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REVIEW ARTICLE

Metabolic and hemodynamic effects of sodium-dependent glucose cotransporter 2 inhibitors on cardio-renal protection in the treatment of patients with type 2 diabetes mellitus

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ABSTRACT

The specific sodium–glucose cotransporter 2 inhibitors (SGLT2 inhibitors) inhibit glucose reabsorption in proximal renal tubular cells, and both fasting and postprandial glucose significantly decrease because of urinary glucose loss. As a result, pancreatic β-cell function and peripheral insulin action significantly improve with relief from glucose toxicity. Furthermore, whole-body energy metabolism changes to relative glucose deficiency and triggers increased lipolysis in fat cells, and fatty acid oxidation and then ketone body production in the liver during treatment with SGLT2 inhibitors. In addition, SGLT2 inhibitors have profound hemodynamic effects including diuresis, dehydration, weight loss and lowering blood pressure. The most recent findings on SGLT2 inhibitors come from results of the Empagliflozin, Cardiovascular Outcomes and Mortality in Type 2 Diabetes trial. SGLT2 inhibitors exert extremely unique and cardio-renal protection through metabolic and hemodynamic effects, with long-term durability on the reduction of blood glucose, bodyweight and blood pressure. Although a site of action of SGLT2 inhibitors is highly specific to inhibit renal glucose reabsorption, whole-body energy metabolism, and hemodynamic and renal functions are profoundly modulated during the treatment of SGLT2 inhibitors. Previous studies suggest multifactorial clinical benefits and safety concerns of SGLT2 inhibitors. Although ambivalent clinical results of this drug are still under active discussion, the present review summarizes promising recent evidence on the cardio-renal and metabolic benefits of SGLT2 inhibitors in the treatment of type 2 diabetes.

INTRODUCTION

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a new class of glucose-lowering drug. There are six SGLT2 inhibitors now available in Japan. These SGLT2 inhibitors share a similar chemical structure with low-affinity, high-capacity, highly specific inhibitors against SGLT2, which is located at the apical surface of the S1 portion of the proximal renal tubule[1,2]. This transporter plays a specific role in the renal tubular reabsorption of more than 90% of glucose filtrated through glomeruli. Therefore, complete inhibition of SGLT2 results in overloading of glucose to SGLT1 at the downstream S3 portion of the proximal renal tubule[2,3], and approximately 60 and 100 g of unabsorbed glucose are excreted in the urine of healthy people and diabetes patients, respectively[4,5]. Among six SGLT2 inhibitors, there are some differences in chemical and relative selectivity against SGLT2/SGLT1 proteins, as well as bioavailability (Table 1)[6–10]. Although clinical usefulness and safety concerns are reported to be roughly similar, previous review articles in this journal indicate that further studies with larger sample sizes and long-term clinical evidences are required to fully evaluate SGLT2 inhibitors as a standard treatment for patients with type 2 diabetes[11,12]. Recent clinical studies have shown multifactorial clinical benefits and unexpected marked protective effects on cardio-renal events with treatment of SGLT2 inhibitors[13,14]. Many metabolic and hemodynamic characteristics of SGLT2 inhibitors are summarized based on recent knowledge, as detailed in many review articles[15,16].

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Table 1 | Chemical and pharmacological characteristics of SGLT2 inhibitors available in Japan

Generic name	Ipragliflozin	Dapagliflozin	Luseogliflozin	Tofogliflozin	Canagliflozin	Empagliflozin
Structural formula						
Initial marketing	2014 April	2014 May	2014 May	2014 May	2014 September	2015 Febrauary
Dosage and administration	50 mg once daily (to 100 mg once daily)	5 mg once daily (to 10 mg once daily)	2.5 mg once daily (to 5 mg once daily)	20 mg once daily	100 mg once daily	10 mg once daily (to 25 mg once daily)
SGLT2/SGLT1	860	610	1,770	2,900	290	2,680–5,000
Half-life (h)	11.71	12.1	11.2	5.4	10.6	9.88–11.7
Bioavailability	90.20%	78%	90%	97.50%	65%	NA
Protein binding	94.6–96.5%	91%	96.0–96.3%	82.3–82.6%	99%	86.20%
Metabolism	UGT2B7	UGT1A9	CYP3A4/5, 4A11, 4F2, 4F3B, UGT1A1	CYP3A4/5, 4A11, 4F3B	UGT1A9, 2B4, 3A4, CYP2D6	UGT2B7, 1A3, 1A9
Excretion	Urinary ex. 67.9% Fecal ex 32.7%	Urinary ex. 75.0% Fecal ex. 21.0%	Urinary ex. 44.2% Fecal ex. 50.0%	Urinary ex. 76.2% Fecal ex. 21.4%	Urinary ex. 32.5% Fecal ex. 60.4%	Urinary ex. 54.4% Fecal ex. 41.2%

CYP, cytochrome P450 superfamily; N/A, not available; UGT, UDP-glucosyltransferase.

In the present review article, we summarize recent advances in our understanding of metabolic and hemodynamic benefits, and safety issues regarding the ambivalent clinical characteristics of SGLT2 inhibitors.

CHARACTERISTICS IN GLYCEMIC CONTROL

Glucose excretion in the urine of patients with diabetes treated with SGLT2 inhibitors is generally reported to be 80–100 g/day[5]. In a phase 2 randomized clinical trial (RCT)[17], patients with type 2 diabetes mellitus were treated with 12.5–100 mg ipragliflozin once daily for 12 weeks. Glycated hemoglobin (HbA1c) levels in the ipragliflozin group dose-dependently decreased by a maximum of −1.31% compared with the placebo group. Similar placebo-adjusted mean changes from baseline HbA1c (−1.24%) were also found in a phase 3 RCT using ipragliflozin[18]. Similarly, patients with type 2 diabetes treated with dapagliflozin 2.5–50 mg once daily, metformin or a placebo for 12 weeks showed a placebo-adjusted mean change in HbA1c to a maximum −0.9% in the dapagliflozin group and −0.73% in the metformin group[19]. In a pooled analysis of phase 2 and 3 trials that included monotherapy or add-on studies with other oral hypoglycemic drugs[20], placebo-adjusted mean changes in HbA1c in patients with type 2 diabetes significantly decreased by −1.17% in the ipragliflozin group. Reductions in HbA1c by ipragliflozin were only weakly associated with reductions in bodyweight. However, reductions in HbA1c were greater in patients with poor glycemic control when compared with good glycemic control groups[17,20]. Consistently, patients with near normal baseline HbA1c did not show further reduction with ipragliflozin treatment.

CLINICAL USEFULNESS OF SGLT2 INHIBITORS IN COMBINATION WITH OTHER ORAL HYPOGLYCEMIC DRUGS

A similar effectiveness of placebo-adjusted reduction in HbA1c was observed in add-on studies using 50 mg ipragliflozin once daily in combination with other oral hypoglycemic drugs, such as sulfonylureas[21], metformin[22] or pioglitazone[23]. Consistently, a similar add-on RCT study (phase 3) was reported that used 100 and 300 mg canagliflozin as compared with a placebo in patients with both metformin plus sulfonylurea for 26 weeks[24]. HbA1c significantly reduced in the canagliflozin vs the placebo groups (100 mg, −0.85%; 300 mg, −1.06 vs −0.13%). Efficacy and safety of canagliflozin vs glimepiride in patients with type 2 diabetes inadequately controlled with metformin[25] in a 52-week, phase 3, non-inferiority RCT, and only canagliflozin 300 mg was found to be superior to glimepiride. Similarly, canagliflozin 300 mg compared with a placebo and sitagliptin 100 mg were studied for 26 weeks in patients with type 2 diabetes who were inadequately treated with metformin[26]. Only canagliflozin 300 mg showed statistical superiority to sitagliptin in lowering HbA1c (−0.88 vs −0.73%). Furthermore, in the Continuous Glucose Monitoring study[27], luseogliflozin 2.5 mg

once daily for 7 days shifted the area under curve (AUC) for glucose to lower levels, and both AUC and peak glucose levels significantly reduced in patients with mildly impaired glycemic control. Similarly, Yamada *et al.*[28] reported that the ipragliflozin treatment improved the entire 24-h glucose AUC without causing hypoglycemia. Finally, Japanese patients with type 2 diabetes inadequately controlled with sulfonylureas were randomly assigned to receive luseogliflozin 2.5 mg or a placebo for 24 weeks, and the placebo-adjusted mean reduction in HbA1c was −0.88% in the treatment group[29].

EFFECTS OF GLOMERULAR FUNCTION ON GLYCEMIC CONTROL

The hypoglycemic effect is mediated by inhibiting SGLT2-dependent reabsorption of glucose in proximal renal tubular cells. Therefore, the usefulness of SGLT2 inhibitors to control hyperglycemia is affected by the glomerular filtration rate of the patients[30–32]. A RCT study was carried out using 252 type 2 diabetes patients with inadequately controlled HbA1c and moderately impaired renal function (estimated glomerular filtration rate 30–60 mL/min/1.73 m^2), who were treated with dapagliflozin and placebo for 24 weeks, respectively. Dapagliflozin at any dose did not show a significant reduction compared with the placebo[30]. However, interestingly, both bodyweight and blood pressure significantly decreased in the dapagliflozin group vs the placebo group. However, another RCT examining canagliflozin using 269 patients with inadequately controlled type 2 diabetes with moderately impaired renal function (estimated glomerular filtration rate 30–50 mL/min/1.73 m^2) showed that canagliflozin significantly decreased HbA1c compared with the placebo group. Furthermore, consistently, both bodyweight and blood pressure also decreased with canagliflozin treatment[31]. A similar renal function-dependent reduction in HbA1c in patients with type 2 diabetes was also reported using luseogliflozin 2.5 mg daily[32].

LONG-TERM DURABILITY OF GLYCEMIC CONTROL

Glycemic control with SGLT2 inhibitors is characterized by long-term durability of excellent glycemic control in not only monotherapy, but also add-on studies with other oral hypoglycemic drugs[33–35]. Glucose-lowering effects of canagliflozin 300 mg were compared with sitagliptin 100 mg, both once daily in a study using type 2 diabetes patients inadequately controlled with metformin and sulfonylureas. In this randomized, double-blind, active-controlled, phase 3 trial, canagliflozin showed non-inferiority in the control of HbA1c. Then in a subsequent assessment, canagliflozin was found to be superior to sitagliptin for the long-term durability of glycemic control[33]. Furthermore, the stable and continuous reductions in both bodyweight and blood pressure were also found with canagliflozin treatment. Similar long-term durability of glycemic improvement, as well as bodyweight reduction, was also reported when compared with glimepiride in a randomized, double-blind study[34]. A total of 1,450 patients with type 2 diabetes, who were inadequately controlled, were assigned to receive canagliflozin 300 mg or glimepiride for a 52-week core period followed by a 52-week extension. At week 104, reductions in HbA1c from baseline values were −0.74 and −0.55% with canagliflozin 300 mg and glimepiride, respectively. Furthermore, reductions in both bodyweight and blood pressure were also well maintained over 104 weeks compared with glimepiride. Long-term durability of glycemic control over 2 years was also found in the dapagliflozin group compared with the glipizide group. In a further extension study, dapagliflozin compared with glipizide showed further sustained reductions of HbA1c, bodyweight and systolic blood pressure over 208 weeks[35]. The long-term durability of better glycemic control, as well as reductions of bodyweight and systolic blood pressure, are major characteristics of SGLT2 inhibitors, and could have a specific usefulness in suppressing chronic diabetic vascular complications.

IMPROVEMENTS IN INSULIN SECRETION, INSULIN SENSITIVITY AND GLUCOSE TOXICITY WITH ENHANCED GLUCAGON SECRETION

Ferrannini *et al.*[36] measured whole-body glucose utilization using the double-tracer glucose administration method after single-dose and chronic empagliflozin 25 mg once daily for 4 weeks compared with baseline levels in 66 patients with type 2 diabetes. Empagliflozin treatment resulted in glucose loss in urine (single 7.8 g/3 h and chronic 9.2 g/3 h during fasting, and 29 g/5 h and 28.2 g/5 h after a meal, respectively). After a 3-h fast, empagliflozin increased endogenous glucose production by 25%, whereas plasma glucose was significantly lower than baseline. After a meal, endogenous glucose production remained higher in the empagliflozin group compared with the placebo group. In contrast, the total glucose disposal rate significantly reduced because of reductions in both glucose oxidation and non-oxidative glucose disposal, with concomitant increases in lipid oxidation during treatment with empagliflozin. At these metabolic conditions after a meal, both glucose and insulin AUCs decreased, whereas the glucagon response increased during empagliflozin treatment. Under such conditions, it is apparent that empagliflozin improves both β-cell function and insulin sensitivity, despite the fall in insulin secretion. Merovci *et al.*[37] also reported a similar improvement of insulin sensitivity in muscle, despite increased fasting glucagon concentration and endogenous glucose production in 18 men with type 2 diabetes, who were randomized to receive either dapagliflozin (n = 12) or a placebo (n = 6) for 2 weeks. Dapagliflozin treatment significantly reduced fasting plasma glucose, and increased insulin-mediated tissue glucose disposal by approximately 18% using the hyperinsulinemic glucose clamp technique as shown in previous rodent models[38,39]. These results provide the first definitive evidence of the applicability of the glucose toxicity hypothesis to humans with type 2 diabetes[37,38].

This interesting evidence on paradoxical increases in endogenous glucose production and glucagon secretion despite an overall reduction of fasting plasma glucose after treatment with

SGLT2 inhibition has been comprehensively reviewed[40]. Recent evidence suggests that SGLT2 is expressed in glucagon-secreting α-cells of the pancreatic islets, and suppresses glucagon secretion[40]. Then, expression of SLC5A2, which encodes SGLT2, is downregulated under chronic hyperglycemic conditions with consequently upregulated glucagon gene expression. Therefore, treatment with SGLT2 inhibitors, which suppresses SGLT2 function in α-cells, might directly further promote glucagon secretion from pancreatic α-cells in type 2 diabetes patients with poor glycemic control[41]. Similar improvements of β-cell function are reported in patients with type 2 diabetes treated with canagliflozin 300 mg daily for 52 weeks[42] and ipragliflozin 50 mg daily for 4 weeks[43]. SGLT2 inhibitors decreased both plasma glucose and insulin levels, and showed significant improvements in insulin resistance as well as insulin secretion. Consistently, Leiter *et al.*[44] reported that canagliflozin provides significant improvements in liver function, such as improved serum levels of liver enzymes compared with the placebo and sitagliptin groups. These reductions might be closely related to improvements in fatty liver in patients with type 2 diabetes.

CLINICAL SIGNIFICANCE OF INCREASED KETONE BODY PRODUCTION

Increased ketone body production is one of characteristics of treatment with SGLT2 inhibitors. Ketone body production in the liver is dependent on a relative ratio of action potentials between insulin and its counterregulatory hormones. Namely, ketone body production increases in the case of relatively insufficient insulin action against insulin counterregulatory hormones, or relatively increased action of counterregulatory hormones against insulin. The increased production is also related to insufficient glucose intake with a low carbohydrate diet and severe energy restriction, as well as increased glucose energy loss in urine[45,46]. Enhanced glycosuria in patients treated with SGLT2 inhibitors could result in relative glucose energy deficiency *in vivo* with a concomitant effective reduction in plasma glucose levels, a concurrent lack of insulin and an excess of glucagon in plasma. Accelerated lipolysis in adipose tissue and the release in free fatty acid results in increased ketone body production in the liver with SGLT2 inhibitor treatment[47]. Pooled analysis of phase 2 and 3 RCTs with tofogliflozin treatment in Japanese patients with type 2 diabetes showed dose-dependent increases in the levels of acetoacetate and β-hydroxybutylic acid[48]. Recently, the US Food and Drug Administration warned that SGLT2 inhibitors for the treatment of diabetes might result in an increased risk for diabetic ketoacidosis (DKA), with mild-to-moderate glucose elevations (euglycemic DKA)[49]. Euglycemic DKA is defined as DKA without marked hyperglycemia. Most cases of DKA are reported in insulin-treated type 2 diabetes patients. The European Medicines Agency has announced that the Pharmacovigilance Risk Assessment Committee has started a review of all three approved SGLT2 inhibitors (canagliflozin, dapagliflozin and empagliflozin) to evaluate the risk of DKA in type 2 diabetes, and have noted 101 cases of DKA have been reported. Although no clinical details are provided, all cases were serious, with some requiring hospitalization and some thought to be type 1 diabetes[50]. Erondu *et al.*[51] reported a relatively low frequency of DKA in the Canagliflozin Cardiovascular Assessment Study, with an estimated incidence rate is 0.8 and 0.2 per 1,000 patient-years with canagliflozin 300 mg and a comparator, respectively. Rosenstock *et al.*[52] reported euglycemic DKA cases as a predictable, detectable and preventable concern with SGLT2 inhibitors. A recent review article[53] reported the incidence of DKA to be <0.1% in the clinical trials using dapagliflozin effect on cardiovascular events (DECLARE) and empagliflozin, cardiovascular outcomes and mortality in type 2 diabetes trial (EMPAREGOUTCOME), and in the other reports in both patients with type 1 and type 2 diabetes[54]. Therefore, patients with insulin-treated diabetes who develop nausea, vomiting and malaise during treatment with SGLT2 inhibitors should be promptly evaluated for the possible coexistence of ketoacidosis.

HEMODYNAMIC AND RENAL EFFECTS WITH BLOOD PRESSURE LOWERING

Hypertension and type 2 diabetes mellitus are major risk factors for cardiovascular events, and frequently coexist. For example, 56% of Japanese type 2 diabetes patients have hypertension[55]. It is well established that lowering blood pressure reduces not only cardiovascular events[56], but also has renoprotective effects in patients with type 2 diabetes[57]. Concerted reductions in both bodyweight and blood pressure are unique characteristics of SGLT2 inhibitors, as shown in many clinical trials, pooled analyses, systemic reviews and meta-analyses[58–60]. Both systolic blood pressure (SBP) and diastolic blood pressure (DBP) significantly reduced by 2.8 and 1.6 mmHg, respectively in pooled analysis of five RCT studies[61]. Blood pressure reduction by ipragliflozin was also consistently found in patients not undergoing cotreatment with other antihypertensive medication[61]. Reductions of both SBP and DBP were significantly greater in patients with baseline SBP ≥140 mmHg than patients with SBP <140 mmHg in a pooled analysis of six RCTs[61]. The percentage reduction of blood pressure was not affected by baseline body mass index. In a systematic review and meta-analysis, SGLT2 inhibitors consistently reduced both SBP and DBP relative to the placebo, with a weighted mean difference of −4 and −1.6 mmHg, respectively[62].

The potential underling mechanisms behind the blood pressure-lowering effects of SGLT2 inhibitors are thought to link multiple factors, such as bodyweight reduction[63], osmotic diuresis and natriuresis[58,59,64–66], and increased degradation of adipose tissue and muscle mass[25,67]. An interesting RCT on the effects of dapagliflozin on 24-h blood pressure, plasma volume and hematocrit compared with hydrochlorothiazide was reported in patients with type 2 diabetes. Dapagliflozin when compared with hydrochlorothiazide showed a significant

reduction in plasma volume with resultant hemoconcentration, and increases in hemoglobin, reticulocyte and hematocrit counts[59]. This increase in red cell counts was explained in part by an increase in plasma erythropoietin concentration in the dapagliflozin treatment group. Hydrochlorothiazide did not show any such increases[59]. However, further studies are required to understand the exact mechanisms behind blood pressure reductions and increases in hematocrit with treatment with SGLT2 inhibitors.

MAJOR ADVERSE EVENTS: HYPOGLYCEMIA, SKIN DISORDERS, AND GENITAL MYCOTIC AND URINARY TRACT INFECTION

A summary of overall safety and selected adverse events in different clinical trials is shown in Table 2.

Hypoglycemia

Monotherapy of any SGLT2 inhibitor is not a cause of clinically significant hypoglycemia. If SGLT2 inhibitors are used in combination with either sulfonylureas or insulin, hypoglycemia becomes a clinical problem in general practice[68,69]. However, patients treated with multiple oral hypoglycemic drugs have fewer hypoglycemic episodes using SGLT2 inhibitors compared with sulfonylureas[34,35]. Real-world evidence on the safety of ipragliflozin in 8,505 elderly Japanese patients with type 2 diabetes Specified drug use resulTs survEy of ipragLifLozintreAtment in ELDERly type 2 diabetes patients (STELLA-ELDER) has been reported (Table 2)[70]. Adverse drug reactions of special interest related to hypoglycemia were found in 0.68% of patients. The incidence of adverse hypoglycemic events was 1 in 10 in the dapagliflozin group compared with the sulfonylurea group[71]. However, in another study, patients treated with a combination of dapagliflozin and insulin showed a higher frequency of hypoglycemia compared with the placebo group, although the dose of insulin was generally 50% of the original dose[68].

Skin disorders with pruritus

A variety of skin disorders with pruritus have been reported in Japanese clinical trials, with an incidence rate of approximately 3–3.5% in both the STELLA-ELDER and preapproval clinical trials[70]. In a phase 3 RCT for glycemic control study with ipragliflozin using Korean patients with type 2 diabetes, skin and subcutaneous tissue disorders were found in 2.3% of patients[72]. In contrast, in clinical trials in Western countries, the adverse events related to skin disorders have not been described, and appear higher in Asian people[25,33,69–73]. Skin disorders in patients treated with SGLT2 inhibitors are often reported between 2 to 4 weeks after initiation of the drug. Although very few cases are suspected to be drug eruption, most skin disorders are possibly diagnosed as dehydration-related dyshidrotic eczema by skin specialists. There are some racial differences in the expression of various adverse events[74].

Table 2 | Summary of overall safety and selected adverse events selected adverse events

Adverse events	Pooled analysis of ipragliflozin[20]		EMPA-REG OUTCOME trial[13]		STELLA-ELDER[70]Japanese type 2 diabetes mellitus[102]		Lavalle-Gonzalez FJ. Type 2 diabetes mellitus study[26]	
	Placebo	Ipragliflozin	Placebo	Empagliflozin	Ipragliflozin	Dapagliflozin	Placebo/sitagliptin	Canagliflozin
No. patients	322	509	2,333	4,687	8,505	728	183	735
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
TEAEs	216 (67.1)	361 (70.9)	2,139 (91.7)	4,230 (90.2)	1,438 (16.9)	544 (74.7)	122 (66.7)	496 (67.5)
Hypoglycemia	3 (0.9)	5 (1)	650 (27.9)	1,303 (27.8)	58 (0.68)	25 (3.4)	5 (2.7)	50 (6.8)
Genital infection								
Male	1 (0.5)	3 (0.9)	25 (1.5)	166 (5.0)	Male+female	Male+female	1 (1.1)	13 (3.8)
Female	2 (1.9)	8 (5.3)	17 (2.6)	135 (10.0)	166 (1.95)	19 (2.6)	1 (1.1)	42 (10.7)
Urinary tract infection								
Male	1 (0.5)	2 (0.6)	158 (9.4)	350 (10.5)	Male+female	Male+female	Male+female	Male+female
Female	7 (6.5)	8 (4.7)	265 (40.6)	492 (36.4)	118 (1.38)	20 (2.7)	12 (6.6)	47 (6.4)
Volume depletion	12 (3.8)	72 (14.2)	115 (4.9)	239 (5.1)	436 (5.13)	49 (6.7)	2 (1.0)	41 (5.6)
Skin complications	NA	NA	NA	NA	269 (3.16)	23 (3.17)	NA	NA

NA, not available; TEAEs, treatment-emergent adverse events.

Genital mycotic infection and urinary tract infection

It is well recognized that the prevalence of genital infections in people with diabetes is higher than that of non-diabetic people[75]. Genital infections were confirmed to have a higher incidence in an empagliflozin-treated group (men 5.0%, women 10.0%) compared with a placebo group (men 1.5%, women 2.6%), respectively[13], and a canagliflozin-treated group (men 3.8%, women 10.7%) compared with a placebo group[26]. Pooled analysis of the incidence of genital infection in Japanese female patients showed a higher incidence in an ipragliflozin-treated group (5.3%) compared with a placebo group (1.9%)[20]. It is generally accepted that genital infections are seen at higher frequencies in female than male diabetes patients (Table 2). The high incidence rate of urinary tract infections is not further increased by treatment with SGLT2 inhibitors, as shown in both pooled analysis of ipragliflozin RCTs20 and the EMPA-REG OUTCOME trial13. However, post-marketing reports for SGLT2 inhibitors show possible risks for complications of acute pyelonephritis and sepsis from a urological origin. Therefore, screening for signs and symptoms of urinary tract infections might be necessary during treatment with SGLT2 inhibitors.

CARDIOVASCULAR BENEFITS LESSONS FROM THE EMPA-REG OUTCOME TRIAL

Beneficial effects for prevention of cardiovascular events by intensive glucose control with medical treatment can only be observed after long-term good control of hyperglycemia in both type 1 and type 2 diabetes mellitus patients[76,77]. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, patients with near normal glycemic control with intensive medical treatments had a 22% higher risk for death compared with the standard group[78]. Therefore, there are unsolved cardiovascular safety concerns with glucose-lowering treatment.

In the EMPA-REG OUTCOME trial[13], 7,020 patients with type 2 diabetes at high risk of cardiovascular diseases with 75–80% coronary artery disease and 23–25% stroke were randomly assigned into three groups (placebo 10 mg/day and empagliflozin 20 mg/day), and were followed for a median of 3.1 years. Mean baseline HbA1c was 8.1%, and more than 57% of patients had greater than a 10-year diabetes duration. Background diabetes treatment was first unchanged for 12 weeks, and was then permitted to change depending on each patient's glycemic conditions. Placebo-adjusted mean reductions in HbA1c in the empagliflozin treatment groups were −0.54% at 12 weeks and −0.24% at 206 weeks. The primary end-points were defined as three-point major adverse cardiovascular events, including death from cardiovascular causes, non-fatal myocardial infarction and non-fatal stroke, decreased by 14% ($P = 0.04$). For secondary end-points, there were significantly lower rates of death from cardiovascular causes (by 38%), hospitalization for heart failure (by 35%) and death from any causes (by 35%). However, there were no significant differences in the rate of myocardial infarction or stroke between the placebo and the treatment groups[13]. Prevention of cardiovascular death in the empagliflozin group was found even in patients who were additionally treated with renin–angiotensin system (RAS) inhibitors (more than 80% of patients), β-blocker (63–68% of patients), diuretics (37 or 59% of patients), statins (75–80% of patients) and/or aspirin (80–83% of patients). In subanalysis of heart failure-related outcomes in the EMPA-REG OUTCOME trial, empagliflozin effectively decreased both re-hospitalization and new hospitalization for heart failure irrespective of the baseline state of heart failure. The number of patients needed to treat to prevent one heart failure hospitalization or cardiovascular death was calculated to be 35 over 3 years[79].

Two possible mechanisms are suggested as the likely mechanisms behind the cardiovascular benefits of SGLT2 inhibitors: (i) hemodynamic effects including blood pressure lowering, diuretic effects and increased hematocrit[58,64–66]; and (ii) metabolic effects relating to negative glucose and energy balance including ketone body production[47,48], and reductions in atherogenic risk factors including reductions of HbA1c, bodyweight, uric acid[80] and triglyceride, as well as increases in HDL-C[17–20,25] (Figure 1). However, the very rapid emergence of cardiac benefits, which were detected 3 months after initiation of the clinical trial, suggests that hemodynamic improvements are a more likely mechanism for the beneficial outcome.

SGLT2 inhibitors as diuretics might be expected to prevent cardiovascular events and heart failure. The mechanisms behind SGLT2 inhibitors as diuretics have been extensively discussed, and SGLT2 inhibitors have a similar effect as loop diuretics without induction of hypokalemia[66,81]. SGLT2 inhibitors increase glucose concentration, and gradually decrease Cl^- concentration in tubular fluid delivered to the loop of Henle because of continuous proximal tubular reabsorption of Cl^- in the presence of a high concentration of unreabsorbed glucose. The reduction of Cl^- concentration in the downstream tubular fluid inhibits reabsorption in the loop of Henle through inhibition of Na^+-K^+-$2Cl^-$ transporter, as a rate-limiting step for reabsorption of water and solute in the loop of Henle is the intraluminal Cl^- concentration[66]. Furthermore, this reduction of Cl-concentration in the tubular fluid as well as osmotic diuresis with volume depletion and natriuresis may additively stimulate renin secretion and result in RAS activation[59]. Interestingly, heat failure hospitalization or cardiovascular death were effectively protected by co-administration with a RAS inhibitor, but not with mineral corticoid receptor antagonists in the EMPA-REG OUTCOME trial[13].

The second hypothetical mechanisms are raised by Ferrannini *et al.*[82] and Mudaliar *et al.*[83]. In the failing heart, the conservation of oxygen consumption is essential to maintain cardiac function. In terms of oxygen cost, the energy yield of beta-hydroxybutyrate (β-HB) is comparable with that of glucose and pyruvate, and lower than palmitate[84]. In perfused working hearts, β-HB addition is readily taken up through a monocarboxylate

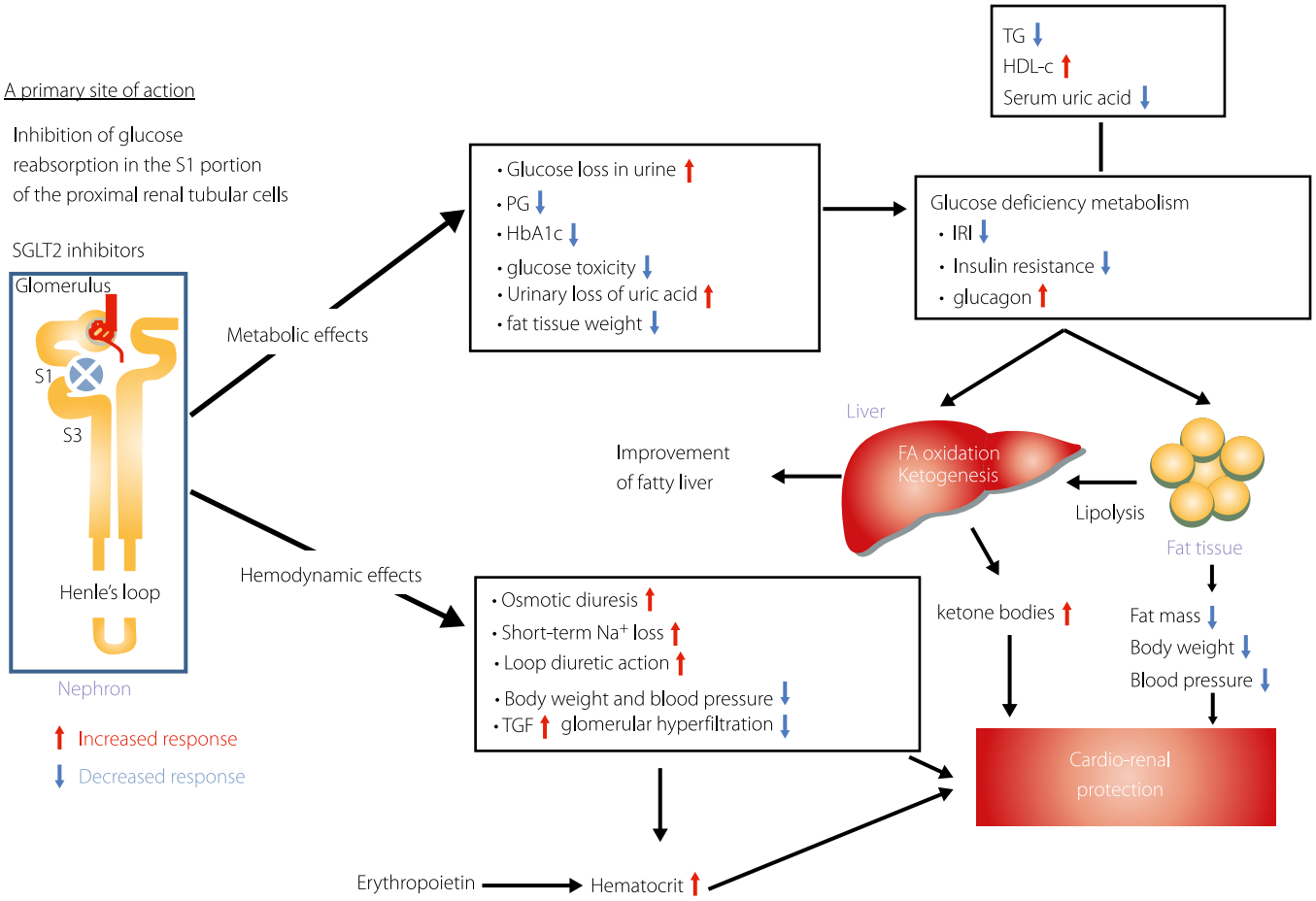

Figure 1 | Multifactorial metabolic and hemodynamic effects of sodium–glucose cotransporter 2 (SGLT2) inhibitors to protect cardio-renal outcomes. A primary site of action of SGLT2 inhibitors is specifically located in the S1 portion of the proximal renal tubular cells, and they inhibit Na/glucose cotransport and then the increased urinary glucose loss. This specific urinary glucose loss triggers profound metabolic and hemodynamic effects *in vivo*. The main parts of these multifactorial effects are shown: (i) reductions of plasma glucose, insulin and body fat mass, as well as bodyweight; (ii) osmotic diuresis and loop diuretic action with reductions of bodyweight and blood pressure, and activation of tubulo-glomerular feedback mechanisms with consequently decreased glomerular hyperfiltration. In addition to those effects, increased plasma glucagon secretion is directly activated with the SGLT2 inhibitor treatment[41], increased hematocrit is possibly related to erythropoietin secretion with an unknown mechanism[59] and serum uric acid decreases[80]. Increased response is shown by a red arrow, and decreased response is shown by a blue arrow. FA, fatty acid; IRI, immunoreactive insulin; TGF, tubulo-glomerular feedback.

transporter into the brain, heart and kidney[85], and preferentially oxidized in mitochondria. β-HB is exclusively produced in the liver, and the serum levels are reported to be increased in people with diabetes treated with SGLT2 inhibitors[47,48]; a finding that might offer significant cardio-protection in the failing heart in type 2 diabetes patients with high coronary risk factors[86]. A similar significant protection of a failing heart with β-HB is reported in patients with chronic heart failure[87,88]. These changes in energy metabolism are beneficial for the protection of chronic heart failure in type 2 diabetes. An increased percentage of hematocrit with SGLT2 inhibitors[59] is another possible underling mechanism for energy supply to the failing heart. These proposed mechanisms could be related to the marked beneficial cardiac outcome in the EMPA-REG OUTCOME trial[13].

RENAL BENEFITS LESSONS FROM EMPA-REG OUTCOME TRIAL

It is generally accepted that both strict glycemic and blood pressure control are essential for protection against the initiation and for the slow-down of diabetic nephropathy. Furthermore, RAS inhibitors might also provide additional benefits for the prevention of diabetic nephropathy in type 2 diabetes[89]. However, there are still substantial residual risks for progression to the advanced stage of renal disease with present medical treatment[90].

In a recent analysis of the EMPA-REG OUTCOME trial, the prespecified secondary microvascular outcomes regarding incident or worsening nephropathy were studied[14]. The end-points occurred in 12.7% in the empagliflozin group and 18.8% in the

placebo group (hazard ratio in the empagliflozin group 0.61, $P < 0.001$). Hazard ratios for progression to macroalbuminuria, doubling of the serum creatinine level, and initiation of renal-replacement therapy in the empagliflozin group were 0.62 ($P < 0.001$), 0.56 ($P < 0.001$) and 0.45 ($P < 0.04$), respectively. In contrast, there was no significant difference in the incidence rate for microalbuminuria in patients with normal albuminuria at baseline between the placebo and treatment groups. The authors concluded that empagliflozin had potent effects preventing the progression from pre- and early diabetic nephropathy into overt diabetic kidney disease, as well as further progression of the advanced stage of diabetic kidney disease in patients with type 2 diabetes at high cardiovascular risk. Interestingly, these results were observed in patients whose blood pressure was well managed with extensive use of RAS inhibitors.

Regarding these beneficial effects of empagliflozin in this trial, increased supply of Na^+ deliveries to the macula densa might exert strong benefits through activating tubulo-glomerular feedback, leading to afferent arteriolar vasocontraction and then a decrease in glomerular hyperfiltration[91]. It has been consistently reported that empagliflozin reduces the intraglomerular hyperfiltration in patients with type 1 diabetes as a result of tubule-glomerular feedback regulation[92,93]. It is possible that beneficial renal effects in the EMPA-REG OUTCOME trial might be partly explained by multifactorial risk reductions including modest diuresis with lowered blood pressure, and reductions of HbA1c, bodyweight and uric acid in the empagliflozin-treatment group compared with the placebo group.

High glucose concentrations in proximal renal tubular cells stimulate Na^+/glucose reabsorption through SGLT2, which activates Na^+/K^+ ATPase and results in increased tubular oxygen consumption, and might be related to tubular hypoxia[94]. In terms of renoprotective action, renal tubular hypoxia should be improved as part of the treatment target in diabetes. A recent study suggests that tubulo-interstitial hypoxia is a significant common pathway in the progression to end-stage renal disease[95]. Renal cortical hypoxia improved with administration of a non-specific SGLT inhibitor, phlorizin[96]. Thus, SGLT2 inhibitors in the treatment of diabetes could lead to less hypoxic stress on the diabetic kidney.

To prevent hypoxia in renal tubular cells, ketone bodies in renal cells are a more efficient fuel than glucose and free fatty acids on a molar basis[97]. Serum ketone concentrations are known to increase twice the level of placebo groups[47,48,86]. Ketone bodies are therefore the preferred renal fuel under the increased supply with treatment with SGLT2 inhibitors. Ketone bodies inhibit the pyruvate oxidation, as well as the uptake and oxidation of oleate, and modulate gene expression to promote resistance to oxidative stress[98,99]. SGLT2 inhibitors can improve fuel efficiency, thereby lowering oxygen consumption, which relieves hypoxic stress, improves renal function and prevents progression of kidney disease in part through an increase of ketone body production.

In terms of renal tubular hypoxia protection in diabetes with treatment with SGLT2 inhibitors, another possible mechanism is suggested to relate to increased hematocrit after treatment. An increased hematocrit concentration might be associated with oxygen delivery to hypoxic tissues. One explanation for the elevated hematocrit in patients treated with SGLT2 inhibitors is generally accepted to be as a result of hemoconcentration due to osmotic diuresis. However, it seems unlikely that hemoconcentration during diuretic therapy is a major cause of increased hematocrit[100,101]. Another new interesting possible mechanism for increased hematocrit is proposed to be an increased erythropoietin concentration with treatment with dapagliflozin in diabetes[59]. In terms of renoprotective effects of SGLT2 inhibitors found in the EMPA-REG OUTCOME trial, multifactorial mechanisms proposed include: (i) activation of a renal factor, such as a tubule-glomerular feedback mechanism; (ii) protection from renal tubular hypoxia through increased ketone body production and an increase in hematocrit concentration; and (iii) improvements of renal risk factors including HbA1c, a specific diuretic action with lowering blood pressure and bodyweight reduction, as well as the serum uric acid concentration in the long-term renal benefits.

CONCLUSION

SGLT2 inhibitors are classified as unique oral glucose-lowering drugs. They have potent glucose-lowering effects, which are insulin-independent and show a negative glucose energy balance because of urinary glucose loss, and then fatty acid oxidation and ketone body production are activated in the liver. They also improve insulin secretion and insulin sensitivity based on relief of glucose toxicity. SGLT2 inhibitors also have a loop-like diuretic action, which is associated with reductions of blood pressure and bodyweight, and then increase in hematocrit with undefined mechanisms. These metabolic and hemodynamic effects of SGLT2 inhibitors showed profound beneficial effects in the prevention of cardio-renal events, as shown in the EMPA-REG OUTCOME trial. However, it should be noted that SGLT2 inhibitors can induce ketoacidosis, increased risks for genital and urinary tract infections, and skin disorders in some patients. The beneficial effects should be further confirmed in future studies using people of different ethnicities and in patients with different stages of type 2 diabetes, as well as in patients treated with other SGLT2 inhibitors.

DISCLOSURE

A Kashiwagi is a consultant for and has received consulting fees/honoraria from Astellas Pharma Inc. and Sunstar Group. H Maegawa has received lecture fees from MSD, Nippon Boehringer Ingelheim, Astellas Pharma, Ono Pharmaceutical, Mitsubishi-Tanabe Pharma, Sanofi, Taisho-Toyama Pharmaceutical, Takeda Pharmaceutical, Kowa Pharmaceutical, Daiichi Sankyo, AstraZeneca, Sanwa Kagaku Kenkyusho, Novartis Pharma and Eli Lilly; research support from Astellas Pharma and AstraZeneca; and

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