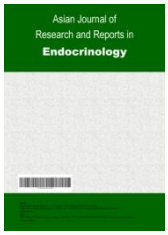

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Combination of Sodium-glucose Co-transporter 2 Inhibitors and Dipeptidyl Peptidase-4 Inhibitor: A Complementary Approach to Diabetes Management

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Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

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ABSTRACT

Diabetes mellitus is a consequence of multiple underlying pathophysiologies. India ranks second in the world with 77 million diagnosed with type 2 diabetes mellitus (T2DM). The unmet need of achieving the targeted glycated hemoglobin (HbA1c) goal along with increased patient compliance is associated with development of novel treatment options, for the diabetes care on individual basis. Diabetes being multifaceted disorder, combination therapy becomes key option either at initiation or later part of the treatment. A "pathophysiological approach" using combination therapy with agents addressing the known 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 by increasing glucose excretion through urine reduces reduce hyperglycemia. SGLT2i works independent of insulin secretion or action. DPP4i improves glucose homeostasis by inhibiting the breakdown of active incretin hormones, increasing insulin secretion and decreasing hepatic glucose production 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 corresponding mechanism of action when combined can achieve significant glycemic control in patients with T2DM, with a reduced adverse events and 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.

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Keywords: Diabetes mellitus; SGLT2i; DPP4i; combination therapy; genito-urinary tract infection; cardiovascular protection.

1. INTRODUCTION

"'Type 2 diabetes mellitus (T2DM) is a multifaceted disorder associated with variety of pathophysiological defects (Fig. 1)" [1].

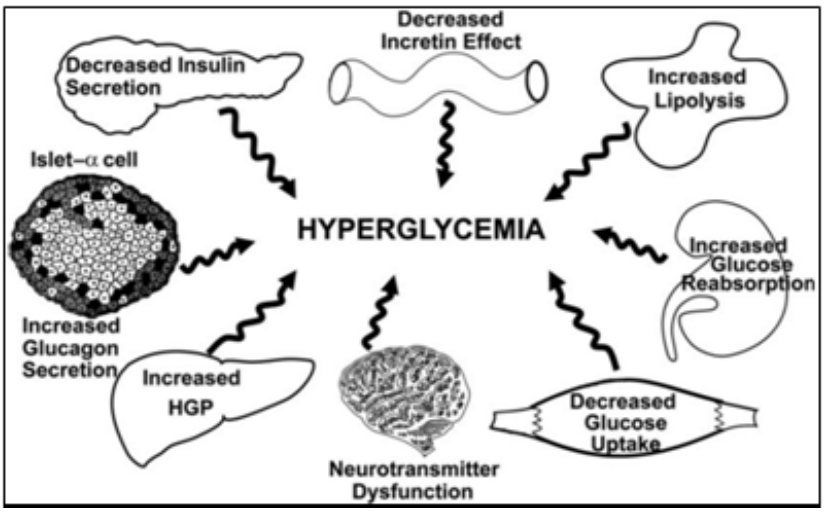


Fig. 1. Ominous octet of diabetes [1]

"India ranks second with highest number of people (77 million) diagnosed with type T2DM in the world" [2]. "Findings from Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) study phase I demonstrated that the prevalence of diabetes in is increasing in both, rural and urban regions of India with a higher rates reported in urban areas due to changes in diet and reduced physical activity compared to rural regions" [2-4]. An alarming trend beought to notice was majority of patients with onset of diabetes were from younger age groups. Clinical study has reported that 69% patients do not achieve the target level of HbA1c goal. [2-4].

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 in achieving the targeted glycated hemoglobin (HbA_{1c}) goal is associated with the need for individualized treatment approach" [2]. Thus, combination therapy becomes key option either at initiation or later part of the treatment [1]. Combination therapy not only reduces the pill burden and improves patient compliance but may also achiever the target HBA_{1c} levels more rapidly compared to monotherapy. Early treatment with combination therapy may improve therapeutic control and provide clinical benefits with better clinical outcomes [2].

2. UNMET NEED

The 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 are less ideal in most cases.
- Decreasing the incidence 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 needs and also increases the patient compliance.

3. "PATHOPHYSIOLOGICAL APPROACH" FOR COMBINATION THERAPY

A "pathophysiological approach" using initial combined 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 complex pathophysiology of diabetes makes it necessary to dictate various crucial implications in managing T2DM [2].

- To manage the various pathophysiological abnormalities two or more drugs should be combined.
- Drugs targeting the known pathophysiological mechanisms and counteracting the effects of these mechanisms should be considered.
- Treatment should focus not only on HbA1c control, or reduction of fasting/postprandial blood glucose.
- Intensified therapy should be initiated to stop the progress of beta-cell failure.
- Various pathophysiological aspects of diabetes can be targeted using combined therapy; however, few agents can work on 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 fulfill unmet needs of multifaceted diabetes pathology" [1].

4. DPP4 INHIBITORS

This novel class of anti-diabetic agents also known as gliptins has revolutionized diabetes treatment. All drugs belonging to this group have different pharmacokinetic and pharmacodynamic profiles and similar anti-diabetic property and safety (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 hormones released from intestinal cells responsible for augmenting insulin response. This amplified insulin response is called as 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 blocks DPP-4 and inhibits the degradation of incretin hormones GLP-1 and GIP. Vildagliptin (approved in EU and other countries) is reversible and competitive inhibitor of DPP-4. Vildagliptin binds DPP4 in two phases (a first rapid phase and consequent slow phase of binding); thus, resulting in both rapid 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 trial conducted in diabetes patients treated with vildagliptin showed that DPP-4 blockade *via* vildagliptin was reported within 45 minutes with maximum concentration attained at 24 hours. Vilagliptin 50 mg can result in 50% DPP4 inhibition within 0.5 hours and at 12 hours about 80% DPP4 inhibition can be observed; thus, making it an ideal candidate for once or twice daily administration. Vildagliption showed dose dependent inhibition of up to 90% after 28 days of regular treatment [6].

5. SGLT2 INHIBITORS

"SGLT2 inhibitors reduce HBA_{1c}, fasting and postprandial plasma hyperglycemia, body weight, and hypertension. It also reduces the risk of cardiovascular and renal events without increasing the risk of hypoglycemic. This novel discovery has foreshowed a remarkable shift in the management of T2DM" [7]. SGLT2i are prescribed either as single therapy 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 high blood sugar levels by blocking SGLT2 (a high-capacity, low-affinity) transporter located on initial segment of the proximal convoluted renal tubule. In normal individuals, SGLT2 results in reabsorption of 90% of the filtered glucose at the glomerulus. The remaining glucose is transported back into the systemic circulation by SGLT1, located at the distal segment of the proximal convoluted tubule. Blocking of SGLT2 receptors results in glycosuria

and lowers blood glucose because SGLT1 is unable to reabsorb all of the filtered glucose. SGLT2i decreses the renal reabsorption of glucose up to 50%" [7].

Dapagliflozin is a highly potent (inhibitory constant 0.55 nmol/L) SGLT2 inhibitor. Dapagliflozin is >1400 times more selective for SGLT2 than SGLT1. Dapagliflozin increased glucose excretion *via* urine and improves fasting (FPG) and post-prandial hyperglycemia in T2DM patients.

After the first dose of dapagliflozin, glucose excretion via urine was continuous with 24 hour dosing interval maintained throughout the course of the treatment. Dapagliflozin-induced glucuresis results in loss of calories and thus causes modest reduction in bodyweight. Dapagliflozin also induces mild osmotic diuresis and transient natriuresis.

The weight loss induced by dapagliflozin is less compared to induced calorie loss due to glucuresis, due to compensatory mechanism which may induce increased caloric intake. Dapagliflozin was associated with modest blood pressure (BP) reduction, which may be a consequence of reduced circulating volume due to induction of diuresis or natriuresis by dapagliflozin [9].

Dapagliflozin lowers blood glucose levels irrespective of insulin concentrations. Dapagliflozin is efficacious in reducing HBA1c, weight and BP. Dapagliflozin decreases the risk of cardiovascular events and heart failure events. Moreover, it does not increases the risk associated with MACE and also decreases the progression of chronic kidney disease along with low hypoglycemia risk. Dapagliflozin is reported to increase the risk of genital infections and diabetic kidney acidosis (DKA) [9].

6. COMBINING DPP4I AND SGLT2I

"Novel anti-hyperglycemic 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 elevates glucose excretion *via* urine irrespective of insulin secretion or action thus, causing decreased blood glucose levels. DPP4i inhibits the degradation of active incretin hormones and improves glucose homeostasis by elevating insulin secretion, and decreasing glucagon secretion in a glucose-dependent manner. Thus, the complimentary mechanisms of the two drugs would be effective and safe for the management of hyperglycemia in patients sub-optimally controlled T2DM" [10].

6.1 Rationale for Combination

SGLT2 inhibitors may elevate the hepatic glucose production and glucagon levels whereas DPP4 inhibitors through increasing insulin secretion, decreasing the hepatic glucose production, and suppressing glucagon secretion reduce hyperglycemia. Thus, the combination can reduce both, fasting plasma glucose levels and post-prandial hyperglycemia [11].

SGLT2 inhibitors may increase calorie intake due to by approx.13% due to increased carbohydrate craving and appetite; whereas, DPP4 inhibitors are reported to increase satiety and result in loss of appetite in pre-clinical studies [12].

Both the classes are also reported to lower the urinary albumin excretion rates, thus suggesting the potential for renal protection in patients with diabetes [12].

"SGLT2 inhibitors are associated with increased risk of genitourinary infections (GTI) and DPP4 inhibitors are reported to reduce this risk moderately in patients with T2DM, when both classes are combined. The combination of SGLT2i and DPP4i reduces glycemia and glycosuria more significantly compared to SGLT2i alone. SGLT2i and DPP4i are membrane proteins located at the kidney and they may interact as proteins at the membrane level" [13]. "Furthermore, DPP4 activity is present within some yeast, moulds, and bacteria. Inhibition of DPP4 may modify function of microorganism. However, this needs to be experimentally evaluated. Lower glycosuria with the DPP4i/SGLT2i combination therapy *versus* SGLT2i monotherapy is the easiest explaination to justify the reduced genito-urinary tract infection risk" [13].

6.2 Complimentary Actions Offered by SGLT2I AND DPP4I in Combination

"DPP-4i and SGLT2i provides complementary mechanisms of action which on combination may result in better glucose control in patients with T2DM and other associated complications, with a low risk of adverse reactions and improved cardiovascular protection. (Table 1)" [1].

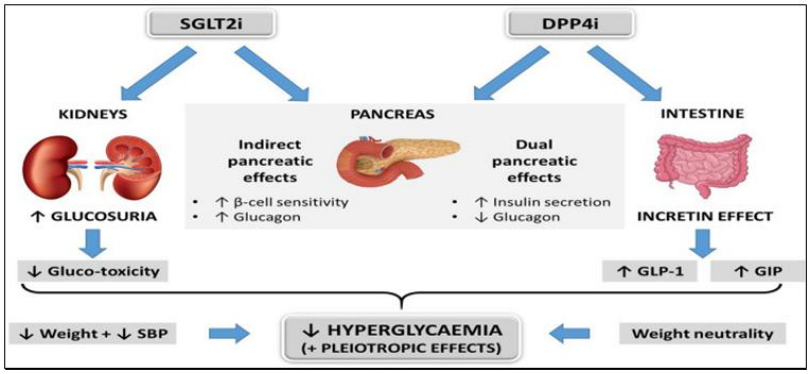


Fig. 2. Complementary mechanisms of action and beneficial effects of SGLT2I and DPP4I [2]

Adapted from: Chadha M, Das AK, Deb P, Gangopadhyay KK, Joshi S, Kesavadev J, Kovil R, Kumar S, Misra A, Mohan V. Expert Opinion: Optimum Clinical Approach to Combination-Use of SGLT2i + DPP4i in the Indian Diabetes Setting. Diabetes Ther. 2022 May;13(5):1097-1114.

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/reduced (due to reduced hyperglycemia)	Elevated (primary effect)
Caloric intake	Slightly reduced (GLP-1-related)	Slightly elevated (compensatory)
Insulin secretion	Elevated (incretin effect, post-meal)	Reduced (sparing effect)
Glucagon secretion	Reduced	Elevated
Endogenous glucose production	Reduced	Elevated
Peripheral insulin sensitivity	Unchanged	Elevated
Fasting plasma glucose	Slightly reduced	Reduced
Postprandial plasma glucose	Reduced	Reduced
HbA1c	Reduced	Reduced
Body weight	Unchanged	Reduced
Systolic blood pressure	Unchanged	Reduced
Lipid profile	Almost unchanged	Almost unchanged
Serum uric acid	Unchanged	Reduced
Cardiovascular outcomes	Non-inferiority versus placebo ((3 trials)	Superiority versus placebo (in EMPA-REG OUTCOME)
Hospitalization for heart failure	Increased (in SAVOR-TIMI 53)	Reduced (in EMPA-REG OUTCOME)
Mortality (cardiovascular and all-cause)	Unchanged (3 non-inferiority trials)	Reduced (in EMPA-REG OUTCOME)
Renal events	Not reported (3 non-inferiority trials)	Reduced (in EMPA-REG OUTCOME)

(**) EXAMINE (alogliptin), SAVOR-TIMI 53 (saxagliptin), TECOS (sitagliptin)

GLP-1 : glucagon-like peptide. GIP : glucose-dependent insulinotropic polypeptide

Adapted from: Scheen AJ. DPP-4 inhibitor plus SGLT-2 inhibitor as combination therapy for type 2 diabetes: from rationale to clinical aspects. Expert Opin Drug Metab Toxicol. 2016 Dec;12(12):1407-1417.

7. SGLT2I AND DPP4I IN COMBINATION: CLINICAL EVIDENCE

I"ndian population belongs to thin fat'' phenotype which is associated with development of T2DM. This phenotype is associated with various exclusive features such as, early age onset of T2DM, early deterioration of beta-cell function, increased insulin resistance, increased intake of carbohydrate and physical inactivity resulting in obesity, increased dyslipidemia risk, increased cardiovascular risk, increased non-alcoholic fatty liver disease, among others" [14–16]. "DPP4i are reported to be highly efficacious in Asian patients as they have increased DPP4 enzyme activity, particularly in patients with T2DM" [17]. "A study comparing the pharmacodynamics, efficacy, and safety of linagliptin among Japanese, Asian, and White patients with T2DM demonstrated better reduction in HbA1c was achieved in the Asian patients as compared to the Caucasians, without any major adverse events" [18]. "In another study conducted in Asian patients demonstrated that linagliptin effectively reduced hyperglycemia in Asian patients with uncontrolled T2DM independent of age, weight, kidney function, or ethnicity. Moreover linagliptin was well tolerated by these patients" [19]. " A recent meta-analysis showed that SGLT2i and DPP4i are associated with superior glucose-lowering efficacy in Asian patients" [20].

7.1 Efficacy of SGLT2i + DPP4i FDC

"Various clinical trials suggests that SGLT2i/DPP4i fixed dose combination (FDCs) are efficacious in controlling glycemic parameters and are well tolerated in patients with T2DM. Long-term studies evaluated the efficacy of available FDCs in patients with T2DM on metformin therapy along with diet and exercise. The efficacy of the empagliflozin/linagliptin combination was assessed in drug-naı¨ve patients" [21–25].

7.1.1 FDC in Drug-Naive Patients with T2DM

"The reduction of HBA_{1c} in drug navie patients using various FDCs of SGLT2i/DPP4i are compared in Table 2" [2].

7.1.2 FDC as Add-on to Metformin Monotherapy

"The reduction in HbA1c with various SGLT2i/DPP4i FDC as add on to metformin therapy is compared in Table 3. A consistent reduction in weight and hypertension was reported in SGLT2i monotherapy group and the FDC group" [2].

7.2 Safety Evidence

"The safety of FDC was similar to its individual components. No significant difference with respect to hypoglycemic events, urinary tract infections, hypovolemia and ketoacidosis between combination and monotherapy was reported. However, the combination was associated with lower rates of GTIs compared to SGLT2i monotherapy. The possible explanation for reduction of GTIs with FDC is

Table 2. Reduction in HBA_{1C} from baseline

HBA_{1C} reduction	Empagliflozin + linagliptin FDC		Dapagliflozin + Saxagliptin FDC	Ertugliflozin + sitagliptin FDC	
	10mg/5mg	25mg/5mg	10 mg/5mg	5mg/100mg	15mg/100mg
HBA1C decrease (%)	-1.2% (baseline 8%)	-1.1% (baseline 8%)	No evidence	-1.4% (baseline 8.3%)	-1.3% (baseline 8.3%)
HBA1C decrease (%)	-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
Adapted from: Chadha M, Das AK, Deb P, Gangopadhyay KK, Joshi S, Kesavadev J, Kovil R, Kumar S, Misra A, Mohan V. Expert Opinion: Optimum Clinical Approach to Combination-Use of SGLT2i + DPP4i in the Indian Diabetes Setting. Diabetes Ther. 2022 May;13(5):1097-1114.

Table 3. Reduction in HBA_{1c} with FDC as add-on to metformin monotherapy

HBA1C reduction	Empagliflozin + linagliptin FDC		Dapagliflozin + Saxagliptin FDC	Ertugliflozin + sitagliptin FDC	
	10mg/5mg	25mg/5mg	10 mg/5mg	5mg/100mg	15mg/100mg
HBA_{1C} decrease (%) (Mean baseline <8.5%)	-1.1%	-1.2%	Not available	Not available	Not available
HBA1C decrease (%) (Mean baseline > 8.5%)	-1.6%	-1.8%	-1.5%	-1.5%	-1.5%

No head-to head comparison data are available

Adapted from: Chadha M, Das AK, Deb P, Gangopadhyay KK, Joshi S, Kesavadev J, Kovil R, Kumar S, Misra A, Mohan V. Expert Opinion: Optimum Clinical Approach to Combination-Use of SGLT2i + DPP4i in the Indian Diabetes Setting. Diabetes Ther. 2022 May;13(5):1097-1114.

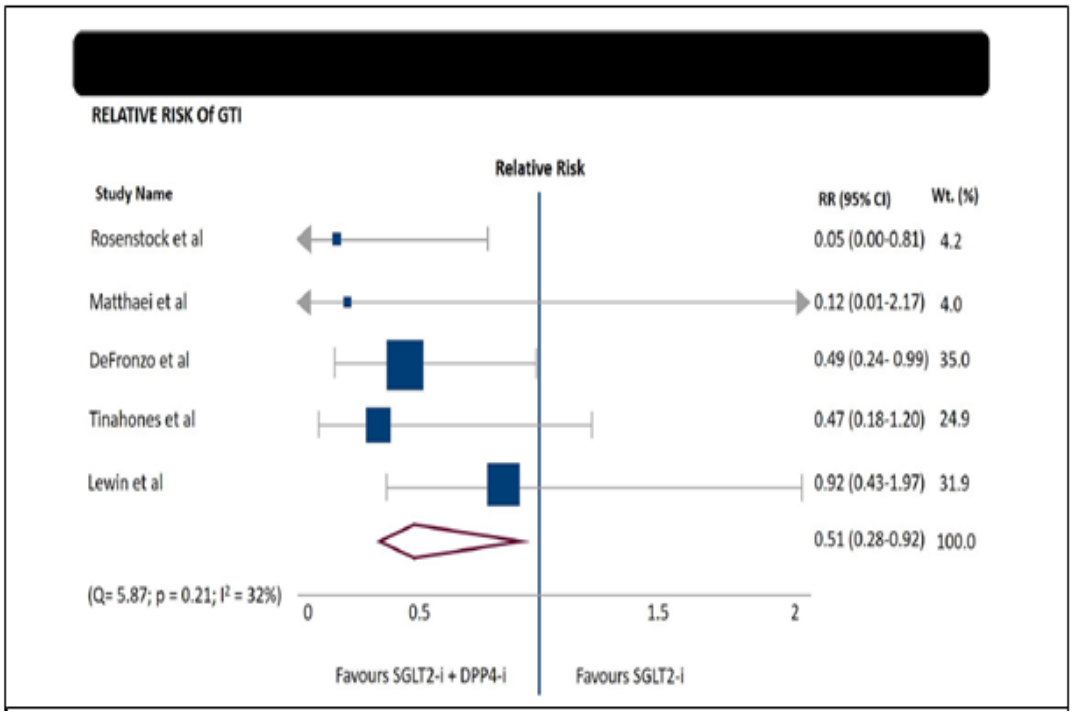


Fig. 3. Incidence of genitourinary tract infections favors the use of the SGLT2i/DPP4i fixed-drug combination

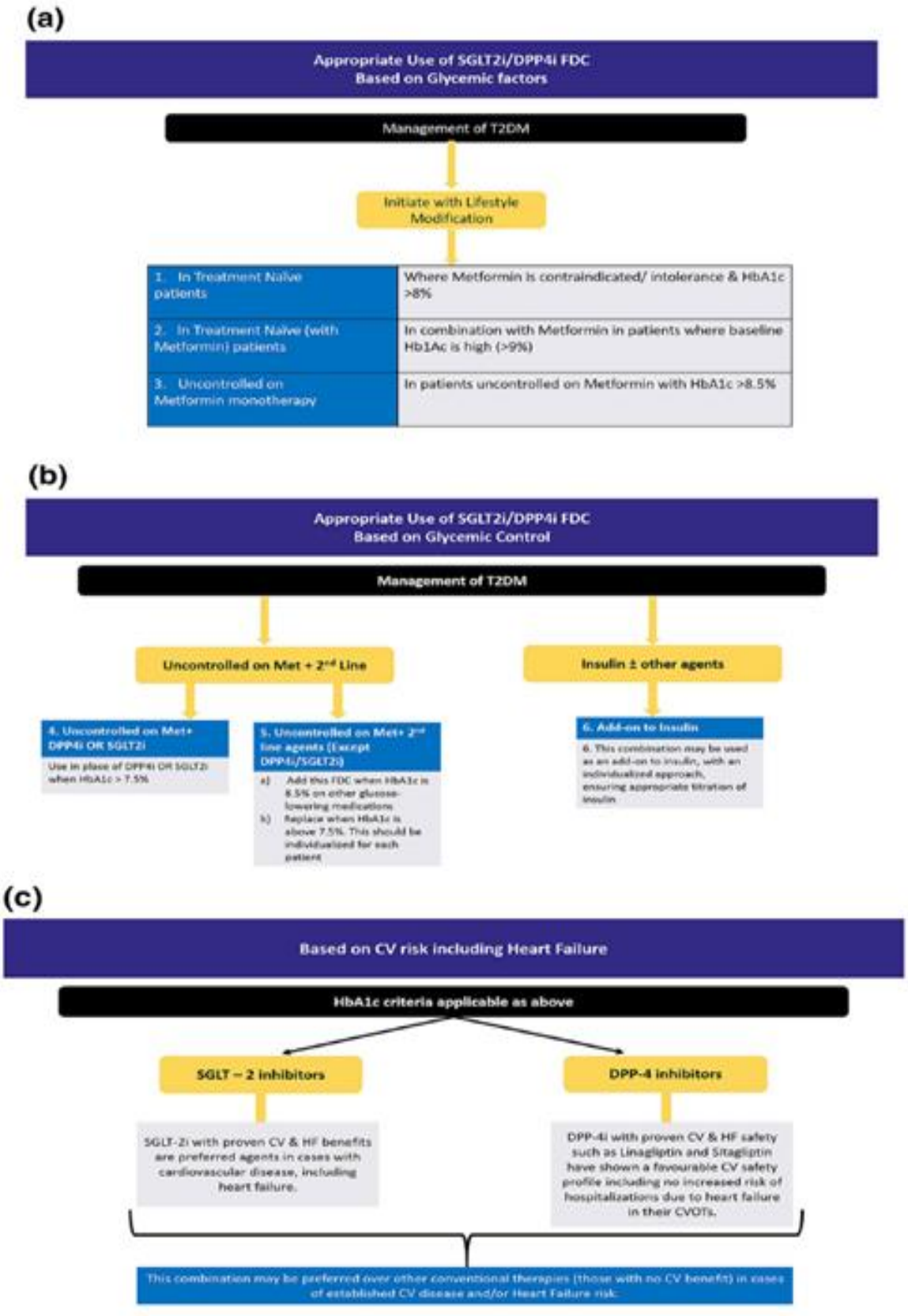
CI: Confidence interval, GTI genitourinary tract infection, RR relative risk.

(Adapted from: Fadini GP, Bonora BM, Mayur S, Rigato M, Avogaro A. Dipeptidyl peptidase-4 inhibitors moderate the risk of genitourinary tract infections associated with sodium-glucose co-transporter-2 inhibitors. Diabetes Obes Metab. 2018 Mar;20(3):740-744.)

probable interaction between DPP4 and SGLT2 proteins present at renal tubular cell-membrane level. Another probable mechanism may include blocking of DPP4 enzyme in certain pathogenic organisms that may result in inactivity of organism (Fig. 3)" [13].

7.2.1 Safety with SGLT2i/DPP4i combination *vs.* sequential addition of SGLT2i to DPP4i therapy

"The effect of SGLT2i /DPP4i for duration of at least 12 weeks was evaluated in a systematic


(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.

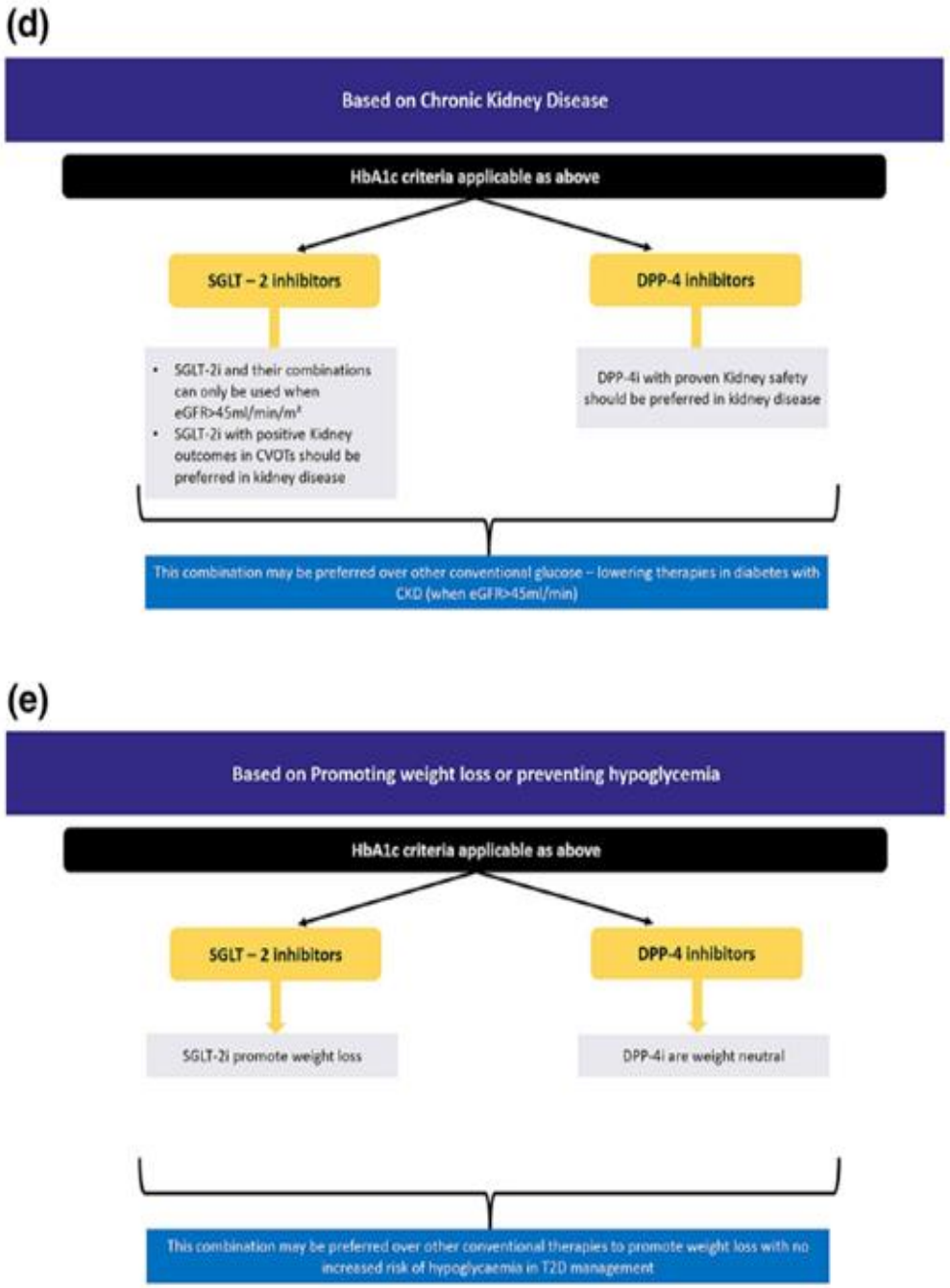


Fig. 4a. Guidance for initiation of SGLT2i/DPP4i FDC based on glycemic factors. b Guidance for appropriate use of SGLT2i/ DPP4i FDC based on glycaemic control. c Guidance for initiation of SGLT2i/ DPP4i FDC based on CV risk. d Guidance for initiation of SGLT2-i/DPP4-i FDC based on CKD risk. e Guidance 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 Adapted from: Chadha M, Das AK, Deb P, Gangopadhyay KK, Joshi S, Kesavadev J, Kovil R, Kumar S, Misra A, Mohan V. Expert Opinion: Optimum Clinical Approach to Combination-Use of SGLT2i + DPP4i in the Indian Diabetes Setting. Diabetes Ther. 2022 May;13(5):1097-1114.

review and meta-analysis of seven RCTs including 2082 patients with T2DM. All the studies included in meta-analysis evaluated the risk of urinary tract infection and GTIs at the end of therapy. The results reported reduced risk of UTI in combination group (relative risk [RR] 0.96, 95% confidence interval [CI] 0.52–1.78) compared to sequential therapy group (RR 0.67, 95% CI 0.28–1.60). The GTI risk was also lower in combination group (RR 1.35, 95% CI 0.55–3.34) compared to sequential therapy group (RR 0.67, 95% CI 0.28–1.60). These results from analysis suggest the lower risk of GTIs and UTIs with the combination therapy compared to sequential treatment with SGLT2i and DPP4i[26].

8. GUIDANCE OF SGLT2I/DPP4I COMBINATION USE

The following algorithm may help healthcare professional for making decision (Fig. 4a–e) regarding the use of SGLT2i/DPP4i combination in clinical practice [2].

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. In addition the DPP4i is suitable for Asian patients and the combination is effective in Asian patients. The combination is suitable in Indian diabetic patients due its safe rapid and sustained glycemic control, improves both insulin resistance and beta-cell function, reduces pill burden, and cost effective treatment option.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that they have no known competing financial interests or non-financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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