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PRACTICAL APPROACH

Expert Opinion: Optimum Clinical Approach to Combination-Use of SGLT2i + DPP4i in the Indian Diabetes Setting

Manoj Chadha · Ashok Kumar Das · Prasun Deb · Kalyan Kumar Gangopadhyay · Shashank Joshi · Jothydev Kesavadev · Rajiv Kovil · Surender Kumar · Anoop Misra · Viswanathan Mohan

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ABSTRACT

The Asian-Indian phenotype of type 2 diabetes mellitus is uniquely characterized for cardio-metabolic risk. In the context of implementing patient-centric holistic cardio-metabolic risk management as a priority, the choice of various combinations of antidiabetic agents should be individualized. Combined therapy with two classes of antidiabetic agents, namely, dipeptidyl peptidase 4 inhibitors and sodium-glucose co-transporter-2 inhibitors, target several pathophysiological pathways. The wide-ranging clinical outcomes associated with this combination, including improvement of glycemia and adiposity, reduction of metabolic and vascular risk, safety, and simplicity for sustainable compliance, are extremely relevant to the Asian Indian patient population living with T2DM. In this review we describe the available evidence in detail and present a rational

M. Chadha
Endocrinology, P.D. Hinduja Hospital, Mumbai, India
e-mail: mchadha59@gmail.com

A. K. Das
Endocrinology, Pondicherry Institute of Medical Science, Puducherry, India
e-mail: ashokdas82@gmail.com

P. Deb
Endocrinology, Krishna Institute of Medical Sciences, Hyderabad, India
e-mail: prasundeb2002@yahoo.co.uk

K. K. Gangopadhyay
Endocrinology, Peerless Hospital, Kolkata, India
e-mail: jaykal69@hotmail.com

S. Joshi
Endocrinology, Joshi Clinic and Lilavati Hospital and Research Centre, Mumbai, India
e-mail: shashank.sr@gmail.com

J. Kesavadev
Jothydev's Diabetes and Research Center, Thiruvananthapuram, India
e-mail: jothydev@gmail.com

R. Kovil
Department of Diabetology, Dr Kovil's Diabetes Care Centre, Mumbai, India
e-mail: drrajivkovil@hotmail.com

S. Kumar
Endocrinology, Sir Ganga Ram Hospital, New Delhi, India
e-mail: doctorsuren@yahoo.co.uk

A. Misra
Fortis-C-DOC Centre of Excellence for Diabetes, Metabolic Diseases and Endocrinology, National Diabetes, Obesity and Cholesterol Foundation (N-DOC), Diabetes Foundation (India) (DFI), New Delhi, India
e-mail: anoopmisra@gmail.com

V. Mohan (✉)
Dr Mohan's Diabetes Specialities Centre and Madras Diabetes Research Foundation, Chennai, India
e-mail: drmohans@diabetes.ind.in

practical guidance for the optimum clinical use of this combination in this patient population.

Keywords: Asian Indian phenotype; Type 2 diabetes; Cardio-metabolic risk; Sodium-glucose cotransporter-2 inhibitor; Dipeptidyl peptidase-4 inhibitor; Fixed-dose combinations

Key Summary Points
Why this expert opinion?
This expert opinion serves as a clinical guidance for the optimum use of the therapeutic combination of dipeptidyl peptidase 4 inhibitor (DPP4i) + sodium-glucose co-transporter-2 inhibitor (SGLT2i) in the management of Asian Indian patients with type 2 diabetes mellitus (T2DM).
The Asian Indian phenotype is characterized by increased visceral adiposity, lower metabolic tolerance, and increased cardio-renal risk.
A personalized approach that is relevant to the unmet needs of each individual patients should be the underlying principle for clinical decision.
It is important to address multiple pathophysiological aspects underlying T2DM; combination therapy with a DPP4i + SGLT2i may be relevant in this regard.
This therapeutic combination may be a pertinent partner to metformin, in providing meaningful glycemia control without increasing risk for hypoglycemia, and in improving the metabolic profile of patients.
The combination of agents with proven benefits may be preferred for patients with higher predisposition to cardiovascular events and kidney disease.
Overcoming clinical inertia and ensuring long-term adherence are important aspects of clinical outcomes optimization; the adoption of a relevant combination therapy can help address these aspects.

INTRODUCTION

India has the second highest number of people (77 million) with type 2 diabetes mellitus (T2DM) in the world. The large Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) study, which is a nationally representative epidemiological study, is currently being conducted throughout the country in a phased manner [1, 2]. To date, the findings suggest an increasing prevalence of T2DM in both urban and rural areas, but with a comparatively steeper rise in the urban setting that is driven by rapid changes in dietary practices and greater physical inactivity compared to rural areas. A particularly alarming trend observed in India is the shift in onset of diabetes to people in younger age groups. In the ICMR-INDIAB study (Phase I), the demographic increase in T2DM was evident in the 25- to 34-year age group, and declined after age 65 years [2]. Of all patients with T2DM in India, the study found that 69% had not achieved the target level of HbA1c. Non-compliance to lifestyle measures and multiple other factors are responsible for nonattainment of glycemic control in Indians [3].

The unmet need of improving/achieving the glycated hemoglobin (HbA1c) goal is strongly associated with the requirement for diverse therapeutic options, namely, for the individualization of care (personalized medicine). Clinicians are currently witnessing a greater choice of therapeutic options, which may be also useful in various combinations to address specific priorities. At the same time, polypharmacy, with its increased pill burden and dosing frequency, is inherently associated with poorer treatment adherence [4, 5]. Even in countries with high access to healthcare, only 39% patients have reported good medication adherence. In a study of 2741 patients on oral antidiabetic drugs, each 10% increase in oral diabetes medication adherence was associated with a 0.1% decrease in HbA1c ($P = 0.0004$). There is evidence suggesting that treatment-adherent patients are more likely to achieve better glycemic control than non-adherent patients [5].

The Indian diabetes setting is also overwhelmed with a plethora of fixed-dose drug combinations (FDCs) for T2DM. The Indian pharmaceutical industry markets > 50 such FDCs in more than 500 brand names. The Drug Controller General of India (DCGI) has recently scrutinized this situation, and citing lack of therapeutic justification, banned 344 such FDCs (27 of which were metformin-based FDCs). While rational FDCs do help in improving drug adherence as well as treatment outcomes, it is important that there be a sound justification for such combinations [4].

In this context, a rational and synergistic FDC of antidiabetic drugs may be considered as a prudent option. In addition to reducing pill burden and improving compliance, combination therapy with two drugs may help patients achieve their target HbA1c faster than monotherapy. Early intensive therapeutic control has proven benefits in clinical outcomes. Long-term studies, such as, for example, the UK Prospective Diabetes Study (UKPDS), have suggested that good glycemic memory leads to a significant reduction in any diabetes-related endpoint. The long-term follow-up of the UKPDS study showed a significant 24% reduction in microvascular disease and a 15% reduction in macrovascular complications, such as myocardial infarction, along with a 13% reduction in all-cause mortality [6]. Results from the long-term follow-up of Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, the Action in Diabetes and Vascular disease study, the PreterAx and DiamicroN-MR Controlled Evaluation (ADVANCE) study, and the Veterans Affairs Diabetes Trial (VADT) also suggested improvements in microvascular outcomes with early intensive glycemia control; however, the macrovascular and mortality outcomes were not consistently improved in these studies. Despite intensive glycemia control having proven clinical benefits for several outcomes, the residual risk of cardiovascular (CV) death has remained a significant unmet need in patients with T2DM. Since 2015, a number of glucagon-like peptide-1 receptor agonists (GLP1-RAs) and sodium-glucose co-transporter-2 inhibitors (SGLT2i) have demonstrated improved CV outcomes regardless of glycemia control; these agents now form an essential part of the armamentarium for appropriate cardiometabolic risk management in T2DM [7]. With this increased availability of therapeutic choices that may address various unmet priority needs, the question of 'rational combination(s)' in T2DM holds deeper and broader implications today. In the current setting of the COVID-19 pandemic, good glycemic control (along with control of other risk factors) has been shown to reduce morbidity and mortality in patients with T2DM [8].

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

UNMET NEEDS AND SCOPE

The four pressing unmet needs in the management of T2DM, within the scope of this paper, include:

1. A need for a combinatorial approach to address multiple pathophysiological mechanisms of hyperglycemia, thus effecting a robust glycemic control.
2. A need for additional treatments that provide both glycemic and non-glycemic benefits, especially since the control of diabetes comorbidities is less than optimal in most patients.
3. Reducing the occurrence of hypoglycemia or weight gain, as recurrent distressing side effects of traditional antidiabetic agents reduces the morale of not only the patient but also the treating physician.
4. An oral treatment option that not only meets all of the pressing needs but additionally improves the compliance of the patients in need.

A synergistic and rational FDC of a SGLT2i and a dipeptidyl peptidase-4 inhibitor (DPP4i), such as an empagliflozin (SGLT2i) and linagliptin (DPP4i) FDC, may address these unmet needs. These issues are elaborated in detail in the subsequent sections of this review.

AIM AND APPROACH IN DEVELOPING THE EXPERT OPINION PAPER

The aim of this expert opinion paper is to evolve an evidence-based clinical guidance for the appropriate consideration and use of combination therapy with SGLT2i + DPP4i, for patients with T2DM in the routine clinical practice setting, in India. With this aim ten experts in the field of diabetes across India came together and developed a pragmatic approach for the optimum use of SGLT2i + DPP4i in FDCs for patients with T2DM through extensive literature reviews and one round of deliberate discussion on available evidence for this class of agents.

PATHOPHYSIOLOGICAL APPROACH TO DIABETES MANAGEMENT

The "ominous octet" is the pathophysiological core of the mechanism of diabetes. As depicted in Fig. 1, various classes of agents act differently on different components of the "ominous octet".

A "pathophysiological approach" using initial combination therapy with agents known to address the established defects in T2DM seems more rational. It is preferable to use combination therapies having complementary mechanisms of action that target different pathways addressing the multiple pathophysiologic abnormalities of T2DM [10–12]. The complementary beneficial effect of this combination is depicted in Fig. 2.

The presence of multiple pathophysiologic abnormalities dictate several important implications in the management of patients with T2DM [10, 14, 15].

- Multiple drugs in combination may be required to manage the various pathophysiological abnormalities.
- Drugs that target the known pathophysiological processes and help to counteract or reverse them should be considered.
- Treatment should not be based on mere reduction of HbA1c, or just controlling fasting/postprandial blood glucose.
- Intensive treatment should be started early to prevent or halt the progression of β-cell failure.
- Few of the various pathophysiological abnormalities can be targeted with multiple anti-hyperglycemic agents, while few of the agents can target multiple pathways as well.

Time-in-range (TIR) is the percentage of time in a 24-h period when glucose levels remain between 70–180 mg/dL. Evidence suggests that TIR complements HbA1c as a parameter of glycemic control, with higher TIR associated with better clinical outcomes [16]. Studies with SGLT2i agents as well as DPP4i agents suggest that these drugs have beneficial effects on TIR. The SGLT2i anti-hyperglycemic agents influence fasting as well as the postprandial components of glycaemia, and DPP4i anti-hyperglycemicagents have more prominent effects on postprandial hyperglycemia; both of these classes of medications are associated with lower risks for hypoglycemia. Glycemic variability (GV) has been an emerging target for preventing complications related to T2DM. Systematic reviews and meta-analyses of 16 randomized controlled trials (RCTs) with SGLT2i and seven RCTs of DPP4i have demonstrated that these agents reduce glycemic variability in patients with T2DM [17, 18]. The Time in Range recommendations for South Asia suggests frequency for repeating TIR evaluation, which may be minimal for therapies such as SGLT2i and DPP4i with minimal glycaemic variability again reducing the cost and complications [19].

- In addition, several RCTs have shown that the DPP4i are also associated with lower insulin dose requirements [17–19].

Thus, the combined use of SGLT2i/DPP4i agents (either separately or as a FDC) not only provides medications that complement each other well, but also targets at least six of the eight components in the "ominous octet" [20]. Hence after metformin initiation or even prior to metformin initiation in suitable patients

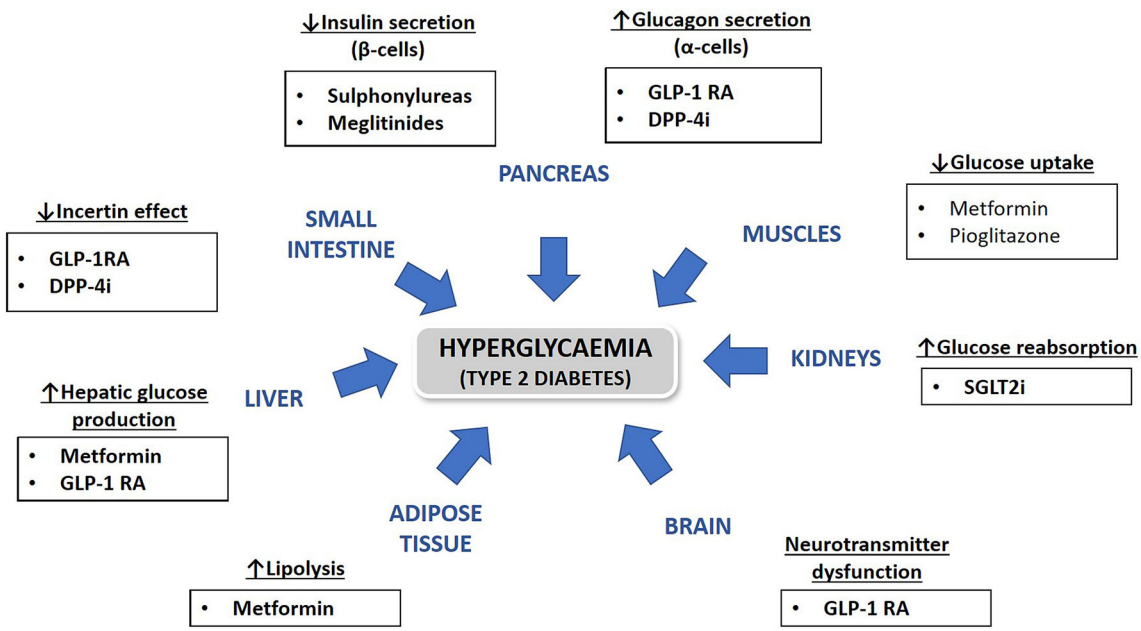


Fig. 1 The "ominous octet" of type 2 diabetes mellitus and the target sites for glucose-lowering therapies. *DDP-4i* Dipeptidyl peptidase-4 inhibitor, *GLP-1RA* glucagon-like peptide-1 receptor agonist, *SGLT2i* sodium-glucose co-transporter-2 inhibitors. (Adapted from Chatterjee and Davies [9])

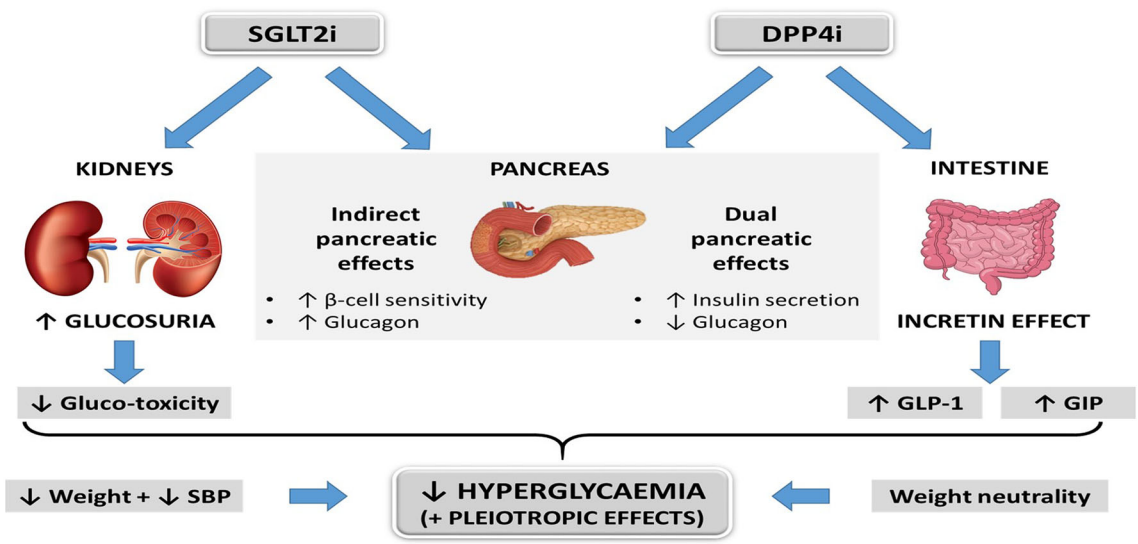


Fig. 2 Illustration of the complementary glucose-lowering activities of DPP4i and SGLT2i in type 2 diabetes mellitus. *GIP* Glucose-dependent insulinotropic polypeptide, *SBP* systolic blood pressure. (Adapted from Scheen [13])

(metformin contraindicated or intolerant), or in patients with high HbA1c who fail on metformin, this combination may give excellent "treat-to-target" benefit to the patients, thus facilitating the "treat early and treat right" approach.

AVAILABLE PRE-CLINICAL AND CLINICAL EVIDENCE WITH SGLT2I AND DPP4I AGENTS

Pre-Clinical Evidence

A study on isolated human islet cells showed that linagliptin restored β-cell function and turnover, which was impaired when islets were exposed to elevated glucose [21]. This demonstrated a direct GLP1-mediated protective effect of linagliptin on β-cell function and survival. Linagliptin was shown to prevent β-cell apoptosis in metabolic and inflammatory stress conditions through the anti-inflammatory interleukin receptor antagonist (IL-1RA) [21].

A study on Wistar rats showed that linagliptin reduced infarct size in an acute model of myocardial infarction by causing an increase in stromal cell-derived factor 1α (SDF-1α) and the respective receptor in infarcted tissue, providing evidence for stem cell recruitment [22]. Linagliptin also improved diastolic function and significantly reduced markers of fibrosis of the heart in a setting of uremic cardiomyopathy [23].

Overall, pre-clinical research on linagliptin has yielded several interesting findings over and above glycemic efficacy, safety, and beta cell preservation. Improved wound healing, reduced inflammation, reduced hepatic fat content, decreased infarct size following myocardial infarction or intracranial stroke, improved vascular function with decreased oxidative stress, improved endothelial dysfunction, and lowering of albuminuria have also been observed in pre-clinical studies [24].

Mechanistic studies suggest that the potential direct cardiovascular benefits of SGLT2i include augmentation of signal transducer and activator of transcription 3 (STAT3), inhibition of sodium hydrogen exchange (sodium-hydrogen antiporter 1 [NHE-1]), improved mitochondrial metabolism, modulation of natriuretic peptides, improved vascular stiffness and autonomic tone, reduction of inflammation, and improved cardiac energetics. There are a few intermediate effects by which SGLT2i may exert cardiovascular benefits that extend beyond glycemic control [25–28].

Clinical Evidence in Asian Indian Patients

The Indian "thin fat" phenotype is more prone to the development of T2DM and is associated with several unique features, such as early age of T2DM onset, early decline in beta cell mass, higher insulin resistance, higher carbohydrate intake and physical inactivity leading to central obesity, unique dyslipidemia pattern, increased CV disease risk, higher association with nonalcoholic fatty liver disease, among others [29–31]. DPP4i have been shown to exert higher efficacy in Asian patients, probably due to increased DPP4 enzyme activity in Asian Indian patients with T2DM [32]. A study comparing the pharmacodynamics, efficacy, and safety of linagliptin among Japanese, Asian, and White patients with T2DM showed that a better reduction in HbA1c was achieved in the Asian patients as compared to the Caucasians, without any added safety issue [33]. In another study, linagliptin effectively reduced hyperglycemia in Asian patients with uncontrolled T2DM, irrespective of age, body mass index, renal function, or ethnic subgroup, and was well tolerated [34].

A recent meta-analysis showed that SGLT2i and, to a lesser extent, DPP4i are associated with greater glucose-lowering efficacy in patients from Asian ethnicity [35]. Subgroup analysis from the EMPA-REG OUTCOME study demonstrated consistent risk reductions for CV outcomes, mortality, and renal outcomes with empagliflozin in Asian patients with T2DM and established CV disease [36–40].

SGLT2i + DPP4i FDCs: Clinical Evidence Overview

Three SGLT2i + DPP4i FDCs are currently by the US Food and Drug Administration (USFDA), but only two of these are approved for use and commercially available in India. These FDCs have been approved as an adjunct to diet and exercise to improve glycemic control in adults

with T2DM when treatment with both an SGLT2i and DPP4i is appropriate (Table 1).

Efficacy of SGLT2i + DPP4i FDCs

Evidence from numerous clinical trials suggest that SGLT2i + DPP4i FDCs are effective and safe in controlling glycemic parameters in patients with T2DM. The efficacy of the available FDCs were evaluated in long-term studies in patients with T2DM on metformin monotherapy and treated with diet and exercise. The efficacy of the empagliflozin + linagliptin FDC was also evaluated in drug-naïve patients [46–50]

Certain anecdotal studies have been conducted in Japan on the effect of sequential therapy with a combination of canagliflozin and teneligliptin in patients with T2DM [46, 47]. However, since the FDC has not been approved in major markets like the USA, Europe, and India, the evidence from these studies is beyond the scope of this review.

Initial Combination in Drug-Naïve Patients with T2DM The reduction of HbA1c in drug-naïve patients receiving different SGLT2i + DPP4i FDCs are compared in Table 2.

As an Add-on to Metformin Monotherapy The reduction in HbA1c in T2DM patients on metformin monotherapy with SGLT2i + DPP4i FDCs is compared in Table 3.

Studies have shown a consistent reduction in body weight and blood pressure in the SGLT2i monotherapy arm and the FDC arm [49–56].

Safety Evidence

The overall safety profile of the FDCs was similar to those of the individual components. There were no significant differences in

Table 1 Global and Indian approval status of sodium-glucose co-transporter-2 inhibitor + dipeptidyl peptidase-4 inhibitor fixed-dose combinations

Fixed-dose combination	USFDA approval	DCGI (CDSCO) approval	Commercial availability in India
Empagliflozin + linagliptin	Yes (2015) [41]	Yes (2017) [44]	Yes (2018)
Dapagliflozin + saxagliptin	Yes (2017) [42]	Yes (2019) [44]	Yes (2020)
Ertugliflozin + sitagliptin	Yes (2017) [43]	No	No
Remogliflozin + vildagliptin	No	Yes (2020) [45]	Yes (2020)
Canagliflozin + teneligliptin	No	No	No

CDSCO Central Drugs Standard Control Organization, *DCGI* Drug Controller General of India, *FDC* fixed-dose combination, *USFDA* US Food and Drug Administration

Table 2 Reductions in glycated hemoglobin from baseline in drug-naïve patients with type 2 diabetes mellitus

HbA1c reduction	Empagliflozin + linagliptin FDC [48]		Dapagliflozin + saxagliptin FDC	Ertugliflozin + sitagliptin FDC [49]	
	10 mg/5 mg	25 mg/5 mg	10 mg/5 mg	5 mg/100 mg	15 mg/100 mg
HbA1c reduction (%)	− 1.2% (baseline 8%)	− 1.1% (baseline 8%)	No evidence	− 1.4% (baseline 8.3%)	− 1.3% (baseline 8.3%)
HbA1c reduction (%)	− 1.9% (baseline 9.3%)	− 1.9% (baseline 9.2%)	No evidence	− 1.8% (baseline 9.6%)	− 2.2% (baseline 9.6%)

No head-to-head comparison data are available
HbA1c Glycated hemoglobin

Table 3 HbA1c response in patients with type 2 diabetes mellitus on metformin monotherapy

HbA1c reduction	Empagliflozin + linagliptin FDC [50]		Dapagliflozin + saxagliptin FDC [53]	Ertugliflozin + sitagliptin FDC [55]	
	10 mg/ 5 mg	25 mg/ 5 mg	10 mg/5 mg	5 mg/ 100 mg	15 mg/ 100 mg
HbA1c reduction (%) (mean baseline < 8.5%)	− 1.1%	− 1.2%	NA	NA	NA
HbA1c reduction (%) (mean baseline > 8.5%)	− 1.6%	− 1.8%	− 1.5%	− 1.5%	− 1.5%

No head-to-head comparison data are available
NA Data not available

hypoglycemia events, urinary tract infections, or events related to hypovolemia and ketoacidosis. Interestingly, slightly lower rates of genitourinary tract infections (GTIs) were reported with the FDC as compared to SGLT2i monotherapy. Some of the probable reasons for such moderation of GTIs with the FDC, beyond improved glycemic control, may be the interaction of DPP4 and SGLT2 proteins at the renal tubular cell-membrane level, or the inhibition of the DPP4 enzyme present in certain pathogenic microbes that may render them inactive (Fig. 3) [52].

Safety with Simultaneous SGLT2i + DPP4i FDC as Compared to Sequential Addition of SGLT2i to DPP4i Therapy

A systematic review and meta-analysis of seven RCTs [57] 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 an UTI was found to be slightly higher in group receiving sequential combination therapy (relative risk [RR] 0.96,

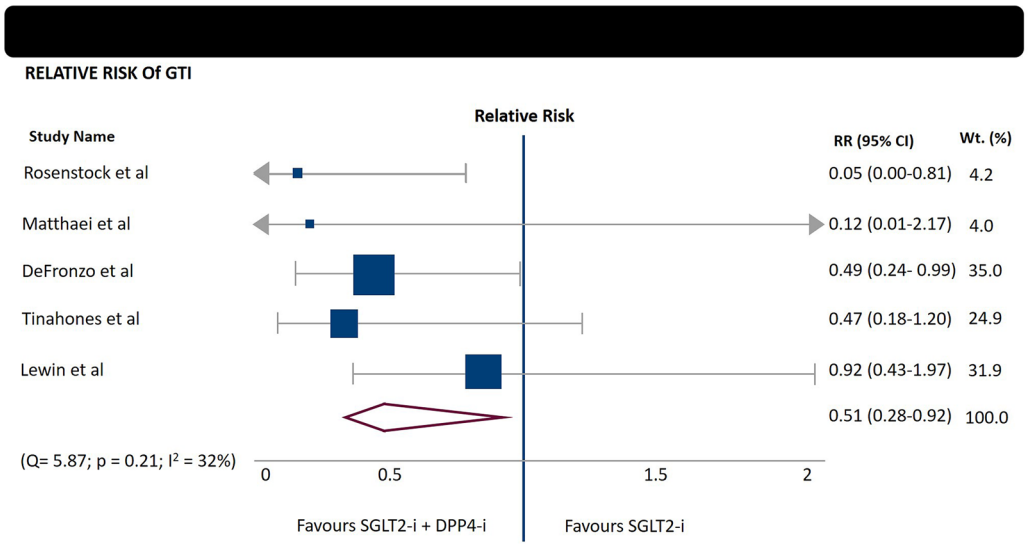


Fig. 3 Incidence of genitourinary tract infections favors the use of the SGLT2i + DPP4i fixed-drug combination. *CI* Confidence interval, *GTI* genitourinary tract infection, *RR* relative risk. (Adapted from Fadini et al. [52])

Table 4 Cardiovascular and renal outcomes with SGLT2i in cardiovascular outcome trials

Clinical outcomes	Cardiovascular outcome trials[a]			
	EMPA-REG OUTCOME [58] (empagliflozin)	CANVAS Program [59] (canagliflozin)	DECLARE-TIMI 58 [60] (dapagliflozin)	VERTIS CV [61] (ertugliflozin)
HHF	HR 0.65[b](95% CI 0.50, 0.85)	HR 0.67[b](95% CI 0.52, 0.87)	HR 0.73[b](95% CI 0.61, 0.88)	HR 0.70[b](95% CI 0.54, 0.90)
CV death	HR 0.62 (95% CI 0.49, 0.77)	HR 0.87 (95% CI 0.72, 1.06)	HR 0.98 (95% CI 0.82, 1.17)	HR 0.92 (95% CI 0.77, 1.11)
3P-MACE	HR 0.86[c](95% CI 0.74, 0.99)	HR 0.86[c](95% CI 0.75, 0.97)	HR 0.93[c] (95% CI 0.84, 1.03)	HR 0.97[c] (95% CI 0.85, 1.11)
Renal outcome	HR 0.54[b](95% CI 0.40, 0.75)	HR 0.59[b](95% CI 0.44, 0.79)	HR 0.55**b**(95% CI 0.41, 0.75)	HR 0.81[b] (95% CI 0.63, 1.04)

Cells with underlining represent significant observations

CI Confidence interval, *CV* cardiovascular, *HHF* hospitalization for heart failure, *HR* hazard ratio, *3P-MACE* 3-point major adverse cardiovascular event

[a]EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; CANVAS, Canagliflozin Cardiovascular Assessment Study; DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events—Thrombolysis in Myocardial Infarction 58; VERTIS CV, Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial

[b]Exploratory outcome

[c]Testing for superiority for 3P-MACE was the primary endpoint

95% confidence interval [CI] 0.52–1.78) than in simultaneous combination group (RR 0.67, 95% CI 0.28–1.60) [57]. The risk of a GTI was also higher in the sequential combination group (RR 5.57, 95% CI 2.33–13.33) than in simultaneous group (RR 1.35, 95% CI 0.55–3.34) [57].

Overall, the results of this analysis suggest a possible lower risk of GTIs and nominal reduction in incidence of UTIs with simultaneous combination as opposed to sequential combination of SGLT-2i and DPP-4i.

Summary of CV and Renal Outcomes with SGLT2i and DPP4i Agents

SGLT2: Inhibitor Cardiovascular Outcome Trials

Cardiovascular outcome trials (CVOTs) have consistently shown that treatment with SGLT2i reduces hospitalization for heart failure (HHF) and secondary renal outcomes in terms of incident or worsening nephropathy in patients with T2DM and CV disease. To date no CVOT has been carried out on remogliflozin. Some differences in 3-point major adverse cardiac event (3P-MACE) and CV death endpoints among patients on SGLT2i have been shown in the CVOTs [58–62], as shown in Table 4.

In patients with T2DM and established CV disease, empagliflozin and canagliflozin have been shown to reduce the of MACE events, although only empagliflozin has demonstrated an ability to reduce the risk of CV death in this population. All SGLT2i CVOTs carried out to date have demonstrated a consistent risk reduction for heart failure-related hospitalizations in patients with established CV disease or high CV risk. The Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE) study demonstrated significant improvement in renal outcomes with canagliflozin in patients with T2DM and advanced macro-albuminuric kidney disease, as compared to placebo [63].

DPP-4i CVOTs

With respect to the primary endpoint (3P-MACE), the CV safety profile of saxagliptin, sitagliptin and linagliptin was established in the respective CVOTs [64–66]. However, there was a heterogeneity seen in the risk for HHF. Saxagliptin showed an increased risk for HHF, whereas both sitagliptin and linagliptin had no increase in the risk of HHF in the respective CVOTs. Vildagliptin does not have a dedicated CVOT, however, in the VIVIDD study, an increase in end systolic and diastolic volumes was noted [67]. Teneligliptin, also does not have a CVOT and may prolong the QT interval at higher doses and needs to be administered with caution [68].

The cardiovascular and renal outcomes of DPP4i have been summarized in Table 5.

Hepatic Safety with SGLT2i and DPP4i

SGLT2i

Meta-analysis and review reports from large phase II–III trials showed that SGLT-2i do not cause hepatotoxicity [65, 66, 69, 70]. No dose adjustment is required in mild to moderate liver dysfunction.

The E-LIFT trial involving patients with T2DM and NAFLD, demonstrated that empagliflozin, in addition to standard diabetes management, causes a significant reduction in liver fat content (as measured by magnetic resonance imaging–estimated proton density fat fraction) and alanine aminotransferase level, and a non-significant reduction in gamma-glutamyl transferase and aspartate aminotransferase levels [71–73].

DPP4i

It is recommended that with the exception of vildagliptin, other DPP-4 inhibitors can be used without dose modification in patients with Child–Pugh Class A liver disease, while their use requires caution in those with Class B disease and is not preferred in patients with severe liver dysfunction (Class C) [74–76].

EXPERT OPINION

The SGLT2i +DPP4i FDCs have been available in India since their introduction in 2018. These are unique non-metformin-based FDCs, which is why there is no clear guidance on their place in T2DM management. The scope of this expert

Table 5 Cardiovascular and renal outcomes with DPP-4 inhibitors in cardiovascular outcome trials

Clinical outcomes	Cardiovascular outcome trials[a]		
	SAVOR TIMI 53 [64] (saxagliptin)	**TECOS [65] (sitagliptin)**	**CARMELINA [66] (linagliptin)**
HHF	HR 1.27[c] (95% CI 1.07, 1.51)	HR 1.00[c] (95% CI 0.83, 1.20)	HR 0.90[c] (95% CI 0.74, 1.08)
CV death	HR 1.03 (95% CI 0.87, 1.22)	HR 1.03 (95% CI 0.89, 1.19)	HR 0.96 (95% CI 0.81, 1.14)
3P-MACE	HR 1.00[d] (95% CI 0.89, 1.12)	HR 0.99[d] (95% CI 0.89, 1.10)	HR 1.02[d] (95% CI 0.89, 1.17)
Renal outcomes[b]	Limited evidence	Limited evidence	HR 1.04[c] (95% CI 0.89, 1.22)

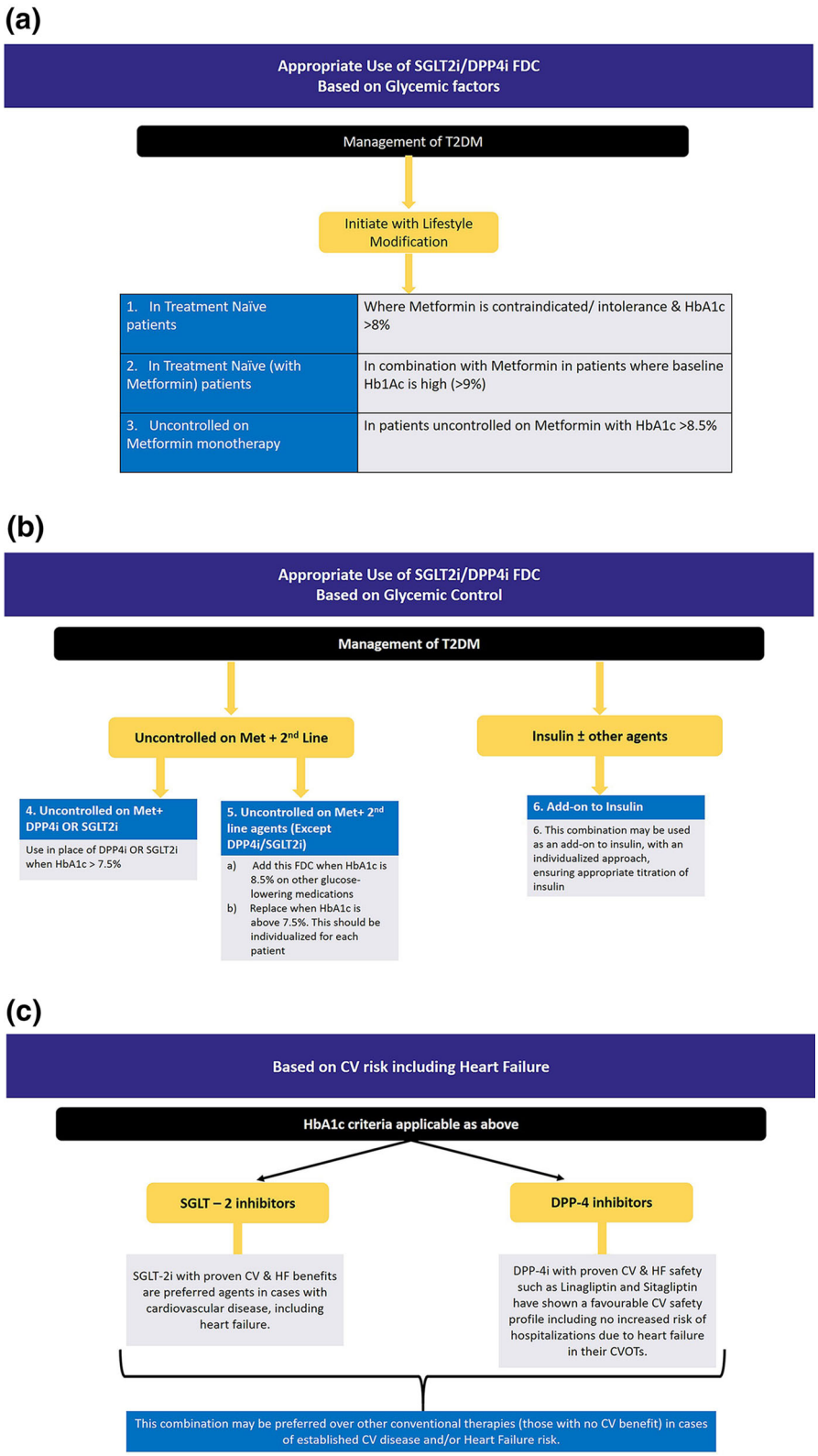
Cells with underlining represent significant observations

[a]SAVOR TIMI 53, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus–Thrombolysis in Myocardial Infarction; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin; CARMELINA Cardiovascular and Renal Microvascular Outcome Study With Linagliptin

[b]Composite of end-stage kidney disease, renal death, or ≥ 40% decrease in estimated glomerular filtration rate

[c]Exploratory outcome

[d]Testing for superiority for 3P-MACE was the primary endpoint (4P-MACE for sitagliptin)


(a)
Appropriate Use of SGLT2i/DPP4i FDC
Based on Glycemic factors
Management of T2DM
Initiate with Lifestyle Modification
1. In Treatment Naïve patients
Where Metformin is contraindicated/ intolerance & HbA1c >8%
2. In Treatment Naïve (with Metformin) patients
In combination with Metformin in patients where baseline Hb1Ac is high (>9%)
3. Uncontrolled on Metformin monotherapy
In patients uncontrolled on Metformin with HbA1c >8.5%
(b)
Appropriate Use of SGLT2i/DPP4i FDC
Based on Glycemic Control
Management of T2DM
Uncontrolled on Met + 2nd Line
Insulin ± other agents
4. Uncontrolled on Met+ DPP4i OR SGLT2i
Use in place of DPP4i OR SGLT2i when HbA1c > 7.5%
5. Uncontrolled on Met+ 2nd line agents (Except DPP4i/SGLT2i)
a) Add this FDC when HbA1c is 8.5% on other glucose-lowering medications
b) Replace when HbA1c is above 7.5%. This should be individualized for each patient
6. Add-on to Insulin
6. This combination may be used as an add-on to insulin, with an individualized approach, ensuring appropriate titration of insulin
(c)
Based on CV risk including Heart Failure
HbA1c criteria applicable as above
SGLT – 2 inhibitors
DPP-4 inhibitors
SGLT-2i with proven CV & HF benefits are preferred agents in cases with cardiovascular disease, including heart failure.
DPP-4i with proven CV & HF safety such as Linagliptin and Sitagliptin have shown a favourable CV safety profile including no increased risk of hospitalizations due to heart failure in their CVOTs.
This combination may be preferred over other conventional therapies (those with no CV benefit) in cases of established CV disease and/or Heart Failure risk.

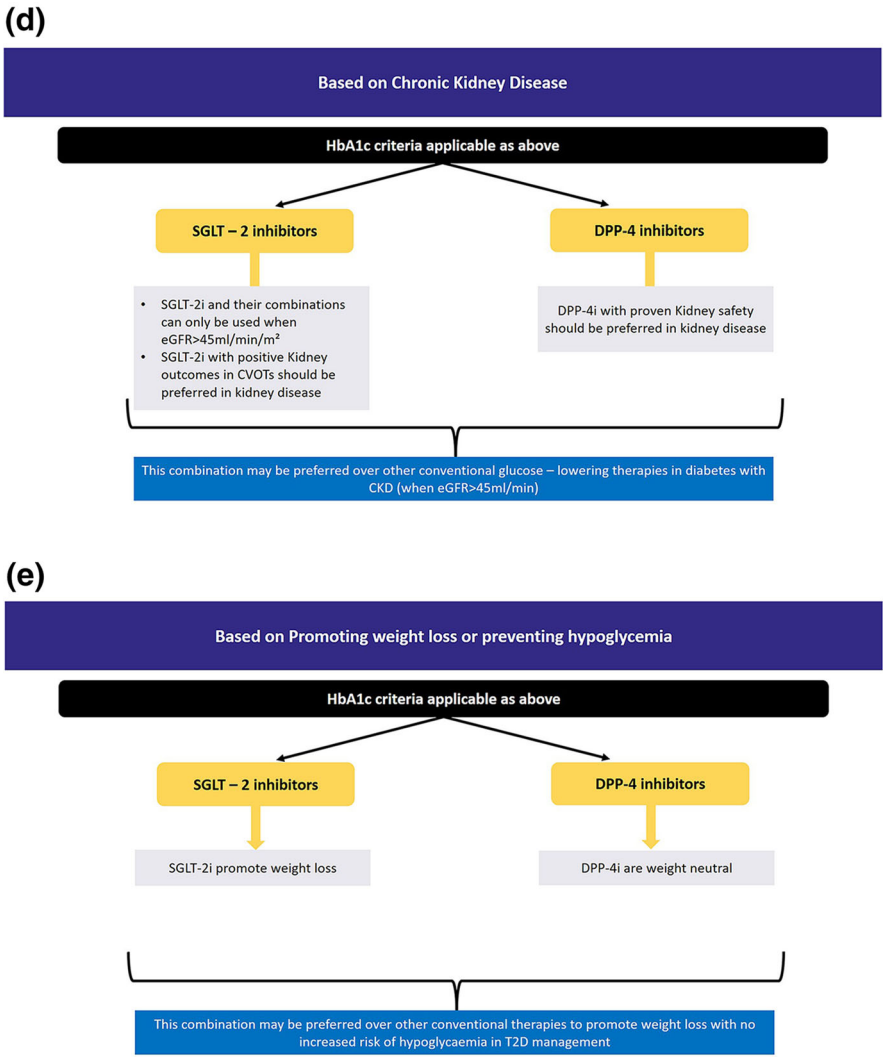


Fig. 4 **a** Guidance for initiation of SGLT2-i + DPP4-i FDC based on glycemic factors. **b** Guidance for appropriate use of SGLT2-i + DPP4-i FDC based on glycaemic control. **c** Guidance for initiation of SGLT2-i + DPP4-i FDC based on CV risk. **d** Guidance for initiation of SGLT2-i + DPP4-i FDC based on CKD risk. **e** Guidance for initiation of SGLT2-i + DPP4-i FDC based on promoting weight loss or preventing hypoglycemia. *CKD* Chronic kidney disease, *CV* cardiovascular, *CVOT* cardiovascular outcome trial, *FDC* fixed-dose combination, *HbA1c* glycated hemoglobin, *HF* heart failure, *Met* metformin, *T2DM* type 2 diabetes mellitus

opinion is to aid in clinical decision-making for the appropriate use of the SGLT-2i and DPP-4i FDCs in T2DM management.

Metformin remains the first-line pharmacological approach to the treatment of T2DM, along with lifestyle modification, with the exception of cases where metformin is not tolerated or contraindicated. Patient preference and clinical characteristics should influence the choice of a second-line glucose-lowering medication. Since the absolute effectiveness of most oral medications rarely exceeds a 1% reduction in HbA1c, the initial combination therapy with a SGLT-2i + DPP-4i FDC may be considered in patients presenting with high HbA1c levels (1.5% above individualized target). In addition, the presence of comorbidities and established CV and kidney safety and/or benefits of

antidiabetic agents may mandate their choice over other conventional options. With the evolving evidence and guidelines across the world, we should now choose second-line agents such as SGLT2i and GLP1-RAs with proven CV benefits in patients with high CV risk followed by agents with proven CV safety if additional glycemic control is required. The combination of an SGLT2i and DPP4i may, therefore, become more relevant in patients with of high CV risk and/or heart failure risk who have HbA1c > 1.5% above the individualized target.

Medications with good glycemic efficacy and a low risk of hypoglycemia and weight loss help to intensify the treatment without introducing common adverse events, such as hypoglycemia and weight gain. These advantages may help overcome clinical inertia for treatment intensification. Targeting multiple pathophysiological pathways for T2DM with DPP4i + SGLT2i combination therapy is a clear benefit which also supports the use of this combination early in T2DM management.

A SGLT2i + DPP4i FDC is a suitable option for Indian T2D patients, for the following reasons:

- Safer, rapid, and sustained glycemic control
- Improves both insulin resistance and beta cell function
- Helps reduce body weight and blood pressure (extraglycemic benefits)
- Reduces pill burden (adherence and compliance improves)
- Overall cost effective

The following decision-making algorithms (Fig. 4a–e) may help guide the use of a SGLT2i + DPP4i combination in clinical practice. Decisions on appropriate use may be made taking into consideration the glycemic parameters together with the status of CV and renal comorbidity and clinically relevant considerations, such as risk of hypoglycemia and weight gain. In treatment-naïve patients with T2DM for whom metformin is contraindicated or who are metformin intolerant and HbA1c is > 8% (as per the inclusion criteria of SGLT2i + DPP4i FDC RCTs), and in patients uncontrolled on metformin with HbA1c of > 8.5% (as per the inclusion criteria of SGLT2i + DPP4i FDC RCTs), we recommend initiating combination therapy with a SGLT2i + DPP4i FDC along with lifestyle modification (Fig. 4a).

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