Review Article

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Vildagliptin Plus Dapagliflozin As A Combination Therapy for Type 2 Diabetes: The Indian Perspective

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Introduction:

The prevalence of diabetes is increasing worldwide; mainly, the prevalence is very high in South Asian countries. India has 77 million diabetes cases, the epicenter of diabetes for the reasons.[1] Though the prevalence of diabetes is higher both in urban and rural areas but in recent years, diabetes has shown a comparatively steeper rise in an urban settings. Rapid changes in dietary practices and greater physical inactivity could be the reason behind this. ICMR-INDIAB study has demonstrated that Indian people are most likely to get diabetes in their early phase of life (25- to 34-year age group).[2] One study found that 69% of patients had not achieved the target level of HbA1c.[3] Non-compliance to lifestyle measures and multiple other factors are responsible for suboptimal glycemic control among Indians. Treatment adherence is very important for effective glycaemic control and achieving the target HbA1c. A study found that a 10% increase in adherence to diabetes medication can reduce HbA1c by 0.1%.[4]

In the Indian diabetes setting, a plethora of anti-diabetes medications is available in the form of fixed-dose combinations (FDC) for the treatment of diabetes. Drug adherence and treatment outcomes can be improved by using rational FDC in the management of diabetes because it reduces pill burden, enhances compliance, and at the same time, patients may achieve their target HbA1c faster than monotherapy.[5] Many long term studies like Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular disease study the Preter Ax and Diamicro N-MR Controlled Evaluation (ADVANCE), Veterans Affairs Diabetes Trial (VADT) suggested that intensive glycaemic control is associated with a reduction in microvascular and other complications which are responsible for morbidity and mortality among diabetes patients.[6,7,8] Despite having good glycemic control, the risk of cardiovascular death persists; hence, addressing this defect by utilizing drugs in the management with proven cardiovascular benefits is of utmost importance.

Vildagliptin as oral incretin-based therapy is increasingly used in managing T2D (type 2 diabetes) as an alternative or add-on therapy to other glucose-lowering agents, especially sulphonylureas. They offer the advantage of an excellent safety profile with no increased risk of hypoglycemia, weight gain, and cardiovascular events.[9]Dapagliflozin has demonstrated cardio-renal benefits and has raised considerable interest among diabetologists and cardiologists. However, the underlying mechanisms of protection remain largely unknown.[10] Fixed-dose combinations (FDCs) of these drugs have been recently commercialized, which could facilitate therapy and improve compliance of patients with T2D.

This article is focused on a review of the studies conducted in the past on the combination of SGLT2i and DPP4i in T2DM management. It highlights the rationale for using this combination therapy in Indian T2DM patients.

Pathophysiological approach to diabetes management:

Current glucose-lowering therapy options target one or more of the eight metabolic and endocrine defects (the ominous octet) underlying the pathophysiology of T2D. These include decreased insulin secretion, reduced incretin effect, increased lipolysis, increased

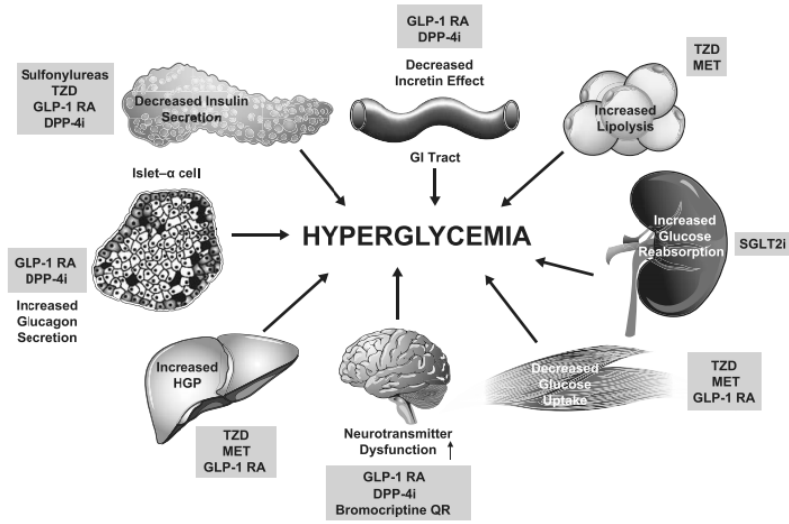

Figure 1. The ominous octet showing the mechanism and site of action of glucose-lowering medications based on pathophysiologic disturbances present in T2DM (adapted from Gude D et.al.[11])

glucose reabsorption, decreased glucose uptake, neurotransmitter dysfunction, increased hepatic glucose production, and increased glucagon secretion.[11] Our better understanding of the pathophysiology of diabetes has enabled a continual churn out of newer antidiabetic agents with varying modes of action. Sodium-Glucose Transport Proteins-2 inhibitors, dipeptidyl peptidase IV inhibitors, glucagon-like peptide analogs, either as monotherapy or combination therapy with the existing oral hypoglycemic agents compound our fight against diabetes.[11]

DPP-4i =dipeptidyl peptidase-4 inhibitor; GI=gastrointestinal; GLP-1 RA=glucagon-like peptide-1 receptor agonist; HGP =hepatic glucose production; MET =metformin; QR =quick release; SGLT2i = sodium glucose cotransporter 2 inhibitor; T2DM = type 2 diabetes mellitus; TZD =thiazolidinedione

Current Challenges of T2DM in India:

Glycemic control in India is poor and this has resulted in a high prevalence of complications. Based on A1chieve study conducted on 66,726 T2DM patients, mean HbA(1c) at time of presentation was 9.2% far away from the HbA1 goal of < 7%. Diabetes control was worse in those with longer duration of diabetes (9.9 +/- 5.5 years). This emphasizes the fact that effective control of T2DM is urgently needed to prevent or reduce the risk of developing the complications of diabetes in Indian T2DM patients.[11] Epidemiological analysis of the UK prospective diabetes study (UKPDS) data showed that for every 1% reduction in HbA1c, the relative risk for microvascular complications decreased by 37%, diabetes-related deaths by 21%, and myocardial infarction by 14%.[6] Hence, early and more aggressive (intensive glucose control) is the strategy to improve patient's chances of reaching HbA1c goal.

Hypoglycemia as a Factor Behind Clinical Inertia:

Although careful selection and titration of anti-diabetic agents can achieve a good glycemic control without significant risk for hypoglycemia, a common limitation of intensive glucose lowering therapy is an increased risk for hypoglycemia. Consequently, today type 2 diabetes is associated with a substantial incidence rate of hypoglycemia. Hypoglycemia has a negative impact for the well-being of the patients, both in the short-term and the long-term. In addition, hypoglycemia also carries a high cost, not only for the individual patient, but also for the health care system and society at large.[12]The risk for hypoglycemia is also an important factor underlying clinical inertia,

which is a key consequence of inadequate glycemic control in patients with type 2 diabetes. Strategies to mitigate the risk of hypoglycemia include awareness of the condition; education of patients, relatives, and health care providers; and selecting appropriate glucose lowering medication that also judges the risk for hypoglycemia to prevent this complication.[12]

Asian Indian Phenotype & Role of Oral Glucose Lowering Agents (OADS):

Indians have distinct clinical and biochemical deformities, which make them the so-called 'Asian Indian Phenotype'. These abnormalities include higher insulin resistance, elevated abdominal adiposity (i.e., higher visceral fat in spite of lower body mass index [BMI]), lower level of adiponectin, higher level of high sensitive C - reactive protein, total GLP‑1 level varied from low to normal after meal, low Intact GLP-1 level and Enhanced DPP-4 activities in plasma so, called Indian Incretin Axis.[13,14] Moreover, Asian Indians have an increased metabolic risk compared to their counterparts; because of a) the existence of high leptin levels; b) leptin concentration is a significant indicator of body fat ($P < 0.0001$), hip circumference, and fasting insulin; c) greater insulin resistance; d) higher insulin sensitivity index and lower acute insulin response to glucose; e) early loss of beta cell function; f) 'thin-fat Indian concept' or 'sarcopenic obesity' (Asian Indians have thinner limbs [smaller muscle mass] with central obesity, with a higher waist-to-hip ratio and higher subscapular-to-triceps skin fold ratio than their British counterparts, which leads to higher insulin resistance); more people suffer from diabetes at a relatively lower BMI compared with those of European descent; elevated mean A1C level (9.0%), which is 2.0% higher than the target suggested by international bodies.[14]

SGLT2i and DPP4 inhibitors could produce multiple benefits in Indian diabetes patients. Table 1 & 2 shows the list of challenges faced by Indian patients and describes how SGLT2i and DPP4i could overcome the challenges.

Table 1. Evolving role of SGLT2i in Indian phenotype with T2DM [13]

Challenges with Indian patients	**Relevant SGLT2i features**
Higher abdominal adiposity and visceral fat at any given body mass index	↓ Body weight (more visceral fat mass loss than subcutaneous fat loss)
Higher waist circumference and waist to hip ratio	↓ Waist circumference
Impaired insulin secretion and increased insulin resistance	↓ Improve b-cell function ↓ and insulin resistance
Low level of adipokine and high plasma leptin increases concentrations of triglycerides	↓ Both triglycerides and leptin
Low rate of glucose disposal	↑ Rate of glucose disposal

Table 2. Evolving role of DPP4i in Indian phenotype with T2DM [14]

Challenges with Indian patients	**Relevant SGLT2i features**
Low adiponectin level in T2DM	Increased adiponectin level
High insulin resistance due to hypoadiponectinemia in T2DM	Improved insulin resistance
Low level of adipokine and high plasma leptin increases concentrations of triglycerides	Both triglycerides and leptin
Low intact GLP‑1 levels and low GLP‑1 response after meals	Strengthen GLP-1 response after meals
Enhanced DPP‑4 activities in type 2 diabetes	Suppress DPP4 activities in T2DM patients

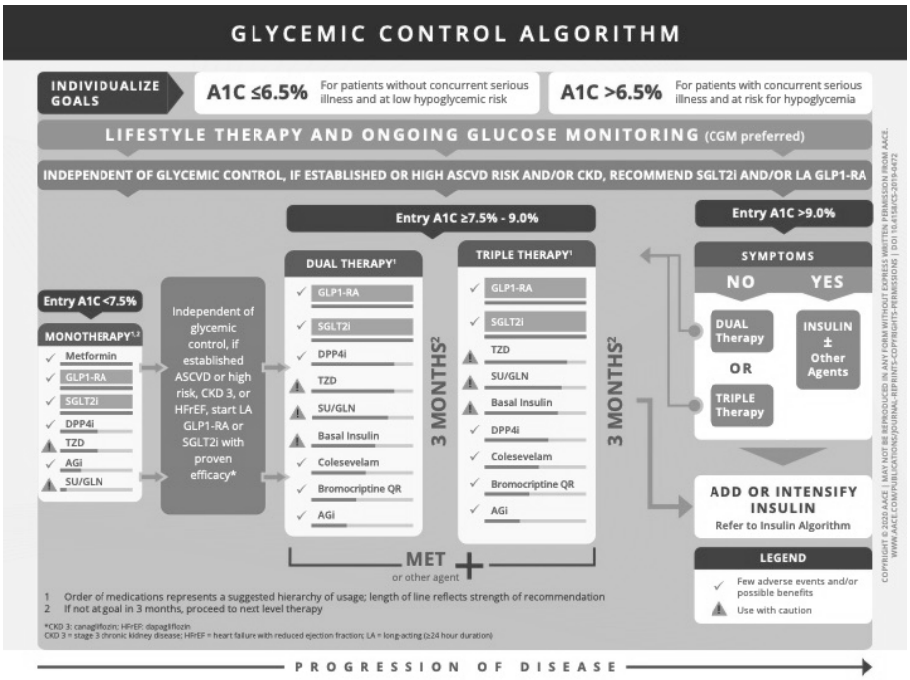

Figure 2. 2020 AACE Comprehensive Type 2 Diabetes Management Algorithm (adapted from Garber AJ et.al.[15])

Guideline Recommendations:

Both American Association of Clinical Endocrinologists (AACE) 2020 and American Diabetes Association (ADA) 2022 guidelines have recommended the combination of SGLT2i and DPP4i therapy for T2DM patients when either of monotherapy is not sufficient to achieve HbA1c target < 7%. At the time of diagnosis, when

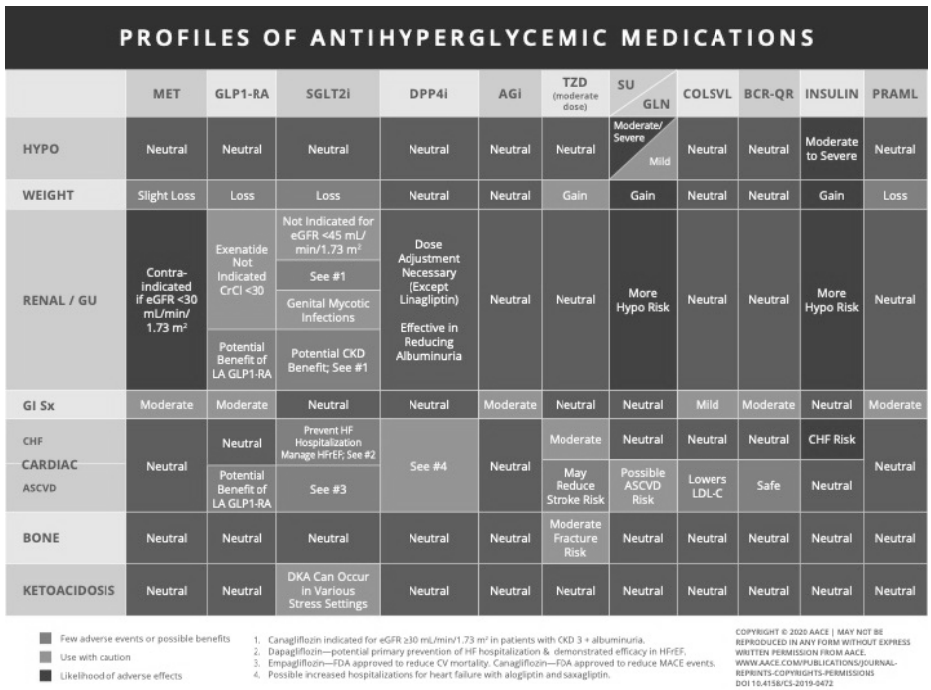

Figure 3. AACE - Safety profiles of SGLT2i and DPP4i: Neutral effect on hypoglycemia risk (adapted from Garber AJ et.al[15])

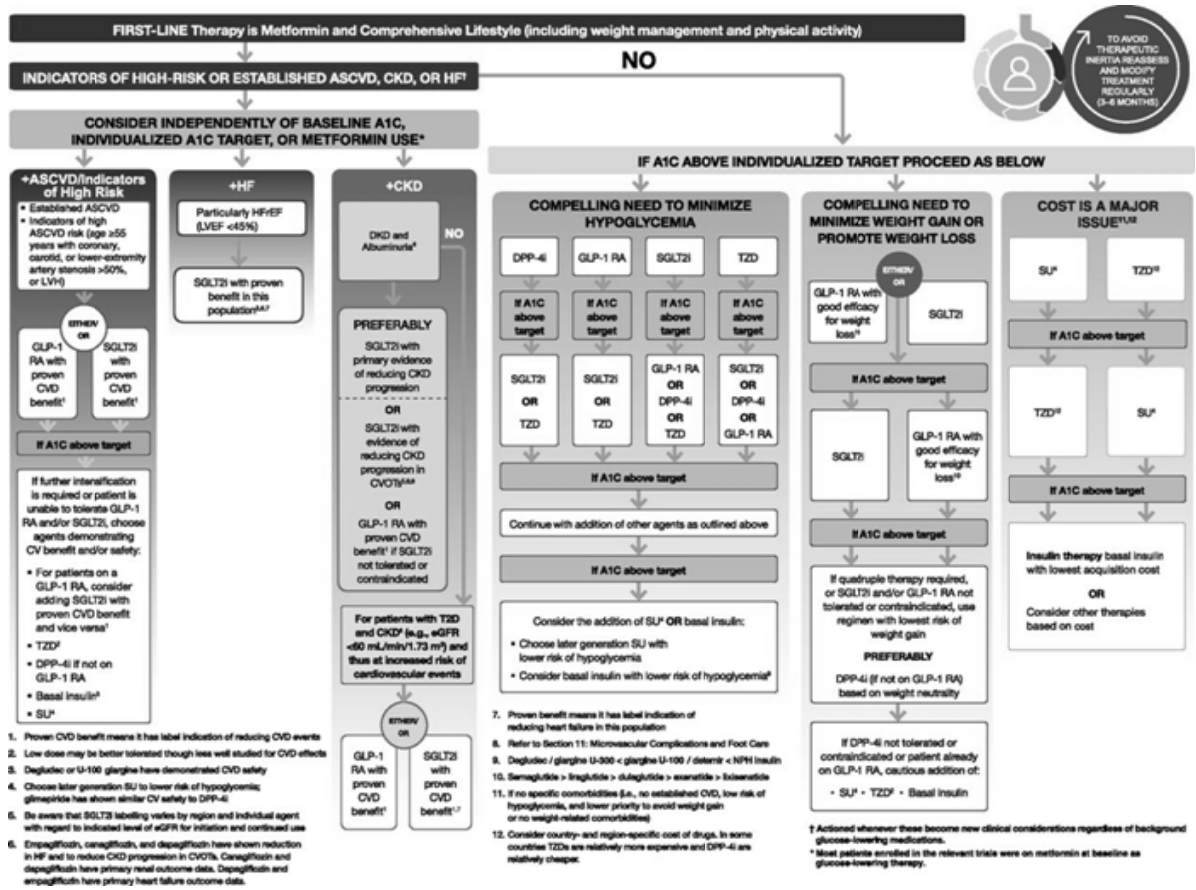

Figure 4. 2022 ADA Comprehensive Type 2 Diabetes Management Algorithm (ADA guidelines 2022[16])

HbA1c is ≥7.5% - < 9% - combination of SGLT2i and DPP4i is recommended by AACE 2020 guideline for T2DM management.[15,16]

Therapeutic Rationale of SGLT2I and DPP4I Combination:

There is a strong rationale for combining a DPP-4i and an SGLT2i in patients with T2D

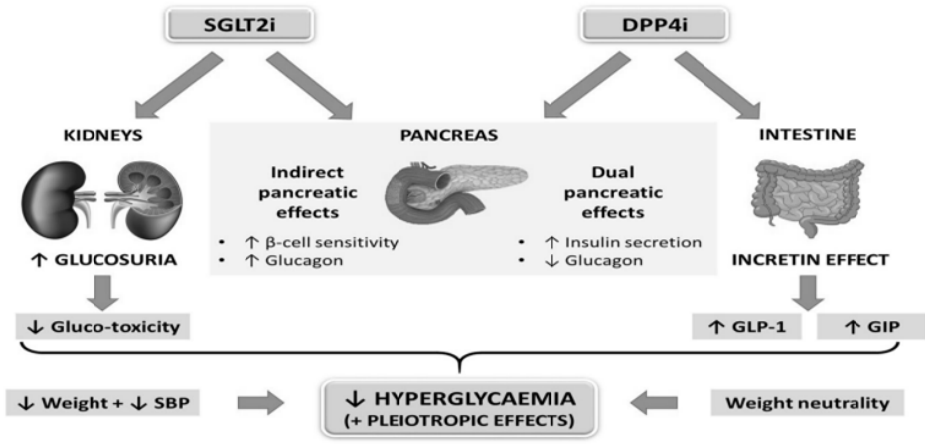

Figure 5. Illustration of the complementary glucose-lowering activities of DPP-4 inhibitors (DPP-4i) and SGLT2 inhibitors (SGLT2i) in type 2 diabetes. (adapted from Scheen et.al.[17])

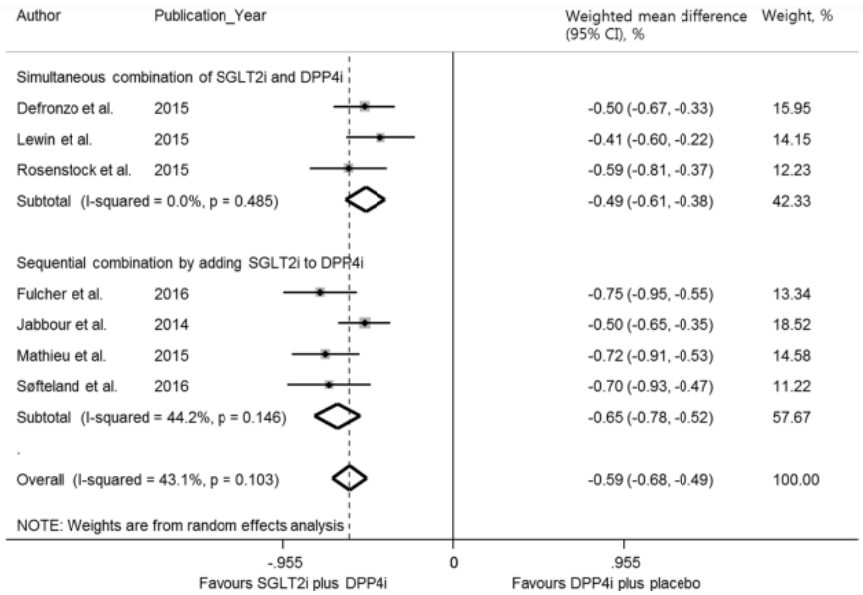

Figure 6. Meta-analysis for the primary efficacy outcome (adapted from Min SH et.al.[18])

because the two drugs exert different and complementary glucose-lowering effects. Dual therapy (initial combination or stepwise approach) is more potent than either monotherapy in patients treated with diet and exercise or already treated with metformin. Combining the two pharmacological options is safe and does not induce hypoglycemia (figure 3), weight gain, and the potential for cardiovascular protection. The addition of a DPP-4 inhibitor which inhibits glucagon and stimulates insulin secretion, may have the potential to block the increase in endogenous glucose production and enhance the glucose-lowering ability of SGLT2. (Figure 5) These findings suggest that combining a DPP-4i with an SGLT2i would potentially provide additional help to individuals with T2D in reaching their glycemic goal. Beyond a glucose-lowering effect, SGLT2i have some added value with reductions in body weight (including abdominal adiposity), blood pressure, and serum uric acid, all markers considered independent cardiovascular risk factors. Thus, combination treatment with a DPP-4i and/or SGLT2i appears to be an attractive option for patients with T2D starting pharmacological therapy or for patients who are already treated with a glucose-lowering agent, especially metformin, but require additional medications to improve glycemic control further. A lesser genito-urinary infection has been observed with combination therapy compared to SGLT2 inhibitors monotherapy. No drug-drug interaction between SGLT2i and DPP4i.[17]

SGLT2I + DPP4I FDCs: Clinical Evidence Overview

Evidence from a meta-analysis suggests that SGLT2i + DPP4i FDCs are effective and safe in controlling glycemic parameters in patients with T2DM. It was a meta-analysis of randomized controlled trials (RCTs) that compared the SGLT2 inhibitor plus the DPP4 inhibitor (SGLT2i/DPP4i) with placebo plus the DPP4 inhibitor (PCB/DPP4i) in patients with type 2 diabetes concurrently treated with or without other antidiabetic agents were included. The study showed that SGLT2i/DPP4i led to greater improvement in HbA1c than PCB/DPP4i (WMD −0.59%, 95% CI −0.68 to −0.49%). Both simultaneous combination and sequential addition of SGLT2 inhibitors to DPP4 inhibitors showed a greater reduction in HbA1c than the respective PCB/DPP4i group (WMD −0.49%, 95% CI −0.61 to −0.38%, and WMD −0.65, 95% CI −0.78 to −0.52%, respectively).[18]

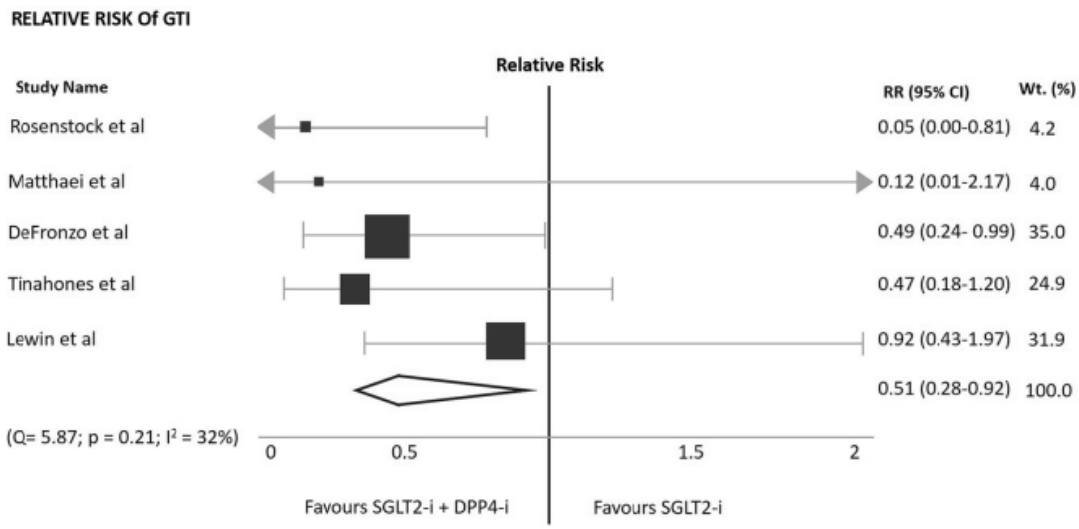

Figure 7: Incidence of genitourinary tract infections favors the use of the SGLT2i + DPP4i fixed-drug combination. CI Confidence interval, GTI genitourinary tract infection, RR relative risk. (Adapted from Fadiniet al.[19])

The study also showed that the combination of the SGLT2i/DPP4i group did not increase the risk of hypoglycemia (RR 1.0, 95% CI 0.4–2.8). The risk of genital infection was increased in the sequential combination subgroup (RR 5.57, 95% CI 2.33–13.333) but not in the simultaneous combination subgroup (RR 1.35, 95% CI 0.55–3.34).[18]

A systematic review and meta-analysis of seven RCTs involving 2082 participants with a duration of at least 12 weeks) investigated the effect of SGLT2i + DPP4i therapy in patients with T2DM. All seven studies assessed the risk of urinary tract infections (UTIs) and GTIs at the end of the treatment. The risk of a UTI was found to be slightly higher in the group receiving sequential combination therapy (relative risk [RR] 0.96, 95% confidence interval [CI] 0.52–1.78) than in the simultaneous combination group (RR 0.67, 95% CI 0.28–1.60). The risk of a GTI was also higher in the sequential combination group (RR 5.57, 95% CI 2.33–13.33) than in the simultaneous group (RR 1.35, 95% CI 0.55–3.34). Overall, the results of this analysis suggest a possible lower risk of GTIs and nominal reduction in the incidence of UTIs with the simultaneous combination as opposed to a sequential combination of SGLT-2i and DPP-4i.[19].

Conclusion:

Type 2 diabetes is a progressive disease that creates a need for earlier and more aggressive intervention to improve patients' chances of reaching treatment goals. Indian diabetes patients are different with respect to phenotypes where OADs like SGLT2i and DPP4i are the best suitable options with a low risk of hypoglycemia. ADA and AACE guidelines on diabetes management have recommended a dual combination of SGLT2i and DPP4i to manage diabetes. Clinical data also shows effectiveness, safety, and tolerability in Indian diabetes patients using SGLT2i and DPP4i for diabetes management. Dapagliflozin plus Vildagliptin FDC offers safe, rapid, and sustained glycemic control, improves insulin resistance and beta-cell function, helps to reduce body weight and blood pressure (extraglycemic benefits), reduces pill burden (adherence and compliance improves) and is cost-effective. Thus Vildagliptin and Dapagliflozin FDC would be a good choice for diabetes management and lifestyle modifications.

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