Review Article

Sodium-glucose co-transporter-2 inhibitors and dipeptidyl peptidase-4 inhibitors combination therapy in type 2 diabetes: A systematic review of current evidence

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ABSTRACT

As type 2 diabetes mellitus (T2DM) is a chronic and progressive disease with multiple pathophysiologic defects, no single anti-diabetic agent can tackle all these multi-factorial pathways. Consequently, multiple agents working through the different mechanisms will be required for the optimal glycemic control. Moreover, the combination therapies of different anti-diabetic agents may complement their actions and possibly act synergistic. Furthermore, these combinations could possess the additional properties to counter their undesired physiological compensatory response. Sodium-glucose co-transporter-2 inhibitors (SGLT-2I) are newly emerging class of drugs, with a great potential to reduce glucose effectively with an additional quality of lowering cardiovascular events as demonstrated very recently by one of the agents of this class. However, increase in endogenous glucose production (EGP) from the liver, either due to the increase in glucagon or compensatory response to glucosuria can offset the glucose-lowering potential of SGLT-2I. Interestingly, another class of drugs such as dipeptidyl peptidase-4 inhibitors (DPP-4I) effectively decrease glucagon and reduce EGP. In light of these findings, combination therapies with SGLT-2I and DPP-4I are particularly appealing and are expected to produce a synergistic effect. Preclinical studies of combination therapies with DPP-4I and SGLT-2I have already demonstrated a significant lowering of hemoglobin A1c potential and human studies also find no drug-drug interaction between these agents. This article aims to systematically review the efficacy and safety of combination therapy of SGLT-2I and DPP-4I in T2DM.

Key words: Combination therapies, dipeptidyl peptidase-4 inhibitors, genitourinary infections, sodium glucose co-transporter-2 inhibitors, type 2 diabetes

Introduction

Pathogenesis of type 2 diabetes mellitus (T2DM) is multi-factorial. Ominous-octet concepts proposed by DeFronzo in recent past suggest that no single anti-hyperglycemic agent (AHA) can correct all the pathophysiological defects in T2DM.[1] Moreover, T2DM and obesity are commonly associated, often referred as diabesity, and considered a major global health problem. Obesity itself triggers insulin resistance and thereby possesses the risk of T2DM. Both obesity and T2DM have been associated with higher morbidity and mortality and this call for institution of effective therapies to deal with this dual menace.[2] Thus, management of T2DM will require multiple agents with complementary mechanisms

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of action to adequately manage progressive hyperglycemia in T2DM and body weight. Currently available AHA either act by increasing insulin secretion (secretagogue) or by sensitizing tissues to insulin action (sensitizers). Secretagogues depend primarily upon pancreatic β-cell function and β-cell mass for its efficacy.

Unfortunately, due to the progressive loss of β-cell function and possibly β-cell mass, many patients eventually fail to achieve target hemoglobin A1c (HbA1c) level, despite using multiple agents.[3] Moreover, conventional secretagogues such as sulfonylureas are associated with hypoglycemia and weight gain that act as a potential barrier to achieve glycemic target and weight control. Insulin sensitizers such as metformin and pioglitazone are also effective agents in treating T2DM; however, pioglitazone is significantly associated with weight gain, fluid retention, edema, and bone fractures. While metformin is already approved as a first-line drug, nevertheless, monotherapy with metformin alone cannot correct hyperglycemia in most of the patients. Therefore, an unmet need still exists which calls for newer AHAs that effectively reduce HbA1c and are either weight neutral or preferably cause weight loss, without potentiating hypoglycemia.

Last decade have witnessed few novel classes of AHAs, that reduce HbA1c effectively, do not cause hypoglycemia, and are either weight neutral or cause weight loss. This includes glucagon-like peptide-1 receptor agonists (GLP-1RA), dipeptidyl peptidase-4 inhibitors (DPP-4I), and sodium glucose co-transporter-2 inhibitors (SGLT-2I). GLP-1RA has been shown to reduce HbA1c effectively and reduce body weight significantly. Reduction in blood pressure is also consistently observed with GLP-1RA; however, these are injectable drugs, costly, and in general, less acceptable by the patients.[4] DPP-4I works by inhibiting the enzyme that degrades the incretin hormones, GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), and thus elevates both plasma GLP-1 as well as GIP concentrations.[5] While both GLP-1 and GIP stimulate insulin secretion from the β-cell, GLP-1 inhibits glucagon secretion from the α-cell. This increase in insulin with a reduction in glucagon inhibits endogenous glucose production (EGP) from the liver and thus helps in reducing plasma glucose in a glucose-dependent manner.[6] Moreover, GIP-mediated augmentation of glucagon by DPP-4I, in the setting of low glucose, may also protect against hypoglycemia.[7,8]

SGLT-2I is another novel class of anti-diabetes drugs, which reduce the plasma glucose by inhibiting renal glucose reabsorption from kidney, independent of β-cell function or mass, thereby inducing glucosuria. This urinary glucose loss results in negative energy balance and weight loss. Moreover, associated inhibition of sodium absorption in the proximal tubule also results in a decrease in blood pressure, seen consistently across their clinical development program.[9,10] Furthermore, a cardiovascular (CV) outcome study with empagliflozin (EMPA-REG CV outcomes trial [CVOT]), a SGLT-2I, recently shown a significant reduction in CV death, all-cause mortality, and hospitalization due to heart failure compared to the conventional arm.[11] However, as the pathogenesis of T2DM is complex and involves multiple metabolic defects, none of the AHA as monotherapy appears to achieve target glycemic control. Thus, use of combination therapy with different mechanisms of action has the potential of producing an additive reduction in HbA1c.

The combination of SGLT-2I with DPP-4I is particularly appealing in the light of recent findings that glucosuria produced by SGLT-2I is associated with an increase in the rate of EGP, which could offset the glucose-lowering effect by ~50%.[12,13] Both Merovci *et al.* and Ferrannini *et al.* reported 17% ($P < 0.05$) and 30% increase ($P < 0.0001$) in EGP, respectively. This increase in EGP has been implicated to either compensatory rise in response to glucosuria or increase in glucagon with SGLT-2I or both.[14] Merovci *et al.* found ~23% increase in fasting glucagon/insulin ratio with dapagliflozin, while Ferrannini *et al.* reported ~25% decrease in insulin/glucagon ratio with empagliflozin.[12,13] Mudaliar *et al.* also reported a 7.8 times increase in glucagon with dapagliflozin, although no rise in EGP was observed in this study.[15] It has been already demonstrated earlier by Paquot *et al.* that the 20–32% increase in fasting plasma glucagon concentration is sufficient to increase EGP.[16]

As DPP-4I significantly lowers glucagon, it can be speculated that the combination of DPP-4I plus SGLT-2I would prevent such increase in EGP, which is triggered by the increase in glucagon. Consequently, this can also produce a synergistic effect in reducing HbA1c.[17] Moreover, pharmacokinetics and pharmacodynamic (PK-PD) studies conducted in healthy volunteers found no drug-drug interaction between SGLT-2I and DPP-4I.[18] Preclinical studies in db/db mice were first to suggest that combination of SGLT-2I with DPP-4I can produce statistically significant better HbA1c reduction, higher glucose-stimulated insulin secretion, and significantly better glucose-disposal rate, compared to the either drug used alone.[19] Human studies also appear to replicate the preclinical data and therefore, we conducted a systematic review of literature to find out safety and efficacy of combination therapies with SGLT-2I and DPP-4I in type 2 diabetes.

Review Method

The studies were identified by conducting a literature search from electronic database till September 2015, using PubMed, The Cochrane library, Google scholar, On-going Trials registers at Clinical Trials (http://www.clinicaltrials.gov), conference abstracts from American diabetes association and European association for the study of diabetes. The search was made using various MeSH terminologies for articles of SGLT2 and DPP-4I combination therapy to assess its safety and efficacy.

Efficacy (change in hemoglobin A1c, fasting plasma glucose, prandial glucose, body weight, and blood pressure) analysis

Several studies which reported these outcomes have been summarized in Table 1.[19-27] All studies were conducted with some background therapies except the study by Lewin *et al.*, which was conducted in treatment naïve patient.

Sitagliptin plus dapagliflozin

In a 24-week placebo-controlled study, Jabbour *et al.* evaluated ($n = 432$) the effect of sitagliptin plus dapagliflozin to dapagliflozin or sitagliptin, with or without background metformin therapy. Result found a significant reduction of HbA1c in dapagliflozin plus sitagliptin with metformin arm (Δ −0.4% vs. sitagliptin with metformin; Δ −0.6% vs. sitagliptin alone; both P < 0.0001). Dapagliflozin plus sitagliptin also reported significant reduction in fasting plasma glucose (FPG) (Δ −29.2 and −26.6 mg/dl with or without background metformin therapy respectively; both $P < 0.0001$) and postprandial plasma glucose (PPG) (Δ −41.6 and −43.7 mg/dl with or without background metformin; both P = not reported), compared to sitagliptin. Moreover, additional 10% of patient achieved the target of HbA1c <7% in dapagliflozin plus sitagliptin arm (with or without background metformin therapy). Significant reduction in body weight (Δ −1.9 kg, $P < 0.0001$) also observed in sitagliptin plus dapagliflozin compared to sitagliptin (with or without background metformin) therapy. No significant difference in blood pressure noted in this study.[19]

Saxagliptin plus dapagliflozin

In a 24-week study, Rosenstock *et al.* ($n = 534$) reported a significant reduction in HbA1c with triple therapy of saxagliptin plus dapagliflozin with metformin (Δ −0.6%, $P < 0.0001$) versus saxagliptin with metformin therapy. HbA1c reduction was also significantly lower in triple therapy (Δ −0.27%, $P = 0.0166$) "compared" to dapagliflozin with metformin therapy. Triple therapy also lowered FPG (Δ −24 mg/dl, *P* not reported) and PPG (Δ −44 mg/dl, $P < 0.0001$) better compared to saxagliptin with metformin therapy. Notably, no significant difference in FPG and postprandial blood glucose reduction observed with triple combination versus dapagliflozin plus metformin therapy. Importantly, additional 23% and 19% patients could achieve the target HbA1c of <7% with triple therapy compared to saxagliptin or dapagliflozin with metformin therapy, respectively. Reduction in body weight by −2.1 kg observed (*P* value not reported) with dapagliflozin plus saxagliptin compared to saxagliptin. However, this study was limited by noninclusion of placebo arm.[20]

Two recently published 24-week studies by Matthaei *et al.* ($n = 315$) and Mathieu *et al.* ($n = 320$) also reported a significant reduction in HbA1c with dapagliflozin plus saxagliptin with metformin, compared to either agent with metformin.[21,22] While Matthaei *et al.* reported a −0.35% HbA1c reduction ($P < 0.0001$) when saxagliptin was added to dapagliflozin plus metformin; Mathieu *et al.* found −0.72% HbA1c reduction ($P < 0.0001$) when dapagliflozin was added to saxagliptin plus metformin versus placebo. Interestingly, Mathieu *et al.* also reported a significant reduction in FPG (Δ −28 mg/dl, $P < 0.0001$) and PPG (Δ −36 mg/dl, $P < 0.0001$) when dapagliflozin was added to saxagliptin plus metformin; however, no significant reduction in FPG and PPG observed, when saxagliptin was added to dapagliflozin plus metformin in Matthaei *et al.* study.[21] Higher proportion of patient achieved the target HbA1c of <7% in dapagliflozin plus saxagliptin plus metformin arm (38%), compared to saxagliptin plus metformin arm (12%) in Mathieu *et al.* study. Similarly, higher proportion of patient achieved the target HbA1c of <7% in saxagliptin plus dapagliflozin plus metformin arm (35%), compared to dapagliflozin plus metformin arm (23%) in Matthaei *et al.* study. Mathieu *et al.* reported significant weight loss (Δ −1.5 kg, $P < 0.0001$) in dapagliflozin plus saxagliptin with metformin, compared to saxagliptin with metformin.[22]

Linagliptin plus empagliflozin

Fixed dose combination (FDC) of empagliflozin plus linagliptin is already approved by US Food Drug Administration and Europeans Agency. Lewin *et al.* ($n = 677$) in a two-point outcome (week 24 and week 52) study in a treatment naïve patients reported a significant lowering of HbA1c reduction at both points of time. FDC of empagliflozin 10 mg plus linagliptin 5 mg reduced HbA1c both at week 24 (Δ −0.41% vs. empagliflozin 10 mg alone and −0.57% vs. linagliptin 5 mg alone; both $P < 0.001$) and week 52 (Δ −0.37% vs. empagliflozin 10 mg alone and −0.71%, vs. linagliptin 5 mg alone, both $P < 0.001$) significantly. While FDC of empagliflozin 25 mg plus linagliptin 5 mg lowered HbA1c significantly both at week 24 (Δ −0.41%, $P < 0.001$) and week 52 (−0.66%, $P < 0.001$) versus linagliptin 5 mg alone,

Table 1: Change in HbA1c, fasting plasma glucose and body weight with combination therapy of SGLT-2 inhibitors and DPP-4 inhibitors

Author, year; (week)	*N*	Intervention	Baseline HbA1c (%)	Δ HbA1c (%)	Δ HbA1c amongst group (95% CI), *P* value	Δ FPG amongst group at week 24 (95%CI), *P* value	Δ Body weight amongst group (95% CI), *P* value
Jabbour *et al*, 2014; (24)	A=113	A=DAPA + SITA + Met	7.80	−0.40	A–B: −0.40 (−0.60, −0.30), *P*<0.0001	A–B: −29.2 (−38.0, −20.4), *P*<0.0001	A–B: −1.9 (−2.6, −1.1), *P*<0.0001
	B=113	B=PBO + SITA + Met	7.90	−0.00			
	C=110	C=DAPA + SITA	8.00	−0.50	C–D: −0.60 (−0.80, −0.30), *P*<0.0001	C–D: −26.6 (−36.3, −16.9), *P*<0.0001	C–D: −1.9 (−2.5, −1.2), *P*<0.0001
	D=111	D=PBO + SITA	8.10	+0.10			
Tanizawa *et al*, 2014; (52)	A=35	A=DPP4i + TOFO 20	8.38	−0.78#	NR	NR	NR
	B=68	B=DPP4i + TOFO 40	8.19	−0.93#			
	C=63	C=TOFO 20	7.83	−0.67#			
	D=127	D=TOFO 40	7.83	−0.66#			
Rosenstock *et al*, 2015; (24)	A=179	A=SAXA + DAPA + Met	8.93	−1.47	A–B: −0.59 (−0.81,−0.37), *P*<0.0001	A–B: −24 (−31.6,−15.9), *P*=NT	A–B: −2.1 (−2.7, −1.4), *P*=NR
	B=176	B=SAXA + Met	9.03	−0.88			
	C=179	C=DAPA + Met	8.87	−1.20	A–C: −0.27 (−0.48, −0.05), *P*=0.0166	A–C: −6 (−13.8, 1.7), *P*=NT	
Lewin *et al*, 2015; (24)	A=134	A=EMPA 25 + LINA (FDC)	7.99	−1.08	A–C: −0.14 (−0.33, 0.06), *P*=0.179	A–C: −5.3 (−12.7, 2.1), *P*=0.161	A–C: −0.1 (−0.9, 1.1), *P*=0.801
	B=135	B=EMPA 10 + LINA (FDC)	8.04	−1.24			
	C=133	C=EMPA 25	7.99	−0.95	A–E: −0.41 (−0.61,−0.22), *P*<0.001	A–E: −23.6 (−31.1,−16.2), *P*<0.001	A–E:−1.2 (−2.2, −0.2), *P*=0.018
	D=132	D=EMPA 10	8.05	−0.83			
	E=133	E=LINA 5	8.05	−0.67	B–D: −0.41 (−0.61, −0.21), *P*<0.001	B–D: −5.8(−13.3, 1.61), *P*=0.125	B–D: −0.5 (−1.5, 0.5), *P*=0.362
					B–E : −0.57 (−0.76, 0.37), *P*<0.001	B–E: −22.3 (−29.7, −14.9), *P*<0.001	B–E: −2.0 (−3.0, −1.0), *P*<0.001
Lewin *et al*, 2015; (52)	A=134	A=EMPA 25 + LINA (FDC)	7.99	−1.17	A–C: −0.16 (−0.39, 0.07), *P*=0.176	NR	A–C: −0.3 (−0.7, 1.4), *P*=0.532
	B=135	B=EMPA 10 + LINA (FDC)	8.04	−1.22			
	C=133	C=EMPA 25	7.99	−1.01	A–E: −0.66 (−0.90,−0.43), *P*<0.001		A–E: −1.7 (−2.8, −0.7), *P*=0.002
	D=132	D=EMPA 10	8.05	−0.85			
	E=133	E=LINA 5	8.05	+0.51	B–D: −0.37 (−0.94, −0.48), *P*<0.001		B–D: 0.8 (−0.3, 1.8), *P*=0.169
					B–E : −0.71 (−0.94, 0.48), *P*<0.001		B–E: −1.3 (−2.4, −0.2), *P*=0.017
DeFronzo *et al*, 2015; (24)	A=134	A=EMPA 25 + LINA (FDC) + Met	7.90	−1.19	A–C: −0.58 (−0.75,−0.41), *P*<0.001	A–C: −16.4(−23.4,−9.5), *P*<0.001	A–C: 0.2 (−0.7,1.0), *P*=0.660
	B=135	B=EMPA 10 + LINA (FDC) + Met	7.95	−1.08	A–E: −0.50 (−0.67,−0.32), *P*<0.001	A–E: −22.2 (−29.3,−15.1), *P*<0.001	A–E: −2.3 (−3.2,−1.4), *P*<0.001
	C=140	C=EMPA 25 + Met	8.02	−0.62	B–D: −0.42 (−0.59, −0.25), *P*<0.001	B–D: −11.3(−18.3, −4.4), *P*=0.002	B–D: −0.1(−0.9, 0.8), *P*=0.876
	D=137	D=EMPA 10 + Met	8.00	−0.66			
	E=128	E=LINA + Met	8.02	−0.70	B–E: −0.39 (−0.56, −0.21), *P*<0.001	B–E: −19.1(−26.2, −12.0), *P*<0.001	B–E: −1.9(−2.8, −1.1), *P*<0.001
DeFronzo *et al*, 2015; (52)	A=134	A=EMPA 25 + LINA (FDC) + Met	7.90	−1.21	A–C: −0.57 (−0.77,−0.37), *P*<0.001	NR	A–C: −0.3 (−1.2,0.6), *P*=0.461
	B=135	B=EMPA 10 + LINA (FDC) + Met	7.95	−1.05	A–E: −0.73 (−0.93,−0.53), *P*<0.001		A–E: −2.9 (−3.8,−2.0), *P*<0.001
	C=140	C=EMPA 25 + Met	8.02	−0.64	B–D: −0.36 (−0.56, −0.17), *P*<0.001		B–D: 0.2(−0.7, 1.1), *P*=0.593
	D=137	D=EMPA 10 + Met	8.00	−0.69			
	E=128	E=LINA + Met	8.02	−0.48	B–E: −0.57 (−0.77, −0.37), *P*<0.001		B–E: −2.4(−3.3, −1.5), *P*<0.001
Seino *et al*, 2015; (52)	A=111	A=DPP4i + LUSEO 2.5	7.88	−0.52*	NR	NR	NR
	B=150	B=SU + LUSEO 2.5	8.07	−0.63*			
Matthaei *et al*, 2015; (24)	A=150	A=SAXA + DAPA + Met	7.95	−0.51	A–B: −0.35 (−0.52, −0.18), *P*<0.0001	A–B: −4 (−11, 3.6), *P*=0.32	NR
	B=160	B=PBO + DAPA + Met	7.85	−0.16			
Mathieu *et al*, 2015; (24)	A=158	A=DAPA + SAXA + Met	8.24	−0.82	A–B: −0.72 (−0.91, −0.53), *P*<0.0001	A–B: −28 (−35.4, −19.6), *P*<0.0001	A–B: −1.5 (−2.12, −0.89), *P*<0.0001
	B=158	B=PBO + SAXA + Met	8.16	−0.10			
Woo *et al*, 2015; (18)	A=111	A=CANA 300 + DPP4i	8.0	−0.64	A–C: −0.75 (−0.95, −0.54), *P*=NT	NR	A–C: −2.7 (−3.5, −2.0), *P*=NT
	B=103	B=CANA 100 + DPP4i	8.1	−0.46			
	C=102	C=PBO + DPP4i	8.1	+0.10	B–C: −0.56 (−0.77, −0.35), *P*=NT		B–C: −2.0 (−2.7, −1.2), *P*=NT

#*P*<0.0001, **P*<0.001, NT: Not tested, NR: Not reported/not retrievable, DAPA: Dapagliflozin, SITA: Sitagliptin, SAXA: Saxagliptin, EMPA: Empagliflozin, CANA: Canagliflozin, LINA: Linagliptin, TOFO: Tofogliflozin, LUSEO: Luseogliflozin, Met: Metformin, PBO: Placebo, DPP4i: Dipeptidyl peptidase-4 inhibitor, SU: Sulfonylurea, FDC: Fixed dose combination, FPG: Fasting plasma glucose

it could not lower HbA1c significantly both at week 24 (Δ −0.14%, $P = 0.179$) and week 52 (Δ −0.16%, $P = 0.176$) versus empagliflozin 25 mg alone. Significant reduction in FPG also observed with FDC of empagliflozin 25 plus linagliptin and empagliflozin 10 mg plus linagliptin (Δ −23.6 and −22.3 mg/dl, respectively, both $P < 0.001$)

compared to linagliptin alone. However, no significant reduction in FPG was observed with FDC (either dosage) versus empagliflozin monotherapy. Significant reduction in body weight was observed with empagliflozin 25 mg plus linagliptin and empagliflozin 10 mg plus linagliptin 5 mg both at week 26 (Δ −1.2, −2.0 kg, respectively; both *P* significant) and week 52 (Δ −1.7, −1.3 kg, respectively; both *P* significant) compared to linagliptin alone. Numerical reduction in blood pressure also noted with empagliflozin combination arm although it was not statistically significant. Notably, this study was limited by the absence of metformin background therapy and noninclusion of placebo.[23]

Similarly, DeFronzo *et al*. in a two-point outcome (week 24 and 52) study (*n* = 686) reported a significant difference in HbA1c reduction ranging from Δ −0.36% to −0.73% (all $P < 0.001$) with both FDC of empagliflozin 25 or 10 mg plus linagliptin 5 mg, versus monotherapy with individual drug, in a background metformin therapy. FDC of empagliflozin 25 mg plus linagliptin 5 mg lowered HbA1c significantly both at week 24 and 52 versus empagliflozin 25 mg alone (Δ −0.58 and −0.57%, respectively, both $P < 0.001$) or versus linagliptin 5 mg alone (Δ −0.50, −0.73%, respectively, both $P < 0.001$). Likewise, FDC of empagliflozin 10 mg plus linagliptin 5 mg also lowered HbA1c significantly both at week 24 and 52 versus empagliflozin 10 mg alone (Δ −0.42 and −0.36%, respectively, both $P < 0.001$) or versus linagliptin 5 mg alone (Δ −0.39, −0.57%, respectively, both $P < 0.001$). FDC of empagliflozin 25 mg plus linagliptin 5 mg also significantly reduced FPG versus empagliflozin 25 mg or linagliptin 5 mg (−16.4, −22.2 mg/dl, both $P < 0.001$) in background metformin therapy. Similarly, FDC of empagliflozin 10 mg plus linagliptin 5 mg reduced FPG significantly versus empagliflozin 10 mg or linagliptin 5 mg (−11.3 mg/dl, $P = 0.002$; 19.1 mg/dl, $P < 0.001$) in background metformin therapy. Notably, PPG reductions were not studied in this study. Interestingly, a significant proportion of patient ranging from 59% to 66% (all $P < 0.05$) could achieve a HbA1c target of <7% with FDC therapy, compared to 40% with empagliflozin 10 mg, 43% with empagliflozin 25 mg, and 34% with linagliptin 5 mg. Significant reduction in body weight observed with empagliflozin 25 mg plus linagliptin and empagliflozin 10 mg plus linagliptin 5 mg both at week 26 (Δ −2.3, −1.9 kg, respectively; both *P* significant) and week 52 (Δ −2.9, −2.4 kg, respectively; both *P* significant) compared to linagliptin alone. The study also found a significant reduction in systolic blood pressure, both with the FDC of empagliflozin 25 mg plus linagliptin (Δ −3.8 mm of Hg, $P = 0.005$) and empagliflozin 10 mg plus linagliptin (Δ −3.1 mm of Hg, $P = 0.022$) compared to linagliptin in a background metformin therapy. However, this study was limited by noninclusion of placebo arms.[24]

Dipeptidyl peptidase-4 inhibitors plus canagliflozin or tofogliflozin or luseogliflozin

From the ongoing subgroup study (*n* = 315) of canagliflozin CV Assessment Study, Woo *et al*. evaluated the change in HbA1c, body weight and composite measure of both, with canagliflozin 100 and 300 mg as an add-on to DPP-4I. Both canagliflozin 100 and 300 mg dose add-on to DPP-4I reduced HbA1c (Δ −0.56 and −0.75%, respectively) effectively. Body weight reduction was also effective with both canagliflozin 100 and 300 mg dose (Δ −2.0 and −2.7 kg, respectively) as add-on to DPP-4I versus placebo.[25] Combination therapy of canagliflozin 100 and 300 mg with DPP-4I also achieved better composite outcome of HbA1c and weight reduction (65% and 78% reduction, respectively) compared to placebo (30%).[25]

Similar reductions in HbA1c have been observed when DPP-4I plus luseogliflozin or tofogliflozin. While addition of DPP-4I to luseogliflozin 2.5 mg reduced the HbA1c by − 0.52% ($P < 0.0001$), tofogliflozin 20 mg plus DPP-4I reduced HbA1c by − 0.78% ($P < 0.0001$) and tofogliflozin 40 mg plus DPP-4I by − 0.93% ($P < 0.0001$).[26,27]

Figure 1 depicts the change in HbA1c and Figure 2 depicts the change in body weight with combination therapy of SGLT-2I plus DPP-4I across these studies.

Safety analysis

No significant exacerbation in hypoglycemia observed with combination therapy of SGLT-2I and DPP-4I compared to either drug alone.[19-27] Most of the studies reported similar genitourinary infection in combination arm, compared to SGLT-2I alone. This side effect is intrinsic to the mechanism of SGL-2TI and well known. Intriguingly, Rosenstock *et al*. reported lesser rate of genital infection in combination arm of dapagliflozin plus saxagliptin (0%), compared to dapagliflozin (6%) or saxagliptin (0.6%) alone.[20] And, lesser rate of urinary infection also observed in combination arm of dapagliflozin with saxagliptin (0.6%), compared to saxagliptin (5%) or dapagliflozin (5%) alone in the same study. Similar trends were observed in DeFronzo *et al*. study, where FDC of empagliflozin plus linagliptin had less genital and urinary tract infections compared to empagliflozin monotherapy.[24] However, volume depletions were apparently similar in all arms. Table 2 summarizes the adverse events noted with this combination therapy. Figure 3 depicts the genital infection with combination therapy of DPP-4 and SGLT-2 seen in these two studies.

To summarize, the use of SGLT-2I or empagliflozin, in particular, is likely to increase in clinical practice, considering its unprecedented CV benefit seen in EMPA-REG CV OUTCOME® Trial. However, a significant reduction of HbA1c to achieve glycemic target and to prevent

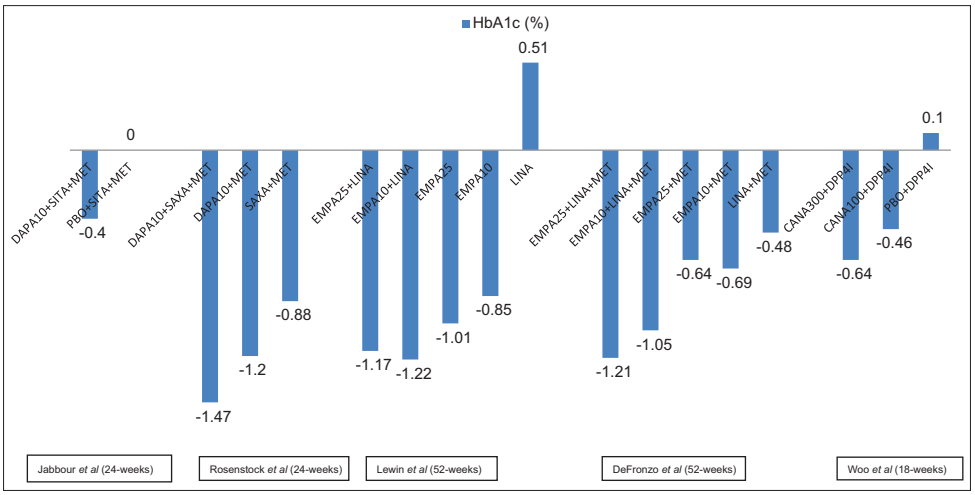

Figure 1: Change in hemoglobin A1c with dipeptidyl peptidase-4 inhibitors and sodium-glucose co-transporter-2 inhibitors combination therapy

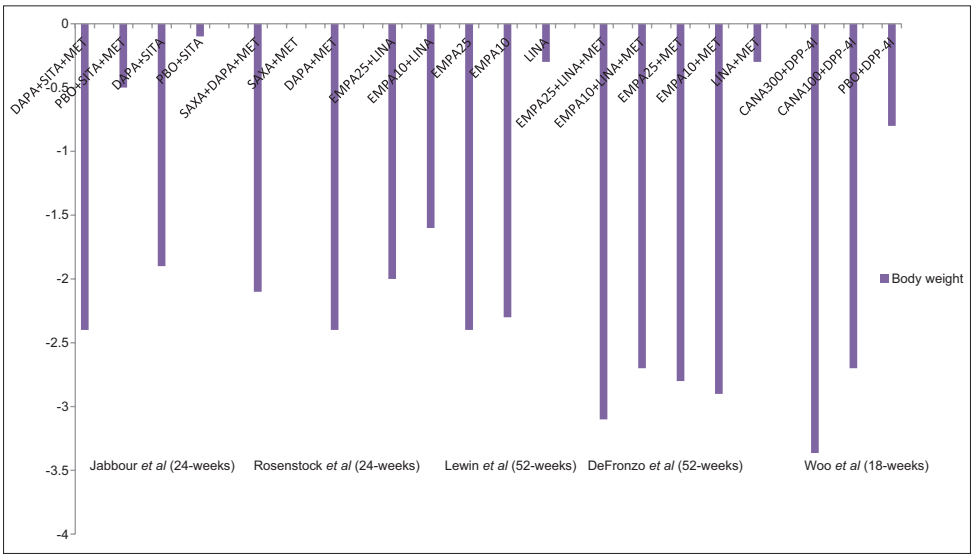

Figure 2: Body weight change (kg) with combination therapies of dipeptidyl peptidase-4 inhibitors and sodium-glucose co-transporter-2 inhibitors

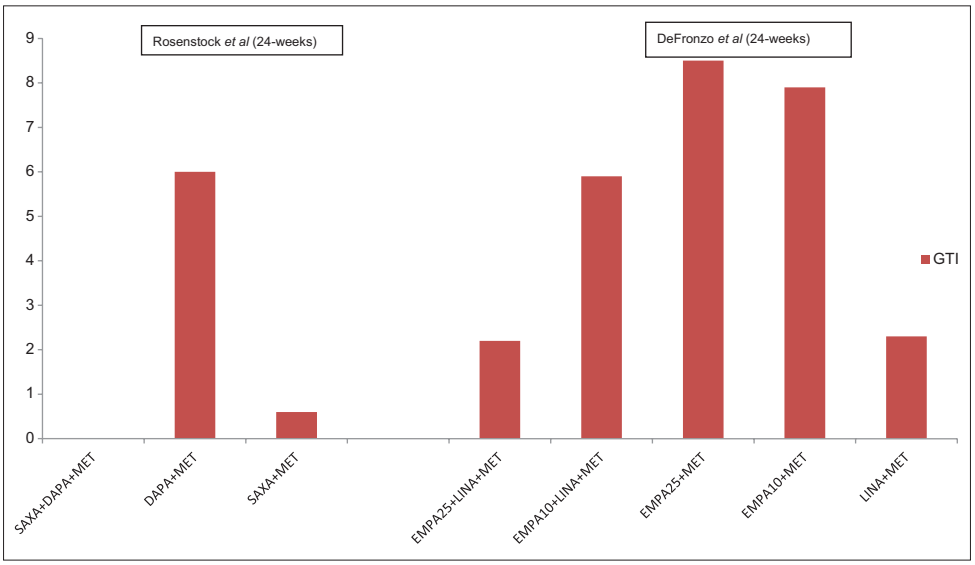

Figure 3: Rate of genital infection (%) with combination therapy of dipeptidyl peptidase-4 inhibitors and sodium-glucose co-transporter-2 inhibitors

micro-vascular benefit has not been demonstrated in this study. Combination of SGLT2-I and DPP-4I appears to lower HbA1c and body weight much more robustly, than either agent alone, without any further increase in hypoglycemia. However, the most pertinent and thought-provoking question is - which order of drugs would yield maximal benefit in HbA1c reduction?

Two studies presented recently, with opposite sequence of adding drugs give some clue in this regard. While addition of dapagliflozin to saxagliptin plus metformin therapy reduced FPG, 2-h PPG, and HbA1c (Δ −28 mg/dl, −36 mg/dl and −0.72%, respectively, all $P < 0.0001$) significantly, addition of saxagliptin to dapagliflozin plus metformin therapy did not reduce FPG and 2-h PPG significantly (Δ −4 mg/dl, $P = 0.32$; −6 mg/dl, $P = 0.20$, respectively), even though HbA1c reduction was significant (Δ −0.35%, $P < 0.001$).[21,22] Figures 4 and 5 depict this result. This may perhaps suggest that sequential addition of DPP-4I first, followed by SGLT-2I, to the background metformin therapy, can yield better glycemic control, compared to initial SGLT-2I, followed by DPP-4I. However, the proportion of patients achieving the target HbA1c of <7% were almost the same at the end of study, irrespective of the sequence used. In addition, the first approach with initial DPP-4I after metformin will miss the opportunity of CV outcome benefit, if at all it is class effect and observed with empagliflozin studies. It would also be worth interesting to find CV outcome, with a combination of DPP-4I and SGLT-2I therapy. Unfortunately, no such study is currently undergoing or being planned as of now.

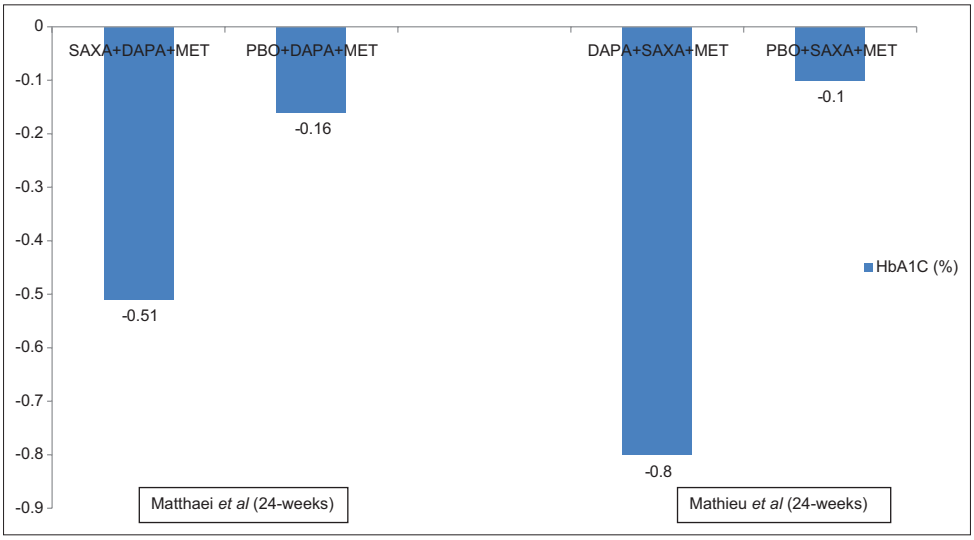

Figure 4: Change in hemoglobin A1c with addition of saxagliptin to ongoing dapagliflozin plus metformin therapy (left panel, Matthaei *et al.*) and addition of dapagliflozin to ongoing saxagliptin plus metformin therapy (right panel, Mathieu *et al.*)

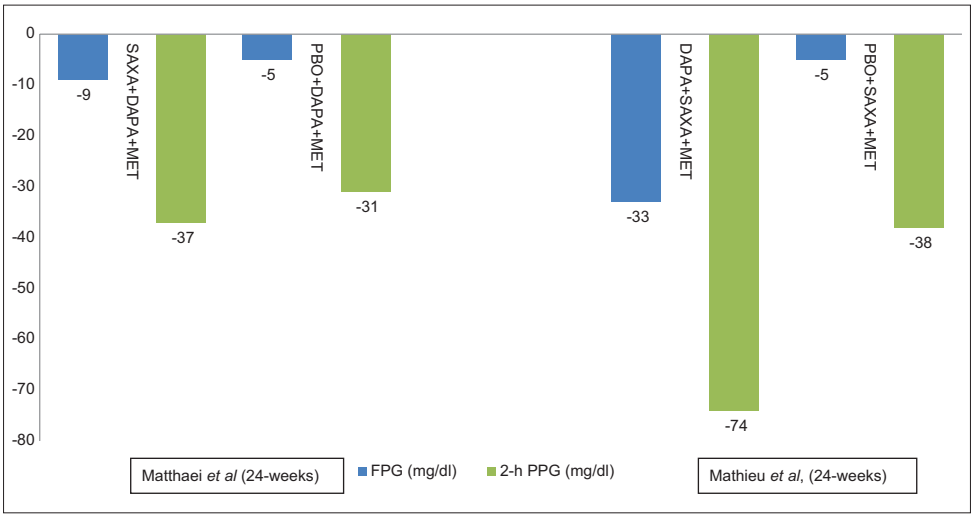

Figure 5: Change in fasting plasma glucose and postprandial plasma glucose with addition of saxagliptin to ongoing dapagliflozin plus metformin therapy (left panel, Matthaei *et al.*) and addition of dapagliflozin to ongoing saxagliptin plus metformin therapy (right panel, Mathieu *et al.*)

Table 2: Safety data of combination therapy with DPP-4 and SGLT-2 inhibitors

Study	Participants	Intervention	Weeks	Hypoglycemia (%)	UTI (%)	GTI (%)	Volume depletion (%)
Tanizawa *et al*	A=35	A=TOFO 20 + DPP4i	52	2.9	2.9	NR	NR
	B=68	B=TOFO 40 + DPP4i		1.5	1.5		
Rosenstock *et al*	A=179	A=SAXA + DAPA + Met	24	1	0.6	0	NR
	B=176	B=SAXA + Met		1	5	0.6	
	C=179	C=DAPA + Met		1	5	6	
Lewin *et al*	A=134	A=EMPA 25 + LINA (FDC)	24	0	12.5	5.9	0.7
	B=135	B=EMPA 10 + LINA (FDC)		0	15.4	2.9	2.2
	C=133	C=EMPA 25		0.7	10.4	4.4	0
	D=132	D=EMPA 10		3.0	16.3	5.2	0
	E=133	E=LINA		0.7	10.4	3.0	0
DeFronzo *et al*	A=134	A=EMPA 25 + LINA (FDC) + Met	24	3.6	10.2	2.2	0.7
	B=135	B=EMPA 10 + LINA (FDC) + Met		2.2	9.6	5.9	1.5
	C=140	C=EMPA 25 + Met		3.5	13.5	8.5	1.4
	D=137	D=EMPA 10 + Met		1.4	11.4	7.9	0.7
	E=128	E=LINA + Met		2.3	15.2	2.3	3.0
Sieno *et al*	A=150	A=LUSEO + SU	24	10.7	0	1.3	0.7
	B=111	B=LUSEO + DPP4i	52	0.9	2.7	1.8	1.8
Matthaei *et al*	A=153	A=SAXA + DAPA + Met	24	1.3	5.2	0	NR
	B=162	B=PBO + DAPA + Met		2.5	3.7	2.5	
Mathieu *et al*	A=160	A=DAPA + SAXA + Met	24	1.3	5.0	5.0	NR
	B=160	B=PBO + SAXA + Met		0	6.3	0.6	
Woo *et al*	A=111	A=CANA 300 + DPP4i	18	4.2	4.5	22.9	3.6
	B=103	B=CANA 100 + DPP4i		3.0	6.8	18.0	0
	C=102	C=PBO + DPP4i		0	1.0	4.1	0

UTI: Urinary tract infection, GTI: Genital tract infection, DAPA: Dapagliflozin, SITA: Sitagliptin, SAXA: Saxagliptin, EMPA: Empagliflozin, CANA: Canagliflozin, LINA: Linagliptin, SU: Sulfonylurea, TOFO: Tofogliflozin, LUSEO: Luseogliflozin, Met: Metformin, PBO: Placebo, DPP4i: Dipeptidyl peptidase-4 inhibitor, FDC: Fixed dose combination, NR: Not reported/not retrievable

Conclusion

Combination therapy with SGLT-2I and DPP-4I is a rational approach, both physiologically and pharmacologically. It is well documented now that SGLT-2I increases glucagon either directly by α-cell of pancreas or indirectly, as a compensatory response to glucosuria. Consequently, there is a significant increase in EGP with SGLT-2I, mediated via glucagon or as a compensatory response to glucosuria. This increase in EGP effectively blunts the glucose-lowering potential of SGLT-2I. DPP-4I, being a potent glucagon lowering agents, will counter this potential increase in EGP or glucagon or both. Thus, combination therapy with these two agents appears appealing and expected to be synergistic in reducing HbA1c. Moreover, PK-PD studies, suggesting no drug-drug interaction between SGLT-2I and DPP-4I, make them a pharmacologically suitable combination.

Several studies conducted so far with the combination therapy of SGLT2-I and DPP-4I, find them an effective tool of HbA1c lowering, without provoking further hypoglycemia. Associated weight loss reduction observed with this combination is an added advantage over DPP-4I monotherapy. Interestingly, some studies also found reduced rate of genito-urinary infections associated with the combination therapy, compared to SGLT-2I alone. This finding is intriguing yet encouraging although, that needs to be confirmed through many more trials. However, these interpretations must be interpreted in light of several limitations, such as different designs, heterogeneity in studies, and noninclusion of placebo arm, in some of these studies. Moreover, further evaluation is also necessary regarding pharmacoeconomic benefits of these combination therapies.

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Conflicts of interest

There are no conflicts of interest.

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