

[ORIGINAL ARTICLE]

Beneficial Effects of Ipragliflozin on the Renal Function and Serum Uric Acid Levels in Japanese Patients with Type 2 Diabetes: A Randomized, 12-week, Open-label, Active-controlled Trial

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Abstract:

Objective To examine the add-on effects, compared to the existing antidiabetes treatment, of the sodium-glucose cotransporter 2 inhibitor ipragliflozin on glycemic control and the risk factors of cardiovascular disease (CVD) and chronic kidney disease (CKD) in patients with inadequately controlled type 2 diabetes.

Methods This 12-week, randomized, open-label, active-controlled trial included 30 patients with type 2 diabetes who were randomized 1:1 to ipragliflozin and control groups (n=15 each). The ipragliflozin group received 50 mg of ipragliflozin once daily in addition to conventional therapy. The primary outcome was the change in hemoglobin A1c (HbA1c) from the baseline. Secondary outcomes were changes from the baseline in indices of glycemic control, uric acid (UA), renal function, and arterial stiffness.

Results The patients' diminished estimated glomerular filtration rate (eGFR) was alleviated in the ipragliflozin group compared to the control group [difference between groups (Δ)=4.6 (95% confidence interval (CI): 1.5-7.7) mL/min/1.73 m², p=0.006] prior to significant improvements in HbA1c and other parameters, including anthropometric indices and arterial stiffness. Furthermore, ipragliflozin add-on therapy resulted in a greater reduction in serum UA levels than control therapy [Δ =-52.3 (95% CI: -85.5-19.1) μ mol/L, p=0.003]. The changes in the eGFR with ipragliflozin treatment were associated with ipragliflozin-mediated changes in the UA, even after adjusting for the age, sex, baseline HbA1c, baseline UA, and baseline eGFR (standardized regression coefficient=-0.535, p=0.010).

Conclusion Ipragliflozin add-on therapy was associated with beneficial renal effects in parallel with reducing serum UA levels.

Key words: a randomized trial, renal function, serum uric acid, sodium-glucose cotransporter 2 inhibitor, type 2 diabetes

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Introduction

Type 2 diabetes is a high-risk factor for cardiovascular disease (CVD), chronic kidney disease (CKD), and dementia (1-4). One particular issue facing patients with diabetes is that the interrelationship between heart and kidney dis-

eases can deleteriously affect both organs simultaneously, leading to heart and/or kidney failure (5). Novel therapeutic strategies for adequately controlling these factors and improving cardiovascular and renal outcomes for patients with diabetes are therefore urgently needed.

Selective sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce the kidney's ability to reabsorb glucose and in-

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crease urinary glucose excretion, thereby reducing plasma glucose concentrations (6, 7). In a recent randomized, double-blind, placebo-controlled trial of cardiovascular outcomes, the SGLT2 inhibitor empagliflozin improved major cardiovascular outcomes in patients with type 2 diabetes with established CVD (8). In a prespecified secondary renal outcome analysis of this trial, empagliflozin reduced the risk of progression of kidney disease, as defined by incident or worsening nephropathy, compared to placebo (9). Due to the fact that these beneficial effects emerged during short-term interventions (8, 9) and there have been reports that glucose-lowering agents other than liraglutide and semaglutide resulted in no significant improvement in cardiovascular outcomes (10, 11), it has been suggested that mechanisms other than glucose reduction may be involved in empagliflozin's cardiovascular and renal benefits (12, 13). Furthermore, an exploratory analysis by the Canagliflozin Cardiovascular Assessment Study (CANVAS) program showed that the SGLT2 inhibitor canagliflozin also has potential renal benefits for patients with type 2 diabetes at a high risk for CVD (14, 15), further highlighting the favorable action of SGLT2 inhibitors on renal dysfunction in patients with diabetes. However, the details of the effects and underlying mechanism of SGLT2 inhibitors on cardiovascular and renal outcomes in patients with inadequately controlled type 2 diabetes remain to be elucidated.

With a cohort comprising Japanese patients with obesity and/or diabetes, we recently demonstrated that, in patients with obesity and type 2 diabetes, CKD indicators such as the urine albumin-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR) correlated significantly with the 10-year Framingham Coronary Heart Disease Risk Score and the cardio-ankle vascular index (CAVI), an index of arterial stiffness (16). In the present study, we examined the add-on effects, compared with existing antidiabetes treatments, of the SGLT2 inhibitor ipragliflozin on glycemic control and the risk factors of CVD and CKD in the patients from our cohort who had type 2 diabetes and mild hyperglycemia.

Materials and Methods

Study design

This study was a two-arm, randomized, open-label, active-controlled, blinded-endpoint trial with a 1:1 allocation ratio. The intervention period was 12 weeks. Randomization was centralized at SATISTA (Kyoto, Japan), a site external to the trial, where computer-generated random number and assignment tables were created. A permuted block randomization algorithm was used with a block size of 4. Stratification factors were based on the patient's age and hemoglobin A1c (HbA1c) level at the baseline. During the randomization procedures, no content was disclosed to the doctors or research staff at the trial site.

This study was registered in the University Hospital

Medical Information Network Clinical Trial Registry (UMIN-CTR) system (ID: UMIN000016563). The study protocol was approved by the ethics committee for human research at Kyoto Medical Center and conducted in accordance with the principles of the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects. Written informed consent was provided by all the participants.

Participants

Participants were selected from a cohort of Japanese patients with type 2 diabetes enrolled at the outpatient clinic at the National Hospital Organization Kyoto Medical Center between January 2015 and December 2016. Eligible participants were those 20-79 years of age with type 2 diabetes, with an HbA1c of 6.5-9.0% and a body mass index (BMI) ≥ 22 kg/m², who were undergoing diet and exercise therapy alone and/or with glucose-lowering medications other than SGLT2 inhibitors, insulin, or glucagon-like peptide-1 (GLP-1) receptor agonists, and who had inadequate glycemic control despite a course of antidiabetes treatment lasting ≥ 12 weeks. The exclusion criteria were as follows: severe ketosis, diabetic coma or precoma, severe infectious disease, a history of surgery with 6 months or scheduled to undergo surgery within 6 months, an external injury, severe liver dysfunction, serum creatinine ≥ 1.5 mg/dL (men) or ≥ 1.3 mg/dL (women), a history of severe vascular diseases in the last 6 months (including stroke or myocardial infarction), dehydration or diarrhea that would cause dehydration, gastrointestinal disorders (including vomiting), pregnancy or lactation, a history of hypersensitivity to SGLT2 inhibitors, and findings that an attending doctor would consider suggestive of ineligibility.

Intervention

The medication intervention for the ipragliflozin group was 50 mg of ipragliflozin once daily in addition to the participants' conventional medications for type 2 diabetes. The control group simply received their conventional type 2 diabetes medications. The prohibited concomitant medicines were SGLT2 inhibitors other than ipragliflozin, insulin preparations, and GLP-1 receptor agonists. Combination-restrictive medicines included sulfonylurea (SU) drugs, biguanides, glinide formulations, and dipeptidyl peptidase-4 (DPP-4) inhibitors.

According to the study protocol, the intervention was not to be changed or discontinued during the study period, although reducing the dose or discontinuing SU drugs, biguanides, glinide drugs, and DPP-4 inhibitors might be acceptable should there be symptoms of hypoglycemia (or an expectation of these), under the judgment of the attending physician. In the event of unfavorable effects, such as serious blood glucose fluctuation, the development or progression of complications/accidental symptoms, or side effects, the weight reduction therapy and/or the administration of the medications would be stopped and switched to more appro-

appropriate treatments, again according to the judgment of the attending physician. There was no restriction on combination therapies, such as diet therapy and exercise therapy. Diuretics or biguanides could be reduced or stopped if there were symptoms of dehydration (or these were expected). For the ipragliflozin group, it was recommended that two or fewer drugs in combination be used in addition to ipragliflozin.

Outcomes and measurements

The primary outcome was the change in HbA1c from the baseline at 12 weeks. The secondary outcomes were changes from the baseline to 12 weeks in the BMI, fasting plasma glucose (FPG), uric acid (UA), creatinine (CRE), UACR, eGFR, and CAVI.

Anthropometric parameters, systolic blood pressure (SBP), diastolic blood pressure (DBP), FPG, HbA1c, total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-cholesterol), and low-density lipoprotein cholesterol (LDL-cholesterol) were determined according to standard procedures (16). We administered detailed questionnaires to the participants to determine the content of their diet (including alcohol consumption), the amount of physical activity that they underwent, and their smoking habit. CAVI was determined using a VaSera VS-1000 vascular screening system (Fukuda Denshi, Tokyo, Japan) (16, 17), which automatically calculated the CAVI values from an electrocardiogram and phonocardiogram with the measured pressures and waveforms of the brachial and ankle arteries. The eGFR and UACR were calculated using the formulas in the guidelines of the Japanese Society of Nephrology (18). Serum UA levels were measured using an enzymatic calorimetric method (19).

Statistical analyses

In a preliminary trial, 20 participants were assigned to an SGLT2 inhibitor group (given an SGLT2 inhibitor for 12 weeks) or a control group. The results of the trial showed a significant effect size of 1.1 points in HbA1c, with mean \pm standard deviation (SD) changes from the baseline at 12 weeks of -0.10 ± 0.45 (SGLT2 inhibitor group) versus -0.65 ± 0.55 (control). Based on these preliminary results and an anticipated dropout rate of 1 per group, we calculated that 32 participants in 2 groups of 16 each would provide 80% power to detect a difference between means at a significance level of 5% in the present study.

The data are presented as the mean \pm SD or median (interquartile range). A logarithmic transformation was applied to variables with a lognormal distribution. We applied a two-way repeated-measures analysis of variance to evaluate between-group differences in outcomes at 12 weeks compared with 0 weeks (baseline), with time and group as the categorical fixed factors, as well as the interaction between time and group. Results are presented as within- or between-group differences with 95% confidence intervals (CIs). Effects were evaluated on an intention-to-treat basis, and participants who did not complete the follow-up period were

considered not to have had any changes in measures. The relationships between the effects on outcomes of ipragliflozin add-on therapy were analyzed using a general or generalized linear model. We first verified the interaction between the presence/absence of ipragliflozin and the change in UA against the change in the eGFR and then determined whether or not an interaction term should be added to the analytical model. In order to adjust for confounding factors, we constructed a model that included the age, sex, baseline HbA1c, and initial values of the independent variables. A two-sided p value <0.05 was considered to indicate statistical significance. The statistical analyses were performed using the SPSS software program, ver. 23.0 for Windows (IBM Japan, Tokyo, Japan).

Results

Study flow

Figure showed the participant flowchart of the selection, randomization, and intervention processes. During the 12-month recruitment period, 32 patients were screened. Two withdrew their consent before randomization, so 30 patients were randomly assigned to the ipragliflozin and control groups ($n=15$ each). One patient in the ipragliflozin group dropped out because of a scheduling conflict; the other 14 completed the 12-week intervention period. Two patients in the control group dropped out (1 withdrew, and the other had a scheduling conflict), leaving 13 who completed the study. There was no marked difference in the background characteristics between the participants who dropped out and those in the study groups. The treatment was not changed for any participant during the study period, and no adverse events were observed in either group.

Baseline characteristics of the participants

The characteristics of the participants ($n=30$) at baseline are shown in Table 1. The mean age was 60.7 ± 12.3 years, 50% were women, and the mean HbA1c was $7.1 \pm 0.6\%$ (53.7 ± 6.3 mmol/mol). The baseline characteristics were reasonably similar between the two groups, except that the values of CAVI were higher in the control group than in the ipragliflozin group.

Effects of ipragliflozin add-on therapy on primary and secondary outcomes

Table 2 shows the changes in the primary and secondary outcomes from the baseline to the end of the 12-week intervention period in the control and ipragliflozin groups. The HbA1c values did not change significantly between the baseline and 12 weeks in either group [ipragliflozin group: -0.2% (95% CI: $-0.3-0.0\%$); control group: -0.1% ($-0.3-0.1\%$)], and there was no significant difference between the groups [$\Delta=-0.1$ ($-0.3-0.2$), $p=0.647$]. In contrast, the UA values decreased significantly after 12 weeks compared to the baseline in the ipragliflozin group [-44.4 ($-71.0-17.8$) $\mu\text{mol/}$

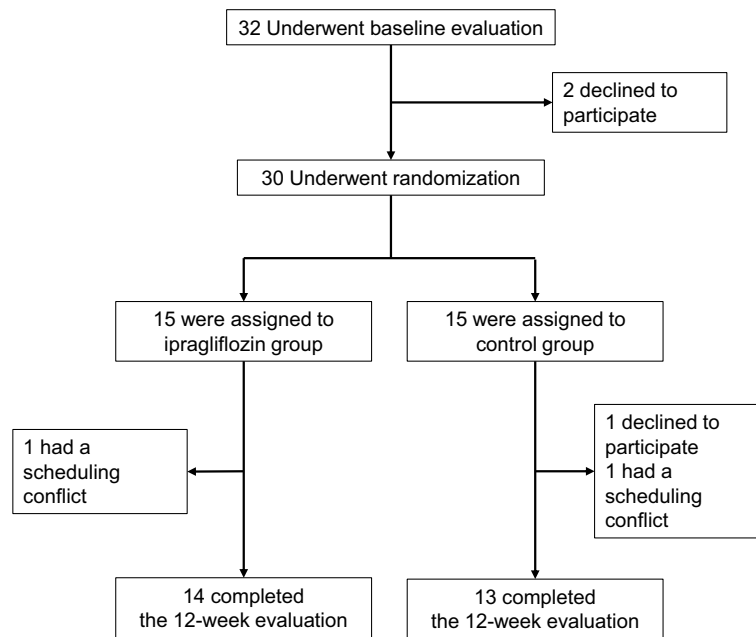


Figure. Patient flowchart for screening, randomization, and completion of the 12-week evaluation.

L], but not in the control group [7.9 (-14.4-30.3) $\mu\text{mol/L}$]; there was therefore a significant difference in the reduction in UA in the ipragliflozin group compared to the control group [$\Delta=-52.3$ (-85.5-19.1) $\mu\text{mol/L}$, $p=0.003$]. The mean eGFR decreased significantly in the control group over 12 weeks [-3.5 (-6.4--0.6) mL/min/1.73 m^2], whereas it remained at a sustained level in the ipragliflozin group [1.6 (-0.5-3.8) mL/min/1.73 m^2]. This appeared as a significant difference between the ipragliflozin group and the control group [$\Delta=4.6$ (1.5-7.7) mL/min/1.73 m^2 , $p=0.006$]. The BMI, FPG, CRE, and UACR values did not change significantly in either group over the course of the study. Similarly, there were no significant changes in the CAVI over 12 weeks [ipragliflozin group: 0.00 (-0.26-0.26); control group: 0.02 (-0.13-0.17)] and no significant difference in the changes in the CAVI between the groups [$\Delta=-0.02$ (-0.31, 0.27), $p=0.866$].

Relationship between the changes in UA and eGFR

Our findings showed that ipragliflozin add-on therapy resulted in improved changes in UA and eGFR compared to the control therapy. Given that the changes in the UA might have influenced the changes in the eGFR, we next examined the relationship between the changes in the UA and eGFR using a general linear model in which the dependent variable was the change in the eGFR (ΔeGFR) and the independent variables were the change in the UA (ΔUA) and the presence/absence of ipragliflozin.

We first investigated whether or not there was an interaction between the presence/absence of ipragliflozin and ΔUA against ΔeGFR , by constructing a preliminary model that included each factor and an interaction term (i.e., ipragliflozin use, ΔUA , and the interaction of ipragliflozin use and ΔUA).

We found no significant interaction between ipragliflozin use and ΔUA [regression coefficient (B)=1.827, standardized B (β)=0.263, $p=0.337$, data not shown]. Accordingly, the potential relationship between ΔUA and ΔeGFR was not limited to only when ipragliflozin was used. The interaction term was therefore excluded from the model thereafter.

We next examined factors that potentially affected ΔeGFR . When ΔUA and ipragliflozin use were evaluated at the same time, only ΔUA showed a significant association with ΔeGFR (ipragliflozin use: $B=2.037$, $\beta=0.220$, $p=0.200$; ΔUA : $B=-0.048$, $\beta=-0.526$, $p=0.004$; $R^2=0.404$) (Model 1 in Table 3). This indicated that the beneficial effects of ipragliflozin add-on therapy on ΔeGFR were attributable to the therapy-mediated ΔUA .

Finally, we examined the relationship between ΔUA and ΔeGFR after adjusting for confounding factors. As shown in Model 2 in Table 3, ΔUA was significantly associated with ΔeGFR after adjusting for age and sex ($\beta=-0.532$, $p=0.007$), classic confounding factors that potentially influence both UA and the eGFR. This association remained significant even after additional adjustment for baseline HbA1c (Model 3 in Table 3: $\beta=-0.537$, $p=0.008$) and after further adjustment for the baseline UA and eGFR (Model 4 in Table 3: $\beta=-0.535$, $p=0.010$).

Discussion

In the present study, we showed that ipragliflozin add-on therapy resulted in better suppression of the exacerbation of the renal function than did control therapy, with no adverse events, in patients with inadequately controlled type 2 diabetes. Our analysis revealed that the suppressive effects of ipragliflozin on the deterioration of the eGFR occurred in

Table 1. Characteristics of the Two Study Groups at Baseline.

Characteristic	Ipragliflozin group	Control group
N	15	15
Gender (n, %)		
Male	8, 53.3	7, 46.7
Female	7, 46.7	8, 53.3
Age (year)	59.1±11.2	62.5±13.5
BMI (kg/m ²)	30.5±7.0	31.4±5.1
Waist circumference (cm)	99.1±16.0	104.6±11.6
SBP (mmHg)	135.4±16.0	135.4±13.3
DBP (mmHg)	82.4±9.7	81.4±13.2
FPG (mmol/L)	7.4±1.2	7.8±1.6
HbA1c (%)	7.0±0.5	7.1±0.6
HbA1c (mmol/mol)	53.4±5.9	54.0±6.8
IRI (pmol/L)	63.9 [46.5, 85.4]	66.0 [59.7, 122.2]
HOMA-R	2.8 [2.2, 4.2]	3.4 [2.5, 6.0]
Triglycerides (mmol/L)	1.2 [0.8, 1.7]	1.4 [1.2, 2.1]
HDL-C (mmol/L)	1.2±0.1	1.3±0.4
LDL-C (mmol/L)	3.2±0.6	3.1±0.7
UA (μmol/L)	339.8±85.2	331.9±73.3
CRE (μmol/L)	75.8±20.6	71.4±19.5
eGFR (mL/min/1.73 m ²)	67.3±18.2	67.9±16.9
UACR (mg/g-Cr)	14.2 [6.5, 30.6]	8.9 [5.4, 32.6]
CAVI	7.8±1.2	8.7±1.5
Diabetes treatment (n, %)		
SU	4, 26.7	6, 40.0
αGI	1, 6.7	1, 6.7
BG	4, 26.7	5, 33.3
DPP-4	7, 46.7	8, 53.3
Thiazolidinedione	1, 6.7	2, 13.3

Data are expressed as mean±SD, median [interquartile range], or the number and percentage of patients.

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, FPG: fasting plasma glucose, HbA1c: hemoglobin A1c, IRI: immunoreactive insulin, HOMA-R: homeostasis model assessment ratio, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, UA: uric acid, CRE: creatinine, eGFR: estimated glomerular filtration rate, UACR: urine albumin-creatinine ratio, CAVI: Cardio-Ankle Vascular Index, SU: sulfonylurea, αGI: alpha-glucosidase inhibitor, BG: biguanide, DPP-4: dipeptidyl peptidase-4

parallel with the ipragliflozin-mediated reduction in serum UA levels. These findings might shed light on the potential novel mechanisms that underlie SGLT2 inhibitors' renal beneficial effects.

In recent large-scale clinical trials, SGLT2 inhibitors exerted beneficial effects on the renal function, such as the eGFR and albuminuria, in patients with type 2 diabetes at a high risk for CVD events and/or with established CVDs (9, 14, 15). In other intervention studies, improvements in the eGFR and UACR with SGLT2 inhibitors in patients with type 2 diabetes have also been reported (20-22). Consistent with these findings, we found that ipragliflozin add-on therapy suppressed the exacerbation of eGFR in patients with type 2 diabetes. Notably, the beneficial effects occurred prior to any remarkable improvements in anthro-

pometric/metabolic profiles, such as body weight and hyperglycemia. Thus, potential novel mechanisms may be implicated in the protective effects of ipragliflozin on renal dysfunction in patients with type 2 diabetes.

In addition to the effects of ipragliflozin on the eGFR, the serum UA levels also decreased in the ipragliflozin group in this study, even though they were within the normal range at the baseline. In several recent studies, SGLT2 inhibitors reduced blood UA levels in both type 1 and type 2 diabetes patients, although these patients were not hyperuricemic at baseline (20, 23-25). Elevated levels of blood UA induce renal injury and have been associated with an increased risk of CKDs and CVDs (23, 26), so a reduction in blood UA would be beneficial for patients with hyperuricemia. However, the clinical significance of reducing blood UA levels in patients with type 2 diabetes without hyperuricemia has not been comprehensively elucidated. Our analysis suggested that the change in serum UA levels might have resulted in a difference between the ipragliflozin and control groups in the changes in the eGFR over the course of the trial, potentially providing novel clues regarding the mechanisms underlying the renal protective effects of SGLT2 inhibitors.

Several possibilities have been proposed for the mechanisms underlying the beneficial effects of SGLT2 inhibitors on renal dysfunction in patients with type 2 diabetes. One is a reduction in the glomerular hyperfiltration, in which the SGLT2 inhibitor activates tubuloglomerular feedback and increases tubular back pressure by increasing the delivery of fluid and electrolytes to the macula densa (7, 13, 27). Another possibility is that pleiotropic effects of SGLT2 inhibitors, such as improvements in hyperglycemia, hypertension, and BMI, contribute to renal protective effects (27). It has also been speculated that the reduction in blood UA levels by SGLT2 inhibitors may be involved in their renal protective effects, based on the high risk for CKD associated with hyperuricemia (7, 26, 27). However, there have been no basic/clinical studies that have comprehensively elucidated the mechanisms underlying the SGLT2 inhibitor-mediated renal protective effects in patients with type 2 diabetes.

In patients with type 2 diabetes, the administration of an SGLT2 inhibitor reportedly improved the eGFR in parallel with the reduction in the UA levels, but improvement in the glucose metabolism was also observed (20). Furthermore, the EMPA-REG OUTCOME trial (8, 9) and the CANVAS program (14, 15) reported that the beneficial effects of SGLT2 inhibitors on the eGFR occurred concomitantly with glycemic improvements. The reduction in the UA levels was also observed concurrently with the improvement in the glucose metabolism following SGLT2 inhibitor administration (28-32). These results suggest that the renal benefits of SGLT2 inhibitors are involved in the changes in several parameters, including UA levels and glucose metabolism. In contrast, however, the present study showed that the beneficial effects of ipragliflozin on the eGFR were obtained in parallel with a reduction in the serum UA levels prior to any substantial improvement in other indices, such as hypergly-

Table 2. Changes in Primary and Secondary Outcomes.

Outcome	Time	Mean change from baseline		Between-group difference	
		Ipragliflozin group	Control group	Ipragliflozin vs. Control	p value
BMI (kg/m ²)	baseline	30.5± 7.0	31.4±5.1		
	week 12	29.8±6.8	30.9±5.1		
	Δ [95%CI]	-0.7 [-1.0, -0.4]	-0.5 [-1.3, 0.4]	-0.3 [-1.1, 0.6]	0.541
FPG (mmol/L)	baseline	7.4±1.2	7.8±1.6		
	week 12	6.8±0.8	7.9±2.0		
	Δ [95%CI]	-0.5 [-0.9, -0.1]	0.1 [-0.5, 0.7]	-0.6 [-1.3, 0.1]	0.088
HbA1c (%)	Baseline	7.0±0.5	7.1±0.6		
	week 12	6.9±0.5	7.0±0.7		
	Δ [95%CI]	-0.2 [-0.3, 0.0]	-0.1 [-0.3, 0.1]	-0.1 [-0.3, 0.2]	0.647
UA (μmol/L)	Baseline	339.8±85.3	331.9±73.3		
	week 12	295.4±77.3	339.8±68.1		
	Δ [95%CI]	-44.4 [-71.0, -17.8]	7.9 [-14.4, 30.3]	-52.3 [-85.5, 19.1]	0.003
CRE (μmol/L)	Baseline	75.8±20.6	71.4±19.5		
	week 12	75.2±23.7	73.8±19.1		
	Δ [95%CI]	-0.5 [-3.8, 2.6]	2.5 [0.6, 4.4]	-3.1 [-6.6, 0.5]	0.091
eGFR (mL/min/1.73 m ²)	Baseline	66.8±18.2	67.9±16.9		
	week 12	68.5±18.6	64.9±15.2		
	Δ [95%CI]	1.6 [-0.5, 3.8]	-3.5 [-6.4, -0.6]	4.6 [1.5, 7.7]	0.006
ln_UACR ^a	Baseline	2.7±0.9	2.6±1.2		
	week 12	2.7±1.0	2.4±1.0		
	Δ [95%CI]	0.0 [-0.3, 0.4]	-0.2 [-0.6, 0.1]	0.2 [-0.3, 0.7]	0.337
CAVI	baseline	7.80±1.20	8.68±1.54		
	week 12	7.80±1.23	8.70±1.51		
	Δ [95%CI]	0.00 [-0.26, 0.26]	0.02 [-0.13, 0.17]	-0.02 [-0.31, 0.27]	0.866

^aUACR values were log-transformed to obtain a normal distribution. Δ represents the difference between the 12-week and baseline values. "Between-group difference" indicates the difference between the ipragliflozin group and the control group values. p values from repeated-measures ANOVA [time (baseline and at 12 weeks)×group (ipragliflozin and control)]. BMI: body mass index, FPG: fasting plasma glucose, HbA1c: hemoglobin A1c, UA: uric acid, CRE: creatinine, eGFR: estimated glomerular filtration rate, UACR: urine albumin-creatinine ratio, CAVI: Cardio-Ankle Vascular Index, 95% CI: 95% confidence interval

cemia. These findings therefore suggest a novel functional significance of ipragliflozin, wherein improving the UA levels rather than factors such as hyperglycemia might contribute to alleviating renal dysfunction from the early phase after intervention. Although the mechanisms by which the serum UA levels are reduced by SGLT2 inhibitors in humans remain to be elucidated, in an experimental study using *Xenopus* oocytes, it was hypothesized that the reduction in the serum UA levels by SGLT2 inhibitors might be attributable to the function of glucose transporter 9 (GLUT9) (7, 26, 27, 33, 34): the SGLT2 inhibitors induce glycosuria, which may in turn result in an increased efflux of UA from the blood into the urine via GLUT9. Higher levels of glucose in the urine would also inhibit GLUT9-mediated UA reabsorption (7, 26, 27, 33, 34). Furthermore, SGLT2 inhibitors were shown to reduce blood UA levels and increase fractional UA excretion in patients with type 1 diabetes (23). Accordingly, our findings imply that ipragliflozin might beneficially affect renal dysfunction by stimulating the SGLT2-blood UA-eGFR axis, mediated by GLUT9. Given that the renal protective effects of ipragliflozin were observed in patients with type 2 diabetes without hyperuricemia, the use of SGLT2 inhibitors might be expected to be widely applicable to mitigating renal dysfunction in patients

with type 2 diabetes, irrespective of the presence of hyperuricemia. Thus, therapies that reduce the blood UA might themselves be novel strategies for suppressing renal dysfunction in patients with type 2 diabetes. Additional basic/clinical studies are needed to elucidate these issues.

The EMPA-REG OUTCOME trial and the CANVAS program reported an initial decline in the eGFR in the SGLT2 inhibitor group after 4 and 13 weeks of SGLT2 inhibitor administration, respectively (9, 15). Thereafter, during long-term administration, the eGFR in the SGLT2 inhibitor group remained stable (9) or increased (15), whereas it declined in the placebo group in both trials. These findings suggest a potential reduction in glomerular hyperfiltration by SGLT2 inhibitors, consequently suggesting the renal protective effects of SGLT2 inhibitors (7, 13, 27). In contrast, however, our study showed that, after 12 weeks, the eGFR remained at a sustained level in the ipragliflozin group but was decreased in the control group compared with baseline. We may therefore not have detected a potential initial decline in the eGFR in our trial, even though it may have occurred during the first several weeks, as this trial was designed to measure parameters at baseline and at the end of the 12-week intervention period. In this respect, time-course measurements would be helpful for analyzing the changes in the

Table 3. Analysis of Factors Affecting Changes in eGFR.

Independent variables	<i>B</i>	<i>SEB</i>	β	p value
Model 1:				
Δ UA	-0.048	0.015	-0.526	0.004
Ipragliflozin use ($R^2=0.404$)	2.037	1.552	0.220	0.200
Model 2: age- and gender-adjusted				
Δ UA	-0.049	0.017	-0.532	0.007
Ipragliflozin use ($R^2=0.409$)	2.464	1.772	0.253	0.178
Model 3: age-, gender-, and baseline HbA1c-adjusted				
Δ UA	-0.050	0.017	-0.537	0.008
Ipragliflozin use ($R^2=0.388$)	2.572	1.816	0.264	0.171
Model 4: age-, gender-, baseline HbA1c-, UA-, and eGFR-adjusted				
Δ UA	-0.050	0.017	-0.535	0.010
Ipragliflozin use ($R^2=0.359$)	2.505	1.887	0.257	0.199

Ipragliflozin use: used=1, not used=0. Relationships between the effects on outcomes of ipragliflozin add-on therapy were investigated using a general or generalized linear model. Model 2: Model 1 adjusted for age and sex, which are classic confounding factors that influence both UA and eGFR. Model 3: baseline HbA1c was added to Model 2. Model 4: baseline UA and eGFR were added to Model 3.

eGFR: estimated glomerular filtration rate, UA: uric acid, HbA1c: hemoglobin A1c, *B*: regression coefficient, *SEB*: standard error of *B*, β : standardized regression coefficient

eGFR in detail.

Another possibility is that the subjects in the present study differed from those in the EMPA-REG OUTCOME trial and the CANVAS program with regard to the presence of a high risk of CVD events (9) and a history of CVD events (15). Since the cardiovascular and kidney functions are closely associated with each other, the effects of SGLT2 inhibitors on the renal function may differ between patients with and without a high risk for CVD events. In this context, a previous study examined the effects of ipragliflozin on the eGFR in patients with type 2 diabetes who had neither heart failure nor a history of myocardial or cerebral infarction but had an eGFR of ≥ 60 to < 90 mL/min/1.73 m² (22). The study found no significant changes in the eGFR between baseline and the end of the 24-week intervention period. Thus, the characteristics of the study patients may affect whether or not the eGFR is initially decreased by SGLT2 inhibitor administration.

Although the mechanistic details underlying the absence of the initial decline in the eGFR with ipragliflozin administration in the present study remain unclear, our results demonstrate that ipragliflozin add-on therapy prevented the decline in the eGFR, in parallel with the significant association between the changes in the eGFR and in UA. These findings therefore suggest that an SGLT2 inhibitor may have beneficial effects on the renal function in a short-term intervention in patients with type 2 diabetes who are not at a high risk for CVD events, compared with those at a high risk for

CVD events, as observed in previous studies (9, 15). These findings further suggest that a longer-term intervention would be required to demonstrate the renal benefits for patients with type 2 diabetes who are at a high risk for CVD events compared with those who are not at a high risk for CVD events.

We observed no adverse effects resulting from the ipragliflozin add-on therapy over the course of this trial. However, HbA1c and FPG were not remarkably improved during the trial. This might be explained by the patients enrolled in this study having only mild hyperglycemia (achieved through antidiabetes treatment), although a ≥ 12 -week course of treatment did not result in further improvement. This explanation is supported by previous studies with a larger sample size reporting that relatively low baseline HbA1c levels may have contributed to the reduced magnitude of glucose-lowering effects by SGLT2 inhibitors (20, 35, 36). Thus, a longer trial may be needed to observe a noticeable improvement in glycemic control in these patients. Similarly, a longer intervention may be required to achieve a substantial improvement in indices such as anthropometric measures and arterial stiffness.

Several limitations associated with the present study warrant mention. First, its open-label design may have resulted in unintentional bias because the physicians and patients knew the type of medication used. Second, the study showed the renal benefits of ipragliflozin prior to any remarkable improvement in anthropometric or metabolic indices, but multiple beneficial effects of ipragliflozin are expected to be potentially favorable to the renal function. Thus, a longer trial would be needed in order for improvements in anthropometric and metabolic indices to manifest and to elucidate the relationships between these benefits and the renal protective effects of ipragliflozin as well as the effects of longer-term administration of ipragliflozin on the renal function in detail. Furthermore, the present study design did not detect the initial changes in parameters that might occur during the early period of intervention. Additional studies conducting time-course measurements would be helpful for improving our understanding of the effects of ipragliflozin add-on therapy. The participants in this study were type 2 diabetes patients with mild hyperglycemia-achieved by treatment-although a ≥ 12 -week course of treatment for diabetes did not bring about further improvement, and they did not have hyperuricemia. Investigating the effects of ipragliflozin on type 2 diabetes patients with elevated HbA1c values with or without hyperuricemia and with a larger sample size would be helpful for comprehensively elucidating the beneficial effects of this treatment on renal dysfunction in this population. Experimental studies using a mouse model that includes GLUT9 knockout mice are also needed to improve our understanding of the detailed mechanisms underlying the SGLT2 inhibitor-mediated renal protective effects in diabetes.

In conclusion, this was the first study showing that ipragliflozin add-on therapy resulted in beneficial effects on re-

nal dysfunction in parallel with a reduction in serum UA levels in patients with type 2 diabetes without hyperuricemia. These findings imply the possible usefulness of SGLT2 inhibitors and the potential novel significance of reducing blood UA levels for renal protection in patients with type 2 diabetes. Future basic or clinical studies that target the functions of SGLT2 and/or GLUT9 could provide further insights into the novel benefits of SGLT2 inhibitors and their underlying mechanisms, leading to novel strategies for reducing the risk of CKD in patients with type 2 diabetes.

Author's disclosure of potential Conflicts of Interest (COI).

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