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GLP-1 RECEPTOR AGONIST CARDIOVASCULAR PROTECTION AMONG TYPE-2 DIABETES PATIENTS: A LITERATURE REVIEW

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ABSTRACT

T2DM (Type 2 Diabetes Mellitus) remains a main global health issue, particularly if cardiovascular complications started to evolve. Type 2 diabetes is the main cause of renal and cardiovascular adverse consequences. Adequate management of T2DM depends on glycemic control and prevent cardiovascular or renal complications. Hence, certain antidiabetic agents have provided cardiovascular protection, of which one of them is the glucose-like peptide 1 receptor agonists. The present literature review aims to assess the cardiovascular efficiency and safety of glucose-like peptide 1 receptor agonists in patients with T2DM. We used the PubMed database, searching for relevant articles to the title. We used the following Mesh words: heart failure, GLP-1 receptor agonist, type 2 diabetes mellitus, cardiovascular consequences. GLP-1 receptor agonists are effective antidiabetic agents in regards to the glycemic control and safety profile for cardiovascular disease. GLP-1 receptor agonists seem to have promising cardiovascular protection in cardiovascular and all-cause mortality, including fatal and non-fatal myocardial infarction, fatal and non-fatal stroke. However, the increased risk of heart failure hospitalization remains debatable, and further clinical trials are recommended to evaluate this concern. A common side effect is related to gastrointestinal upset, and overall, it is transient and generally does not require discontinuation of the treatment.

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Introduction

T2DM is a chronic cardiometabolic disease correlated with increased risk of cardiovascular disease, heart failure, and Chronic Kidney Disease (CKD), which all represent a significant risk to high mortality and morbidity, poor life quality, and increased global health financial burden [1-3]. In 2017, diabetic patients accounted for approximately 425 million, and its prevalence will keep rising to 629 million by 2040. This was attributed to the population aging and the increasing rate of obesity among adults and children. Also, economic development and urbanization may contribute to the rise of a diabetic pandemic. Further, enhanced recognition, early detection, and improved management of T2DM patients increase longevity, which further increases the diabetic prevalence [4].

Almost 5 million deaths were attributed to diabetes, and the total global health cost secondary to diabetes was estimated at 673 Us dollars in 2015 [5]. Importantly, T2DM is the foremost common form of diabetes, accounting for 90-95% of detected DM, and proceeds to be rapidly growing around the world and in the USA. The risks for T2DM comprise a mixture of both metabolic

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and genetic factors, which contributes to its high outbreak. **Table 1** summarizes the most important modifiable and non-modifiable risk factors for T2DM [6].

Cardiovascular Disease (CVD) represents an individual and societal burden in patients with T2DM. The life expectancy of 50-year-old diabetic patients is shorter than an average of 6 years, which is mainly related to vascular complications [7]. Moreover, diabetes is accounted for a two-fold enhanced risk of Coronary Artery Disease (CAD), major stroke subtypes, and deaths related to other vascular etiologies [8]. Fortunately, strict control of the modifiable risk factors resulted in a progressive decline in major cardiovascular events (MACE) for the last two decades in the US and Europe. However, fatal CV consequences remain high among T2DM patients compared with nondiabetic. The more intensified glycemic control will improve CV outcomes is remains an area of controversy. Further, reduction in glycated hemoglobin (HbA1c) and duration of glycemic intensification play a major role that might influence CV outcomes. Hence, the US Food and Drug Administration (FDA) required all antidiabetic agents to proven CV safety and effectiveness [7].

Table 1. Modifiable and non-modifiable risk factors for T2DM

Modifiable	**Non-modifiable**
Obesity	Ethnicity
Unhealthy diet	Family history
Poor physical activities	Previous gestational diabetes
Smoking	Older age

While microvascular complications of T2DM (retinopathy, nephropathy, neuropathy) are related to two factors: 1) HbA1c level, representing the severity of hyperglycemia 2) the duration of hyperglycemia; the primary cause of death among T2DM patients is the CVD, accounting for 70-80%. The optimal treatment for T2DM is controlling microvascular (hyperglycemia) and macrovascular (blood pressure, lipids, insulin resistance) complications. Therefore, clinicians are encouraged to consider several points in T2DM management: 1) Keep HbA1c persistently low, which controls the pathophysiological disturbances 2) Reduction of CV risk and mortality, and finally, provides renal protection from CKD, independently from glycemic control [9]. Although the CVD burden is globally declined, T2DM patients still experience a high rate of MACE. Hence, managing diabetes-related cardiovascular risk remains a significant challenge [10].

GLP-1RA Background and Mechanism of Action

Glucose Like-Peptide 1 (GLP-1) is an incretin glucoregulatory hormone secreted from the enteroendocrine L cells of the intestinal mucosa after meal ingestion, which stimulates decreases glucagon secretion and insulin release when plasma glucose levels are raised [11-13]. It was initially discovered as an insulinotropic hormone produced in and released from the gut after food ingestion. Since then, it has received clinical attention due to its role in glycemic metabolism and control [14]. GLP-1 hormone exerts its efficacy via the GLP-1 receptor (GLP-1R) that belongs to the G-protein-coupled receptors family [12]. GLP-1R is expressed in various body tissues, including the brain, heart, pancreas, blood vessels of several organs, such as the gastrointestinal tract, lungs, and the kidneys [11, 12]. Notably, the GLP-1 insulinotropic properties are maintained in human subjects with T2DM showing response failure to sulphonylurea [13]. While the exact mechanism by which GLP-1 restores glucose sensitivity is incompletely understood, it was suggested that the involvement of crosstalk between intracellular glucose metabolism, cyclic AML (cAMP)-dependant signaling, and membrane ion channels [13]. Further, GLP-1 plays a vital role in neural transmission for GLP-1 initiated signals controlling glycemia, gastrointestinal motility, and body weight, although the exact mechanism remains unclear [13]. Importantly, GLP-1 post-prandial glycemic reduction was no longer effective in non-diabetic patients who underwent vagotomy and pyloroplasty [13].

GLP-1 receptor agonists (GLP-1RA) are synthetic, subcutaneously administered mimetics or analogs of the natural human GLP-1 with adjusted pharmacokinetics and a more stable pharmacodynamic profile [9, 10]. Hence, it provides greater pharmacological effects compared to the endogenous GLP-1. GLP-1RA are generally divided based on their duration of action; Short-active GLP-1 RAs (lixisenatide and exenatide) exert short-lived receptor activation and provide greater post-prandial glucose reduction through delaying gastric discharging and facilitate slower delivery of glucose to the duodenum; The longer-acting (dulaglutide, liraglutide-OD and exenatide ER, and semaglutide-OW) agents offer continual receptor activation at their suggested doses and provide longer half-lives pharmacokinetics (>3 hours). Therefore, the GLP-1RAs significantly reduce fasting blood glucose via agitating insulin release and hindrance of glucagon secretion from the pancreas, which makes them ideal for once-weekly dosing [11]. Multiple pharmaceutical industries have developed GLP-1RAs, of which six agents gained approval to treat diabetes and/or obesity [15].

GLP-1RA Cardiovascular Protection in Patients with T2DM

GLP-1RAs is a glucose-lowering agent with favorable effects in weight loss, systolic BP reduction, lipid profile, and low risk of hypoglycemia. These favorable CV benefits make GLP-1RAs biologically plausible. Six GLP-1RAs have been approved for the treatment of T2DM, including exenatide, liraglutide, lixisenatide, dulaglutide, albiglutide, and semaglutide). Four large CV outcomes trials in a total of 33,457 participants have investigated the safety and efficacy of several GLPL-1RAs; The investigation of Lixisenatide in Acute Coronary Syndrome (ELIXA), The Liraglutide Effect and Action in Diabetes:

Evaluation of Cardiovascular Outcome Results (LEADER), Samiglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (SUSTAIN-6), and impacts of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes (EXSCEL) [16]. All the aforementioned trials have demonstrated GLP-1RAs safety "non-inferiority" compared to placebo or standard of care. Two trials have demonstrated a reduction in rates of CVD "superiority": LEADER and SUSTAIN-6 [16].

Moreover, another meta-analysis of the above four trials revealed that cardiovascular protection of GLP-1RAs is considered to be a class impact. With some limitations to be considered, two previous meta-analyses have concluded that myocardial infarction (MI), cardiovascular mortality, and all-cause mortality were considerably lower in the GLP-1RAs group than the comparator group. On the contrary, no beneficial outcomes were observed in regards to stroke and heart failure. Overall, these agents emerge to decrease cardiovascular mortality, all-cause mortality, and the incidence of MI at mid-term follow-up [17]. Marsico *et al*. have also conducted a meta-analysis of the four above mentioned trials in addition to three trials (total of seven): Researching CV Events with a Weekly Incretin in Diabetes (REWIND), Peptide Innovation for Early Diabetes Treatment 6 (PIONEER 6), and Safety and Efficacy of once-weekly GLP-1 RA albiglutide (HARMONY). This meta-analysis concluded that GLP-1RAs significantly reduce the three-point MACE composite endpoint hazard by 12%, risk of CV mortality, and all-cause mortality, heart failure, non-fatal stroke, and fatal hospitalization. Nevertheless, no significant effects were noticed in fatal and non-fatal MI [18].

Furthermore, Nreu *et al*. have conducted an updated meta-analysis on 43 trials of GLP-1RAs compared to placebo. The result supported the beneficial impact of GLP-1RAs on main cardiovascular events, cardiovascular and all-cause mortality, stroke, and possibly MI. On the other hand, GLP-1RAs did not enhance the risk of atrial fibrillation and were not related to a significant beneficial effect on heart failure [19]. When Bethel *et al*. conducted a meta-analysis for ELIXA, SUSTAIN 6, EXSCEL, and LEADER trials, the result showed that the GLP-1RAs group had an overall 10% relative risk decrease in the three-point composite result of nonfatal MI, non-fatal stroke, and cardiovascular mortality, and a comparative risk decrease in all-cause mortality and overall cardiovascular mortality [20]. Importantly, no safety concerns were reported in the GLP-1RAs, such as the hypoglycemia risk, pancreatitis, medullary thyroid cancer, or pancreatic cancer [20].

Besides, Yang *et al*. have conducted a nationwide population-based cohort study comparing GLP-1RAs with dipeptidyl peptidase-4 inhibitor (DPP-4 inhibitor), sulphonylurea, and insulin in a real-world population with T2DM. While the initial result was a combination of CVD incidents, the GLP-1RAs group showed a lower risk of composite CVD incidents [21]. This real-world cohort study also supported the evidence of GLP-1RAs cardiovascular protection in the diabetic population. In supporting the latter cohort study, Kristensen *et al*. analyzed the cardiovascular outcomes for GLP-1RAs in different trials. While no statistically significant heterogeneity across the investigated group, GLP-1RAs were found to reduce heart failure hospitalization by 9%, MACE and all-cause mortality by 12%, and broad renal composite by 17%. Similarly, there was no increased risk of pancreatitis, pancreatic cancer, and hypoglycemia [22].

Regarding the risk of heart failure hospitalization, incretins-based agents were observed due to the enhanced risk of heart failure hospitalization, especially after the SAVOR-TIMI 53 trials, which showed a significant increase in heart failure hospitalization T2DM patients with pre-existing CVD who received saxagliptin compared with placebo. Nevertheless, this impact was not approved in other trials by different DPP-4 inhibitors, and GLP-1 RAs were found to not, or only slightly and inconsistently, improve myocardial function in patients with CAD or heart failure with reduced Left Ventricular Ejection Fraction (LVEF). Also, the risk of heart failure hospitalization was not elevated in many meta-analyses of phase-II/III RCTs including various GLP-1RAs, which demonstrate the safety of these agents in regards to the risk of heart failure hospitalization [23].

GLP-1RA Adverse Outcome

The American Diabetes Association and the European Society of Cardiology were recommended in 2019 using GLP-1RAs in managing diabetes patients with cardiovascular disease, at high risk of CVD, or kidney disease with poor glycemic control [24]. It is commonly observed that GLP-1RAs is initiated later than previously recommended [21]. This may be attributed to the novelty of GLP-1RAs, and thus diabetic patients were not exposed to this agent. Also, physician's or patients' adoption of new agents may not be as fast as expected due to the uncertainty of long-term real-world drug effectiveness and safety considerations. Besides, patients or physicians usually discourage the injectable form of GLP-1RAs until treatment failed [21].

In regards to the adverse outcomes, gastrointestinal symptoms, such as nausea and diarrhea, are the most commonly reported adverse effects of GLP-1RAs (>1/10), where abdominal pain, dyspepsia, vomiting, and constipation were relatively common (>1/100 to <1/10). However, gastrointestinal symptoms gradually decreased with the continuous use of these agents. Nausea is the most common adverse effect up to 50% of patients experienced, and it seems to be dose-dependent. It is worth mentioning that 4% of patients in clinical trials discontinued the study due to nausea. Notably, long-acting GLP-1RAs exert lesser gastrointestinal effects, which could be associated with less nausea [25].

Moreover, pancreatic inflammation or pancreatitis have been an area of concern secondary to GLP-1RAs usage. The animal studies revealed a potentially harmful effect on the pancreatic tissue. Nonetheless, in human clinical trials, a study of 90 T2DM patients who received GLP-1RAs or DPP-4 inhibitors showed that 36% of them had elevated serum amylase or lipase (or both) levels in comparison to 18% of T2DM patients not receiving these agents. In a recent analysis of the LEADER trial, serum amylase and/or lipase were raised at baseline in 22.7% of patients. More precisely, serum lipase levels were elevated in 16.6% and amylase levels in 11.8% of patients with no symptoms of acute pancreatitis. Furthermore, several recent studies and meta-analyses have failed to confirm the association between GLP-1RAs use and increased risk of pancreatitis. Yet, until

this issue is finally resolved, it may be prudent that GLP-1RAs should not be prescribed to patients with several risk factors of pancreatitis, such as hypertriglyceridemia or alcohol intake.

Injection site reactions, including rash, erythema, or itching, are common with GLP-1RAs and reported more frequently with long-acting GLP-1RAs. The predominant injection site reaction is pruritis, and still, these reactions are self-limiting and generally do not require discontinuation of the treatment. Certain infections were reported frequently after the initiation of GLP-1RAs, such as urinary tract infection, nasopharyngitis, influenza, and viral infection. However, no serious infection has been observed with GLP-1RAs use. Headache is also frequently reported adverse effect and generally does not require discontinuation of the treatment [25]. The indirect impact of GLP-1RAs on the kidneys and the potential association of medullary thyroid cancer is beyond the scope of this literature review.

Conclusion

Cardiovascular disease remains a significant global burden in the diabetic population. GLP-1 receptor agonists are recently developed antidiabetic agents, demonstrating favorable cardiovascular protection in diabetes patients and even without diabetes. More specifically, these agents showed beneficial effects on cardiovascular and all-cause mortality, including coronary artery disease and fatal and non-fatal stroke. Nonetheless, the increased risk of heart failure hospitalization remains an area of controversy. Further randomized clinical trials are warranted to establish the safety and efficacy of GLP-1 receptors agonist in heart failure hospitalization. The current data support the initiation of GLP-1 receptor agonists earlier in the diabetic population who are at high risk for renal or cardiovascular outcomes.

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