SGLT2I + DPP4I combination: A complementary approach to diabetes management

ABSTRACT

Diabetes mellitus is a consequence of multiple underlying pathophysiologies. India ranks second in the world with 77 million people suffering from Type 2 diabetes mellitus (T2DM). The unmet need of improving/achieving the glycated hemoglobin (HbA1c) goal along with improve patient compliance is associated with need of developing diverse therapeutic options, for the individualization of care. Diabetes being multifaceted disorder, combination therapy becomes key option either at initiation or later part of the treatment. A "pathophysiological approach" using initial combination therapy with agents known to address the established defects in T2DM seems more rational. A synergistic and rational fixed dose combination of a Sodium-glucose co-transporter 2 inhibitors (SGLT2i) and a dipeptidyl peptidase-4 inhibitor (DPP4i), may address these unmet needs. SGLT2i reduce hyperglycemia by increasing urinary glucose excretion independent of insulin secretion or action. DPP4i, which inhibit the breakdown of active incretin hormones, improve glucose homeostasis by increasing insulin secretion and decreasing glucagon secretion in a glucose-dependent manner. Moreover, the combination is safe and effective with reduced side-effects such as genito-urinary tract infection. DPP-4i and SGLT2i fulfill provides complementary mechanisms of action that can be combined to achieve better glucose control over a wide spectrum of patients with T2DM, with a low risk of adverse events and the potential of cardiovascular protection. The current review provides insights on this combination along with clinical evidences for safety and efficacy and guidance on the use of the combination.

Key words: Diabetes mellitus, SGLT2i, DPP4i, Combination therapy, Genito-urinary tract infection, Cardiovascular protection

1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a complex multifaceted disorder associated with different pathophysiological defects (Figure 1) [1].

India has the second highest number of people (77 million) with type T2DM in the world [2]. To date, the findings from Indian Council of Medical

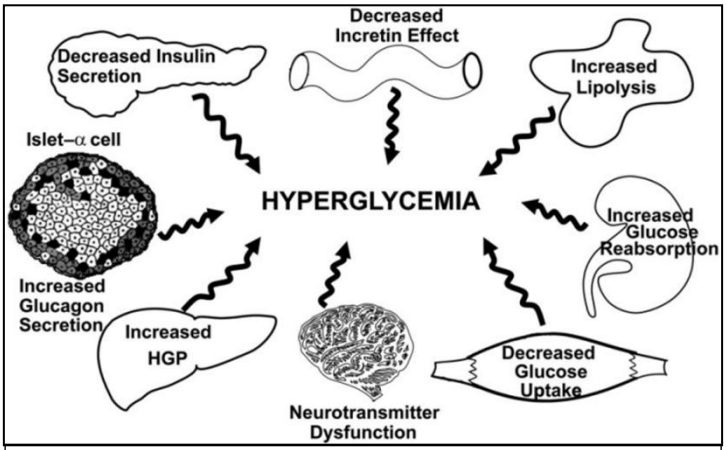


Figure 1: Ominous octet of diabetes [1]

Research-India Diabetes (ICMR-INDIAB) study phase I 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 [2,3,4]. An alarming trend associated with shift in onset of diabetes to people in younger age groups. Clinical study has reported that 69% patients do not achieve the target level of HbA1c goal. [2,3,4].

As T2DM is associated with multiple pathological defects, monotherapies generally fails to achieve or maintain the targeted HBA1c goals, and diabetes progresses in patients increasing the risk of microvascular and macrovascular complications [1]. The unmet need of improving/achieving the glycated hemoglobin (HbA_{1c}) goal is strongly associated with the requirement for diverse therapeutic options, namely, for the individualization of care (personalized medicine) [2]. Thus, combination therapy becomes key option either at initiation or later part of the treatment [1]. In addition to reducing pill burden and improving compliance, combination therapy with two drugs may help patients achieve their target HbA_{1c} faster than monotherapy. Early intensive therapeutic control has proven benefits in clinical outcomes [2].

2. UNMET NEED

The pressing unmet needs in controlling of T2DM, includes a need for [2]:

- Combination approach to address various underlying pathophysiological defects, thus making it easier for reaching the target HBA1c.
- Additional treatments providing glycemic and non-glycemic profits, as control comorbidities associated with diabetes is less than optimal in most cases.
- Reducing the occurrence of recurrent distressing side effects (hypoglycemia or weight gain) of traditional antidiabetic agents, which affects the patient compliance and the treating physician.
- A novel oral therapy that meets all of the pressing needs and also improves the patient compliance.

3. “PATHOPHYSIOLOGICAL APPROACH” FOR COMBINATION THERAPY

A “pathophysiological approach” using initial combination therapy with complimentary modes of action addressing various underlying pathophysiology associated with diabetes may prove to be beneficial and may improve patient compliance [2].

The presence of multiple pathophysiologic abnormalities dictates several important implications in the management of patients with T2DM [2].

- To manage the various pathophysiological abnormalities multiple drugs in combination may be required.
- Drugs that specifically target the known pathophysiological processes and help to counteract or reverse them should be considered.
- Treatment should not be focused on HbA1c reduction, or fasting/postprandial blood glucose control.
- Intensive treatment should be an initial approach to halt the progression of β-cell failure.
- Few of the various pathophysiological abnormalities can be targeted with combination treatment, while few of the agents can target multiple pathways.

A synergistic and rational fixed dose combination (FDC) of a SGLT2i and a dipeptidyl peptidase-4 inhibitor (DPP4i), such as a Dapagliflozin (SGLT2i) and vildagliptin (DPP4i) FDC, may address these unmet needs. These issues are elaborated in detail in the subsequent sections of this review [1].

4. DPP4 INHIBITORS

This new class of anti-diabetic agents also known as gliptins has revolutionized diabetes treatment. Although various DPP-4 inhibitors have different pharmacokinetic and pharmacodynamic profiles, they are remarkably similar with regards anti-hyperglycemic properties with a very safe adverse effect profile (weight neutral without causing hypoglycemia) [5]. Available and marketed gliptins are Sitagliptin, Vidagliptin, Saxagliptin, Linagliptin, Alogliptin, Dutogliptin, Gemiglaptin, and teneligliptin.

Incretins (glucagon like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP)) are gut hormones released from intestinal cells responsible for augmenting insulin response. This augmented insulin response has been termed the 'incretin effect'. However, this effect is lasts for some minutes as GIP and GLP are degraded by DPP-4 enzyme [6].

Gliptins like Vildagliptin, selectively inhibits DPP-4 and prevents the degradation of incretin hormones GLP-1 and GIP (incretin enhancer). Vildagliptin (available in the EU and other countries) is a potent reversible and competitive inhibitor of DPP-4, an effect that is not species specific. Vildagliptin has two phases of binding: an initial rapid phase and subsequent slow phase of binding, providing both prompt and persistent DPP-4 inhibition [6]. Thus, gliptins significantly reduces post-prandial hyperglycemia and controls fasting plasma glucose levels by inhibiting hepatic glucose production [5,6].

In clinical trials of T2DM patients, DPP-4 inhibition by vildagliptin is demonstrated within 45 min, and reaching a maximum at 24 h. In T2DM patients, 50 mg of vildagliptin is associated with 50% DPP-4 inhibition within 0.5 h; at 12 h, approximately 80% DPP-4 inhibition is still evident, allowing once- or twice-daily administration. Durable, dose-dependent DPP-4 inhibition by vildagliptin has been demonstrated by documentation of up to 90% inhibition after 28 days continuous treatment [6].

5. SGLT2 INHIBITORS

SGLT2 inhibitors lower glycated hemoglobin, fasting and postprandial plasma glucose levels, body weight, and blood pressure. It also reduces the risk of a range of cardiovascular and renal outcomes without increasing hypoglycemic risk. This novel discovery has foreshowed a paradigm shift in the management of T2DM [7]. SGLT2i are prescribed as monotherapy or in combination with other anti-diabetic agents. Common SGLT2i used and marketed includes canagliflozin, dapagliflozin, empagliflozin, remogliflozin, ertugliflozin, etc. [8].

The SGLT2 inhibitor ameliorates hyperglycemia by inhibiting SGLT2 (a high-capacity, low-affinity) transporter located on early segment of the proximal convoluted renal tubule. Under normal circumstances, SGLT2 is responsible for reabsorption of 90% of the filtered glucose at the glomerulus, with the remainder being transported back into the systemic circulation by SGLT1, located at the distal segment of the proximal convoluted tubule. Inhibition of SGLT2 receptors results in glycosuria and lowers blood glucose because SGLT1 cannot reabsorb all of the filtered glucose. However, because of physiological changes that occur in response to SGLT2 inhibitor administration, these agents only reduce renal glucose reabsorptive capacity by up to 50% [7].

Dapagliflozin, highly potent (inhibitory constant 0.55 nmol/L) and reversible SGLT2 inhibitor, is > 1400 times more selective for SGLT2 than SGLT1. Dapagliflozin increased glucose excretion in the urine and improves both, both fasting (FPG) and post-prandial plasma glucose (PPG) levels in T2DM patients. After the first dose of dapagliflozin urinary glucose excretion (glucuresis) was continuous during the 24 h dosing interval and was maintained throughout therapy course. Dapagliflozin-induced glucuresis is associated with caloric loss and a modest reduction in bodyweight in T2DM patients. Dapagliflozin is also mild osmotic diuresis and transient natriuresis in T2DM patients. The loss in bodyweight with SGLT2 inhibitors is less than that calculated from calorie loss due to glucuresis, which may be because of compensatory mechanisms such as increased energy intake. A modest

decrease in blood pressure (BP) was also reported with dapagliflozin, which may be due to reduction in circulating volume as a consequence of the diuretic/natriuretic properties of the drug [9]. Dapagliflozin lowers blood glucose levels independently of insulin action. It provides effective glycemic, weight, and BP control. It also reduces rate of CV death or HHF, does not adversely affect MACE and possibly reduces progression of renal disease. Dapagliflozin offers low risk of hypoglycaemia, while genital infections and diabetic kidney acidosis (DKA) are more commonly reported.

6. COMBINING DPP4I AND SGLT2I

Newer anti-diabetic agents such as SGLT2i and DPP4i are very effective with lower incidence of common adverse effects of other oral hypoglycemic agents (weight gain and hypoglycemia). SGLT2i increases urinary glucose excretion independent of insulin secretion or action resulting in reduced blood glucose levels. DPP4i inhibits the breakdown of active incretin hormones, improves glucose homeostasis by increasing insulin secretion, and reducing glucagon secretion in a glucose-dependent manner. In this regard, the combination of these two drugs could be effective and safe for the treatment of hyperglycemia in patients with sub-optimally controlled T2DM [10].

6.1. Rationale for combination

SGLT2 inhibitors could increase endogenous (Hepatic) glucose production (EGP/HGP) and plasma glucagon concentrations. DPP-4 inhibitors exert their hypoglycemic effects by preventing the degradation of endogenously released incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide to enhance postprandial insulin secretion and suppress glucagon secretion, likewise, decrease endogenous (hepatic) glucose. In addition, a study indicated that DPP-4 inhibitors could improve endothelial function and reduce renal and vascular oxidative stress, which was independent of albuminuria-lowering or improvement in glucose control, in patients with T2DM and chronic kidney disease [11].

SGLT2i induced glycosuria results in ~13% increase in calorie intake as an anabolic response, attributed to increase in appetite and carbohydrate craving. A few pre-clinical studies have also found DPP4i to increase satiety and cause loss of appetite. As both the drug classes have shown lowering in urinary albumin excretion rates, this combination has been speculated to possess the potential of renal protection as well [12].

Moreover, DPP4i may moderate SGLT2i-associated genito-urinary tract infection risk. The DPP4i/SGLT2i combination reduced glycaemia and glycosuria more than SGLT2i alone, thereby resulting in protection from GTI. SGLT2i and DPP4i are membrane proteins expressed at high levels in the kidney and they may interact as proteins at the membrane level (Figure S6). Furthermore, DPP4 activity is present within some yeast, moulds, and bacteria, and its inhibition may directly modify micro-organismal function. These highly speculative and sophisticated hypotheses need to be tested experimentally. Lower

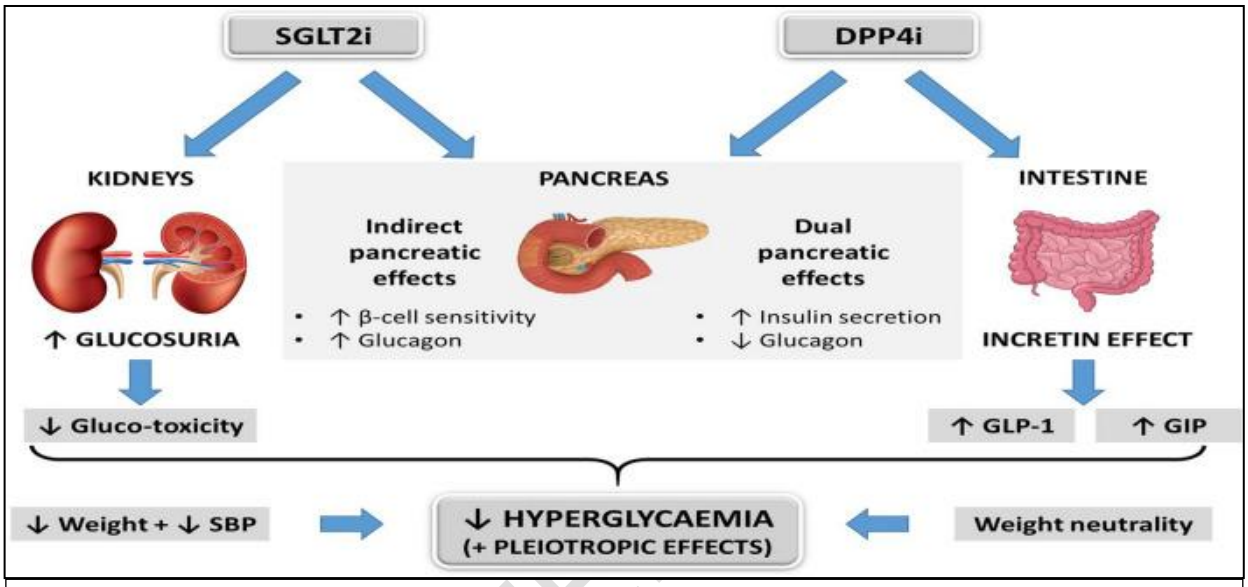


Figure 2. Complementary mechanisms of action and beneficial effects of SGLT2i and DPP4i [2]

glycosuria with the DPP4i/SGLT2i combination therapy *versus* SGLT2i monotherapy is the simplest explanation for moderation in genito-urinary tract infection risk [13].

6.2. COMPLIMENTARY ACTIONS OFFERED BY SGLT2I AND DPP4I IN COMBINATION

DPP-4i and SGLT2i fulfil provides complementary mechanisms of action that can be combined to achieve better glucose control over a wide spectrum of patients with T2DM, with a low risk of adverse events and the potential of cardiovascular protection. (Table 1) [1].

Table 1. Complimentary effects of SGLT2i and DPP4i [1]

Parameters	**DPP-4 inhibitor (Vildagliptin)**	**SGLT2 inhibitor (Dapagliflozin)**
Target organ	Gut	Kidney
Mode of action	Inhibition of degradation of GLP-1 and GIP (incretins)	Inhibition of tubular reabsorption of glucose
Glucosuria	Unchanged/decreased (due to reduced hyperglycemia)	Increased (primary effect)
Caloric intake	Slightly decreased (GLP-1-related)	Slightly increased (compensatory)

Insulin secretion	Increased (incretin effect, post-meal)	Decreased (sparing effect)
Glucagon secretion	Decreased	Increased
Endogenous glucose production	Decreased	Increased
Peripheral insulin sensitivity	Unchanged	Increased
Fasting plasma glucose	Slightly decreased	Decreased
Postprandial plasma glucose	Decreased	Decreased
HbA1c	Decreased	Decreased
Body weight	Unchanged	Decreased
Systolic blood pressure	Unchanged	Decreased
Lipid profile	Almost unchanged	Almost unchanged
Serum uric acid	Unchanged	Decreased
Cardiovascular outcomes	Non-inferiority versus placebo ((3 trials)	Superiority versus placebo (in EMPA-REG OUTCOME)
Hospitalization for heart failure	Increased (in SAVOR-TIMI 53)	Decreased (in EMPA-REG OUTCOME)
Mortality (cardiovascular and all-cause)	Unchanged (3 non-inferiority trials)	Decreased (in EMPA-REG OUTCOME)
Renal events	Not reported (3 non-inferiority trials)	Decreased (in EMPA-REG OUTCOME)
(**) EXAMINE (alogliptin), SAVOR-TIMI 53 (saxagliptin), TECOS (sitagliptin) *GLP-1 : glucagon-like peptide. GIP : glucose-dependent insulinotropic polypeptide*		

7. SGLT2I AND DPP4I IN COMBINATION: CLINICAL EVIDENCE

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 non-alcoholic fatty liver disease, among others [14–16]. DPP4i have been shown to exert higher efficacy in Asian patients, probably due to increased DPP4 enzyme activity in Asian Indian patients with T2DM [17]. 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 [18]. 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 [19].
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 [20].

7.1. Efficacy of SGLT2i + DPP4i FDC

Evidence from numerous clinical trials suggests 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-naı¨ve patients [21–25].

7.1.1. Initial Combination in Drug-Naive Patients with T2DM: The reduction of HbA1c in drugnaı ¨ve patients receiving different SGLT2i/DPP4i FDCs are compared in Table 2 [2].

***7.1.2. 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 [2].

Table 2. Reduction in glycemic hemoglobin from baseline

HBA1C reduction	**Empagliflozin + linagliptin FDC**		**Dapagliflozin + Saxagliptin FDC**	**Ertugliflozin + sitagliptin FDC**	
	10mg/5mg	25mg/5mg	10 mg/5mg	5mg/100mg	15mg/100mg
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 2diabetes mellitus on metformin monotherapy

HBA1C reduction	**Empagliflozin + linagliptin FDC**		**Dapagliflozin + Saxagliptin FDC**	**Ertugliflozin + sitagliptin FDC**	
	10mg/5mg	25mg/5mg	10 mg/5mg	5mg/100mg	15mg/100mg
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

7.2. Safety evidence

The overall safety profile of the FDCs was similar to those of the individual components. There were no significant differences in 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) [13].

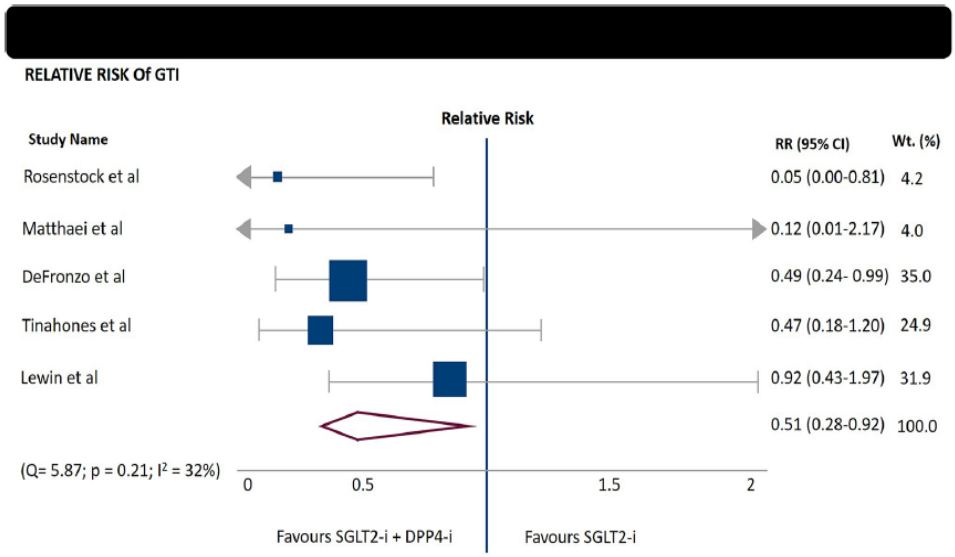
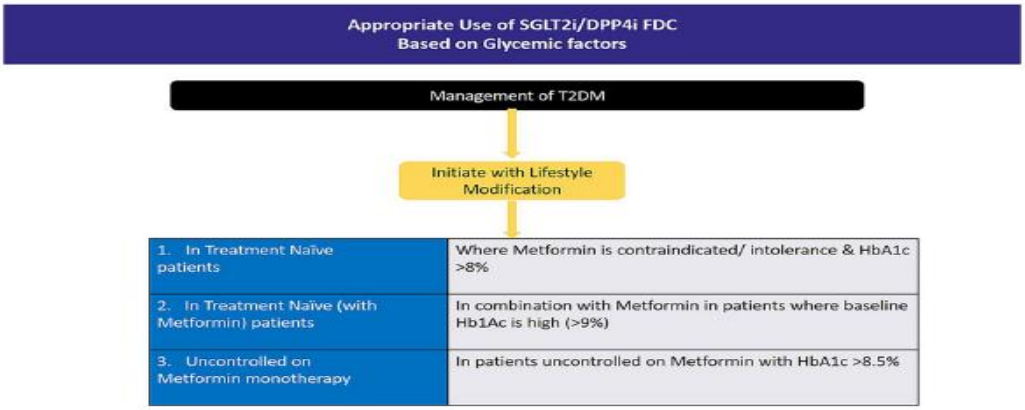


Figure 3 : Incidence of genitourinary tract infections favors the use of the SGLT2i/DPP4i fixed-drug combination. *CI: Confidence interval, GTI genitourinary tract infection, RR relative risk. (Adapted from Fadini et al. [13])*

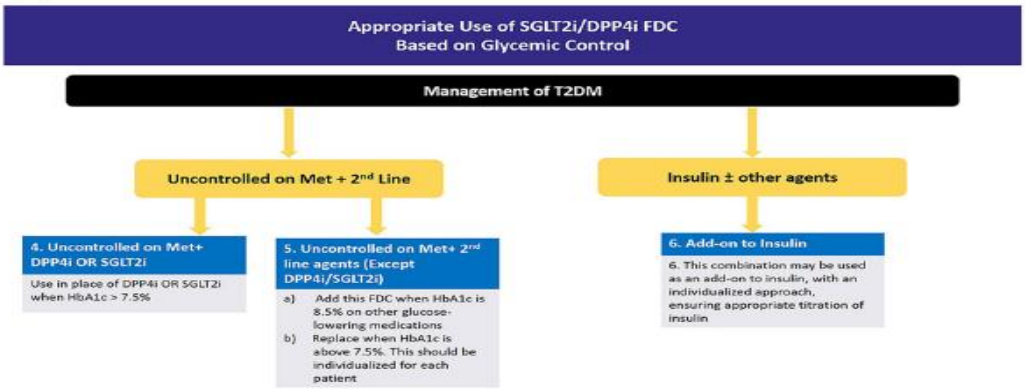
8. GUIDANCE OF SGLT2I/DPP4I COMBINATION USE

The following decision-making algorithms (Fig. 4a–e) may help guide the use of a SGLT2i/DPP4i combination in clinical practice [2].

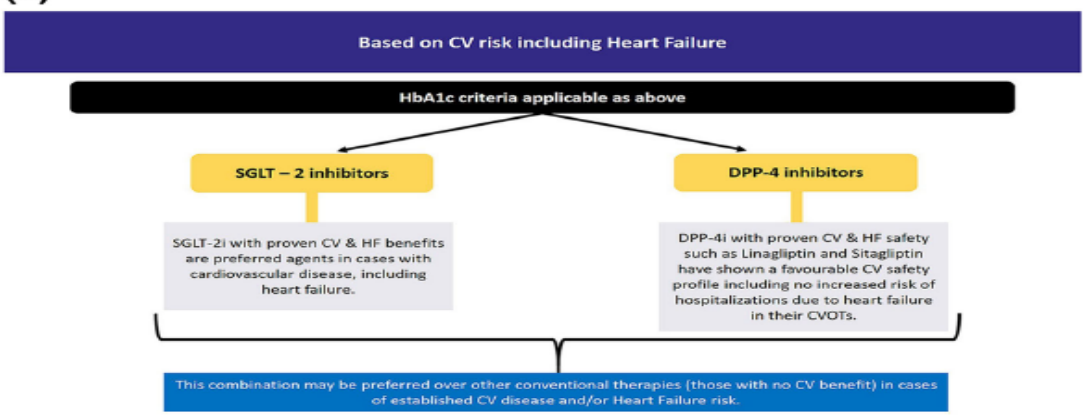
(a)


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.

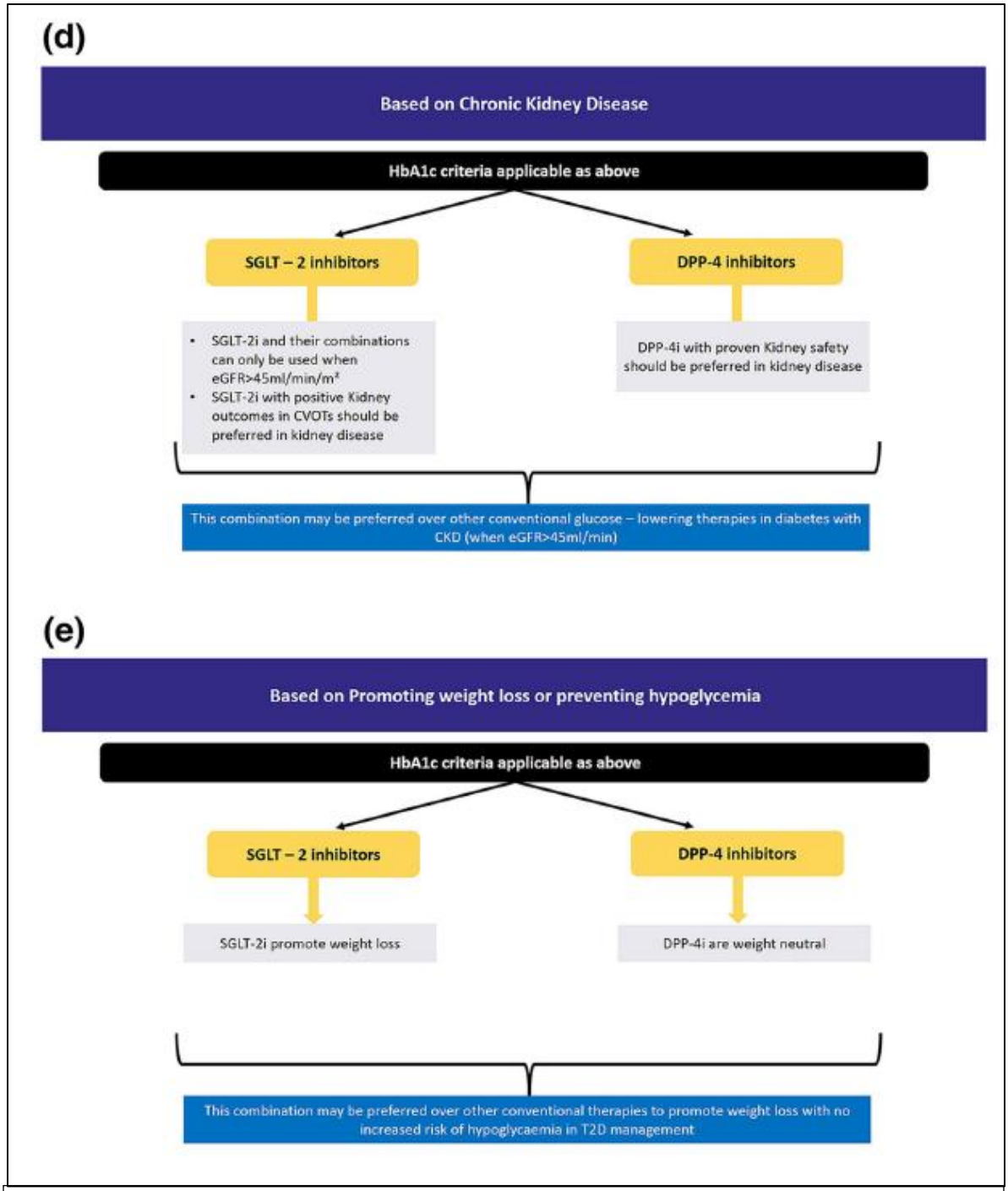


Figure 4 : a. Guidance for initiation of SGLT2i/DPP4i FDC based on glycemic factors. b Guidance for appropriate use of SGLT2i/ DPP4i FDC based on glycaemic control. c Guidance for initiation of SGLT2i/ DPP4i FDC based on CV risk. d Guidance for initiation of SGLT2-i/DPP4-i FDC based on CKD risk. e Guidance for initiation of SGLT2i/DPP4i 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

9. CONCLUSION

Thus, based on theory and clinical evidences, it can be concluded that SGLT2i and DPP4i combination is effective and safe in patients with type 2 diabetes mellitus. Together the combination of SGLT2i and DPP4i provides:

- Complementary mechanism of action
- Improved beta-cell function
- Reduced urogenital infections
- Combined cardio and reno-protective effects
- Weight reduction
- Reduced craving for carbohydrates
- Additive anti-hyperglycemic effects
- Can be used concomitantly in patients not responsive to metformin alone

Moreover, 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

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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