Review Article

Combination treatment with SGLT2-i and DPP4-i : Glycemic-control and beyond

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Type 2 diabetes is chronic and progressive metabolic disorder involving multiple metabolic defects. The use of combination therapy with anti-diabetes drugs with different mechanisms of action has the potential of producing complementary metabolic action including a robust reduction in HbA1c along with cardiovascular and renal benefits. The availability of a dual sodium glucose co-transporter 2/ dipeptidyl peptidase-4 inhibitor combination represents a new therapeutic alternative for patients with type 2 diabetes. Present review considers the range of evidence for combining SGLT2-I and DPP4-I with a focus on their respective role on cardiovascular and related benefits of each agent in patients.

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Key words **: SGLT2-i and DPP-4i combination, cardioprotection, renoprotection.**

T2 D Mellitus (T2 DM) is one of the most widely prevalent conditions causing pandemic across the globe. As evidenced by major landmark trials, although intensive glycemic control achieved by conventional agents demonstrated reduction in risk of microvascular manifestation, its relationship with macrovascular outcomes or all-cause mortality appeared to be multifaceted. Furthermore, metabolic risk factors like hypertension and obesity, and macrovascular manifestations are shown to be positively linked together for their development and progression. There is a clinical unmet need of an effective antidiabetic treatment that can ameliorate residual risk of cardiovascular disease, still having lower propensity for hypo-glycemic events and weight gain. Two classes of glucose-lowering agents that meet the criteria are sodium glucose cotransporter-2 (SGLT2) inhibitors and dipeptidyl peptidase-4 (DPP4) inhibitors. In 2017, Drug Controller General of India (DCGI) approved empagliflozin and linagliptin combination therapy as an adjunct to diet and exercise to improve glycemic control when treatment with both empagliflozin and linagliptin is appropriate.

Present review considers the range of evidence for combining (DPP4-i) and (SGLT2-i) with a focus on their respective role on cardiovascular and related benefits in patients.

Complementary Effects of SGLT2-i and DPP4-i Combination :

SGLT2-i is a class of novel oral glucose lowering agents that mediates glucose lowering action by increasing urinary glucose excretion via inhibition of the sodium-glucose cotransporter-2 in the proximal tubule of the kidney. The salutary effect is its ability to act independent of insulin secretion and action and render it suitable to administer at any stage of disease course. DPP4-i exerts its glucose lowering effect by the elevation of incretin hormones and subsequent augmentation of glucose dependent insulin secretion and inhibition of glucagon release. SGLT2-i associated with 17-30% rise in endogenous hepatic glucose output, perhaps mediated by compensatory increase in plasma glucagon in response to glycosuria as suggested by experimental study. Combined DPP-4i with gliflozin is speculated to prevent such increase in glucagon level resulting in optimum glucose control. Combination of these agents has potential to show the additive glycemic control due to their complementary effects (Fig 1).

Glycemic Control with Complementary Effects :

Various pivotal phase III trials suggest that combining SGLT2-i and DPP4-i in T2DM adults result in clinically

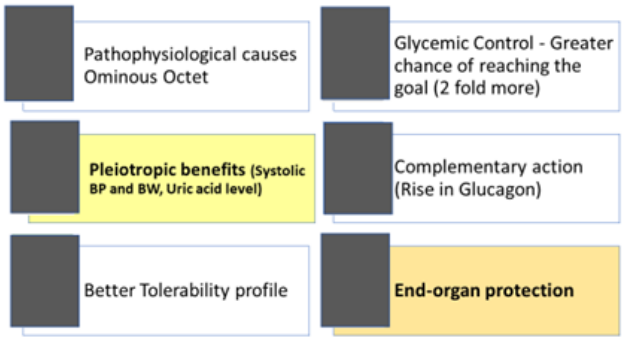

Fig 1—The need of using the combination of SGLT2-i and DPP4-i

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meaningful reductions in HbA1c (-1.2–1.5%) which was significantly more than either agent alone. In two randomized, placebo controlled trials, empagliflozin (10mg) and linagliptin (5mg) produced statistically significant reductions in HbA1c (-1.24) at week 24, in the treatment-naïve patients, and (-1.08) add on to metformin compared to linagliptin (P<0.001)[1,2]. The benefits on glycemic control were maintained at week 52 in the treatment-naïve and metformin treated groups, and a higher percentage of patients achieving HbA1c <7% were reported for combinations.

Table 1 — *Glycemic control with combination of SGLT2i and DPP4i versus SGLT2i or DPP-4i alone*

Combination of SGLT2-i and DPP4-i	HbA1c	FPG
vs. DPP-4i in treatment naïve	-0.69 (-1.00, -0.38)	-32.18 (-46.40, -17.96)
vs. DPP-4i on metformin background	0.70 (-0.80, -0.60)	-23.49 (-39.80, -7.17)
vs. SGLT2i in treatment naïve	-0.25 (-0.34, -0.15)	-7.13 (-13.28, -0.97)
vs. SGLT2i on metformin background	-0.38 (-0.48, -0.28)	-10.55 (-13.58, -7.52)

Adapted from Li et al.meta-analysis (2018).

Results were consistent with other combination therapy like dapagliflozin and saxagliptin in patients with uncontrolled glycemia[3]. Large metaanalysis with different combination agents analyzed glucose lowering potential with consistent results (Table 1).

End Organ Protection :

Hypertension and cardiovascular disease (CVD) are the most common comorbidities in T2D patients[4]. Overall, CVD with significant morbidity and mortality accounts for half (50.3%) of deaths in this population[5]. Approximately 40% of patients with diabetes upon screening for decreased eGFR and albuminuria have evidence of CKD[6].

Cardiovascular Benefits :

Due to the conflicting reports of increased risk of cardiovascular event with antidiabetic agents, USFDA (2008)[7]and EMA (2012)[8] issued a guidance to provide CV safety data for new antidiabetic medications. Empagliflozin was first SGLT2-i to demonstrate cardio-renal benefit in T2D patients with established cardiovascular disease (eCVD) (99% of cohort)[9]. DPP4-i demonstrated CV safety in patients, although with increased risk of heart failure reported with saxagliptin that led to the incorporation of heart failure risk warning in all USFDA-approved DPP4-i labels in August 2017[10]. Combinations of SGLT2-i and DPP4-i are not retested in similar clinical trial programs to the individual drug because the agents are bioequivalent[11].

Empagliflozin Cardiovascular Outcome Event Trial in T2D Mellitus Patients (EMPA-REG OUTCOME) reported that 3P-MACE outcome occurred in a significantly lower percentage (HR 0.86; 95.02% CI: 0.74-0.99; P = 0.04) in the Empagliflozin compared to placebo on top of standard care. Treatment with Empagliflozin resulted in a 38% (HR 0.62, 95% CI 0.49, 0.77p<0.001) reduction of death from CV causes, and 35% reduction of hospitalization for HF (HR 0.65, 95% CI 0.50, 0.85; p <0.002)[12]. There were around 11% patients on DPP4-i in background therapy. Empagliflozin is the only SGLT2i (FDA 2016) to reduce the risk of CV death in patients with T2D and established CV disease to date[13].

In CANVAS program, a total of 10,142 patients with T2 DM and either established CV disease or multiple CV risk factors (34.4%) demonstrated a significant reduction (by 14%) in the composite primary endpoint (HR 0.86, 95% CI 0.75, 0.97) in canagliflozin group compared to placebo[14]. A total of 17,160 patients with T2 DM were assessed for CV Safety in Dapagliflozin Effect on Cardiovascular Events (DECLARE-TIMI 58) study for a median period of 4.2 years[15]. Treatment with Dapagliflozin resulted in a 17% reduction of the composite outcome of CV death or hospitalization for HF, while no effect was reported for the 3P-MACE[16].

Mechanism behind the impressive CV benefits exhibited by SGLT2-i is mostly unknown, however, closely interconnected to its hemodynamic effects (Fig 2).

With the range of evidence with DPP4-i, overall cardiac safety was quite evident in patients with high risk of cardiovascular disease compared to placebo.

CV safety of DPP4-i further elucidated in CARMELINA (CARdiovascular Safety & Clinical outcoME with LINAgliptin) trial in T2D patients with renal impairment which recruited a substantial proportion of patients with T2 DM; 74% had prevalent kidney disease. Linagliptin has demonstrated the CV and renal safety (secondary

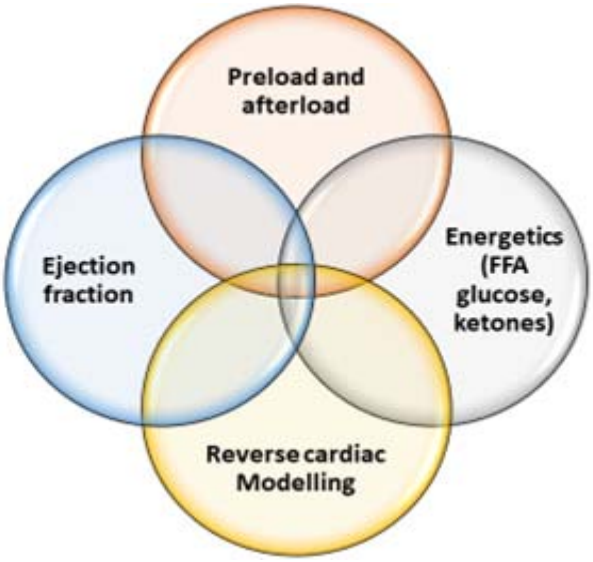

Fig 2 — Proposed mechanism for cardiovascular benefits of empagliflozin

endpoint) of linagliptin versus placebo when in addition to standard care in patients with T2 DM who were at high risk of vascular complications[17]. CAROLINA (Cardiovascular Outcome Study of LINAgliptin versus Glimepiride in Patients with Type 2 Diabete) trial similarly demonstrated CV safety compared to active comparator in 6041 patients with relatively early T2 DM[18].

Preservation of Renal Function :

Growing evidence showed that SGLT2-i has the potential to offer renoprotective effects in patients with T2 DM and CKD. In a sub-analysis from EMPA Reg study, empagliflozin decreased new-onset or worsening of nephropathy by 39% (HR 0.61, 95% CI 0.53–0.70) as compared to placebo, on the top of RAS-blocker therapy[19]. Although HbA1c reduction observed with SGLT2-i declines with progressive eGFR reduction, the CV and renal benefits seem to be maintained independent of eGFR level (< 30 mL/min/1.73 m2). SGLT2-I demonstrated preservation of eGFR, as compared to glimepiride or placebo in a four-year duration studies[20].

Restoration of tubule-glomerular feedback reducing intraglomerular pressure and decreased glomerular hyperfiltration, have been postulated for renal benefits of SGLT2-i[21]. Initially after institution of therapy, clinical presentation may report a decline in eGFR value by 4-5 mL/min/1.73 m^2 during the first weeks of treatment and then gradually improve after 6-12 months[22,23] with stabilization of renal function.

CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial which is first dedicated renal outcomes trials for canagliflozin reported renal benefits including patients with eGFR value of 30ml/min/1.73m^2.

DPP4-i may have beneficial effects on renal outcomes primarily by reducing albuminuria compared to placebo in patients with T2D.

Extra Glycemic Effects :

Body weight reduction :

In contrast to conventional anti-glycemic agents, SGLT2-i demonstrated moderate weight loss in patients, mechanism mostly unknown. It is estimated that 75 gm glucose per day are lost in the urine with a diuresis of 400 mL/day. The EMPA-REG study showed that patients on empagliflozin 10 and 25 mg lost a mean of around 2 kg and almost 3 kg of body weight, respectively. Weight loss seem to occur rapidly in the first weeks of treatment, followed by gradual decline which reaches a plateau after 6 months and is maintained for a long time.

Blood pressure lowering :

It is widely known that the reduction of arterial BP is closely linked to reduction of CV morbidity and mortality in patients with DM[24]. More specifically, SGLT2-i reduce 24-h ambulatory systolic and diastolic BP by 3.76 mmHg and 1.83 mmHg, respectively[25,26]. Several mechanism has been suggested like plasma volume contraction; weight loss; improvements in vascular stiffness by reductions in body weight, reduced sympathetic nervous system activity; and lower serum uric acid concentrations[27].

Arterial Stiffness :

Diabetes is likely to be closely linked to the increased arterial stiffness without coexisting hypertension.

SGLT2-i has also shown amelioration of aortic stiffness measured noninvasively[28]. SGLT2i induce natriuresis, which might improve whole-body sodium balance and volume status[29], and are associated with improved endothelial function and reduced vascular stiffening, decreasing the demand placed on cardiac tissue that causes left ventricular hypertrophy[30].

Effect on liver fat :

SGLT2is (empagliflozin, luseogliflozin, canagliflozin) attenuate several factors associated with nonalcoholic steatohepatitis (NASH) and nonalcoholic fatty liver disease (NAFLD), such as weight gain, elevated alanine amino-transferase, high liver fat index, and visceral fat[31].

Post-hoc study of EMPA Reg showed the improvement in amino-transferase level at 28 week [-2.98 ±0.18 versus placebo -0.73±0.25U/L ($p<0.0001$)]. In (E-LIFT) trial[32] empagliflozin was significantly better at reducing liver fat over control in standard of care diabetes treatment.

Lipid modifying effects:

Dyslipidemia is a common comorbidity of T2 DM that increases CV morbidity and mortality[33]. The administration of Empagliflozin or Canagliflozin increased both low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) according to the EMPA-Reg outcome and CANVAS program. SGLT2-i administration modestly alter lipid profiles by reductions in plasma triglycerides and increase in HDL cholesterol and LDL cholesterol[34,35], while triglyceride and small dense LDL levels tend to modestly decrease SGLT2is[36].

Uric acid lowering effect :

Elevated uric acid in T2D is a common finding in metabolic syndrome. The mechanism is not clearly understood. However, some studies suggested that it may possibly involve the renal SLC2A9 (GLUT9) transporter[37]. A recent post hoc analysis of EMPA-REG trial has shown that 24.6% of the empagliflozin effect on the observed decrease in the risk of cardiovascular death may be mediated by changes in uric acid[38].

Tolerability Profile :

Combination therapy of SGLT-2i and DPP4-i was observed to have less risk of hypoglycemia (2.4%)

compared to either drug alone. Most of the studies reported similar genitourinary infection in combination arm, compared to SGLT2-i alone which is intrinsic to the mode of action of SGLT-2i. Frequent adverse reaction observed with 10 mg empagliflozin / 5 mg linagliptin and (8.50 % with 25 mg empagliflozin / 5 mg linagliptin) was urinary tract infection (7.5 %). Interestingly, the rate of genital infections is lowered by 26% when used with the combination, which has been postulated to be attributed to DPP-4i effect on the immune system[39]. The adverse reactions like ketoacidosis (<0.1%), pancreatitis (0.2%) were rare with this combination. Certain precautions advised during the administration and follow-up are to check eGFR periodically, to check electrolytes level, background therapies like diuretic, Insulin and insulin secretagogues, reinforcement on advice of perineal hygiene, advice on the fasting, keto diet or acute illness, watch on serum creatinine level.

Current Place of SGLT2i and DPP4-i in T2D Management :

Empagliflozin and linagliptin is the first-in class available combination of SGLT2-i and DPP4-i in India. This anti-diabetic class appear to be a promising add-on in therapeutic armamentarium of T2D management due to their various complementary effects on incretin and renal glucose excretion, more proportion of patients achieving target than either drug alone, better tolerability profile with substantial cardiorenal benefits. ADA (2016) guidelines on use of triple drug combination suggests that if A1c targets are not achieved after 3 months of dual therapy, begin triple therapy by adding third hypoglycemic agent to the dual combination.

Summaries of product characteristics suggests that DPP-4/SGLT2i combinations can be instituted in case of inadequate glycemic control with metformin and/or sulphonylureas (SU) or when already being treated with the free combination of individual components. Rather than using a conventional stepwise treatment strategy, early use of triple therapy (add-on dual therapy to metformin) could be considered in patients who have failed to achieve glycemic control on metformin. SGLT-2i are not recommended in patients with advanced kidney disease (eGFR <45 mL/min/1.73 m2 for canagliflozin, dapagliflozin and empagliflozin and <60 mL/ min/1.73 m^2 for ertugliflozin).

Conclusion :

In the era of patient-centered care, the novel combination of SGLT2-i and DPP4-i by virtue of its unique features will prove as an important contribution in diabetes health care system to address the medical unmet need of ever growing epidemic of diabetes in Indian population.

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