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Therapeutic Potential of SGLT2 Inhibitors in Treating Type 2 Diabetes Mellitus

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Abstract

Current therapies in type 2 diabetes management lose their efficacy because of their dependence on β-cell function which decreases with the passage of time. In kidneys, filtered glucose is reabsorbed mostly by the sodium glucose cotransporter-2 (SGLT-2) proteins which are located in the S1 segment of proximal convoluted tubules. SGLT2 inhibitors reduce this reabsorption process by blocking SGLT2 proteins and reduce glycemic levels by promoting urinary glucose excretion which is an insulin independent phenomenon. This loss of glucose in urine is also associated with decrease in body weight by creating an energy deficit and to some extent reduction in blood pressure due to an osmotic diuretic effect. This review focuses on therapeutic potential of SGLT2 inhibitors with a view to identify their role in diabetes management. The available evidence suggests that SGLT2 inhibitors are safe, efficacious and well tolerated across a large group of patients. Provided that the long term safety of this class is established, it is very likely that these agents shall assume a major role in diabetes management.

Key word: Type 2 diabetes mellitus, HbA1c, Sodium glucose cotransporter-2, Dapagliflozin, Canagliflozin, Ipragliflozin.

INTRODUCTION

Nearly 285 million people suffer from diabetes mellitus and impaired glucose tolerance around the globe and by 2030, its prevalence shall increase to 438 million.[1,2] Consequences of hyperglycemia are overwhelming; it contributes to microvascular complications namely retinopathy, neuropathy, nephropathy; and macrovascular complications namely cardiovascular and cerebrovascular disease conditions besides increased apoptosis of β-cell mass.[3-5] Normoglycemia is the goal of diabetes therapy; however, current therapeutic options fail to provide the desired level of protection against hyperglycemic threats. Type 2 diabetes which accounts for 90 percent of diabetes cases is the result of impaired insulin secretion and increased resistance to insulin action.[3,4] It is estimated that only half of the patients with a baseline HbA1c of < 7% receiving monotherapy maintain American Diabetes Association recommended targets of glycemic control over a period of three years and this figure decreases to a quarter over 9 years period.[6] Currently available therapeutic choices have their own limitations. Metformin, the first line drug in management of type 2 diabetes is associated with gastrointestinal adverse effects, sulfonylureas causes weight gain and hypoglycemia; besides this their efficacy is lost over the passage of time due to loss of β-cell mass,[7] DPP-4 Inhibitors and GLP-1 analogues are also dependent upon β-cell function and insulin has its own complications due to its injectable form, hypoglycemic risk and propensity for weight gain.[8]

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Thus a new non-insulin dependent therapeutic option was required to alleviate the risks of hyperglycemia without having any serious adverse event leading to discontinuation of therapy or seriously affecting the quality of life of patient. In quest of such a therapeutic agent, sodium glucose co-transporter 2 (SGLT2) inhibitors are developed to provide a novel mechanism of action free from pancreatic activity. This review shall focus on three agents in the class namely dapagliflozin, canagliflozin and ipragliflozin as most of the clinical data is available for these agents presently. Status of SGLT2 inhibitors in different stages of development are showed in table 1.

Table 1. Status of each SGLT2 inhibitors in late 2013

Name of Drug	Development Stage	Manufacturer
Dapagliflozin	Authorized in EU; Under review in US; Phase 3 in Japan	BMS/Astra Zeneca
Canagliflozin	Authorized in US; Under review in EU; Phase 3 in Japan	Johnson & Johnson /Mitsubishi Tanabe
Ipragliflozin	Filed in Japan; Phase 3 in Asian countries	Astellas/Kotobuki
Empagliflozin	Phase 3 in US/EU/Japan	Boehringer Ingelheim
Tofogliflozin	Phase 3 in Japan	Chugai
Luseogliflozin	Phase 3 in Japan	Taisho

EU= European Union, US= United States

Kidney and glucose homeostasis

SGLTs are the transport proteins located in different parts of the body which are responsible for transport of different substrates.[9] The most studied are SGLT1 and SGLT2 transport proteins. SGLT1 transport 10% of glucose in the kidney being located in S2/S3 segments of proximal convoluted tubule (PCT) and also absorb glucose and galactose in the intestine while SGLT2 are exclusively located in the S1 segmentof the PCT and reabsorb nearly 90 percent of the filtered glucose (figure 1).[9,10] Glucose being a polar compound needs a carrier protein for transport across the brush membranes of the lumen of PCT which occurs as 1:1 stoichiometry with sodiumion in SGLT2 while it occurs as 1:2 stoichiometry in the SGLT1 transport system.[9] This reabsorption process relies on electrochemical sodium gradient developed by sodium-potassium adenosine tri-phosphatase (ATPase) which serves as driving force for glucose entry into the cells. Once glucose is reabsorbed across the membrane and entered into PCT cells, it is then transported into the interstitium and then into systemic circulation by facilitative glucose transporters mainly GLUT2.[12,13] SGLT2 is a high capacity and low affinity transport protein while SGLT1 is a low capacity and high affinity transport protein.[9] Thus, most of the glucose reabsorption in the kidney occurs through SGLT2 which is the target of this new class of drugs under discussion.

Table 2. Characteristics of SGLT1 and SGLT2 proteins[9,10]

Parameter	SGLT2	SGLT1
Site	Primarily in kidney	Mostly located in intestine. Also in kidney and heart.
Substrate	Glucose	In intestine, galactose and glucose. In kidney, glucose only.
Renal Location	S1 segment of PCT	S2/S3 segment of PCT
Capacity	High	Low
Affinity	Low	High
Glucose reabsorption percentage	≈90%	≈10%

PCT= Proximal Convoluted Tubule, SGLT= Sodium Glucose Co-transporter.

Body filters about 160-180 gram of glucose per day for a healthy individual with an average plasma glucose level of 90-100 mg/dL.[14] Almost all of this filtered glucose is reabsorbed and re-entered into systemic circulation. Theoretically, the maximum capacity of the kidney to reabsorb filtered glucose, often called tubular maximum (T_{max}) is ≈ 370-375 mg/min which is exceeded when plasma glucose level reaches approximately 400 mg/dL in a hyperglycemic individuals.[14,15] However, in real life cases when plasma glucose levels exceed 200-250 mg/dL, it starts excreting into urine which may either be due to low affinity of SGLT2 proteins or due to the reason that not all the nephrons have the same capacity to reabsorb glucose maximally; a process called S-play.[12] Once this threshold is crossed, glucose starts excreting into the urine owing to the saturation of SGLT2 proteins mainly and to a lesser extent SGLT1.[14] Healthy individuals normally do not cross this threshold level, therefore, concentration of glucose in urine is almost negligible. However, for a diabetic patient, it is normal to cross this threshold level which leads to the glycosuria. Although glycosuria is an indication of uncontrolled glycemia but evidence supports the notion that renal threshold for glucose excretion is much higher in diabetic patients which lead to reduced glucose excretion despite higher glucose levels in the plasma.[11] This situation further aggravates glucotoxicity and associated complications. SGLT2 inhibitors work by reducing this renal threshold for glucose excretion.

If an average plasma glucose concentration of 200 mg/dl is assumed in a diabetic patient, this will lead to the excretion of nearly 360 grams of glucose in 24 hours at a normal GFR. If an inhibition of 25 percent of re-absorptive capacity is attained, then this would lead to a loss of nearly 90 grams of glucose in urine which equals a loss of 360 kcal per day. This is a two pronged strategy; first loss of glucose in urine shall decrease glycemic levels in plasma and second, the energy deficit caused by loss of calories shall be met by excess nutrients in the body if appropriate diet and exercise is maintained; this shall result in weight loss which is highly desirable in diabetes management. Thus, SGLT2 inhibitors act by inhibiting SGLT2 transport system in the kidney to exert their desired effect on the body.

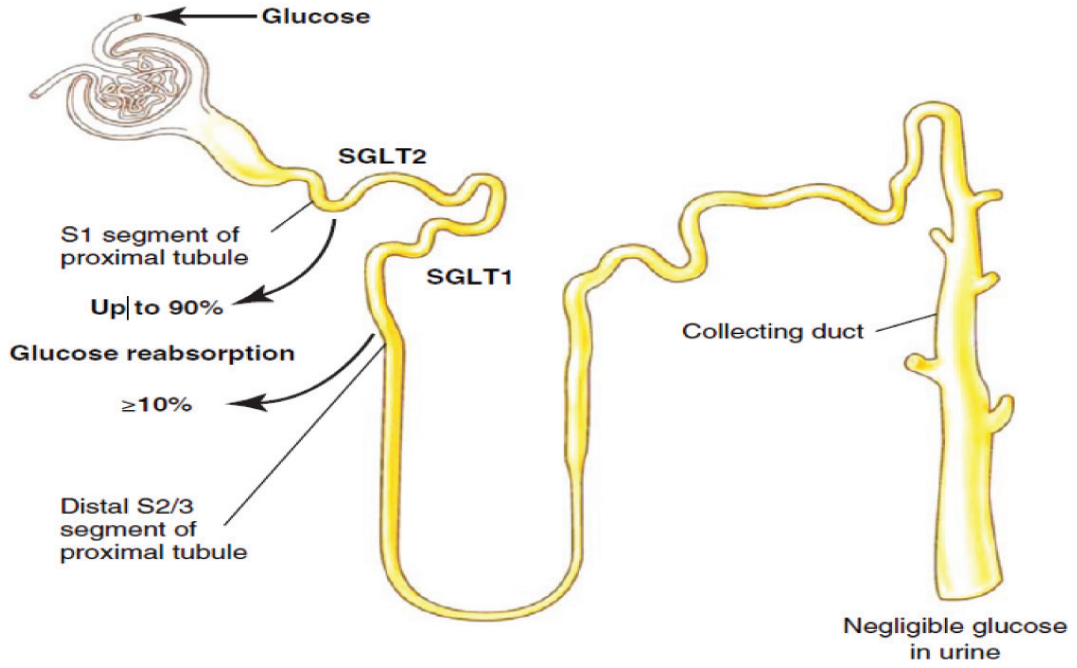


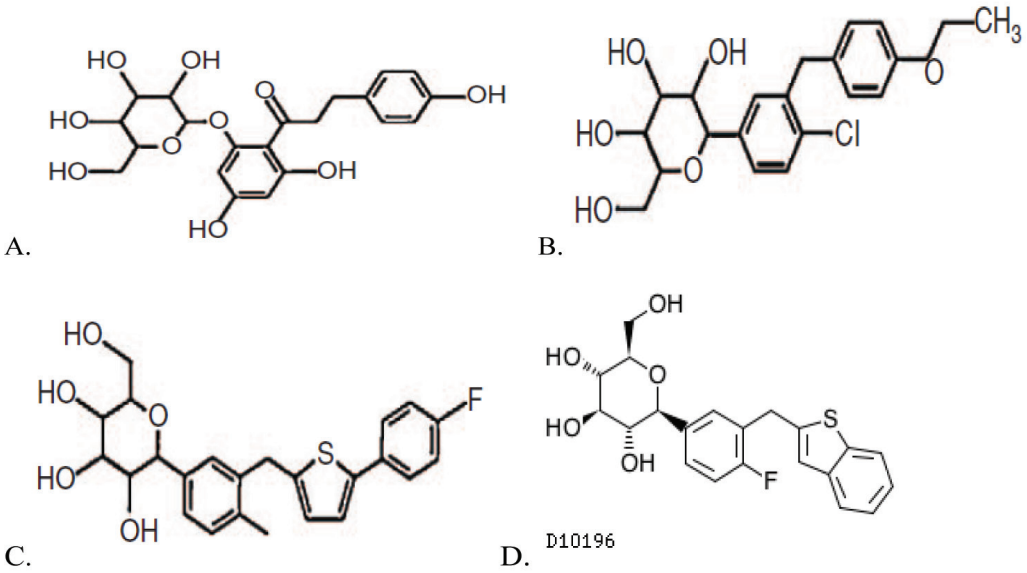
Figure 1. Glucose transport in the kidney[12]

Origin and development of SGLT2 inhibitors

The O-glucoside, phlorizin was the first compound discovered in this novel class of drugs in 1835 by a French chemist from the root bark of apple tree.[16] Experiments of the phlorizin in animal models was a success in inhibiting renal glucose reabsorption but this compound was not further developed due to its low absorption from gastrointestinal tract and degradation by β-glucosidases.[16] Further, it was a non-selective SGLT inhibitor which had a potential to block SGLT1 in the intestines also. Patients with SGLT1 gene mutations lead to malabsorption of glucose and galactose, diarrhea and dehydration.[16] Thus, interest was shifted towards development of SGLT2 specific inhibitors.

This quest for knowledge leaded towards development of first generation SGLT2 inhibitors, T-1095, sergliflozin and remogliflozin which were also O-glucosides and possessed greater SGLT2 selectivity.[17,18] Early experiments with the compounds were successful in increasing urinary glucose excretion (UGE) but their further development was stopped due to poor pharmacokinetic profile of these drugs mainly because of O-glucoside linkage which made them susceptible to degradation by β-glucosidase enzymes.

To cope with the challenge of degradation in the gastrointestinal tract, second generation SGLT2 inhibitors were developed with C-glucoside linkages instead of O-glucoside linkages which provided better stability in the gastrointestinal tract and better selectivity towards SGLT2. Dapagliflozin is the first compound in the group which has been granted marketing authorization in Europe and it is under regulatory review in the United States. The next compound in the group is canagliflozin which has been granted marketing authorization in United States and it is under regulatory review in Europe. Ipragliflozin ranks third in the group which has completed phase 3 trials and it is under regulatory review in Japan. Figure 2 shows the chemical structure of SGLT2 inhibitors.[16, 19-21]



A = Phlorizin, B = Dapagliflozin, C = Canagliflozin, D = Ipragliflozin

Pharmacodynamics and pharmacokinetics

All the SGLT2 inhibitors are different in their selectivity and IC_{50} value towards SGLT2 and SGLT1 proteins. Dapagliflozin is >1,200 folds selective towards human SGLT2 than for human SGLT1 with an IC_{50} value of 1.1 nmol/l and 1,390 nmol/l respectively.[19] Likewise, selectivity of canagliflozin and ipragliflozin for human SGLT2 is 155 and 254 folds respectively with an IC_{50} value of 4.4 nmol/l and 7.38 nmol/l, respectively.[20,21] Their respective IC_{50} values for human SGLT1 are 681 nmol/l and 1,876 nmol/l.[20,21]

Currently available evidence suggests that all the SGLT2 inhibitors induce glycosuria in a dose dependent manner in healthy volunteers and in type 2 diabetes patients.[22] When dapagliflozin was administered to healthy volunteers for two weeks in the dose range of 2.5 to 100 mg/day, the UGE was in the range of 20.4 to 55.4 gram per day[22] which shows a maximum inhibition of appriximately 30% if an average value of 180 gram per day is considered for glucose filtration. In type 2 diabetes patients this value was in the range of 52 to 85 gram per day when the drug was administered in the range of 2.5 to 50 mg/day for two weeks.[23] When the same experiment was conducted in healthy volunteers with canagliflozin in the dose range of 10 to 800 mg/day, the maximum UGE was 70 gram per day.[24] This maximal effect was observed at doses > 200 mg/day with a maximal renal threshold for glucose (RTg) of 3.4 mmol/l,[24] which is an indication that SGLT2 inhibition is self-limiting in the range of 30-40%. In a 28-day randomized controlled trial (RCT) of the drug in previously treated type 2 diabetes patients with uncontrolled glycaemia, the maximum UGE was 67 gram and 154 gram per day with a dose of 100 and 300 mg respectively.[25] Similar experiments with ipragliflozin produced a maximal UGE of 59 gram per day and 90 gram per day with different dosage ranges in healthy and diabetic patients, respectively.[26]

Unlike O-glucosides, C-glucoside compounds are rapidly and extensively absorbed after oral administration. Dapagliflozin has a bioavailability of ≥ 75% which is not limited by P-glycoprotein.[27,28] It can be administered without regard to meal as time to maximum plasma concentration after taking the drug with a fatty meal was increased from approximately 1 to 2 hours without any clinically significant change in systemic exposure of the drug.[27,28]

Similar results have also been observed with canagliflozin; however bioavailability of this drug is 65%[29] while bioavailability of ipragliflozin is 90%.[30]

SGLT2 inhibitors are not the substrates and also not the inducers or inhibitors of CYP450 enzyme system; rather they are metabolized by glucuronidation process.[27] Dapagliflozin is metabolized into inactive metabolites mainly dapagliflozin 3-O-glucuronide which is mediated by uridine 50-diphospho-glucuronosyltransferase 1A9 (UGT1A9).[27,28] After a 50 mg oral dose, nearly 75% of drug is detected in urine in the form of its metabolite while < 2% drug is detected in unchanged form.[27,28] Half-life of the drug ranges between 12 to 14 hours in different studies which makes it a suitable candidate for once daily dosing. Plasma protein binding capacity of drug is more than 91%.[27]

Likewise, canagliflozin also undergoes glucuronidation process and its main metabolites are ether (O)-glucuronides M5 and M7 which are also inactive pharmacologically.[29] Up to 60% of drug and its metabolites are excreted in feces while 32.2% is excreted in urine. It is more than 99% protein bound.[29] Ipragliflozin metabolism is also mediated by glucuronidation process in liver mainlyuridine 50-diphospho-glucuronosyltransferase (UGT) and sulphatation enzymes. M1, M2, M3, M4 and M6 are main metabolites of the drug which are inactive.[31] Route of elimination for the drug and its main metabolite M2 is primarily in feces followed by urine. Half-life of the drug ranges from 15-16 hours which also makes this drug suitable for once daily dosing.[31,32] The pharmacodynamic and pharmacokinetic parameters of SGLT2 inhibitors are shown in table 3.

Table 3. Pharmacodynamic and pharmacokinetic parameters of SGLT2 Inhibitors[19-32.]

Parameter	Dapagliflozin	Canagliflozin	Ipragliflozin
Oral bioavailability (%)	78	65	90
T_{max}	1–2 h	1–2 h	1 h
IC_{50} for SGLT2 (nM)	1.12	4.4	7.38
IC_{50} for SGLT1 (nM)	1391	684	1876
SGLT2 selectivity (fold)	1242	155	254
Elimination half-life	12.9 h (typical range 12–14 h)	10.6 h (100 mg) 13.1 h (300 mg)	15 - 16 h
Metabolism	Conversion to inactive metabolites by glucuronidation	Conversion to inactive metabolites by glucuronidation	Conversion to inactive metabolites by glucuronidation
Elimination	Mainly urine and to a lesser extent feces	Mainly feces and to a lesser extent urine	Mainly feces followed by urine

Special populations

Data from pharmacokinetic studies suggest that SGLT2 inhibitors are safe for administration during mild and moderate hepatic impairment defined as Child Pugh score of A and B respectively.[27,33] However, for severe hepatic impairment (Child Pugh score C) these agents may not be suitable. When dapagliflozin was administered to patients with mild and moderate hepatic impairment, area under the plasma concentration time curve from 0 to infinity (AUC∞)

was increased by 3% and 36% in comparison to healthy subjects.[33] However, for severe hepatic impairment cases it increased by 67% indicating a reduced dosage requirement in such patients.[27,33] Similarly, relative to healthy subjects, geometric mean ratios (GMRs) for AUC∞ of canagliflozin in subjects with mild to moderate hepatic disease was 110% and 111% respectively after a 300 mg dose which is not considered important clinically.[29] Currently no data is available in severe disease condition hence not recommended in such cases. Likewise, when ipragliflozin 100 mg dose was administered to subjects with moderate hepatic impairment, GMR for AUC∞ was 125% in comparison to controls without having any effect on elimination half-life.[34] The slight increase in systemic exposure of SGLT2 inhibitors in mild to moderate hepatic impairment is due to the reason that glucuronidation process is less sensitive to liver ailments as compared to CYP isozymes.[34]

Studies of dapagliflozin in renal impairment suggest that systemic exposure of the drug increases by 32%, 60% and 87% in mild, moderate and severe renal impairment respectively.[27] Therefore, it is not recommended for patients with eGFR (estimated glomerular filtration rate) < 60 ml/min. Similarly, canagliflozin should be used with caution in patients with eGFR > 45 ml/min to < 60 ml/min. It is supposed to cause a reduction in renal function in patients with eGFR < 60 ml/min therefore dose reduction may be required if used in such patients.[29] In patients with eGFR < 30 ml/min, it is not recommended. However, in patients with eGFR > 60 ml/min, no dosage reduction is required.[29] Limited data is available to assess safety of ipragliflozin in renal impairment cases at this stage.

Drug interactions

Generally, propensity of SGLT2 inhibitors for drug interactions is low as these drugs are unlikely to affect CYP isozymes.[28] Dapagliflozin has been studied with other antidiabetic drugs like metformin, glimepiride, pioglitazone, sitagliptin and insulin but no pharmacokinetic interaction has been reported.[35] Similar finding were also observed when the drug was used in combination with valsartan, warfarin, digoxin and simvastatin in healthy volunteers.[36] When the drug was administered with a UGT inducer rifampicin, systemic exposure of the drug was reduced but not to a clinically significant degree.[37] When the drug was administered with UGT inhibitor mefenamic acid, systemic exposure was increased by nearly 50% but this was not considered relevant clinically.[37]

Likewise, canagliflozin has also been studied successfully with antidiabetic drugs such as metformin, sulfonylureas, pioglitazone and insulin but no pharmacokinetic interaction has been reported.[29] When drug was co-administered with UGT inducer rifampicin, systemic exposure of the drug was increased by more than 50%.[29] Therefore, when a UGT inducer like rifampicin, phenytoin or ritonavir is co-administered with canagliflozin, a higher dose is recommended based upon the patient's tolerance level. Co-administration of digoxin with canagliflozin increases digoxin exposure by approximately 36%, therefore such patients may need appropriate monitoring.[38] Canagliflozin is a highly plasma protein bound drug but it is not affected by protein bonding interactions due to its low extraction ratio. Ipragliflozin has also been studied with other antidiabetic drugs like metformin, sulfonylureas, sitagliptin and pioglitazone and no pharmacokinetic interaction has been reported. No data is currently available for other groups of drugs.

Therapeutic efficacy

Therapeutic efficacy of SGLT2 inhibitors have been assessed in various monotherapy and combination therapy trials. Primarily, the efficacy endpoints of interest in all the studies on the topic were mean HbA1C level, FPG (fasting plasma glucose)

level and mean change in body weight. In the current review, main trials for each drug either conducted as monotherapy or as combination therapy shall be focused to assess their therapeutic potential. Most of the data is available for dapagliflozin being first in the group followed by canagliflozin and ipragliflozin. This may limit our assessment of therapeutic efficacy and safety due to some differences in time period of studies, patient characteristics and active comparators. However, this comparison shall provide an overview of clinical potential of these drugs and help identify their place in diabetes therapy.

Effects on glycemic parameters and body weight in monotherapy trials

One of the key phase III study for dapagliflozin includes a 24 week double blind, placebo controlled trial with 485 patients.[39] In the main cohort, 274 patients were randomized to receive once daily dapagliflozin in the doses of 2.5, 5 and 10 mg in the morning after a two week diet / exercise lead in period. The exploratory cohort comprised of 211 patients who received the study drug in the same dosage range in the evening.[39] An additional exploratory cohort of 73 patients with HbA1c 10.1 - 12% was also randomized to receive dapagliflozin 5 and 10 mg in the morning. Mean baseline HbA1c and body weight of the participants in the intervention group was in the range of 7.86 to 8.01% and 87.6 to 94.2 kg, respectively while the placebo group had a mean HbA1c of 7.84% and a mean body weight of 88.8 kg.

At the end of study, the mean reduction in HbA1c from the baseline was 0.58, 0.77 and 0.89% in 2.5, 5 and 10 mg dose groups in the main cohort receiving morning dose, while the placebo arm had a mean reduction of 0.23% only.[39] This decrease was statistically significant in 5 and 10 mg dose groups (P= 0.0005 and < 0.0001 respectively versus placebo). Likewise, a mean reduction of fasting plasma glucose (FPG) from the baseline was in the range of 0.8 to 1.6 mmol/l while the placebo group had a reduction of 0.2 mmol/l only. This reduction also achieved statistical significance in 5 and 10 mg dose groups. Although statistically non-significant, a trend in reduction of body weight was also observed which was in the range of 2.8 to 3.3 kg in the main cohort while in the placebo it was 2.2 kg only. In the exploratory cohort of patients with higher HbA1c, a greater reduction in HbA1c values was reported. Percentage of patients who achieved target glycemic control of < 7% was 41, 44 and 51% for 2.5, 5 and 10 mg cohorts, respectively while in the placebo group it was 32% only. A similar trend was also observed in the patients receiving evening dose of the drug.

The comparative monotherapy trial of canagliflozin is a 26 week double blind placebo controlled trial with 584 participants.[40] The study included subjects with inadequate glycemic control with diet/ exercise or antihyperglycemic agents (AHAs). Before randomization all subjects underwent a washout period followed by a placebo run in period. The subjects were assigned to receive once daily doses of canagliflozin 100 and 300 mg or placebo.[40] Mean baseline HbA1c was 8.1 and 8.0% in the two intervention groups while in the placebo it was 8.0%. Similarly mean baseline body weight in intervention group was 85.8 and 86.9 kg versus 87.6 kg in the placebo.

Results of the study indicated a mean HbA1c reduction from baseline which was 0.77 and 1.03% in the 100 and 300 mg canagliflozin groups versus an increase of 0.14% in the placebo (P < 0.001 versus placebo). The respective placebo corrected change was a statistically significant reduction of 0.91 and 1.16%. Similarly, reduction in mean FPG from baseline was also observed which were 1.5 mmo/l and 1.9 mmol/l in intervention group versus an increase of 0.15 mmol/l in the placebo group. Mean reduction in body weight from the baseline was 2.5 and 3.5 kg in the intervention arm versus 0.5 kg reduction

in placebo (P< 0.001). Percentage of patients achieving glycemic goal of < 7% was 44.5% and 62.4 % in 100 and 300 mg cohorts versus 20.6% in placebo arm (P< 0.001) .[40]

Likewise, efficacy of ipragliflozin was assessed in a 12-week double blind placebo controlled trial with 412 patients.[41] Study participants were either naïve or previously treated with AHAs. Patients on AHAs underwent a washout period followed by a run in period for all participants. Patients were randomized to receive ipragliflozin in once daily doses in the range of 12.5, 50, 150 or 300 mg, placebo or metformin. Maximum dose of metformin received was 1,500 mg. Mean baseline HbA1c was in the range of 7.83% to 8.05% in ipragliflozin group versus 7.84% in the placebo and 8.03 in metformin group. Similarly, mean baseline body weight was in the range of 83.3 kg to 90.7 kg in intervention arm versus 81.8 in placebo and 84.1 in metformin group.

The mean change in HbA1c from the baseline at the end of 12 week study period was a decrease of 0.22, 0.39, 0.47 and 0.55% in 12.5, 50, 150 and 300 mg group versus an increase of 0.26% in placebo. The respective placebo corrected change was a reduction of 0.49, 0.65, 0.73 and 0.81% with a p-value of <0.001. Placebo corrected decease in metformin arm was 0.72%. The placebo corrected reduction for FPG was in the range of 0.84 mmol/l to 1.68 mmol/l while in metformin arm it was 1.18 mmol/l. All these results were statistically significant.[41] Similarly, a placebo corrected reduction of body weight ranged from 0.50 kg to 1.67 kg while metformin arm had an increase of 0.12 kg. Statistical significance was achieved only for 300 mg group where a reduction of 1.67 kg was observed.[41]

Table 4. Comparative efficacy of SGLT2 inhibitors in monotherapy trials.

			Mean change from baseline‡			
Intervention	Duration (weeks)	N	HbA1c (%)	FPG (mmol/l)	Body Wt. (kg)	Ref
Dapa- monotherapy	24	274	-0.58 to -0.89	-0.84 to -1.6	-3.3 to -3.2	39
Cana- monotherapy	26	584	-0.77 to -1.03	-1.5 to -2.4	-2.5 to -3.4	40
Ipra- monotherapy	12	412	-0.22 to – 0.55	-0.84 to -1.6*	-0.50 to -1.67*	41

Dapa= Dapagliflozin, Cana= Canagliflozin, Ipra= Ipragliflozin

‡ Data are ranges across all dosing regimens involved in the study.

* Placebo corrected change.

Effects on glycemic parameters and body weight in combination therapy trials

Efficacy of SGLT2 inhibitors have been assessed in various combination therapies with AHAs. In a 24 week double blind placebo controlled trial, 546 patients with inadequate glycemic control on metformin monotherapy were randomized to receive dapagliflozin as add on therapy to metformin in comparison to placebo.[42] Dapagliflozin was administered as 2.5, 5 and 10 mg once daily dose in the morning while pre-study regimen of metformin was continued in all randomized patients. Mean baseline HbA1c was in the range of 7.92% to 8.17% in intervention arm versus 8.11% in the placebo. Mean Body Mass Index (BMI) was 31 kg/m^{2}across all groups with slight variations.

At the end of study, a statistically significant reduction in mean HbA1c level from the baseline was observed in intervention

group. The mean decrease was 0.67, 0.70 and 0.84% for 2.5, 5 and 10mg dose regimens of dapagliflozin versus 0.30% in the placebo group. Likewise, a statistically significant decrease in mean FPG level of 0.99, 1.99 and 1.30 mmol/l was observed in intervention arm versus 0.33 mmol/l in the placebo group. A similar pattern of decrease in body weight was also noticed. The mean decrease was 2.2, 3.0 and 2.9 kg for 2.5, 5 and 10 mg dose groups of dapagliflozin versus 0.9 kg in placebo (P= <0.0001). In addition, percentage of patients who achieved glycemic goal of < 7% was 33.0, 37.5 and 40.6% in 2.5, 5 and 10 mg dapagliflozin groups versus 25.9 % in the placebo group.

A long term extension of the same study was also conducted for 102 weeks.[43] A statistically significant reduction in mean HbA1c, FPG and body weight from baseline was observed at week 102. This decrease was 0.48, 0.58 and 0.78% for 2.5, 5 and 10 mg dose regimens of the drug while in the placebo group there was an increase of 0.02% (P = 0.0008 for 2.5 and < 0.001 for 5 and 10 mg). Similarly, mean reduction in FPG levels was 1.07 (P = 0.05), 1.47 (P = 0.0003) and 1.36 mmol/l (P = 0.001) for the three regimens while there was a decrease of 0.58 mmol/l in placebo arm. Reduction in mean body weight was 1.55, 2.52 and 2.24 kg for 2.5, 5 and 10 mg regimens while an increase of 1.36 kg in placebo arm was observed (P < 0.0001). Additionally, percentage of patients with HbA1c levels < 7.0% was 20.7, 26.4, and 31.5% for three dosage groups while in the placebo arm this percentage was only 15.4. Results were statistically significant for 5 (P = 0.01) and 10 mg (P = 0.001) regimens.

Dapagliflozin was also compared to placebo in a 24 week study as add on therapy to pioglitazone in a group of 420 participants.[44] This study was further extended to a total of 48 weeks with the same group of patients. Patients enrolled in the study were either treatment naïve or receiving an oral anti-diabetic drug (OAD) who underwent a dose optimization period of 10 weeks with pioglitazone. Mean HbA1c in the dapagliflozin arm was 8.40 and 8.37% for 5 and 10 mg regimens while it was 8.34% in the placebo arm. Mean body weight was 87.8 and 84.8 kg in intervention arm while placebo group had a mean body weight of 86.4 kg.

For the primary efficacy measure at week 24, mean reduction in HbA1c from the baseline was 0.82 and 0.97% for 5 (P= 0.0007) and 10 mg (P= <0.0001) regimens and at week 48, there was a mean reduction of 0.95 and 1.21%.44 In the placebo arm, this reduction was 0.42 and 0.54% at week 24 and 48, respectively. Both dosage regimens of dapagliflozin also had a statistically significant decrease in mean FPG level and body weight at week 24. The decrease in FPG level was 1.38 and1.64 mmol/l in dapagliflozin arm versus a decrease of 0.31 mmol/l in placebo group.[44] Mean reduction in body weight was 0.09 to 0.14 kg in intervention arm while the placebo group had an increase of 1.64 kg. In the extension period, decrease in FPG level was maintained while the mean body weight was increased.

In the 24-week double blind placebo controlled trial, efficacy of dapagliflozin was assessed as add on therapy to glimepiride in 597 patients.[45] Mean HbA1c was 8.0% across all groups with slight variations and nearly half of the patients were with BMI > 30 kg/m^2. Eligible patients were either continued with or switched to open label 4 mg glimepiride after an 8 week lead in period and then randomized to double blind dapagliflozin in 2.5, 5 and 10 mg daily regimens. At week 24, mean decrease in HbA1c from the baseline was 0.58, 0.62 and 0.83% for 2.5, 5 and 10 mg dose groups while in placebo group there was a decrease of 0.13% only (P < 0.0001 for all groups).[45] The mean change in FPG was a significant decrease of 1.18 and 1.58 mmo/l for 5 (P < 0.0001) and 10 mg (P < 0.0001) regimens, respectively. Similarly, the mean decrease in body weight from the baseline was 1.18, 1.56 and 2.26 kg

for three regimens. Results were significant for 5 and 10 mg dose groups (P= 0.009 and < 0.0001 respectively). Proportion of patients with HbA1C < 7% at week 24 was 30.3% for 5 mg regimen (P < 0.0001) and 31.7% for 10 mg regimen (P < 0.0001) compared to 13.0% in placebo group.

In a similar double blind placebo controlled trial, efficacy of canagliflozin in the dose range of 50 to 300 mg twice daily was assessed in 451patients as add on therapy to metformin in comparison to placebo for 12 weeks.[46] Patients included in the study had inadequate glycemic control with metformin monotherapy. Mean HbA1c in canagliflozin group was in the range of 7.61 to 8.0% while in placebo group it was 7.75%. The active comparator sitagliptin 100mg group was also added in the study which also had a mean HbA1c level of 7.75%. Mean body weight ranged from 86.0 to 87.6 kg in the intervention arm while it was 85.9 and 87.2 kg in placebo and sitagliptin group respectively. At week 12, mean reduction in HbA1c in canagliflozin group was in the range of 0.70 to 0.95% while in placebo and sitagliptin group this decrease was 0.22 and 0.74%, respectively (P < 0.001).[46] Mean reduction in FPG level ranged from 0.9 to 1.5 mmol/l while in placebo group an increase of 0.2 mmol/l was observed. The active comparator sitagliptin 100 mg group had a decrease of 0.7 mmol/l which was lower than all canagliflozin dosage ranges (P < 0.001). Besides this, a decrease in mean body weight was also observed across all canagliflozin dosage ranges which ranged from 2.3 to 3.4 kg (P < 0.001). The respective decrease in mean body weight in placebo and sitagliptin arm was 1.1 and 0.6 kg only.

Efficacy of canagliflozin was also compared to sitagliptin in a 52 week, randomized, double blind, active controlled trial in 755 type 2 diabetes patients who had inadequate glycemic control with metformin and a sulfonylurea drug.[47] Patients were randomized to receive canagliflozin 300 mg or sitagliptin 100 mg in once daily dosage regimens as add on therapy to stable doses of metformin and a sulfonylurea agent. Means HbA1c in both study arms was 8.1% while mean body weight was 87.4 kg in canagliflozin group versus 89.1 kg in sitagliptin group. At the end of study, mean reduction in HbA1c from the baseline in canagliflozin arm was 1.03% while in sitagliptin group it was 0.66% only.[47] Reduction in FPG level from the baseline was 1.7 mmol/l in canagliflozin group versus 0.3 mmol/l in sitagliptin arm. Similarly, a decrease of 2.3 kg in mean body weight was also achieved in intervention arm against a decrease of 0.1 kg in comparator. Percentage of the patients achieving target glycemic levels of < 7.0% was 47.6% in canagliflozin arm versus 35.3% in sitagliptin group. Statistical comparisons were not performed in the study.

A similar 12 week study was also conducted with ipragliflozin in dose ranges of 12.5 to 300 mg once daily in 343 subjects with inadequate glycemic control on metformin monotherapy.[48] Mean HbA1c was in the range of 7.73 to 7.78% in ipragliflozin group versus 7.68% in placebo arm. Mean body weight ranged from 86.7 to 89.5 kg while placebo group had a mean value of 89.0 kg. At the end of week 12, mean reduction in HbA1c level in intervention arm was in the range of 0.53 to 0.79% while placebo group observed a decrease of 0.31% only (P < 0.001 for 50, 150 and 300 mg dose groups).[48] A reduction of 0.47 to 1.54 mmol/l was also observed for mean FPG levels in ipragliflozin group versus 0.06 mmol/l in placebo arm (P < 0.001 for 150 and 300 mg dose). Likewise, decrease in mean body weight was in the range of 0.92 to 2.21 kg in intervention arm versus 0.48 kg in placebo (P < 0.001 for 50, 150 and 300 mg dose groups). Besides this, percentage of patients achieving glycemic target of < 7.0% was 33.3, 54.5, 53.0 and 52.1% in 12.5, 50, 150 and 300 mg group versus 33.8% in placebo arm.

Table 5. Comparative efficacy of SGLT2 inhibitors in combination therapy trials.

			Mean change from baseline‡			
Intervention	Duration (weeks)	N	HbA1c (%)	FPG (mmol/l)	Body Wt. (kg)	Ref
Dapa as add on to Met	24	546	-0.67 to -0.84	-0.98 to -1.3	-2.2 to -2.9	42
Extension period	102		-0.48 to -0.78	-1.07 to 1.36	-1.10 to – 1.74	43
Dapa as add on to Pio	24	420	-0.82 to -0.97	-1.38 to -1.64	-0.09 to -0.14	44
Extension period	48		-0.95 to -1.21	-1.27 to -1.84	+1.35 to 0.69	44
Dapa as add on to Glim	24	597	-0.58 to -0.82	-1.18 to -1.58	-1.18 to -2.26	45
Cana as add on to Met	12	451	-0.79 to -0.95	-0.90 to -1.4	-2.3 to -3.4	46
Cana* as add on to Met & SU	52	755	-1.03	-1.7	-2.3	47
Ipra as add on to Met	12	343	-0.53 to –0.79	-0.47 to -1.51	-0.94 to -2.21	48

Dapa = dapagliflozin, Cana = canagliflozin, Ipra = ipragliflozin, Met = metformin, Pio= pioglitazone, Glim = glimepiride, SU= sulfonylurea, FPG= fasting plasma glucose.

‡ Data are ranges across all dosing regimens involved in the study.

* Canagliflozin 300 mg only.

Other effects

Besides reducing the glycemic levels and body weight, SGLT2 inhibitors have also been associated with many other effects like reduction in blood pressure, some important changes in lipid profile and decrease in serum uric acid levels.

Effects on blood pressure

Reduction in blood pressure associated with SGLT2 inhibitors is attributed to osmotic diuretic effect of the class owing to increased UGE. In the 24 weeks, monotherapy trial of dapagliflozin mean decrease in systolic blood pressure (SBP) and diastolic blood pressure (DBP) from the baseline was in the range of 2.3 to 5.7 mmHg and 1.7 to 3.3 mmHg respectively across all study regimens. In the placebo group, this decrease was 0.9 and 0.7 mmHg only.[39] In the 24 week study comparing dapagliflozin as add on therapy to metformin against placebo, the mean decrease in SBP and DBP from the baseline ranged from 2.1 to 5.1 mmHg and 1.5 to 2.5 mmHg, respectively.[42] However, this effect did not remain consistent in the 102 week extension period of the same study.[43] In the 24 week study comparing dapagliflozin to placebo as add on therapy to pioglitazone, the mean decrease in SBP was 0.8 and 3.4 mmHg for 5 and 10 mg dose regimens while in the placebo group an increase of 1.3 mmHg was observed.[44] The respective DBP decrease was 1.0 and 3.1 mmHg against an increase of 0.7 mmHg in placebo. In the 48 week extension phase of this study, this effect remained consistent for both regimens of dapagliflozin. Statistical significance was not reported for these effects in dapagliflozin studies.

In the 26 week canagliflozin monotherapy study, mean decrease in SBP from the baseline was 3.3 and 5.0 mmHg for 100 and 300 mg regimens against an increase of 0.4 mmHg in the placebo arm. Thus, the placebo corrected change was 3.7 and 5.4 mmHg ($P < 0.001$). The respective, decrease

in DBP was 1.7 and 2.1 mmHg for intervention arm and 0.1 mmHg in placebo.[40] Statistical comparison was not performed for this effect. In the 52 week study of canagliflozin 300 mg as add on to metformin and a sulfonylurea agent in comparison to sitagliptin 100 mg, mean decrease in SBP from the baseline was 5.1 mmHg compared to 0.9 mmHg in comparator arm (P= 0.001).[47] Similar effects have also been observed in monotherapy and combination therapy studies with ipragliflozin.[41,48] Although statistically nonsignificant, in the 12 week monotherapy study, placebo corrected decrease in SBP was in the range of 2.6 to 3.1 mmHg in the regimens above 50 mg while a decrease of 0.1 to 1.2 mmHg in DBP was observed in 150 and 300 mg regimens.[41] In the 12 week combination therapy trial with metformin, mean decrease in SBP from the baseline ranged from 1.9 to 4.8 mmHg while in placebo arm this reduction was 0.5 mmHg only. The respective decrease in DBP was in the range of 1.1 to 4.2 mmHg against a decrease of 0.5 mmHg in placebo. Statistical significance was achieved for 300 mg regimen only.[48]

Effects on lipid profile

SGLT2 inhibitors are reported to affect lipid profile as well. In the 24 week monotherapy trial of dapagliflozin, lipid profile was not altered very much. A placebo subtracted small increase in higher density lipids (HDL) levels in all dapagliflozin arms was observed which ranged from 0.02 to 0.17 mmol/l.[39] In the 24 week study of dapagliflozin as add on to metformin, a general trend of increase in cholesterol level was observed. There was an increase in lower density lipids (LDL) levels from the baseline in the range of 3.1 to 9.5% versus an increase of 3.1% in placebo. Likewise, HDL levels also increased in the range of 1.8 to 4.4% across all dapagliflozin regimens while placebo arm displayed an increase of 0.4% only.[42] Conversely, triglycerides displayed a trend of decrease which was in the range of 2.4 to 6.4% while an increase of 2.1% was observed in placebo arm. In the 48 week study of dapagliflozin with pioglitazone as add on therapy, an increase in both LDL and triglyceride levels from the baseline was observed, however, this increase was lower than that observed in the placebo group.[44] On the contrary, HDL levels increased more in the dapagliflozin arm as compared to placebo which was in the range of 4.1 to 7.2% versus 1.3% in the placebo. Statistical significance was not reported for these observations.[44]

In the monotherapy study of canagliflozin, the placebo corrected increase in HDL levels was 6.4% in 100 mg group (P < 0.001) and 6.1% in 300 mg group (P < 0.01).[40] Similarly, LDL levels decreased by 4.0% in 100 mg arm and a modest increase of 1.9% were observed in 300 mg group (statistical comparison not performed). The respective change in triglyceride level was a decrease of 5.4 and 10.2%; however this result was not significant. In the combination therapy study with metformin, canagliflozin significantly increased HDL levels in 300 mg twice daily dose regimen (P = 0.001).[46] Similarly, a significant reduction in triglyceride levels in 300 mg once daily (P = 0.025) and twice daily (P= 0.001) regimens was observed. In the 300 mg twice daily regimen there was an increase in LDL levels in comparison to placebo, however, in the once daily regimen, there was no notable change. In the study, comparing canagliflozin 300 mg once daily to sitagliptin 100 mg daily dose, increase in HDL level was higher in canagliflozin arm in comparison to sitagliptin cohort (7.6 % versus 0.6% respectively).[47] However, an increase in LDL level was also observed in both arms which were high in canagliflozin group in comparison to sitagliptin arm (11.7% versus 5.2% respectively). A modest increase in triglyceride levels was also observed in both groups[47]. In the add on therapy of ipragliflozin with metformin, no clinically relevant changes in lipid profile was observe in study arms

while in the monotherapy study of ipragliflozin this outcome was not reported.[41,48] Further studies on ipragliflozin are in the pipeline which shall help provide an answer in this respect.

Changes in uric acid levels

Across all the studies of SGLT2 inhibitors in humans, a decrease in serum uric acid levels in the range approximately 1 mg/dL have been observed.[39-48] These findings indicate that these drugs have potential to excrete uric acid into the urine thus decreasing its levels in circulation. Hyperuricemia together with hyperglycemia have important role in decreasing efficiency of renal function. Long term effects of this effect on renal function is yet to be determined, however, it is expected that this will have an additional beneficial effect by improving renal function of diabetic patients.

Safety and tolerability

SGLT2 inhibitors are generally well tolerated. The rate of serious adverse events are not different from the placebo or active comparators. Adverse events of special interest in all SGLT2 inhibitors studies are urinary tract infections (UTIs), genital infections, hypoglycemia and diuresis related adverse events due to their relation with mechanism of action. Below is an overview of adverse effect profile of SGLT2 inhibitors.

Urinary tract infections

Initially there was a concern that SGLT2 inhibitors may promote UTIs due to higher level of glucose in the urine but this notion is losing ground as more studies are becoming available. In an initial monotherapy study of dapagliflozin, incidence of UTIs was 9.0% in intervention arm versus 4.0% in the placebo group.[39] When dapagliflozin was administered as add on therapy to metformin, rate this event was 6.0% in intervention arm in comparison to 8.0% in placebo arm.[42] Likewise, when dapagliflozin was administered as add on therapy to pioglitazone, rate of this event was 6.7% while in the placebo arm this event was 7.9%.[44] In a pooled analysis report of placebo controlled trials (n= 4500), incidence of UTI was 4.3% in dapagliflozin group versus 3.7% in the placebo.[49]

Likewise, in canagliflozin studies, rate of UTIs ranged from 4-8% in canagliflozin arms while in non-canagliflozin groups it ranged from 2-6%.[40,46,47] Results from the pooled analysis reports indicate a related finding with 8.2 and 6.7% in canagliflozin and non-canagliflozin group respectively.[29] Similar observations were also noticed in ipragliflozin studies.[41,48] Glycosuria is thought to promote microbial growth in urinary tract environment but urine is generally sterile and high glucose levels in urine have not been associated with infectious growth in diabetic patients.[50]

Genital infections

Although association of glycosuria with UTIs is low, its association with genital infections is high. Due to its strong association a higher incidence of this event was reported in all SGLT2 studies especially in women which are not unexpected. Different studies of dapagliflozin either administered as monotherapy or as add on, reported this incidence in the range of 5 to 10% while in the non-dapagliflozin arms it was in the range of 0.7 to 5.0%.[39,42-47] In the pooled analysis of dapagliflozin studies, genital infections in the intervention arm (n= 3291) had an incidence of 6.8% while in the non-dapagliflozin group (n= 1393), 2.1% suffered from this adverse event. However, these infections were not severe and responded to routine therapy.

In the canagliflozin studies, incidence of genital infections ranged from 5 to 12% in intervention arms, while in the non-canagliflozin groups, genital infections were in the range of 2 to 4%.[40,46,47] From the pooled analysis it was observed that the rate of female genital infections were 14.3% in

canagliflozin group (n= 6177) while in non-canagliflozin group (n= 3262) 3.1% suffered from this adverse event. Similarly in the same population, male genital infections in canagliflozin group were 8.3% versus 1.6% in non-canagliflozin arm.[29] Similar findings were also reported in ipragliflozin studies.[41,48]

Hypoglycemia

SGLT2 inhibitors are associated with a low risk of hypoglycemia due to its insulin independent action. It is mainly affected by combination therapy like sulfonylurea drug or insulin which is strongly associated with hypoglycemic risk. Incidence of hypoglycemia in dapagliflozin monotherapy and combination therapy trials (except insulin) ranged from 1.05 to 7.0% while in placebo group it was in the range of 0.7 to 4.8%.[39,42-45] This also includes a study of glimepiride as add on therapy; excluding this study event rate was in the range of 1.2 to 3.6% in the intervention arm. In the study comparing dapagliflozin as add on therapy to insulin, hypoglycemia occurred in 56.5% of patients while in the placebo group 51.8% experienced hypoglycemia.[52] Thus background therapy is more important than dapagliflozin itself for this event to happen.

Likewise in canagliflozin studies, hypoglycemia was experienced by 2.2 to 3.3% of patients against a value of 2.0 to 2.6% in non-canagliflozin arm.[40,46] However, these studies did not include a sulfonylurea agent or insulin as combination therapy. When canagliflozin was compared to sitagliptin with background therapy of metformin and a sulfonylurea agent, event rate was 43 and 40% respectively.[47] In the pooled analysis, incidence hypoglycemia was 8.0% in canagliflozin group (n= 6177) while in non-canagliflozin group (n= 3262) its incidence was 8.9%.[29] Ipragliflozin studies were also found to be consistent with the findings of other two drugs in the group with the incidence in the range of 0.7 to 3.3% versus 0 to 3.0% in non-ipragliflozin arms.[41,48]

Cardiovascular safety

SGLT2 inhibitors have generally beneficial effects on the cardiovascular system of the human body. They are associated with reduction in blood pressure and in supra-therapeutic doses they do not have a clinically significant effect on QTc interval in healthy subjects.[53]

Results of a meta-analysis on the cardiovascular safety of dapagliflozin indicate a potential decrease in cardiovascular events. For the primary composite outcome of myocardial infarction, cardiovascular death, unstable angina and stroke, the hazard ratio was 0.82 (95% CI 0.583 – 1.152).[49] A similar finding was also reported in a canagliflozin meta-analysis on the same primary composite outcome. The hazard ratio in this case was 0.91 (95% CI 0.68 – 1.22) which indicates a lower rate of these events in canagliflozin group as compared to non-canagliflozin arm. However, it was noticed that the hazard ratio for the stroke (fatal/non-fatal) was 1.47 (95% CI 0.83 – 2.59)[27] which represents a higher incidence of this event in intervention group. The long term CANVAS trial is under way to assess cardiovascular safety of the drug the results of which shall be available by 2018 to answer these questions. In a pooled analysis of canagliflozin, it was observed that a mean increase of 4.5 and 8.0% in LDL levels occur with 100 and 300 mg regimens of the drug.[51] Therefore, lipid profile of the patient should be monitored continuously. However, these drugs also increase HDL cholesterol and decrease triglyceride levels, so a combined effect of this phenomenon is yet to be known. The data on the cardiovascular safety of ipragliflozin is limited therefore a clear picture cannot be delineated at this stage; however, reduction in blood pressure and effects on lipid profile are nearly similar to other drugs in the group as per available data.[41,48]

Osmotic diuresis and volume depletion related adverse events:

In view of mechanism of action

of the SGLT2 inhibitors, volume related adverse events (hypotension, syncope, orthostatic hypotension, urine flow decrease) and osmotic diuresis related adverse events (polyuria, pollakiuria and thirst) are expected to be associated strongly.[27] According to EU SPC, polyuria is the common adverse event of dapagliflozin treatment with the incidence ranging from >1/100 to <1/10.[27] Overall results of the pooled analysis report of dapagliflozin studies on volume related adverse events indicate a clinically non-significant difference of 0.3% between the two groups. Incidence of hypotension was slightly high as compared to non-dapagliflozin group (0.5 versus 0.1%) but this may not be clinically meaningful due to its low rate of incidence.[27]

In the canagliflozin pooled analysis studies, osmotic diuresis related adverse events were 7.3 and 7.9% in 100 and 300 mg regimens compared to 2.4% in non-canagliflozin arm.[51] Volume related adverse events in individual studies were in the range of 0-3% versus 0% in placebo groups.[40,46,47] In the pooled analysis, incidence rate was 3.2 and 4.6% for 100 and 300 regimens compared to 2.4% in non-canagliflozin groups.[51]

Risk of cancer

Although there is no direct association of cancer with SGLT2 proteins being exclusively located in kidneys but a non-significant increase in incidence of bladder and breast cancer has been reported in dapagliflozin pooled analysis. There were 9 cases of bladder cases out of 5,478 patients receiving dapagliflozin in comparison to 1 out of 3,156 patients.[54] For breast cancer there were 9 cases out of 2,223 patients in dapagliflozin arm in comparison to 1 out of 1,053 in non-dapagliflozin group. Detection bias is thought to be a cause of these findings as most of cases were detected in less than two years period which is considered too short for a cancer to develop.[54] In animal studies, there was no signal of carcinogenicity or mutagenicity despite the drug was given in high doses for long period of time.[27] Overall risk of malignancy was same in the dapagliflozin and comparator group (1.47 versus 1.35%).[27] Although the point estimate was > 1 for certain tumors like bladder and breast, for certain tumors like blood, lymphatic and ovary it was < 1 however, statistical significance for the cancer risk was not achieved for any organ system.[27] Post marketing studies of the drug shall provide an answer to this ambiguity. Other drugs in the group have not been reported to be associated with cancer risk.

Other data

Results of a pooled analysis with over 3,000 patients showed that dapagliflozin was not associated with decline in renal function. Parameters assessed were estimated glomerular filtration rate (eGFR), albuminuria and serum creatinine. Also there was no clinically meaningful effect on serum electrolytes.[55] However, in renal impairment patients SGLT2 therapy may deteriorate renal function. In a 24 week study with extension period of 52 weeks in type 2 diabetes patients with moderate renal impairment (eGFR 30 - 60 ml/min), an initial rapid decline in renal function was observed followed by a minimal change with no improvement in glycemic levels.[56] In another study, effects on bone mineral density (BMD) were assessed owing to the mechanism of action of drug which is thought to be associated with tubular transportation of minerals. No effect on markers of bone formation, reabsorption and BMD was noticed.[57] In all SGLT2 inhibitor studies, hematocrit level was increased slightly. Long term impact of this effect is unknown.[39-48]

From the pooled analysis of canagliflozin studies, incidence of rash and urticaria was 1.6 and 0.4% versus 1.3 and 0.3% in comparator group.[51] After 52 week treatment with canagliflozin, small reductions

in BMD of elderly patients were observed but thought to be associated with decrease in body weight.[51] Results of the pooled analysis indicate that 3.1 and 3.6% patients are exposed to renal related adverse events comparing to 2.5% in non-canagliflozin group. Incidence was high in the patients with eGFR < 60 ml/min; thus these drugs are generally not recommended below this threshold level.[51]

CONCLUSION

SGLT2 inhibitors provide a promising future for type 2 diabetes patients due to its insulin independent action. Reduction in glycemic levels due to increase in urinary glucose excretion is a unique phenomenon which in combination with reduction in body weight is thought to decrease insulin resistance, improve β-cell function and prevent microvascular and macrovascular complications. These drugs are generally safe, efficacious and well tolerated in monotherapy and in combination therapy studies. Propensity of these agents for drug interactions is also low especially with the other AHAs. Long term safety studies of the drugs in the class are underway which shall further determine the scope of SGLT2 inhibitors therapy. Because of the unique mechanism of action of this new group of drugs it is very likely that SGLT2 inhibitors shall assume a major role in diabetes management in the near future.

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