), and a 12% decrease in deaths from all causes [HR, 0.88 (0.82–0.94)]. Individuals with T2D who had CKD or not were included in these eight trials. Notably, for the 3-point MACE main outcome, there was no apparent connection with eGFR status. The cardiovascular effects remained consistent regardless of eGFR status[59].

GLP1-RAs have been recommended by the American College of Cardiology (ACC)[60], the European Society of Cardiology (ESC)[10], and the American Diabetes Association (ADA)[61] for use in treatment regimens aimed at reducing ASCVD in high-risk patients with T2D. Furthermore, the KDIGO diabetes management recommendation for people with CKD promotes GLP1-RA above other glucose-lowering medications because of its good cardiovascular profile. This recommendation recommends GLP1-RA as a follow-up medication for high-risk patients or those who require further A1c reduction after initiating SGLT2i[62,63]. It is necessary to highlight a few points about the CVOTs discussed before. Efpeglenatide is not available in the United States, and albiglutide has been discontinued globally. The PIONEER 6 trial, designed to explore the cardiovascular risks linked with oral semaglutide in individuals with T2D but lacking the power to demonstrate superiority, revealed the cardiovascular safety of oral semaglutide compared to placebo. Despite observing a favorable trend, such as a 21% reduction in risk, statistical significance was not attained[34].

Underutilization of glucagon-like peptide-1 receptor agonists

Even though GLP1-RAs has received approval from several organizations to treat diabetes, cardiovascular disease, and renal disease, its use in clinical practice is still rather limited[10,60,61]. Only 1.6% of nearly 21 000 patients who developed CVD and T2D at an esteemed academic healthcare institution received GLP1-RA treatment during a retrospective analysis spanning

from 2013 to 2019[64]. Merely 1.4% of these medications were given by cardiologists, whereas 90% were prescribed by general practitioners and endocrinologists combined. In the same way, only 7.9% of cases in the GOULD registry—which focused on the highest-risk individuals with ASCVD and T2D—saw the administration of GLP1-RAs[65]. The challenges of cost and insurance pre-authorization approvals continue to impede GLP1-RA usage in clinical settings. However, the low acceptance of this pharmaceutical class in ordinary clinical practice is primarily owing to treatment inertia, a lack of understanding of its cardiovascular advantages, and uncertainty among non-endocrinologists about changing other glycemic medications (such as insulin and sulfonylureas) to commence GLP1RA therapy.

Cardiologists have a crucial role to play in advocating for the use of proven cardioprotective medications, such as GLP1-RAs, for people with T2D. According to research from two well-known US healthcare systems, people with T2D were twice as likely to see a cardiologist during clinical visits as they were an endocrinologist, and people with T2D plus ASCVD were four times as likely to see a cardiologist[66]. Cardiovascular practitioners must encourage the utilization of evidence-supported GLP1-RAs in eligible patients within a collaborative therapy framework, given the increased frequency of visits to cardiologists.

Adverse effects of glucagon-like peptide-1 receptor agonists

The GLP-1 RAs are mimetics of a peptide produced in the GI tract and thus often produce GI side effects such as nausea, vomiting, and diarrhea. Effects are dose-dependent, so the dose must be titrated[67]. Patients must be educated about the fact that GLP-1 RAs delays gastric emptying, and early satiety can result. Nausea will result if they attempt to eat when they are already full. Meta-analysis of 34 trials found that once weekly, exenatide has the lowest risk of vomiting compared to the other GLP-1 RAs[68]. In comparison with other therapies, hypoglycemia is considered low risk with GLP-1 RAs, but no significant difference in incidences between the different agents. Additions of insulin and insulin secretagogues like sulfonylureas increase the risk. Injection site reactions and erythema are more familiar with once-weekly exenatide compared to its twice-daily administration and also more frequent than with once-daily liraglutide. Exenatide has been noted to increase the INR in patients on warfarin. Semaglutide, on the other hand, has been linked to a temporary worsening of pre-existing diabetic retinopathy due to rapid improvements in glycemic control. Its long-term effects on retinopathy have not been studied. In a trial of liraglutide, 3.1% of patients developed gallbladder disease versus 1.9% on placebo, so assessment of gallbladder disease for the development of cholelithiasis or cholecystitis should be considered. Formation of antibodies is shallow with once-weekly injectables but more common with twice-a-day exenatide and once-a-day lixisenatide. As seen during the development of these antibodies, exenatide or lixisenatide efficiency gets reduced, but not when patients are switched to liraglutide[13]. Since dulaglutide is associated, for example, with sinus tachycardia, PR interval prolongation, and first-degree AV block, this drug should be prescribed with caution to patients with pre-existing arrhythmias[30,69].

Future directives

In the future, cardiovascular problems in T2D will need to be addressed through multimodal approaches to better clinical practice and research. More study on the long-term cardiovascular consequences of GLP-1RAs is urgently needed. This research should include people with varying degrees of cardiovascular risk and comorbidities. Longitudinal studies and real-world data analysis can provide a better understanding of the safety and sustained efficacy features of GLP-1RAs across extended treatment periods. Comparative effectiveness research comparing GLP-1RAs to other anti-diabetic drugs and combination regimens is also required in order to enhance treatment algorithms and facilitate evidence-based clinical decision-making. Eliminating barriers to the use of GLP-1RA is crucial, even beyond research initiatives. This means resolving concerns about insurance coverage and cost accessibility in addition to increasing patient and healthcare provider understanding of the cardiovascular benefits of these agents. Educational campaigns targeting patients, pharmacists, and physicians should promote a greater understanding of the role of GLP-1RAs in cardiometabolic regulation and overcoming treatment inertia. Furthermore, it is anticipated that as research advances, the therapeutic spectrum of GLP-1RAs would widen.

With more modern development technologies, oral and injectable formulations that are longer-acting could very well boost treatment compliance and patient convenience. Therefore, interdisciplinary cooperation with very good coordination among the endocrinologist, cardiologist, primary care physician, and other healthcare providers and specialists is of great importance in order to achieve the best possible reduction in cardiovascular risk among patients with T2D. Incorporation of multidisciplinary care teams and integrated care models can optimize cardiovascular outcomes, with probable comprehensive treatment plans designed as per individual patients requirements. Finally, it is really important to look at and follow-up on the real-world outcomes that are being delivered with reference to the safety and efficacy of GLP-1RAs in standard clinical practice. This information, from this final useful data, will be useful in informing clinical recommendations and practice guidelines from patient registries and from post-marketing surveillance about treatment patterns, adverse events, and long-term cardiovascular outcomes.

Conclusion

In summary, GLP-1 RAs have emerged as critical agents in controlling T2D while also lowering cardiovascular risk. CVOTs show effectiveness in lowering MACE, cardiovascular mortality, and stroke, particularly in high-risk T2D groups. The various mechanisms of GLP-1 RAs, including as glycemic control, vasodilation, weight loss, and anti-inflammatory actions, highlight their therapeutic potential beyond glucose management. However, issues such as cost and treatment inertia limit their wider use. Overcoming these hurdles and encouraging multidisciplinary teamwork among healthcare professionals are critical to improving cardiovascular health in T2D patients. Further study into long-term results and real-world data will help to optimize treatment regimens, ultimately increasing patient outcomes and lowering the burden of cardiovascular disease in T2D populations.

Ethical approval

As this is a review article without involvement of patients, no ethical approval was necessary.

Consent

As this is a review article without patient involvement, ethical considerations regarding patient consent and privacy do not apply.

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