

## Ipragliflozin: A novel sodium-glucose cotransporter 2 inhibitor developed in Japan

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### Abstract

Sodium-glucose cotransporter 2 (SGLT2) inhibition induces glucosuria and decreases blood glucose levels in diabetic patients and lowers hypoglycemic risk. SGLT1 is expressed in the kidney and intestine; SGLT1 inhibition causes abdominal symptoms such as diarrhea and reduces incretin secretion. Therefore, SGLT2 selectivity is important. Ipragliflozin is highly selective for SGLT2. In type 2 diabetes mellitus (T2DM), urinary

glucose excretion increased to 90 g/24 h after 28 d of treatment with ipragliflozin 300 mg/d. Twelve weeks of ipragliflozin 50 mg/d *vs* placebo reduced glycated hemoglobin and body weight by 0.65% and 0.66 kg, respectively, in Western T2DM patients, and by 1.3% and 1.89 kg, respectively, in Japanese patients. Ipragliflozin (highly selective SGLT2 inhibitor) improves glycemic control and reduces body weight and lowers hypoglycemic risk and abdominal symptoms. Ipragliflozin can be a novel anti-diabetic and anti-obesity agent.

**Key words:** Sodium-glucose cotransporter 2 inhibitor; Type 2 diabetes mellitus; Ipragliflozin; Japan

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**Core tip:** Ipragliflozin is highly selective for sodium-glucose cotransporter 2 (SGLT2) inhibitor. Twelve weeks of ipragliflozin 50 mg/d *vs* placebo decreased HbA1c and body weight by 0.65% and 0.66 kg, respectively, in Western patients, and by 1.3% and 1.89 kg, respectively, in Japanese patients. The highly selective SGLT2 inhibitor ipragliflozin improves glycemic control and reduces body weight, and lowers hypoglycemic risk and abdominal symptoms. Ipragliflozin has potential as a novel anti-diabetic and anti-obesity agent.

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### INTRODUCTION

Type 2 diabetes mellitus (T2DM) is characterized by insulin resistance and defective insulin secretion<sup>[1]</sup>. Hyperglycemia

is caused by glucose influx exceeding glucose outflow from the plasma compartment<sup>[2]</sup>. In the fasting state, hyperglycemia is related to increased hepatic glucose production<sup>[2]</sup>. In the postprandial state, further glucose excursions result from insufficient glucose output suppression and defective insulin stimulation of glucose disposal in target tissues<sup>[2]</sup>. Once the renal tubular transport maximum for glucose exceeds, glycosuria curbs, but does not prevent further hyperglycemia<sup>[2]</sup>.

Oral hypoglycemic agents include insulin secretagogues [sulfonylureas, meglitinides, and dipeptidyl peptidase-4 (DPP-4) inhibitors] and insulin sensitizers [metformin and thiazolidinediones (TZDs)]<sup>[3]</sup>.  $\alpha$ -glucosidase inhibitors decrease glucose absorption. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes recommend metformin as the first-line oral therapy<sup>[2,3]</sup>. If the glycated hemoglobin (HbA1c) target is not achieved by 3 mo, either sulfonylurea, TZD, DPP-4 inhibitor, GLP-1 receptor agonist, or basal insulin should be combined with metformin<sup>[2]</sup>.

The ADA recommends lowering HbA1c to < 7.0% to reduce microvascular disease incidence<sup>[4]</sup>. However, only approximately half of T2DM patients achieve this<sup>[3,5]</sup>. Oral hypoglycemic agents have side effects: hypoglycemia and weight gain (sulphonylureas)<sup>[6]</sup>; peripheral edema, weight gain, and fractures (TZDs)<sup>[7]</sup>; a possible increased risk of bladder cancer (pioglitazone)<sup>[8]</sup>; and abdominal symptoms (metformin and  $\alpha$ -glucosidase inhibitors). Metformin can also cause lactate acidosis.

Few insulin sensitizers and anti-obesity agents exist. Mazindol maintains body weight after obesity therapy and treats obesity-related diseases such as diabetes, hypertension, and hyperlipidemia<sup>[9]</sup>, but has side effects including tremor, nausea, vomiting, and diarrhea. Therefore, novel anti-diabetic and anti-obesity agents are required.

## SODIUM-GLUCOSE COTRANSPORTER

### TYPE 2

The kidney is important in glucose metabolism; it is a target for therapeutic intervention<sup>[10]</sup>. Sodium-glucose cotransporter 2 (SGLT2) mediates glucose reabsorption from the proximal renal tubule<sup>[10]</sup>. SGLT2 inhibition induces glucosuria and lowers blood glucose in diabetes, and a lowers hypoglycemic risk<sup>[10]</sup>.

Ipragliflozin is an SGLT2 inhibitor first released in Japan (Figure 1)<sup>[3]</sup>. Here studies on ipragliflozin and other SGLT2 inhibitors are reviewed.

## PHARMACOLOGY, MODE OF ACTION, AND PHARMACOKINETICS

### *In vitro* SGLT inhibition

Two types of SGLT exist: SGLT1 and SGLT2. SGLT1 is expressed in the kidney and intestine; intestinal SGLT1 inhibition causes abdominal symptoms such as diarrhea.

It is pivotal for intestinal mass absorption of d-glucose and triggers glucose-induced secretion of gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1)<sup>[11]</sup>. Therefore, SGLT1 inhibition reduces incretin secretion. Miglitol ( $\alpha$ -glucosidase inhibitor) suppresses GIP and increases GLP-1, reducing body weight and improving glycemic control<sup>[12]</sup>, but suppression of GLP-1 reduces insulin secretion<sup>[13]</sup>. Therefore, SGLT2 selectivity is important. The selectivity of currently available SGLT2 inhibitors is presented in Table 1<sup>[3,14-19]</sup>.

### *Urinary glucose excretion*

Healthy Japanese subjects receiving ipragliflozin excreted approximately 70 and 50 g of glucose/24 h after a single 300 mg dose or after multiple 50 or 100 mg doses, respectively<sup>[20]</sup>. In healthy European subjects, ipragliflozin dose-dependently increased urinary glucose excretion (UGE) to a maximum of approximately 59 g/24 h (327 mmol/24 h) (dose: 5-600 mg/d) without affecting plasma glucose levels<sup>[21]</sup>. In T2DM, ipragliflozin increased UGE to a maximum of approximately 90 g/24 h after 28 d of treatment with 300 mg/d<sup>[22]</sup>. Therefore, SGLT2 inhibitors increased UGE more in T2DM patients compared with healthy subjects<sup>[3]</sup>. Human exfoliated proximal tubular epithelial cells (HEPTECs) from T2DM patients expressed significantly more SGLT2 and the facilitative glucose transporter GLUT2 than cells from healthy individuals<sup>[23]</sup>. Renal glucose uptake in HEPTECs isolated from T2DM patients was markedly increased compared with that in healthy controls<sup>[23]</sup>. Therefore, renal glucose transporter expression and activity is increased in T2DM<sup>[23]</sup>. In T2DM patients, ipragliflozin increases glycosuria directly proportional to the glomerular filtration rate (GFR) and degree of hyperglycemia, so it can be reliably predicted for individuals<sup>[24]</sup>. Although absolute glycosuria decreases with declining GFR, ipragliflozin efficiency is maintained in patients with severe renal impairment<sup>[24]</sup>.

### *Effect of ipragliflozin on the pharmacokinetics of other medications*

AUC<sub>inf</sub> or C<sub>max</sub> of single doses of sitagliptin, pioglitazone, or glimepiride<sup>[25]</sup> were unaffected by multiple doses of ipragliflozin; the combination was well tolerated in healthy subjects<sup>[25]</sup>. Ipragliflozin (300 mg qd) and metformin together were well tolerated in T2DM patients; the addition of ipragliflozin did not result in a clinically relevant change in the pharmacokinetic properties of metformin<sup>[26]</sup>. Dose adjustments may not be required when ipragliflozin is administered with other glucose-lowering drugs<sup>[25]</sup>.

### *Effect of moderate hepatic impairment on the pharmacokinetics of ipragliflozin*

Moderate hepatic impairment had no clinically relevant effects on the single-dose pharmacokinetics of ipragliflozin and its major metabolite<sup>[27]</sup>. A single oral dose of ipragliflozin 100 mg was well tolerated in healthy subjects

**Table 1 Sodium-glucose cotransporter 2 selectivity of sodium-glucose cotransporter 2 inhibitors**

Company	IC <sub>50</sub> for human SGLT1/SGLT2 (nmol/L)	SGLT2 selectivity (fold)
Phlorizin	210/34.6	6
Ipragliflozin	1876/7.38	254
canagliflozin	684/4.4	155
Dapagliflozin	1391/1.12	1242
Empagliflozin	8300/3.1	2680
Tofogliflozin	8444/2.9	2912
luseogliflozin	3990/2.26	1770

SGLT2 selectivity was calculated by using the following formula: IC<sub>50</sub> value for SGLT1/IC<sub>50</sub> value for SGLT2. IC<sub>50</sub>: Half maximal (50%) inhibitory concentration; SGLT: Sodium-glucose cotransporter.

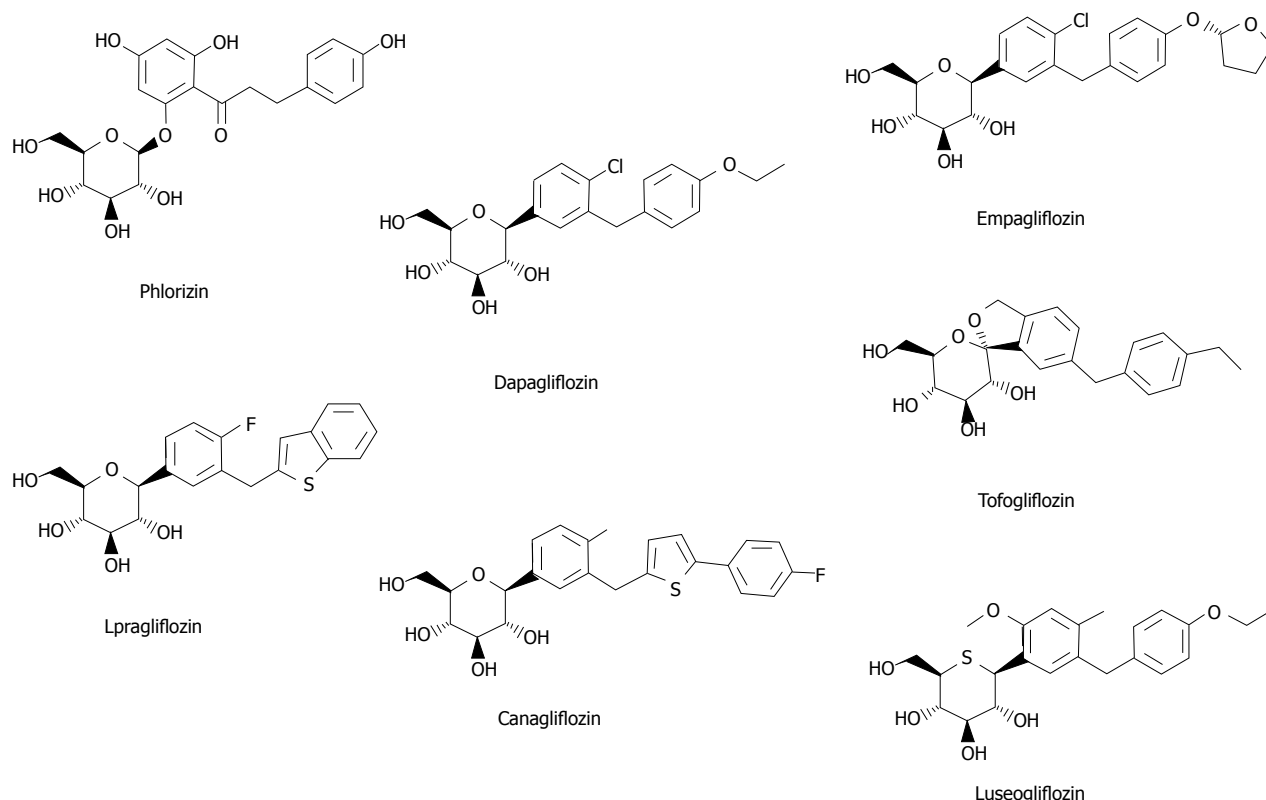


Figure 1 Chemical structure of sodium-glucose cotransporter 2 inhibitors in late-stage clinical trials.

and those with moderate hepatic impairment<sup>[27]</sup>.

## EFFICACY AND COMPARATOR STUDIES WITH OTHER SGLT2 INHIBITORS

### HbA1c

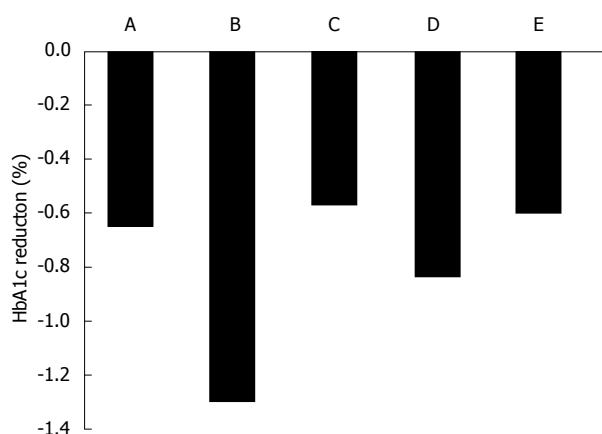
In Western T2DM patients, a 12-wk treatment with ipragliflozin 12.5, 50, 150, and 300 mg/d reduced HbA1c by 0.49%, 0.65%, 0.73%, and 0.81%, respectively, compared with placebo treatment (Figure 2)<sup>[28]</sup>. In Japanese patients, 12-wk treatment with ipragliflozin 12.5, 25, 50, and 100 mg/d reduced HbA1c by 0.61%, 0.97%, 1.29%, and 1.31%, respectively, compared with placebo treatment<sup>[29]</sup>.

Canagliflozin 50, 100, 200, 300 mg/d and 300 mg

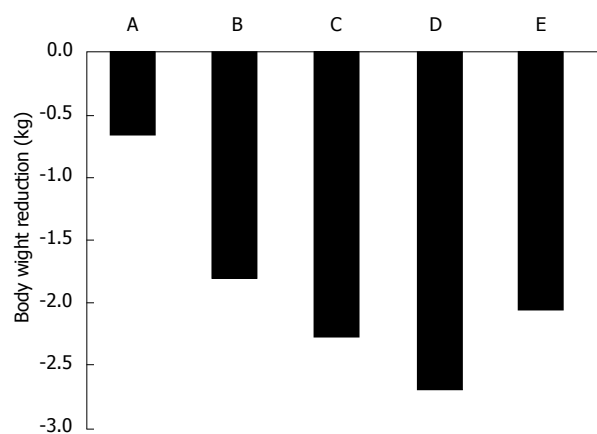
twice daily for 12 wk significantly reduced HbA1c by 0.79%, 0.76%, 0.70%, 0.92%, and 0.95%, respectively, compared with reductions of 0.22% for placebo (all  $P < 0.001$ ), and 0.74% for sitagliptin<sup>[30]</sup>. The adjusted mean difference in HbA1c between placebo and 100 mg canagliflozin was -0.54%<sup>[30]</sup> (Figure 2). Dapagliflozin 2.5, 5, and 10 mg reduced HbA1c by 0.67%, 0.70%, and 0.84%, respectively<sup>[31]</sup>. Empagliflozin 5, 10, and 25 mg for 12 wk reduced HbA1c by 0.4%, 0.5%, and 0.6% compared with placebo (+0.09%)<sup>[32]</sup>. Ipragliflozin reduced HbA1c levels when added to metformin ( $-0.87 \pm 0.66$ ), pioglitazone ( $-0.64 \pm 0.609$ ), or sulfonylurea ( $-0.83 \pm 0.717$ )<sup>[3,33]</sup>.

### Fasting plasma glucose

In Western T2DM patients, 12-wk of ipragliflozin



**Figure 2** The adjusted mean difference in HbA1c from baseline to 12 wk between placebo and the standard dose of sodium-glucose cotransporter 2 inhibitors. A: 50 mg ipragliflozin in Westerners; B: 50 mg ipragliflozin in Japanese; C: 100 mg canagliflozin in Westerners; D: 10 mg dapagliflozin in Westerners; E: 25 mg empagliflozin in Westerners.



**Figure 3** The adjusted mean difference in body weight from baseline to 12 wk between placebo and the standard dose of sodium-glucose cotransporter 2 inhibitors. A: 50 mg ipragliflozin in Westerners; B: 50 mg ipragliflozin in Japanese; C: 100 mg canagliflozin in Westerners; D: 10 mg dapagliflozin in Westerners; E: 25 mg empagliflozin in Westerners.

treatment at 12.5, 50, 150, and 300 mg/d decreased fasting plasma glucose (FPG) by 0.84, 1.10, 1.30, and 1.68 mmol/L, respectively compared with placebo<sup>[28]</sup>. In Japanese T2DM patients, 12.5, 25, 50, and 100 mg ipragliflozin decreased FPG from baseline by 15.6, 23.7, 34.1, and 46.9 mg/dL (0.87, 1.32, 1.89 and 2.60 mmol/L) compared with +12.0 mg/dL for placebo<sup>[29]</sup>.

### Body weight

In T2DM patients, SGLT2 inhibitors ipragliflozin, dapagliflozin, and canagliflozin reduced body weight by approximately 2 kg<sup>[3]</sup> (Figure 3). In Western individuals, the standard dose of 50-mg ipragliflozin for 12 wk reduced body weight by 0.66 kg<sup>[28]</sup>. In Japanese T2DM patients, 12-wk of placebo or 12.5-100 mg ipragliflozin treatment reduced body weight by 0.39 kg and 1.46-2.10 kg, respectively<sup>[29]</sup>. Twelve-weeks of canagliflozin 100 mg<sup>[30]</sup>, dapagliflozin 10 mg<sup>[34]</sup>, or empagliflozin 25 mg<sup>[32]</sup> reduced body weight by 2.28, 2.7, and 2.06 kg, respectively.

Most weight loss in patients receiving dapagliflozin is related to visceral and subcutaneous fat loss<sup>[3,35]</sup>. After 24-wk of dapagliflozin treatment at 10 mg/d, placebo-corrected changes were -2.08 kg body weight, -1.52 cm waist circumference, -1.48 kg total body fat mass, -258.4 cm<sup>3</sup> visceral adipose tissue, and -184.9 cm subcutaneous adipose tissue<sup>[3,35]</sup>. Compared with placebo, 26.2% more patients achieved weight reduction of at least 5%<sup>[3,35]</sup>.

### Blood pressure

SGLT2 inhibitors decrease blood pressure *via* osmotic diuresis induced by glucose in the urine earlier during treatment<sup>[3]</sup>. Ipragliflozin 50 mg for 16 wk reduced systolic blood pressure by 3.2 mmHg and diastolic blood pressure by 2.5 mmHg, without hypotension<sup>[36]</sup>. Dapagliflozin for 12 wk reduced systolic blood pressure by 2.6-6.4 mmHg, with no clear dose-dependent relationship, but changes in diastolic blood pressure and heart rate were small and

inconsistent<sup>[34]</sup>. Small dose-related increases in 24-h urine volumes were observed (107-470 mL above baseline volumes of 1.8-2.2 L)<sup>[34]</sup>.

Canagliflozin 100 and 300 mg for 26 wk significantly reduced systolic BP by 3.7 and 5.4 mmHg, respectively, compared with placebo (both  $P < 0.001$ )<sup>[37]</sup>. Diastolic BP was also reduced by 1.6 and 2.0 mmHg, respectively<sup>[37]</sup>. Minimal changes in heart rate were observed with canagliflozin 100 and 300 mg compared with placebo (-1.6, -0.5, and +1.4 beats/min, respectively)<sup>[37]</sup>. Empagliflozin 25 mg for 12 wk decreased systolic blood pressure by 3.4 mmHg, and diastolic blood pressure by 1.7 mmHg, but there was no significant difference compared with placebo<sup>[32]</sup>. Overall, SGLT2 inhibitors reduced blood pressure by approximately 2-6 mmHg.

### Beta-cell function

Chronic hyperglycemia induces  $\beta$ -cell dysfunction and insulin resistance<sup>[38]</sup>. SGLT2 inhibitors improve glucose toxicity and glycemic control<sup>[3]</sup>. There are no clinical reports on effect of ipragliflozin on  $\beta$ -cell function but ipragliflozin increased insulin content in the pancreas and suppressed the loss of insulin-positive cells in islets of db/db mice, an animal model of T2DM<sup>[3,39]</sup>.

Compared with placebo, canagliflozin 100 mg/d for 12 wk significantly improved  $\beta$ -cell function as assessed by homeostasis model assessment 2 (HOMA2)-%B (measure of fasting insulin secretion)<sup>[30]</sup>. Another study reported improvements in  $\beta$ -cell function following 26-wk treatment with canagliflozin 100 and 300 mg compared with placebo, with increases in HOMA2-%B of 12.4 and 22.8, respectively<sup>[37]</sup>.

Proinsulin/insulin (PI/I) ratio reflects  $\beta$ -cell dysfunction associated with the onset and progression of T2DM<sup>[40,41]</sup>. Mitiglinide improved the postprandial insulin secretion profile, suppressed the postprandial glucose spike, and improved the PI/I ratio in T2DM patients with low insulin resistance and low triglyceride levels<sup>[42]</sup>.

Dose-related decreases in proinsulin/insulin ratio of 0.5 and 0.8 pmol/mIU were observed with canagliflozin at 100 and 300 mg, respectively, compared with placebo, and decreases in proinsulin/C peptide ratio were also seen with both doses of canagliflozin<sup>[37]</sup>. These results suggest that SGLT2 inhibitors improve  $\beta$ -cell function.

### Insulin resistance

To date, there are no clinical reports on effect of ipragliflozin on insulin resistance. However, reductions in HOMA2 insulin resistance after dapagliflozin treatment at 2.5 and 10 mg for 12 wk were significantly larger compared with placebo<sup>[43]</sup>. The most precise method to assess insulin resistance is the glucose clamp technique<sup>[44]</sup>. Results of a hyperinsulinemic-euglycemic clamp study demonstrated that within 3 d of completing 2-wk of dapagliflozin treatment, Zucker diabetic fatty rats displayed improved glucose utilization accompanied by reduced glucose production and enhanced glucose influx into liver tissue<sup>[16]</sup>. In a clamp study of T2DM patients, 12-wk of dapagliflozin treatment increased glucose disposal rates<sup>[3,45]</sup>. There are few glucose clamp studies of SGLT2 inhibitors because the method is complex and expensive<sup>[46]</sup>. Recently, a novel insulin resistance index “20/(fasting C-peptide  $\times$  fasting plasma glucose),” to estimate the insulin resistance index was derived from the glucose clamp method<sup>[46]</sup>. This index will evaluate insulin resistance in clinical studies.

## SAFETY, EFFICACY, AND TOLERABILITY

### Genito-urinary tract infections

A meta-analysis of 45 clinical trials indicated that SGLT2 inhibitors increased the risk of urinary and genital tract infections [odds ratios, 1.42 (95%CI: 1.06-1.90) and 5.06 (95%CI: 3.44-7.45)], respectively, probably a result of glucosuria<sup>[47]</sup>.

In ipragliflozin phase 3 trial, treatment-emergent urinary tract infections (UTIs) were reported in 32/412 patients across all treatment groups, including placebo<sup>[28]</sup>. Infections were symptomatic and asymptomatic in 9 and 23 patients, respectively<sup>[28]</sup>. A total of 14 patients experienced treatment-emergent genital tract infections but there was no evidence that the frequency was related to the dose of ipragliflozin<sup>[28]</sup>. All events were treated with antifungal or antibacterial agents and were resolved prior to the final study visit (except three)<sup>[28]</sup>. In canagliflozin phase 3 trial, the incidence of genital mycotic infections, UTIs, and osmotic diuresis-related adverse events was higher in the treatment group<sup>[37]</sup>. UTIs were observed in 5%-12% of dapagliflozin-treated patients (with no clear dose relationship) compared with 6% of placebo-treated patients and 9% of metformin-treated patients<sup>[34]</sup>. Genital infections were observed in 2%-7% of dapagliflozin treated patients, 0% of placebo-treated patients, and 2% of metformin-treated patients<sup>[34]</sup>. Therefore, SGLT2 inhibitors might increase the risk of UTIs.

### Hypoglycemia

In a multi-center Japanese study of 361 patients randomized to receive either ipragliflozin (12.5, 25, 50, or 100 mg/d) or a placebo for 12 wk, a single mild symptomatic hypoglycemic event (not confirmed by plasma glucose measurement) occurred in one patient in the 100-mg ipragliflozin group<sup>[29]</sup>. In ipragliflozin phase 3 trial, only one patient in each of the ipragliflozin 50 mg (67 patients) and 300 mg (68 patients) dose groups experienced treatment-emergent hypoglycemia<sup>[29]</sup>. In T2DM patients, ipragliflozin did not significantly increase the incidence of hypoglycemic events compared to placebo, even in combination with other hypoglycemic agents<sup>[3,48]</sup>. Hypoglycemic events were reported in 6%-10% of patients treated with dapagliflozin, with no dose-dependent relationship, compared with 4% and 9% for placebo and metformin, respectively<sup>[34]</sup>. There were no symptomatic hypoglycemic events with a fingerstick glucose of  $\leq 50$  mg/dL<sup>[34]</sup>. In canagliflozin phase 3 trial, the incidence of hypoglycemia was similar for canagliflozin 100 and 300 mg and placebo (3.6%, 3.0%, and 2.6%, respectively), with no report of severe hypoglycemia<sup>[37]</sup>. Therefore, these data suggest that SGLT2 inhibitors lowers hypoglycemic risk.

### Osmotic diuretic effect

Ipragliflozin caused a mild 1.5%-2.0% increase in hematocrit at all doses<sup>[29]</sup>. Similarly, blood urea nitrogen (BUN) was also mildly increased by 1.0-2.2 mg/dL compared with placebo<sup>[29]</sup>.

### Cancer risk

An increased incidence of bladder and breast cancer was indicated in patients receiving dapagliflozin compared with controls<sup>[47]</sup>. Data on bladder and breast cancer were retrieved from regulatory databases and other sources to produce a pool of 5501 patients (at least 5000 patient-years of exposure to dapagliflozin), and a total of 3184 patients (at least 2350 patient-years of exposure to placebo or an active comparator)<sup>[49,50]</sup>. Nine cases of bladder cancer were identified in patients treated with dapagliflozin compared with one case in patients receiving placebo<sup>[49,50]</sup>. The number of observed cases exceeds the expected number in the general diabetic population<sup>[47]</sup>. UTIs may increase the risk of bladder cancer. However, early detection after short exposure and potential detection bias related to frequent urinalysis mitigate against a causative relationship<sup>[47]</sup>. Therefore, no robust conclusions can be drawn, pending accumulation of long-term data<sup>[47]</sup>.

There were 9 cases of breast cancer in the dapagliflozin group (2223 patients) compared with one case in the placebo group (1053 patients), diagnosed within the first year of the study<sup>[47]</sup>. These figures were higher than the predicted number of 7.1 cases based on the Surveillance Epidemiology and End Results (SEER) program<sup>[51]</sup>. It remains uncertain whether the use of dapagliflozin is associated with an increased risk of breast cancer and further studies are needed<sup>[47]</sup>. There are no reports

indicating that other SGLT2 inhibitors are associated with an increased risk of cancer<sup>[3]</sup>.

### Safety and tolerability of metformin combination therapy

A meta-analysis of 20 randomized, double-blind studies demonstrated SGLT2 inhibitors administered with metformin significantly decreased the incidence of diarrhea<sup>[52]</sup>. However, the addition of SGLT2 inhibitors increased the risk of genital infection<sup>[52]</sup>. Despite some limitations, SGLT2 inhibitors have a favorable safety profile, and combination therapy with metformin is well tolerated<sup>[52]</sup>.

### Patient-focused data on quality of life, satisfaction, and acceptability

One study investigated effect of ipragliflozin on quality of life<sup>[28]</sup>. Outcomes were assessed using the European Quality of Life-5 Dimensions (EQ-5D)<sup>[53]</sup>, Audit of Diabetes-Dependent Quality of Life (ADDQoL)<sup>[54]</sup>, and Diabetes Medication Satisfaction (Diab-MedSat) questionnaires<sup>[55]</sup>. No differences were observed in EQ-5D domains or ADDQoL scores at week 12<sup>[28]</sup>. However, mean changes in EQ-5D visual analogue scale scores from baseline to week 12 showed positive changes in the treatment groups, suggesting improvements in perceived health status<sup>[28]</sup>. Changes in Diab-MedSat scores for burden and symptoms were small and similar across all treatment groups, but changes in the efficacy score from baseline to week 12 were greater for the ipragliflozin groups<sup>[28]</sup>. Another study reported that changes from baseline to week 12 in EQ-5D domains and ADDQoL scores were small across all treatment groups but with a non-statistically significant trend for improvement in the ipragliflozin treatment groups<sup>[33]</sup>. These results suggest that the SGLT2 inhibitor ipragliflozin may improve the quality of life in T2DM patients.

### Ethnic differences

There are no clinical reports on ethnic differences in effects of ipragliflozin. However, past reports imply that ipragliflozin reduces HbA1c more in Japanese patients compared with Western patients (Figure 2)<sup>[28,29]</sup>. The mechanism is unclear, but a meta-analysis reported that DPP-4 inhibitors were associated with a reduction in HbA1c of 0.65% in non-Japanese randomized, controlled trials (RCTs; 55 patients), compared with 1.67% in Japanese RCTs<sup>[56]</sup>. There may be pharmacogenetic or cultural lifestyle differences that contribute to the larger reduction in HbA1c in Japanese patients. Japanese people have a greater amount of abdominal visceral fat relative to abdominal subcutaneous fat compared with Caucasians<sup>[57]</sup>. Dapagliflozin reduced visceral adipose tissue more than subcutaneous adipose tissue<sup>[35]</sup>. Therefore, the difference in visceral adipose tissue between Japanese and Western T2DM patients may contribute to the difference in effect of SGLT2 inhibitors.

Japanese and Asian patients often show reduced  $\beta$ -cell function<sup>[46]</sup> and East Asians may have a limited innate

capacity for insulin secretion<sup>[58,59]</sup>. The body mass index (BMI) of Japanese T2DM patients was significantly correlated with insulin secretion ability in a meal tolerance test; the insulin secretion ability diminished in patients with BMI < 20 kg/m<sup>2</sup><sup>[60]</sup>. Other reported complications associated with familial renal glucosuria include episodes of ketosis, UTIs, and natriuresis<sup>[61]</sup>. SGLT2 inhibitors increase blood ketone bodies<sup>[62]</sup>. Low insulin secretion ability and lean stature in Asian patients receiving SGLT2 inhibitors may increase the risk of ketosis; therefore, caution is required.

## CONCLUSIONS AND PLACE IN THERAPY ALONGSIDE OTHER SGLT2 INHIBITORS

SGLT2 inhibitor ipragliflozin improves glycemic control and reduces body weight, especially in Japanese T2DM patients. Furthermore, ipragliflozin lowers hypoglycemic risk and abdominal symptoms and can be safely used with sulphonylureas, metformin, pioglitazone, and DPP4 inhibitors. SGLT2 inhibitors are likely to improve  $\beta$ -cell function and insulin sensitivity. They offer great potential as novel anti-diabetic and anti-obesity agents. Ipragliflozin is particularly effective for Japanese T2DM patients with a greater abdominal visceral fat relative to abdominal subcutaneous fat than Caucasians. Ipragliflozin is a highly selective SGLT2 inhibitor, and lower hypoglycemic risk and abdominal symptoms.

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