Review Article

Exploring the safety of combination therapy with SGLT-2 and DPP-4 inhibitors in type 2 Diabetes mellitus

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ABSTRACT

Type 2 diabetes mellitus (T2DM) presents a complex pathogenesis involving various mechanisms, necessitating multiple therapeutic approaches for effective glycemic control. While metformin remains the first-line therapy, additional agents are often required to maintain optimal glucose levels. The combinatory use of anti-diabetic agents with complementary mechanisms of action, such as sodium-glucose co-transporter 2 (SGLT2) inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors, has emerged as a promising strategy. This review explores the safety profile of different combinations of SGLT2 inhibitors and DPP4 inhibitors. SGLT2 inhibitors offer glucose-lowering effects with potential cardiovascular benefits but come with considerations such as the risk of hypoglycemia, urinary tract and genital infections, diabetic ketoacidosis, and fractures and amputations. Conversely, DPP-4 inhibitors provide effective glycemic control with a low risk of hypoglycemia, although concerns exist regarding infections, hypersensitivity reactions, pancreatitis, and cardiovascular safety. Evaluating combination therapies, including Empagliflozin + Linagliptin, Canagliflozin + Teneligliptin, Dapagliflozin + Saxagliptin, and Dapagliflozin + Sitagliptin, reveals a generally favorable safety profile, with manageable risks consistent with individual component therapies. Notably, these combinations mitigate the risk of hypoglycemia while offering efficacy in glycemic control. Further research and monitoring are warranted to fully elucidate the long-term safety and efficacy of these combination therapies in managing T2DM.

Keywords: *Type 2 diabetes mellitus, Empagliflozin, Linagliptin, Canagliflozin, Teneligliptin, Dapagliflozin, Saxagliptin .*

How to cite this article: Shemeer PS, Khan FA, Ashraf H. Exploring the safety of combination therapy with SGLT-2 and DPP-4 inhibitors in type 2 Diabetes mellitus. J Pharmacovig Drug Safety 2024;21(1):1-4.

Source of Support: Nil, **Conflict of Interest:** None

Received:20.12.23
Accepted:17.02.24

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INTRODUCTION

The pathogenesis of type 2 diabetes is intertwined with multiple different mechanisms, which encompasses decreased insulin secretion, decreased insulin sensitivity, increased hepatic glucose production, decreased responses to Incretin hormones, and increased renal reabsorption of glucose[1].

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DOI: 10.21276/jpds.2024.21.01.01	Contact at editorjournalsopi@gmail.com

Therefore, multiple strategies are often required to effectively control hyperglycemia in patients with type 2 diabetes. The combinatory use of different anti-diabetic agents with complementary mechanisms of action may enhance the glucose-lowering effect without compromising drug safety. Metformin is the recommended first-line pharmacotherapy for patients with type 2 diabetes[2], but most patients will ultimately require additional therapies to maintain glycemic control[3,4]. Maintaining intensive glucose control early in the disease process may lead to legacy benefits that persist beyond the period of treatment[5].

Therefore, when metformin fails to achieve glycemic control, add-on combination therapy with two oral anti-diabetes agents are needed.

Inhibition of the sodium–glucose co-transporter 2 (SGLT2), located in the proximal tubule of the kidney, reduces renal glucose reabsorption, thereby increasing urinary glucose excretion and reducing hyperglycemia in patients with type 2 diabetes[6]. Since this mechanism is independent of insulin, SGLT2 inhibition is associated with a low risk of hypoglycemia. Additional benefits include weight loss[7] and reduction in blood pressure[8].

Inhibitors of Di-Peptidyl Peptidase-4 (DPP-4) reduce blood glucose in patients with type 2 diabetes by preventing degradation of Incretin peptides such as GLP-1, stimulating insulin release and inhibiting glucagon secretion[9]. As DPP-4 inhibition leads to a glucose dependent release of insulin, it is associated with a low risk of hypoglycemia[10].

There are many SGLT-2 Inhibitor, DPP-4 inhibitor combinations.In this review we are exploring the safety profile of different sglt2 inhibitor DPP-4 inhibitor combinations in the treatment of type 2 Diabetes Mellitus.

SAFETY PROFILE OF SGLT2 INHIBITORS

Sodium-glucose linked transporter 2 (SGLT2) inhibitors have emerged as a promising class of drugs for the management of type 2 diabetes mellitus (T2DM), offering glucose-lowering effects with potential cardiovascular benefits. However, like any medication, they come with a set of adverse events that warrant careful consideration. Here, we delve into the safety profile of SGLT2 inhibitors, exploring both their benefits and potential risks.

Hypoglycemia

One of the common concerns with glucose-lowering agents is the risk of hypoglycemia. However, recent meta-analyses have shown that SGLT2 inhibitors alone do not increase the risk of hypoglycemia, consistent with their mechanism of action. Nonetheless, when combined with other glucose-lowering agents, particularly insulin, the risk of hypoglycemia may rise[11].

Urinary Tract and Genital Infections

While initial concerns regarding urinary tract infections (UTIs) associated with SGLT2 inhibitors have not been substantiated, there is evidence suggesting a higher risk of genital infections, particularly in women. Regulatory agencies have updated product information to include warnings about genital infections, including serious conditions like Fournier's gangrene[11].

Diabetic Ketoacidosis (DKA)

DKA, though rare, is a potentially fatal event associated with SGLT2 inhibitor use. Mechanistically, SGLT2 inhibitors can lead to reduced insulin secretion and increased glucagon secretion, predisposing individuals to ketone body formation. The risk of DKA is heightened in patients with type 1 diabetes mellitus and those on insulin therapy[11].

Hypotension and Cardiovascular Benefits

SGLT2 inhibitors have been shown to reduce blood pressure, potentially contributing to their cardiovascular benefits. They have demonstrated reductions in cardiovascular outcomes and mortality, making them a valuable addition to the armamentarium against T2DM and cardiovascular disease[11].

Fractures and Amputations

Controversy surrounds the risk of fractures and amputations with SGLT2 inhibitors. While some trials have reported increased risks, others have not found significant associations. Nonetheless, caution is warranted, and patients should be monitored for signs of fractures and foot complications[11].

SAFETY OF DPP4 INHIBITORS

DPP-4 inhibitors are a valuable addition to diabetes treatment, offering effective blood sugar control with a low risk of hypoglycemia. Studies have shown that when used alone or with certain antidiabetic medications, DPP-4 inhibitors do not increase the risk of hypoglycemia. However, caution is needed when combining them with insulin or sulfonylureas, as this may elevate the risk[12].

Concerns about infections with DPP-4 inhibitors have been raised due to their role in immune functions, but recent analyses have not shown an increased risk compared to placebo. Similarly, gastrointestinal adverse events are rare with DPP-4 inhibitors, making them well-tolerated[12].

Reports of hypersensitivity reactions like angioedema have been noted, particularly with vildagliptin, especially in patients also taking ACE inhibitors. However, the overall incidence remains low, and further investigation is needed[12].

Pancreatitis has been a concern, with reports of acute pancreatitis associated with sitagliptin and vildagliptin. While some studies have suggested an increased risk, others have not confirmed this association. Close monitoring is advised[12].

Cardiovascular safety trials have not shown a significant increase in cardiovascular events with DPP-4 inhibitors. However, Saxagliptin has been associated with a higher rate of hospitalization due to heart failure, requiring further investigation[12].

Malignancy risk, particularly pancreatic cancer, has been a topic of concern, but clinical trial data have not shown an increased risk[12].

Renal and hepatic toxicity have been observed in rare cases, necessitating monitoring of renal function with Sitagliptin and caution with Vildagliptin and Alogliptin, particularly in patients with impaired liver function[12].

In conclusion, DPP-4 inhibitors offer effective glycemic control with a favorable safety profile overall, but careful monitoring and consideration of individual patient factors are essential in their use.

SAFETY PROFILE OF SGLT2, DPP4 INHIBITORS COMBINATION

Empagliflozin + linagliptin

Based on the findings of the three trials, the combination therapy of empagliflozin and linagliptin demonstrated a safety profile consistent with the individual components. In trial 1, the risk of hypoglycemia was similar to empagliflozin or linagliptin with metformin, with comparable incidences of urinary tract and genital infections across all groups[13]. In another trial, while severe adverse events were reported with empagliflozin/linagliptin or empagliflozin alone compared to linagliptin, all treatments were generally well tolerated, and no confirmed hypoglycemic events were observed with empagliflozin/linagliptin[14]. Similarly, one trial revealed a

slightly higher occurrence of hypoglycemic events with empagliflozin 25 mg compared to placebo when added to linagliptin and metformin, alongside a higher incidence of genital infections, but no increase in UTIs. Overall, the combination therapy demonstrated a safety profile consistent with individual component therapies, with manageable risks and tolerability[15].

Canagliflozin + teneligliptin

In comparing the safety of canagliflozin combined with teneligliptin versus canagliflozin with placebo, it was noted that the incidence of adverse events (AEs) was higher in the group receiving teneligliptin and canagliflozin compared to the placebo group. Specifically, there were slightly more AEs related to gastrointestinal and skin disorders in the group receiving both medications. However, it's important to note that the numbers of such events were relatively low. Notably, adverse events commonly associated with SGLT2 inhibitors, like genital infections or osmotic diuresis, were not observed in this study. Additionally, neither group experienced hypoglycemia during the trial period[16].

Dapagliflozin + saxagliptin

The combination of Dapagliflozin with Saxagliptin and Metformin, as seen in , showed a participant experiencing a decrease in glomerular filtration rate (GFR), while occurrences of urinary tract and genital infections were lower compared to the other group. Hypoglycemic events were rare and consistent across treatment groups, affecting only 1% of patients receiving this combination. The incidence of adverse events (AEs) was similar across all groups[17]. In another trial the addition of dapagliflozin to saxagliptin and metformin was well tolerated, with comparable rates of AEs between treatment groups over a 24-week period. However, genital infections were more frequent with dapagliflozin therapy, consistent with previous findings, while no significant increase in urinary tract infections was observed[18].

Dapagliflozin + sitagliptin

In the comprehensive safety analysis, there was a slightly higher proportion of patients reporting at least one adverse event (AE) in the dapagliflozin group compared to the placebo group. Regarding safety concerns, instances of signs, symptoms, and events indicative of genital infections, as well as diagnosed urinary tract infections (UTIs), were more prevalent in patients receiving dapagliflozin, aligning with the anticipated mechanism of action. A minor imbalance in events related to renal impairment was noted in this study, although such a discrepancy was not observed in the broader dapagliflozin program's general population. These events resulted from transient, reversible, nonserious changes in laboratory parameters, necessitating no treatment and consistent with a mild diuretic effect. Modest alterations in total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides were identified with dapagliflozin compared to placebo, but they were deemed unlikely to have clinical significance.

CONCLUSION

In conclusion, the combination therapy of SGLT2 inhibitors and DPP4 inhibitors, as demonstrated in the various trials with empagliflozin and linagliptin, canagliflozin and teneligliptin, dapagliflozin and saxagliptin, and dapagliflozin and sitagliptin, exhibits a generally favorable safety profile. Across these trials, the combination therapies were generally well tolerated, with adverse event rates comparable to individual component therapies or placebo. While there were instances of specific adverse events such as genital infections, urinary tract infections, and renal impairment, these were largely manageable and consistent with the known mechanisms of action of the medications. Notably, the combination therapy did not result in an increased risk of hypoglycemia, which is a significant concern in diabetes management. Overall, these findings suggest that the combination of SGLT2 inhibitors and DPP4 inhibitors could be a viable treatment option for patients with type 2 diabetes, offering both efficacy and a reasonable safety profile. However, ongoing monitoring and further research are warranted to fully elucidate the long-term safety and efficacy of these combination therapies.

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