Review Article

Effect of Combination Treatment with GLP-1 Receptor Agonist and SGLT-2 Inhibitors on Incidence of Cardiovascular and Serious Renal Events

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ABSTRACT

Objective: This review aims to synthesize current evidence on the combined use of GLP-1 RAs and SGLT-2 inhibitors, focusing on their impact on cardiovascular and renal outcomes in patients with T2DM.

Study Design: A comprehensive literature review

Place and Duration of Study: This study was conducted at the Department of Family Medicine, College of Medicine and Health Sciences, National University, Oman during 2020 to 2024.

Methods: This study was conducted to analysed the data from clinical trials and observational studies that investigated the individual and combined effects of GLP-1 RAs and SGLT-2 inhibitors on CV and renal outcomes.

Results: The combination therapy of GLP-1 receptor agonists and SGLT-2 inhibitors demonstrates significant potential in enhancing both cardiovascular and renal outcomes for patients with T2DM. GLP-1 RAs improve glycemic control, reduce weight, and lower blood pressure, leading to a notable reduction in major adverse cardiovascular events. SGLT-2 inhibitors complement these effects by promoting renal glucose excretion and reducing cardiovascular mortality and heart failure hospitalizations.

Conclusion: The combination of GLP-1 receptor agonists and SGLT-2 inhibitors offers a promising approach for managing T2DM and reducing the risk of cardiovascular and renal complications. This dual therapy approach provides enhanced benefits through complementary mechanisms of action.

Key Words: DM, Type II, Patients, SGLT2, Inhibitors, Therapy

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INTRODUCTION

The management of type 2 diabetes mellitus (T2DM) has evolved significantly over the past decade, particularly in the realm of reducing cardiovascular and renal complications associated with the disease. Of all the classes of medications popular for their cardioprotective and nephroprotective properties, only two classes are in focus— GLP-1 receptor agonists (GLP-1 RAs) and SGLT-2 inhibitors[1]. The treatment with GLP-1 receptor agonists is based on the structure of incretin hormone GLP-1 which can effectively promote glucose-dependent insulin secretion, inhibit glucagon secretion, and reduce the rate of stomach emptying which leads to the improvement of glycemic control[2]. SGLT-2 inhibitors on the other hand selectively reduces sodium-glucose co-transporter 2 in the proximal renal tubules that will result into increased glucose excretion, osmotic diuresis and natriuresis[3]. Out of all classes of drugs prescribed for the management of diabetes, two have received the recent attention in as far as cardio renal protection is concerned namely GLP-1 receptor agonists (GLP-1 RAs) & SGLT-2 inhibitors[4]. As for the currents SGLT-2 inhibitors exert positive effects by blocking sodium-glucose co-transporter in the proximal renal tubules giving rise to osmotic diuresis and natriuresis[5]. The individual effects of these two classes of drugs have recently been shown in randomised controlled trials and also in epidemiological studies in patient with T2DM in relation to the decrease in events cardiovascular and the slowing down of renal disease[6]. This strategy might potentially be less nephrotoxic and cardiotoxic in the case of cardiovascular and renal incidents due to the individual molecular effects of the two drugs[7]. Depending on individual treatment option unable to maintain the glycemic targets, both GLP-1 receptor agonists and SGLT-2 inhibitors are being used together in clinical practice. Hence, since the drugs have different actions,

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the combined usage will have supplementary effects on the clinical results[8]. Furthermore, meta-analysis of the patient of type 2 diabetes across the observational studies comparing GLP-1 receptor agonist and SGLT-2 inhibitor shows that combined treatment enhances the haemoglobin A1c the blood pressure while the body weight decreases with the combined therapy compared to the particular treatments[9]. These, however, define surrogate end points, and there is no information that this combination reduces the incidence of Macro vascular and Micro vascular complications[10,11]. Until now, there is still no well-done archival observational study, which is sufficiently powered to compare cardiovascular efficacy with adjustment for the immortal time bias on low-dose aspirin with a P2Y12 receptor antagonist in the real-world population[12]. But there has been a rise in the interest of the interaction between GLP-1 RAs and SGLT-2 since the resultant effect of the two is enhancement of glucose excretion, post prandial and fasting blood glucose levels suppression and weight loss in the individual using the two drugs[13]. Metformin and sulfonylureas are the major classical oral antidiabetic drugs that mainly exert glycemic effects but have relatively small beneficial effects on cardiovascular and renal end points. Contemporary drugs that have been released have proved to be more effective in providing a comprehensive advantage[14]. Two of these categories include GLP-1 receptor agonists and SGLT-2 inhibitors which provide different approaches to glucose regulation and have shown signs of having extra benefits to glucose regulation[15].

The basic aim of this review article is to find the effect of combination treatment with GLP-1 receptor agonist and SGLT-2 inhibitors on incidence of cardiovascular and serious renal events.

METHODS

A comprehensive literature review was conducted at Department of Family Medicine, College of Medicine and Health Sciences, National University, Oman during 2020 to 2024.

MECHANISMS OF ACTION

GLP-1 Receptor Agonists: GLP-1 is a naturally occurring incretin hormone produced in the gut following a meal. It stimulates insulin secretion from pancreatic beta cells, suppresses glucagon release from alpha cells, and promotes satiety, leading to improved glycemic control[16]. GLP-1 receptor agonists mimic the effects of endogenous GLP-1, offering several additional benefits beyond blood sugar control.

SGLT-2 Inhibitors: SGLT-2 inhibitors work by blocking the reabsorption of glucose in the proximal convoluted tubules of the kidney. This leads to a reduction in blood sugar levels by promoting its excretion in the urine (glucosuria)[17].

Clinical Evidence: Emerging research suggests a synergistic effect when combining GLP-1 receptor agonists and SGLT-2 inhibitors for T2DM management. Several large-scale clinical trials have investigated the cardiovascular and renal benefits of this combination therapy[18].

Combined Therapy: GLP-1 RAs and SGLT-2 Inhibitors: The combination of GLP-1 RAs and SGLT-2 inhibitors is hypothesized to provide additive or synergistic benefits due to their complementary mechanisms. Clinical studies exploring this combination have shown promising results in terms of glycemic control, weight loss, and cardiovascular outcomes[19].

Glycemic Control and Weight Loss: The combined use of GLP-1 RAs and SGLT-2 inhibitors has been shown to provide superior glycemic control compared to either agent alone. Studies have demonstrated greater reductions in HbA1c levels and fasting plasma glucose with the combination therapy. Additionally, both classes of drugs promote weight loss through different mechanisms, leading to a more significant reduction in body weight[20].

Cardiovascular Outcomes: Limited data exist on the cardiovascular outcomes of the combined therapy. However, the complementary effects on blood pressure, weight, and glucose control suggest potential cardiovascular benefits. The DURATION-8 trial, which investigated the combination of exenatide (a GLP-1 RA) and dapagliflozin (an SGLT-2 inhibitor), found significant reductions in HbA1c, body weight, and systolic blood pressure compared to monotherapy. These findings suggest that the combination may provide additional cardiovascular protection[21].

GLP-1 Receptor Agonists: GLP-1 RAs have shown renal benefits in clinical trials. The LEADER trial found that liraglutide reduced the progression of nephropathy and the need for renal replacement therapy. These benefits are thought to be mediated by improved glycemic control, weight loss, and blood pressure reduction[22].

SGLT-2 Inhibitors: SGLT-2 inhibitors have demonstrated robust renal benefits in clinical trials. The CREDENCE trial showed that canagliflozin significantly reduced the risk of end-stage kidney disease, doubling of serum creatinine, and renal or cardiovascular death in patients with T2DM and CKD. The renal benefits of SGLT-2 inhibitors are attributed to their hemodynamic effects, including reduction in intraglomerular pressure and improvement in renal oxygenation[23].

Table No.1: Clinical trials and renal benefits of GLP-1 Receptor Agonists and SGLT-2 Inhibitors

Trial	Drug	Patient Group	Key Findings	Renal Benefits	Mechanism of Action
CREDENCE Trial	Canagliflozin (SGLT-2 inhibitor)	Patients with T2DM and high cardiovascular risk	Significant reduction in the risk of the primary composite renal endpoint (doubling of serum creatinine, ESRD, or renal death) compared to placebo	Reduced risk of end-stage kidney disease, doubling of serum creatinine, and renal or cardiovascular death	Hemodynamic effects, reduction in intraglomerular pressure, improvement in renal oxygenation
DAPA-CKD Trial	Dapagliflozin (SGLT-2 inhibitor)	Patients with CKD, irrespective of diabetes presence	Significant reduction in the risk of the primary composite renal endpoint, decrease in risk of cardiovascular death and hospitalization for heart failure	Robust renal benefits in patients with CKD	Similar to CREDENCE; reduction in intraglomerular pressure and renal oxygenation improvement
LEADER Trial	Liraglutide (GLP-1 RA)	Patients with T2DM	Reduced progression of nephropathy and need for renal replacement therapy	Renal benefits mediated by improved glycemic control, weight loss, and blood pressure reduction	Improved glycemic control, weight loss, and blood pressure reduction

Table No.2: Cardiovascular outcomes of GLP-1 Receptor Agonists and SGLT-2 Inhibitors based on the mentioned trials:

Trial	Drug	Patient Group	Key Findings	Cardio- Benefits	Mechanism of Action
DECLARE-TIMI 58 Trial	Liraglutide (GLP-1 RA)	Patients with T2DM at high cardiovascular risk	Significant reduction in the risk of major adverse cardiovascular events (MACE) including cardiovascular death, myocardial infarction, and stroke	Reduced risk of MACE	Improved glycemic control, weight loss, blood pressure reduction, direct cardioprotective effects, reduced inflammation, improved endothelial function
SUSTAIN-SIX Trial	Semaglutide (GLP-1 RA)	Patients with T2DM with established ASCVD	Statistically significant reduction in the risk of MACE compared to placebo	Reduced risk of MACE and favorable cardiovascular outcomes	Similar to DECLARE-TIMI 58; improved glycemic control, weight loss, blood pressure reduction, direct cardioprotective effects, reduced inflammation, improved endothelial function
LEADER Trial	Liraglutide (GLP-1 RA)	Patients with T2DM	Significant reduction in the risk of MACE, including cardiovascular death, non-fatal MI, and non-fatal stroke	Reduced risk of MACE	Improved glycemic control, weight loss, blood pressure reduction, direct cardioprotective effects, reduced inflammation, improved endothelial function
EMPA-REG	Empagliflozin	Patients with	Lower	Reduced risk of	Impact on blood

OUTCOME Trial	(SGLT-2 inhibitor)	T2DM with established cardiovascular disease	cardiovascular mortality, heart failure hospitalization, and all-cause mortality	cardiovascular mortality, heart failure hospitalization, and all-cause mortality	pressure, body weight, and volume; enhanced cardiac performance, lessened arterial stiffness, and lowered oxidative stress
CANVAS Program	Canagliflozin (SGLT-2 inhibitor)	Patients with T2DM	Decreased risk of MACE and heart failure hospitalization	Reduced risk of MACE and heart failure hospitalization	Similar to EMPA-REG OUTCOME; impact on blood pressure, body weight, and volume; enhanced cardiac performance, lessened arterial stiffness, and lowered oxidative stress

Combined Therapy: GLP-1 RAs and SGLT-2 Inhibitors: The combination of GLP-1 RAs and SGLT-2 inhibitors holds promise for enhancing renal protection. Both classes of drugs have complementary effects on renal physiology, including reduction in hyperfiltration, proteinuria, and blood pressure. Clinical studies are needed to confirm the renal benefits of the combined therapy, but the existing evidence is encouraging[24].

Synergy and Potential Mechanisms:

The combined use of GLP-1 receptor agonists and SGLT-2 inhibitors appears to offer a more comprehensive approach to managing T2DM and its associated complications. This synergy might be attributed to the complementary mechanisms of action of each drug class.

- **Improved glycemic control:** The combined effect of enhanced insulin secretion, glucagon suppression, and reduced glucose reabsorption can lead to more robust blood sugar control, potentially reducing the risk of long-term diabetic complications.
- **Enhanced cardiovascular protection:** The combined effects of improved blood pressure control, reduced inflammation, and modulation of lipid profiles might offer a more potent cardiovascular protective effect than either drug class alone.

Synergistic renal benefits: SGLT-2 inhibitors may offer direct renal protection by reducing workload and inflammation, while GLP-1 receptor agonists might contribute by improving hemodynamics and reducing oxidative stress, further protecting the kidneys.

CONCLUSION

Combination therapy with GLP-1 receptor agonists and SGLT-2 inhibitors emerges as a promising strategy for managing T2DM and potentially reducing cardiovascular and renal complications. Existing clinical data demonstrates a synergistic effect in improving glycemic control, reducing cardiovascular risk, and protecting kidney function. While some safety considerations require monitoring, the potential benefits of this combination therapy are significant. Further research is necessary to optimize treatment protocols and identify the most suitable patient populations. This novel approach holds immense promise for improving the lives of patients with T2DM and reducing their burden of associated complications.

Author's Contribution:

Concept & Design of Study:	Rizwan Qasim
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Data Analysis:	Kamran
Revisiting Critically:	Rizwan Qasim
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