OPINION

Expert Opinion: Use of sodium glucose co-transporter type-2 inhibitors in South Asian population -The Pakistan perspective

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Abstract

Sodium-glucose co-transporter type 2 inhibitors (SGLT 2-i)are increasingly being used in the management of type 2 diabetes mellitus (T2DM). With the novel insulin-independent glycosuric action, these agents help to attain glycaemic goals by lowering HbA1c and fasting blood glucose. In addition, these agents improve metabolic control in diabetes and ameliorate comorbidities like obesity and hypertension. Beneficial effects on cardiovascular outcomes have been a key attraction for physicians. These agents are used alone or in combination with oral antidiabetic agents and insulin to attain glycaemic and metabolic targets. A major disadvantage with these agents is the increased risk for genital and urinary infections. When used in appropriate settings, there is no additional increased risk of hypoglycaemia or volume depletion with these agents. Available evidence suggests good efficacy and safety of these agents in diabetes management. The easy and convenient once-daily dosing should be customized according to patient needs and glycaemic profiles.

Keywords: Diabetes, SGLT-2, dapagliflozin, canagliflozin, empagliflozin, ertugliflozin

Introduction

Diabetes is a global public health problem. The burden of diabetes is specifically high in the South East-Asia (SEA) region. The region is currently home to more than 72 million patients with diabetes and the numbers are projected to increase to 123 million in 2035. This can be explained by the changing lifestyle in this region given the evolution towards urbanization. T2DM is the predominant type (>95%) of diabetes in this region.[1]

T2DM characterized by high plasma glucose levels, has a chronic and progressive course which can culminate in end-organ damage. Novel therapies are continuously being evaluated to help attain glycaemic targets with ease and convenience.

Sodium-glucose co-transporter type 2 (SGLT-2) is an emerging target in the management of diabetes. Located at the proximal convoluted tubules, SGLT-2 has an important physiological role in renal glucose reabsorption. Pharmacological inhibition of SGLT-2 increases urinary glucose excretion and decreases plasma glucose levels. Additional metabolic effects including development of a calorie restricted and ketogenic state, SGLT-1 inhibition, and optimization of insulin:glucagon ratio, can lead to glycaemic benefits with SGLT-2 inhibitors.[2]

The action of SGLT-2 inhibitors is independent of insulin and these agents can be used as monotherapy or in addition to oral antidiabetic drugs (OADs) or insulin to control hyperglycaemia.[24] SGLT-2 inhibitors have been used in both the initiation and intensification of therapy of T2DM. The approved drugs in this class include dapagliflozin (2012), canagliflozin (2013), empagliflozin (2014), and ertugliflozin (2017). SGLT-2 inhibitors are indicated as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM. Another agent, ipragliflozin has been approved in Japan. The available SGLT-2 inhibitors differ in their relative selectivity for SGLT-2 versus SGLT-1. Empagliflozin is the most selective for SGLT-2 (42500:1), followed by dapagliflozin (41200:1) and canagliflozin (4250:1).[3]

In SEA, experience with SGLT-2 inhibitors is limited. Many of the key trials for SGLT-2 have Asian centers but there are no reports for the comparison of outcomes in the Asian and rest of the population. Real-world experience with SGLT-2 has been reported for SEA. In a post-hoc analysis, canagliflozin 100 and 300 mg provided clinically meaningful reductions in glycohaemoglobin (HbA1c) in Indian patients (124) and in overall population (n=2313)

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Table-1: Efficacy and safety of monotherapy with SGLT-2 inhibitors.

Reference (Sample, duration)	Pharmacotherapy	Key efficacy parameters				Key safety parameters		
		Baseline HbA1c (%)	Baseline FBG (mg/dl)	ΔHbA1c from baseline (%)	ΔFBG from baseline (%)	Hypoglycemic events (%)	Genital tract infections (%)	Urinary tract infections (%)
Kaku 2013 (n=279; 12 W)	D: 1, 2.5, 5 or 10 mg or P	8.1	162	D: -0.11 to -0.44 P: 0.37	D: -15.6 to -31.9 P: 11.2	0-2 vs. 2	0-2 vs. 0	0-4 vs. 2
Roden 2013 (n=899; 24 W)	Em: 10 or 25 mg or S or P	7.9	151.6	Em: -0.66, -0.78 S: -0.66 P: 0.08	Em: -19.4, -24.5 S: -6.8 P: 11.7	<1 vs. <1	5-12 vs. 0	14-17 vs. 9
Terra 2017# (n=461; 26+26 W*)	Er: 5 or 15 mg or P	8.2	183	Er: -0.79, -0.96 P: 0.20		2, 2 vs. 4	14, 19 vs. 5	13, 11 vs. 6

C: Canagliflozin; D: Dapagliflozin; Em: Empagliflozin; Er: Ertugliflozin; HbA1c: Glycosylated hemoglobin; M: Metformin; OD: Once daily; P: Placebo; S: Sitagliptin; SGLT-2: Sodium-glucose cotransporter type 2; W: weeks. All studies were in treatment-naïve patients of T2DM; #Washout allowed; *26 weeks of placebo control followed by 26 weeks of active control (Metformin). All SGLT-2inhibitors were administered in once daily dosing.

from four pooled Phase 3 studies (-0.74% and -0.88% vs. -0.81% and -1.00%). The reductions in fasting blood glucose (FBG), body weight, and blood pressure (BP) in the Indian subgroup were consistent with findings in the overall population.[4] In a prospective experience from clinical practice in India (n=100), SGLT-2 inhibitors lead to significant reductions in HbA1c(1.02±0.24%) and body weight (2.64±1.27 kg) irrespective of the background treatment regimen for T2DM.[5] In a retrospective review of a clinical database in India (n=9; follow up: 16 weeks), canagliflozin reduced HbA1c from 9.0% at baseline to 6.8% at follow up (P <0.005). There was reduction in body weight and requirement or dose of OADs during follow up.[6]

The treatment with SGLT2-inhibitors in T2DM patients is associated with improved glycaemic control and other non-glycaemic outcome including relative risk reduction in cardiovascular death and in all-cause mortality among those with T2DM and cardiovascular disease.The survival benefit in the EMPREG OUTCOME trial was greater for younger patients and diminished compared with placebo as the study patients aged: The mean differences between patients taking empagliflozin and those taking placebo were 4.5 years at age 45, 3.1 years at age 50, 2.5 years at age 60, 2.0 years at age 70, and 1 year at age 80.[7]

In this paper, we review the existing evidence for the efficacy and safety of SGLT-2 inhibitors to guide the adoption of these agents in Pakistan.

Monotherapy with SGLT-2 inhibitors

Monotherapy with SGLT-2 inhibitors has helped to improve glycaemic control in T2DM (Table 1).

Dapagliflozin has shown good efficacy in both placebo and active controlled trials in treatment-naive patients with T2DM. When compared to placebo, significant reductions in HbA1c are reported with dapaglifozinin patients with poorly controlled T2DM.[8]

In a placebo-controlled, phase 3 trial, patients of T2DM who had not received pharmacological treatment in the last 12 weeks were randomized to receive once daily dose of placebo (n=228), empagliflozin10 mg (n=224), empagliflozin 25 mg (n=224), or sitagliptin 100 mg (n=223). At week 24, adjusted mean differences in change from baseline HbA1c when compared to placebo were -0·74% (95% CI -0·88 to -0·59; p<0·0001) for empagliflozin 10 mg, -0·85% (-0·99 to -0·71; p<0·0001) for empagliflozin 25 mg, and -0·73% (-0·88 to -0·59; p<0·0001) for sitagliptin.[9]

In a 26-week, placebo controlled, phase 3 study, 461 patients with T2DM were randomized to receive ertugliflozin 5 or 15 mg, or placebo. For the two doses of ertugliflozin, the placebo-adjusted least squares (LS) mean HbA1c changes from baseline were -0.99% and -1.16%, respectively (P<0.001 for both).[10]

Add-on therapy with SGLT-2 inhibitors

SGLT-2 inhibitors have been used with OADs (Table 2) as well as insulin (Table 3) for the achievement of glycaemic targets in T2DM.

Table-2: Efficacy and safety of SGLT-2 inhibitors as add-on treatment with oral hypoglycemic agents.

Reference (Sample, duration)	Pharmacotherapy	Key efficacy parameters				Key safety parameters		
		Baseline HbA1c (%)	Baseline FBG (mg/dl)	ΔHbA1c from baseline (%)	ΔFBG from baseline (%)	Hypoglycemic events (%)	Genital tract infections (%)	Urinary tract infections (%)
Lavalle Gonzalez 2013 (n=1020; 52 W)	Add-on to M C: 100 or 300 mg or P or S	7.9	169.2	C: -0.73, -0.88 P: -0.6 S: -0.73	C: -26.2, -35.2 P: -17.8 S: -17.7	NR	12-16 vs. 1	5-8 vs. 7
Wilding 2013 (n=469; 26 W)	Add-on to M+SU C: 100 or 300 mg or P	8.1	170	C: -0.85, -1.06 P: -0.13	C: -18.0, -30.6 P: 3.6	33.8, 36.5 vs. 17.9	5.7-18.8 vs. 1.3-5.0	8.3 vs. 7.7
Forst 2014 (n=342; 26+26 W*)	Add-on to M+PIO C: 100 or 300 mg or P	7.9	165.8	C: -0.89, -1.03 P: -0.26	C: -26.8, -33.2 P: 2.5	4.4, 6.1 vs. 6.1**	3.9-16.7, 4.8-21.6 vs. 7.7**	5.3, 7.9 vs. 7.8**
Schernthaner 2013 (n=755; 52 W)	Add-on to M+SU C: 300 mg or S	8.1	167.4	C: -1.03 S: -0.66	C: -30.6 S: -5.4	43 vs. 41	12 vs. 2	4 vs. 6
Haring 2014 (n=637; 24 W)	Add-on to M Em: 10 or 25 mg or P	7.9	155	Em: -0.70, -0.77 P: -0.13	Em: -20, -22 P: 5.0	1.8, 1.4 vs. 0.5	3.7, 4.7 vs. 0	5.1, 5.6 vs. 4.9
Rosenstock 2018 (n=621; 26 W)	Add-on to M Er: 5 or 15 mg or P	8.1	167	Er: -0.7, -1.0 P: -0.2	Er: -1.5, -2.2 P: -0.1	3.4, 3.4 vs. 1.9	3.1-5.5, 3.2-6.3 vs. 0.9	2.9, 3.4 vs. 1.0
Pratley 2018^ (n=1233; 26+26 W)	Add-on to M vs. S or Er+S Er: 5 or 15 mg	8.6	180	E5: -1.0 E15: -1.1 S100: -1.1 E5/S100: -1.5 E15/S100: -1.5	E5: -35.7 E15: -36.9 S100: -25.6 E5/S100: -44.0 E15/S100: -48.7	E5: 2.4 E15: 2.4 S100: 2.4 E5/S100: 2.5 E15/S100: 4.9	E5: 4.9 E15: 7 S100: 1.1 E5/S100: 5 E15/S100: 7.6	E5: 5.2 E15: 5.6 S100: 3.2 E5/S100: 3.3 E15/S100: 3.7
Dagogo-Jack 2018^^ (n=463; 26+26 W)	Add-on to M+S Er: 5 or 15 mg or P	8.0	169.7	E: -8.9, -9.4 P: -1.7	E: -26, -31 P: -2.5	3.8, 0.7 vs. 2.6	4.9-8.0, 3.7-12.7 vs. 1.9	2.6, 4.6 vs. 2.0
Miller 2018 (n=291; 26 W)	Add-on to S Er: 5 or 15 mg or P	8.9	197.8	E: -1.7, -1.7 P: -0.8	E: -48.2, -55.4 P: -9.3	3.1, 3.1 vs. 1	5.3-4.9, 1.9-7.0 vs. 5	8.2, 3.1 vs. 5.2
Hollander 2018 (n=1326; 52 W)	Add-on to M Er: 5 or 15 mg or Gm	7.8	160	E: -0.6, -0.6 Gm: -0.7	E: -20, -24 Gm: -16	3.1, 5.2 vs. 19.2	4.4-7.7, 2.1-10.0 vs. 1.4	6.7, 6.4 vs. 0.7

C: Canagliflozin; D: Dapagliflozin; Em: Empagliflozin; Er: Ertugliflozin; Gm: Glimepiride; Gp: Glipizide; HbA1c: Glycosylated hemoglobin; M: Metformin; NR: Not reported; OD: Once daily; OHA: Oral hypoglycemic agents; P: Placebo; PIO: Pioglitazone; S: Sitagliptin; SGLT-2: Sodium-glucose cotransporter type 2; SU: Sulphonylurea; W: weeks. *26 weeks of placebo control followed by 26 weeks of active control (Sitagliptin); **Over 52 weeks. All SGLT-2inhibitors were administered in OD dosing; ^Genital infections in females; ^^Data reported for 26 weeks.

SGLT-2 inhibitors with OADs

Dapagliflozin has been studied as add-on therapy to metformin, glimiperide, pioglitazone, and sitagliptin. As add-on therapy to metformin, canaglifozin has been compared to placebo, sitagliptin, and glimepiride.[11] In a 52-week phase 3 trial, 1020 patients with T2DM inadequately controlled with metformin were randomized to receive canagliflozin 100 mg, 300 mg, sitagliptin 100 mg, or placebo. At 26 weeks, canagliflozin (100 mg and 300 mg/day) significantly reduced HbA1c relative to placebo (-0.62% and -0.77%, respectively). At 52 weeks, both doses of canagliflozin were non-inferior and canagliflozin 300 mg was superior to sitagliptin in lowering HbA1c (-0.73%, -0.88%, and -0.73%, respectively).[11]

Benefits are also reported for add-on therapy with canagliflozin in patients of T2DM who are being treated with one or more sulphonylureas. In a phase 3 study, 469 patients of T2DM inadequately controlled with metformin and sulphonylurea, received canaglifozin 100 or 300 mg or placebo in once daily dosing. At week 26, HbA1c was significantly reduced with canagliflozin 100 and 300 mg vs. placebo (-0.85%, -1.06%, and -0.13%; p <0.001). These reductions were sustained at week 52 (-0.74%, -0.96%, and 0.01%).[12] Schernthaner et al. (2013) compared canagliflozin 300 mg/day with sitagliptin 100 mg/day in patients of T2DM inadequately controlled with metformin plus sulfonylurea. At 52 weeks, canagliflozin 300 mg was superior to sitagliptin 100 mg in reducing HbA1C (-1.03% and -0.66%, respectively; least squares mean difference between groups, -0.37% [95% CI, -0.50 to -0.25]).[13] In another phase 3 study in patients with T2DM inadequately controlled with metformin and pioglitazone (n=342),

Table-3: Efficacy and safety of SGLT-2 inhibitors as add-on treatment with insulin.

Reference (Sample, duration)	Pharmaco-therapy	Key efficacy parameters				Key safety parameters			Changes in weight and BP	
		Baseline HbA1c (%)	Baseline FBG (mg/dl)	ΔHbA1c from baseline (%)	ΔFBG from baseline (%)	Hypoglycemic events (%)	Genital tract infections (%)	Urinary tract infections (%)	Reduction in weight	Reduction in BP
Neal 2015 (n=2072; 52 W)	C: 100 or 300 mg or P	8.3	165	C: -0.55, -0.69 P: -0.03	NR	80 vs. 66	15 vs. 3	7 vs. 8		
Wilding 2012 (n=800; 48 W)	D: 2.5, 5 or 10 mg or P	8.6	177.5	D: -0.79 to -1.01 P: -0.47	D: -12.4 to -16.9 P: NR	60 vs. 52	11 vs. 3	11 vs. 5	D: Reduced by 0.92 to 1.61 kg P: Increased by 0.43 kg	
Wilding 2013 (n=808; 104 W)	D: 2.5, 5 or 10 mg or P	8.6	179.0	D: -0.64 to -0.78 P: -0.43	D: -20.5 to -23.4 P: -18.0	61-70 vs. 62	13-35 vs. 6	17-20 vs. 11	D: Reduced by 0.9 to 1.4 kg P: Increased by 1.8 kg	
Rosenstock 2015 (n=494; 78 W)	Em: 10 or 25 mg or P	8.2	143	E: -0.5, -0.6 P: 0	E: -18, -20 P: 10	33-35 vs. 33	10-12 vs. 8	4-8 vs. 4	Em 10 mg: −2.2 ± 0.5 kg Em 25 mg: −2.0 ± 0.5 kg P: 0.7 ± 0.5 kg	Em 10mg vs. P: SBP: −4.1 ± 1.0 mmHg vs 0.1 ± 1.0 mmHg; DBP: −2.9 ± 0.7 mmHg vs. −0.3 ± 0.6 mmHg (p = 0.004 for both). No significant changes with 25 mg Em.

BP: Blood pressure; C: Canagliflozin; D: Dapagliflozin; Em: Empagliflozin;HbA1c: Glycosylated hemoglobin; NR: Not reported; OD: Once daily; P: Placebo; S: SGLT-2: Sodium-glucose cotransporter type 2; W: weeks.All SGLT-2inhibitors were administered in OD dosing.

canagliflozin 100 or 300 mg significantly lowered HbA1c compared with placebo at week 26 (-0.89%, -1.03% and -0.26%; p <0.001).[14]

In a 24-week trial, subjects with T2DM and HbA1c levels ≥7% to ≤10% while on treatment with metformin (≥1,500 mg/day) were randomized to receive once-daily treatment with empagliflozin 10 mg (n=217), empagliflozin 25 mg (n=213), or placebo (n=207) for 24 weeks. The mean (SE) changes from baseline in HbA1c with placebo, empagliflozin 10 mg, and empagliflozin 25 mg were -0.13% (0.05), -0.70% (0.05), and -0.77% (0.05) respectively (P <0.001 for both doses).[15]

In the 26-week VERTIS MET trial, add-on therapy with ertugliflozin 5 or 15 mg or placebo was studied in 621 patients with T2DM receiving metformin (≥1,500 mg/d for ≥8 weeks). In this study, the placebo-adjusted LS mean change from baseline HbA1c was -0.7% and -0.9% for the two doses of ertugliflozin, respectively (both P<0.001).[16] In the 52-week VERTIS FACTORIAL trial (n=1233), patients receiving metformin were randomized to add-on therapy with ertugliflozin 5 (E5) or 15 (E15) mg/d, sitagliptin 100 mg/d (S100), E5/S100 or E15/S100. At 26 weeks, the least square mean HbA1c reductions from baseline were -1.0%, -1.1%, -1.1%, -1.5%, and -1.55, respectively for the dosing groups (P <0.001 for all comparisons).[17] In another trial (VERTIS SITA 2) for add-on ertugliflozin in patients receiving metformin ≥1,500 mg/day and sitagliptin 100 mg/day, ertugliflozin 5 and 15 mg reduced HbA1c at 26 weeks by -0.7%, and -0.8%, respectively (both P<0.001) compared with placebo.[18] In the 26-week VERTIS SITA study, the least squares mean HbA1c change (95% confidence intervals) from baseline was - 0.4% (- 0.7, - 0.2), - 1.6% (- 1.8, - 1.4), and - 1.7% (- 1.9, - 1.5) with ertugliflozin 5 mg+ sitagliptin 100 mg, ertugliflozin 15 mg+ sitagliptin 100 mg, and placebo, respectively.[19] In the VERTIS SU study, 1326 patients inadequately controlled on metformin (≥1500 mg/day) were randomized (1:1:1) to ertugliflozin receive 5 or 15 mg once-daily, or glimepiride (titrated from 1 mg/day; Mean daily dose: 3 mg). At week 52, the least squares mean change (95% CI) from baseline in HbA1c was - 0.6% (- 0.6, - 0.5), - 0.6% (-0.7, -0.5), and - 0.7% (-0.8, -0.7) in the three groups, respectively.[20]

SGLT-2 inhibitors with insulin

In the double-blind, placebo-controlled CANagliflozin CardioVascular Assessment Study (CANVAS), patients of T2DM who were being treated with insulin were randomized to receive canagliflozin 100 mg (n = 692), canagliflozin 300 mg (n = 690), or placebo (n = 690). Reductions in HbA1c with canagliflozin 100 and 300 mg versus placebo were -0.62% (95% CI -0.69, -0.54; P <0.001) and -0.73% (95% CI -0.81, -0.65; P <0.001) at 18 weeks and

-0.58% (95% CI -0.68, -0.48) and -0.73% (95% CI -0.83) at 52 weeks.[21]

In a double-blind, three-arm parallel-group (1:1:1) trial, 71 patients were randomly assigned to placebo, 10 mg dapagliflozin, or 20 mg dapagliflozin, plus OAD(s) and 50% of their daily insulin dose. At 12 weeks, the 10- and 20-mg dapagliflozin groups demonstrated -0.70 and -0.78% mean differences in A1C change from baseline versus placebo.[22] In a double-blind, four-arm parallel-group (1:1:1:1) trial, 800 patients were randomly assigned to receive placebo or 2.5, 5, or 10 mg of dapagliflozin, once daily. At 24 weeks, mean HbA1c decreased by 0.79% to 0.96% with dapagliflozin compared with 0.39% with placebo while the daily insulin dose decreased by 0.63 to 1.95 U with dapagliflozin and increased by 5.65 U with placebo.[23] In another placebo-controlled, double-blind study, 808 patients with T2DM inadequately controlled with insulin ≥30 IU/day with or without up to two OADs, were randomly assigned to receive placebo or 2.5, 5 or 10 mg/day of dapagliflozin. At 104 weeks, mean HbA1c changes from baseline were -0.4% in the placebo group and -0.6 to -0.8% in the dapagliflozin groups.[24] In a 78-week phase 3 clinical trial of empagliflozin as add-on to basal insulin in adults with T2DM, empagliflozin when compared to placebo, significantly reduced the HbA1c levels at 18 and 78 weeks. The study was designed to include an 18-week constant-dose period for insulin after which the dose was adjusted at investigator's discretion. At 18 and 78 weeks, the placebo-adjusted changes in HbA1c for empagliflozin 10 mg and 25 mg were -0.6% and -0.7% (P <0.001), respectively, and -0.5% and -0.6%, respectively (P <0.001). At week 78, empagliflozin therapy resulted in significant reduction in the required daily insulin dose.[25]

In another randomized, double-blind, placebo-controlled, parallel-group study (n=563) empagliflozin 10 mg and 5 mg reduced insulin doses (-9 to -11 IU/day) at week 52.[9]

Non-glycemic benefits of SGLT-2 inhibitors

Besides control of glucose levels, metabolic goals in the management of T2DM include targets for weight, lipids, and blood pressure (BP) and cardiovascular risk reduction. The effect of SGLT-2 inhibitors on these parameters have been reported in various clinical studies.

Effects on weight

Insulin, insulin secretagogues, and other OADs are known to cause an increase in weight. This makes a metabolic paradox for the achievement of therapeutic targets in T2DM. Experience with SGLT-2 inhibitors in clinical studies yields evidence for weight reduction with these agents as monotherapy as well combination therapy with OADs and insulin.

Dapagliflozin monotherapy was associated with a significant weight reduction (-1.9 kg) relative to placebo in a 12-week study in Japanese patients [8]. Similarly, canagliflozin 300 mg added to metformin plus sulfonylurea mitigated the increase in weight(-2.3 kg) when compared with sitagliptin (+0.1 kg).[13]

The reduction in weight is of relevance to plan pharmacotherapy for the management of T2DM as obesity is a common problem in SEA. This is a desirable effect for SGLT-2 inhibitors when used in combination with agents known to increase weight (example, insulin and pioglitazone).[2]

Effects on blood pressure

SGLT-2 inhibitor therapy has shown favourable and sustained improvements in BP in patients with T2DM. The lowering of BP may be attributable to the physiological effects of SGLT-2 inhibitors including osmotic diuresis, natriuresis, reductions in arterial stiffness, and modulations in nitric oxide release.[2] Hypertension in a common comorbidity with T2DM in the SE Asian region where benefits of SGLT-2 inhibition can be potentially multifold. Over 52 weeks, canagliflozin (300 mg/day) achieved a significant reduction (-5.1 mmHg) in systolic BP compared to sitagliptin (100 mg/day) (+0.9 mmHg).[13] Favourable reductions in systolic BP are also reported with empagliflozin when compared to placebo and sitagliptin [9]. In a 24-week study, empagliflozin (10 and 25 mg/day) led to greater reductions in systolic BP (-2.9 and -3.7, respectively) when compared to placebo (-0.3 mmHg).[9]

Effects on lipids

Variable and inconsistent effects of SGLT-2 inhibitors are reported for HDL, LDL and total cholesterol levels [2]. Insignificant effects on LDL levels are reported for dapagliflozin in some studies.[8,12] Rise in LDL levels was reported with canagliflozin (300 mg) when compared to placebo (4.3 and 6.8 mg/dl) and sitagliptin (5.9 mg/dl).[12,13]

Effects on cardiovascular outcome risk reduction

Improved cardiovascular outcomes have been demonstrated with use of SGLT2 inhibitors. Empagliflozin significantlyreduced the risk of cardiovascular death when compared to placebo (3.7 vs 5.9%; HR 0.62, 95% CI 0.49-0.77).[7] In the CANVAS trial (n=10142), cardiovascular death or hospitalizations for heart failure were reduced in patients treated with canagliflozin compared with placebo (16.3% vs 20.8% per 1000 patient-years; HR: 0.78; 95% CI: 0.67-0.91).[26]

In the placebo-controlled, phase III (n=17150) DECLARE-TIMI 58 cardiovascular outcomes trial (CVOT), dapagliflozin resulted in a lower rate of CV death or hospitalization for heart failure (4.9% vs. 5.8%; HR: 0.83; 95% CI, 0.73-0.95; P=0.005) but not a lower risk of major adverse cardiovascular event (8.8% vs. 9.4%; HR: 0.93; 95% CI, 0.84 -1.03; P=0.17).[27]

The ongoing VERTIS CV Study is evaluating the cardiovascular outcomes with ertugliflozin in patients of T2DM having vascular disease (NCT01986881). Such studies may find relevance to the SEA populations given the higher risk of cardiovascular complications in these patients.

Effects on NASH/ NAFLD

Dapagliflozinis associated with significant reduction in liver fat content. In the EFFECT-II study, dapagliflozin, either alone or in combination with omega-3 carboxylic acids (OM3CA) reduced liver fat content when compared to baseline values (relative changes: OM-3CA, -15%; dapagliflozin, -13%; OM-3CA + dapagliflozin, -21%). The combination treatment reduced total liver fat volume (relative change, -24%, p = 0.037) in comparison with placebo.[28] Although these effects are very significant and important for this patient population, but mechanism is poorly understood.

Effects on albumin-to-creatinine ratio

Independent of glycaemic control and effects on body weight and BP, SGLT2 inhibitors have renoprotective effects. Empagliflozin has shown significant improvement in albumin-to-creatinine ratio (UACR) (-32% and -41%, respectively vs placebo) in T2DM patients with microalbuminuria (UACR: 30-300 mg/g; n = 636) and macroalbuminuria (UACR >300 mg/g; n = 215).[29] Safety and Monitoring of use of SGLT-2 inhibitors.

Various adverse events (AEs) have been reported with SGLT2 inhibitors. Genital and urinary tracts infections, volume depletion and hypoglycaemia are of key concerns when using SGLT2 inhibitors. Patients taking SGLT2 inhibitors and experiencing symptoms such as dizziness, difficulty in breathing, nausea, vomiting, pain in abdominal and atypical fatigue or sleepiness need to seek medical attention immediately. In case, diagnosis of acidosis/ ketoacidosis is confirmed, SGLT2 inhibitor use should be discontinued and acidosis should be treated. In addition, it is essential to monitor glucose levels. There is no experience for the use of SGLT2 inhibitors in pregnant women and use in this group of special population should always be on the discretion of the treating physician. Clinical symptoms for genital mycotic infection (pain during urination, itching, etc.), hypoglycaemia (abnormal sweat, increased hunger, fainting, unusual fatigue, nausea, vomiting, dryness in mouth, tingling lips, etc.), hypotension (fatigue, dizziness, nausea, loss of consciousness, blurry vision, etc.), impaired renal function (frequent urination, etc.), high lipid levels, UTIs (increased urinating urge, pain with urination, etc.), need to be monitored while using any SGLT2 inhibitor.

Genital and urinary tract infections: Higher rates of genital and urinary tract infections are reported with monotherapy (Table 1) and combination therapy (Table 2: OADs; Table 3: Insulin) with SGLT-2 inhibitors when compared to placebo and other active controls. The occurrence of these infections can be explained by the glycosuric action of SGLT-2 inhibitors in T2DM which is a risk factor for the development of infections. This is a class-effect with SGLT-2 inhibitors without any significant differences in one agent over another.[2] These infections are of relevance to the SE Asian population due to the cultural inhibitions in seeking treatment and the compromise in hygiene in the lower socioeconomic segments. A rare but severe complication is necrotizing fasciitis (Fournier's gangrene). At initiation of the treatment with SGLT2-inhibitors, consider taking history of current or recurrent UTI.

Hypoglycaemia- Role of SGLT-2 inhibitors in Ramadan: SGLT-2 inhibitors have a lower risk of hypoglycaemia when compared to placebo, OADs, or insulin (Tables 1-3). This can be explained by the insulin-independent mechanism of action of these agents. However, it is important to monitor patients for the risk and occurrence of hypoglycaemia and make adjustments in doses of SGLT-2 inhibitors and/or other treatments for diabetes. Religious

and cultural practices of prolonged fasting (for example, Ramadan) may predispose the SE Asian population to a higher risk of hypoglycaemia. Benefits of switching to SGLT-2 inhibitors during fasting are reported SEA population. Hypoglycaemic episodes in patients observing the Ramadan fast were significantly lower (P = 0.002) in those who switched to dapagliflozin plus metformin (6.9%) than in those who continued the earlier prescribed SU plus metformin treatment (28.8%).[30] In the Canagliflozin in Ramadan Tolerance Observational Study (CRATOS), fewer people receiving canagliflozin (n=162) experienced hypoglycaemia compared to those receiving sulphonylurea (n=159) (adjusted odds ratio: 0.273 [95% CI: 0.104, 0.719]).[31]

Volume depletion: SGLT-2 inhibitors can produce a state of volume depletion due to osmotic diuresis caused by glycosuria. This can lead to a fall in BP, postural dizziness, syncope, dehydration and reduced urinary output. A higher occurrence of these adverse events (AEs) have been reported with SGLT-2 inhibitors when compared to placebo and other active comparators.[9,12,14,20] The hot and humid weather in SE Asian countries may cause cutaneous vasodilation and compromise the orthostatic responses in patients with T2DM predisposing them to dehydration with SGLT-2 inhibitors. The cultural trends for fasting may also predispose these patients to a higher risk of dehydration. In a pooled analysis (4 randomized placebo-control and 1 active-control studies), 917 patients residing in hot climatic regions and receiving capagliflozin (100 and 300 mg) demonstrated no increased risk for volume-depletion related AEs with reductions in HbA1c, FBG, weight, and BP consistent with the rest of the population.[32] However, patients should be advised for adequate hydration and monitored for potential risk of dehydration with SGLT-2 inhibitors.

Others: Other less common AEs with SGLT-2 inhibitors include development of euglycaemic ketoacidosis, ischaemic events, reductions in bone mineral density and potentially increased risk for bladder and breast cancer.[2] These complications are very rare but should be taken into account when selecting a patient for the use of this class.

Expert Opinion

SGLT-2 inhibitors are used alone or in combination with OADs and insulin for the attainment of glycaemic targets in patients with T2DM. The insulin-independent mechanism of action makes these agents suitable for both the initiation and intensification of treatment in T2DM. SGLT-2 inhibitors, alone or in combination with OADs and insulin, help to achieve glycaemic goals by reducing HbA1c, fasting blood glucose (FBG), body weight, BP and risk of cardiac complications. These agents reduce HbA1c in patients receiving high doses of insulin along with insulin sensitizers and may also help to stabilize the dose of insulin in patients with T2DM. Favourable effects on weight, BP, and lipids explain the benefits of SGLT-2 in T2DM patients with cardiovascular and renal complications.[29,33]

The once daily oral dosing and lower risk of hypoglycaemia offer ease and convenience for treatment. Patients should be monitored for the development of genital and urinary tract infections and signs of volume depletion during treatment with SGLT-2 inhibitors.

Before initiating treatment with SGLT2 inhibitors, baseline assessments should include vitals, renal function and urine complete analysis. Cangliflozin and Empagliflozin should be discontinued at eGFR <45 mL/min/1.73 m^2 and dapagliflozin at <60 mL/min/1.73 m.[13] SGLT2 inhibitors should be discontinued in patients experiencing ketoacidosis. In the absence of sufficient data in pregnant population, treatment with SGLT2-ihibitors during pregnancy cannot be advocated, till more scientific information is available for potential benefit and risk to the fetus.

SGLT-2 inhibitors can benefit patients with T2DM who are overweight and obese, at higher risk of hypoglycaemia with OADs and insulin, and have contraindications or intolerance to other pharmacological options. Additionally, SGLT-2 inhibitors may benefit patients of T2DM with high risk of cardiovascular and renal complications. Treatment in patients in the SE Asian countries should be customized according to the patterns of diet, weather conditions, and lifestyle.

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