Original Article

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Investigation of efficacy and safety of low-dose sodium glucose transporter 2 inhibitors and differences between two agents, canagliflozin and ipragliflozin, in patients with type 2 diabetes mellitus

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Summary **Sodium glucose transporter 2 inhibitors (SGLT2is), new antidiabetic agents, were reported to improve not only glycemic parameters but also metabolic and circulatory parameters. Whereas, several adverse events caused by SGLT2is were also reported. We aimed to investigate the changes of glycemic, metabolic, and circulatory parameters as well as safety with low-dose administration of two SGLT2is, canagliflozin and ipragliflozin, and also the difference between the two agents. 25 individuals with type-2 diabetes mellitus (T2DM) were recruited and administered with low-dose SGLT2is, canagliflozin (n = 10, 50 mg/day) and ipragliflozin (n = 15, 25 mg/day). We examined glycemic, metabolic, and circulatory parameters at baseline and 24 weeks after administration. All patients completed the study without complications. Compared with baseline, levels of glycated hemoglobin, fasting plasma glucose, and homeostasis model assessment of β-cell function improved significantly at 24 weeks after administration ($p < 0.05$). Levels of body weight, low-density lipoprotein-cholesterol, aspartate transaminase, γ-glutamyl transferase, and urinary excretion of albumin also improved significantly ($p < 0.05$). Moreover, systolic/diastolic blood pressure and levels of brain natriuretic peptide improved significantly ($p < 0.05$). The comparison of improvement ratio (values of improvement/values of basement) of each agent revealed that there was a significant difference between low-dose canagliflozin and low-dose ipragliflozin for brain natriuretic peptide (0.4404 *vs.* 0.0970, p = 0.0275). Hence, low-dose SGLT2is could be useful for patients of T2DM not only for hyperglycemia but also for metabolic and circulatory disorders without eliciting adverse events. In addition, with regard to the efficacy upon cardiovascular function, canagliflozin could be more suitable than ipragliflozin.**

Keywords: Sodium glucose transporter 2 inhibitors, type-2 diabetes mellitus, canagliflozin, ipragliflozin

1. Introduction

Sodium glucose transporter-2 inhibitors (SGLT2is) are new antidiabetic agents for patients with type-2 diabetes mellitus (T2DM). Sodium glucose transporter-2 (SGLT2) is a member of the sodium glucose transporter (SGLT)

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family of solute transporters and expressed highly in the proximal tubules of kidneys. SGLT2 has an important role in glucose reabsorption, and inhibition of SGLT2 prevents hyperglycemia caused by reduced reabsorption of glucose (*1-3*). SGLT2is were proposed as an insulin-independent approach for treatment of hyperglycemia (*4*), and have the effects of reducing body weight and fat mass (*5,6*). SGLT2is were also reported to improve several metabolic parameters other than glycemic parameters (*7-10*). Moreover, some studies revealed that the SGLT2is reduce the prevalence of death from cardiovascular causes and hospitalization for heart failure (*11-13*).

On the other hand, it was reported SGLT2is often caused adverse events. In detail, infection of the urinary and genital tracts, dehydration, diabetic ketosis/ketoacidosis have been reported as adverse events of SGLT2is (*14,15*). A way to prevent these adverse effects of SGLT2is have yet to be established.

Interestingly, it was reported that the inhibition of sodium glucose transporter-1 (SGLT1) led to same diuretic effect as that of SGLT2 (*16,17*). It was also reported that SGLT2is could inhibit SGLT1 as well as SGLT2, implying differences in potencies of inhibition of SGLT1 among available SGLT2is (*18,19*).

Hence, we investigated the efficacy of low-dose SGLT2is, 50 mg/day of canagliflozin (a half of commonly used dose: 100 mg/day) or 25 mg/day of ipragliflozin (a half of commonly used dose: 50 mg/day), upon glycemic parameters, metabolic parameters, and circulatory parameters, and also checked the safety of low-dose administration of these two SGLT2is to seek whether it can circumvent the adverse effects of SGLT2is that have been reported to be problematic recently. Besides, we also investigated the difference of effects upon available parameters between the two SGLT2is, canagliflozin and ipragliflozin.

2. Subjects and Methods

2.1. *Ethical approval of the study protocol*

The study protocol was approved by the Ethics Review Committee of Nagasaki Prefecture Iki Hospital (Nagasaki, Japan). All participants provided written informed consent to participate in the study.

2.2. *Subjects*

We recruited 25 individuals with T2DM at Nagasaki Prefecture Iki Hospital and Shinagawa Surgical Hospital from April 2015 to March 2018. Participant characteristics are shown in Table. 1 and Table. 2. None of the drugs of patients were changed during the study.

2.3. *Study design*

To examine the efficacy and safety of low-dose SGLT2is (canagliflozin 50 mg/day, ipragliflozin 25 mg/day), we administered them and continued treatment for 24 weeks.

Table 1. Clinical characteristics of patient cohort

	All (n = 25)	Canagliflozin (n = 10)	Ipragliflozin (n = 15)
Age (years)	62.4 ± 11.0	60.9 ± 9.4	63.5 ± 12.2
Male/female	12/13	5/5	7/8
Body weight (kg)	69.0 ± 14.2	69.3 ± 13.3	68.8 ± 14.1
Fasting plasma glucose (mg/dL)	147.7 ± 30.9	144.3 ± 30.3	149.9 ± 32.1
Glycated hemoglobin (%)	7.68 ± 0.61	7.78 ± 0.55	7.59 ± 0.65
HOMA-β	31.8 ± 21.6	31.0 ± 26.5	32.3 ± 18.6
HOMA-IR	2.69 ± 2.05	2.51 ± 2.10	2.81 ± 2.08
Low-density lipoprotein-cholesterol (mg/dL)	106.6 ± 19.8	106.4 ± 19.8	106.7 ± 20.4
High-density lipoprotein-cholesterol (mg/dL)	56.5 ± 15.2	59.6 ± 17.6	54.5 ± 13.6
Triglyceride (mg/dL)	117.8 ± 62.8	134.0 ± 89/7	107.0 ± 35.7
Aspartate transaminase (U/L)	22.4 ± 10.8	22.0 ± 6.2	22.7 ± 13.3
Alanine aminotransferase (U/L)	24.1 ± 17.9	19.4 ± 7.0	27.3 ± 22.2
γ-glutamyl transferase (U/L)	26.6 ± 14.5	31.3 ± 15.4	23.4 ± 13.5
Urinary albumin (mg/gCr)	164.1 ± 393.3	183.1 ± 406.0	151.5 ± 398.4
Estimated glomerular filtration rate (mL/min/1.73 m^2)	75.3 ± 21.2	81.8 ± 21.3	71.0 ± 20.3
Brain natriuretic peptide (pg/mL)	26.8 ± 21.0	25.7 ± 10.2	27.6 ± 26.2
Systolic blood pressure (mmHg)	137.0 ± 17.3	135.1 ± 14.9	138.2 ± 19.2
Diastolic blood pressure (mmHg)	74.7 ± 10.2	77.1 ± 7.8	73.1 ± 11.6
Detail of medication for diabetes mellitus			
Only dipeptidyl peptidase-4 inhibitor	3	2	1
Only biguanide	4	2	2
Dipeptidyl peptidase-4 inhibitor and biguanide	11	3	8
Sulfonylurea and dipeptidyl peptidase-4 inhibitor	5	2	3
Sulfonylurea and biguanide	1	0	1
Sulfonylurea, dipeptidyl peptidase-4 inhibitor, and biganide	1	1	0

Data are shown as means ± standard deviation (SD). HOMA-β: homeostasis model assessment of β-cell function, HOMA-IR: homeostasis model assessment of insulin resistance.

Table 2. Glycemic parameters, the metabolic parameters, and circulatory parameters at baseline and 24 weeks after administration of low-dose SGLT2is

	baseline	24 weeks after	*p*
Body weight (kg)	69.0 ± 14.2	66.0 ± 13.4	< 0.0001*
Fasting plasma glucose (mg/dL)	147.7 ± 30.9	134.3 ± 21.4	0.0023*
Glycated hemoglobin (%)	7.68 ± 0.61	7.12 ± 0.62	0.0002*
HOMA-β	31.8 ± 21.6	39.0 ± 31.0	0.0201*
HOMA-IR	2.69 ± 2.05	2.46 ± 1.99	0.1582
Low-density lipoprotein-cholesterol (mg/dL)	106.6 ± 19.8	97.6 ± 20.4	0.0034*
High-density lipoprotein-cholesterol (mg/dL)	56.5 ± 15.2	57.6 ± 13.4	0.2959
Triglyceride (mg/dL)	117.8 ± 62.8	102.1 ± 49.6	0.2149
Aspartate transaminase (U/L)	22.4 ± 10.8	18.4 ± 3.9	0.0203*
Alanine aminotransferase (U/L)	24.1 ± 17.9	20.0 ± 12.2	0.0644
γ-glutamyl transferase (U/L)	26.6 ± 14.5	23.7 ± 14.0	0.0128*
Urinary albumin (mg/gCr)	164.1 ± 393.3	69.8 ± 153.6	0.0492*
Estimated glomerular filtration rate (mL/min/1.73 m^2)	75.3 ± 21.2	75.2 ± 21.2	0.4558
Brain natriuretic peptide (pg/mL)	26.8 ± 21.0	17.3 ± 16.3	0.0013*
Systolic blood pressure (mmHg)	137.0 ± 17.3	124.6 ± 16.5	0.0003*
Diastolic blood pressure (mmHg)	74.7 ± 10.2	69.6 ± 13.0	0.0152*

Data are shown as means ± standard deviation (SD). The significance of differences between means was estimated by paired *t*-test. $p < 0.05$ were considered to indicate statistical significance (*). HOMA-β: homeostasis model assessment of β-cell function, HOMA-IR: homeostasis model assessment of insulin resistance.

The following variables were measured at baseline and 24 weeks after administration of parameters of glycemic control (glycated hemoglobin (HbA_{1c}), fasting plasma glucose (FPG), homeostasis model assessment of insulin resistance (HOMA-IR), homeostasis model assessment of β-cell function (HOMA-β); markers of lipid metabolism (low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG)); liver enzymes (aspartate transaminase (AST), alanine transaminase (ALT), γ-glutamyl transferase (γ-GTP)), estimated glomerular filtration rate (eGFR), urinary albumin (U-Alb), brain natriuretic peptide (BNP), systolic and diastolic blood pressure (SBP and DBP), and body weight (BW). Blood samples were obtained after an overnight fast, and HOMA-IR was calculated using the following formula: HOMA-IR = FPG × fasting insulin/405. HOMA-β was calculated using the following formula: HOMA-β = 360 × fasting insulin/(FPG − 63). Adverse events (including side effects) were examined based on patient data and interviews with patients. In addition, to evaluate the difference between two agents, canagliflozin and ipragliflozin, glycemic, metabolic, and circulatory parameters at baseline and 24 weeks after administration were investigated and the comparison of improvement ratio (values of improvement/values of basement) in each parameter of the two different agents was performed.

2.4. *Statistical analyses*

Data are the mean ± standard deviation (SD). Statistical analyses were performed using STATA® SE version 13.1 (Stata Corporation, College Station, TX, USA). Significance of differences between mean values was estimated by paired *t*-test (for investigations except comparison of improve ratio) and unpaired *t*-test (for comparison of improve ratio). $p < 0.05$ was considered significant.

3. Results

All patients completed the present study without adverse events such as infection of urinary or genital tracts, dehydration, diabetic ketosis/ketoacidosis. Changes in glycemic parameters (HbA_{1c}, FPG, HOMA-IR, HOMA-β), metabolic parameters (BW, LDL-C, HDL-C, TG, AST, ALT, γ-GTP, eGFR, U-Alb), circulatory parameters (BNP, SBP, DBP) at baseline and 24 weeks after administration of low-dose SGLT2is for all patients are shown in Table 2. In terms of glycemic parameters, levels of HbA_{1c}, FPG, and HOMA-β improved significantly after 24 weeks of SGLT2is administration compared to baseline (HbA_{1c}: 7.68 ± 0.61 *vs.* 7.12 ± 0.62 %, $p = 0.0002$; FPG: 147.7 ± 30.9 *vs.* 134.3 ± 21.4 mg/dL, $p = 0.0023$; HOMA-β: 31.8 ± 21.6 *vs.* 39.0 ± 31.0, $p = 0.0201$). HOMA-IR also improved but not significant (2.69 ± 2.05 *vs.* 2.46 ± 1.99 mg/dL, $p = 0.1582$). BW decreased significantly (69.0 ± 14.2 *vs.* 66.0 ± 13.4 kg, $p < 0.0001$). Concerning lipid metabolism, levels of LDL-C improved significantly (106.6 ± 19.8 *vs.* 97.6 ± 20.4 mg/dL, $p = 0.0034$), while levels of HDL-C and TG also improved but were not significant (HDL-C: 56.5 ± 15.2 *vs.* 57.6 ± 13.4 mg/dL, $p = 0.2959$; TG: 117.8 ± 62.8 *vs.* 102.1 ± 49.6 mg/dL, $p = 0.2149$, respectively). As for liver enzymes, levels of AST and γ-GTP were reduced significantly (AST: 22.4 ± 10.8 *vs.* 18.4 ± 3.9 U/L, $p = 0.0203$; γ-GTP: 26.6 ± 14.5 *vs.* 23.7 ± 14.0 U/L, $p = 0.0128$, respectively), though the reduction of ALT was not significant (24.1 ± 17.9 *vs.* 20.0 ± 12.2 U/L, $p = 0.0644$). U-Alb levels were improved significantly (164.1 ± 393.3 *vs.* 69.8 ± 153.6 mg/gCr, $p = 0.0492$), while there was not significant change of eGFR level

(75.3 ± 21.1 *vs.* 75.2 ± 21.2 mL/min/1.73 m^2, $p = 0.4558$). Concerning circulatory parameters, all parameters improved significantly (BNP: 26.8 ± 21.0 *vs.* 17.3 ± 16.3 pg/mL, $p = 0.0013$; SBP: 137.0 ± 17.3 *vs.* 124.6 ± 16.5 mmHg, $p = 0.0003$; DBP: 74.7 ± 10.2 *vs.* 69.6 ± 13.0 mmHg, $p = 0.0152$, respectively).

The differences between baseline and 24 weeks after administration for patients with low-dose canagliflozin and those of low-dose ipragliflozin are shown in Table 3. The change of parametric values were similar, except for those of HOMA-IR, AST, ALT, and DBP, that were significantly decreased for low-dose canagliflozin ($p = 0.0221$, $p = 0.0243$, $p < 0.0001$, $p = 0.0140$, respectively) but not for low-dose ipragliflozin ($p = 0.3219$, $p = 0.0979$, $p = 0.1613$, $p = 0.1982$, respectively). There was a significant increase for HOMA-β and decrease for γ-GTP with low-dose ipragliflozin ($p = 0.0334$ and $p = 0.0010$) but not for low-dose canagliflozin ($p = 0.1672$ and $p = 0.2849$). Improvement ratio (values of improvement/values of basement) in glycemic parameters, metabolic parameters, and circulatory parameters of both low-dose canagliflozin and low-dose ipragliflozin is shown in Table 4. Among the parameters, low-dose canagliflozin significantly improved BNP compared to low-dose ipragliflozin (0.4404 *vs.* 0.0970, $p = 0.0275$).

4. Discussion

T2DM is known for its hyperglycemia symptoms due to impaired glucose homeostasis, which is a result of an imbalance of concerted secretion of pancreatic hormones such as insulin and glucagon, and which is accompanied with insulin resistance in peripheral tissues (*20*). Appropriate blood glucose control in T2DM patients can be achieved through diet and exercise therapy but is discontinued in most patients. Most of them come to rely on antidiabetic agents (*21,22*).

SGLT2is are a distinct category of anti-diabetic agents that lower blood glucose level by increasing urine glucose excretion (*4*).This is a result of decreased reabsorption of glucose by inhibiting SGLT2 (*1-3*). Unexpectedly, SGLT2is improve various pathological

Table 3. Respective data of each parameter at baseline and 24 weeks after administration of low-dose of canagliflozin and ipragliflozin

	baseline	24 weeks after	*p*
Canagliflozin ($n = 10$)			
Body weight (kg)	69.3 ± 15.1	65.5 ± 13.2	0.0056*
Fasting plasma glucose (mg/dL)	144.3 ± 30.3	130.3 ± 19.2	0.0359*
Glycated hemoglobin (%)	7.78 ± 0.55	7.03 ± 0.62	0.0115*
HOMA-β	31.0 ± 26.5	33.3 ± 29.6	0.1672
HOMA-IR	2.51 ± 2.11	1.75 ± 1.36	0.0221*
Low-density lipoprotein-cholesterol (mg/dL)	106.4 ± 19.8	100.4 ± 21.5	0.0424*
High-density lipoprotein-cholesterol (mg/dL)	59.6 ± 17.6	61.4 ± 12.6	0.3402
Triglyceride (mg/dL)	134.0 ± 89.7	101.3 ± 59.1	0.1169
Aspartate transaminase (U/L)	22.0 ± 6.2	17.9 ± 4.3	0.0243*
Alanine aminotransferase (U/L)	19.4 ± 7.0	15.9 ± 5.9	< 0.0001*
γ-glutamyl transferase (U/L)	31.3 ± 15.4	30.2 ± 17.8	0.2849
Urinary albumin (mg/gCr)	183.1 ± 406.0	116.9 ± 238.0	0.1240
Estimated glomerular filtration rate (mL/min/1.73 m^2)	81.8 ± 22.2	81.4 ± 21.3	0.4128
Brain natriuretic peptide (pg/mL)	25.7 ± 10.2	13.3 ± 7.4	0.0024*
Systolic blood pressure (mmHg)	135.1 ± 14.9	124.5 ± 19.8	0.0243*
Diastolic blood pressure (mmHg)	77.1 ± 7.8	67.9 ± 12.0	0.0140*
Ipragliflozin ($n = 15$)			
Body weight (kg)	68.8 ± 14.1	66.3 ± 14.0	< 0.0001*
Fasting plasma glucose (mg/dL)	149.9 ± 32.1	137.0 ± 23.0	0.0194*
Glycated hemoglobin (%)	7.59 ± 0.65	7.17 ± 0.63	0.0022*
HOMA-β	32.3 ± 18.6	42.9 ± 32.4	0.0334*
HOMA-IR	2.81 ± 2.08	2.94 ± 2.23	0.3219
Low-density lipoprotein-cholesterol (mg/dL)	106.7 ± 20.4	95.7 ± 20.2	0.0163*
High-density lipoprotein-cholesterol (mg/dL)	54.5 ± 13.6	55.1 ± 13.7	0.3779
Triglyceride (mg/dL)	107.0 ± 35.7	102.6 ± 44.4	0.3476
Aspartate transaminase (U/L)	22.7 ± 13.3	18.7 ± 3.7	0.0979
Alanine aminotransferase (U/L)	27.3 ± 22.2	22.8 ± 14.6	0.1613
γ-glutamyl transferase (U/L)	23.4 ± 13.5	19.4 ± 9.0	0.0010*
Urinary albumin (mg/gCr)	151.5 ± 398.4	38.4 ± 37.6	0.1370
Estimated glomerular filtration rate (mL/min/1.73 m^2)	71.0 ± 20.3	71.0 ± 20.8	0.4879
Brain natriuretic peptide (pg/mL)	27.6 ± 26.2	20.0 ± 20.0	0.0446*
Systolic blood pressure (mmHg)	138.2 ± 19.2	124.6 ± 14.7	0.0028*
Diastolic blood pressure (mmHg)	73.1 ± 11.6	70.7 ± 13.9	0.1982

Data are shown as means ± standard deviation (SD). The significance of differences between means was estimated by paired *t*-test. $p < 0.05$ were considered to indicate statistical significance (*). HOMA-β: homeostasis model assessment of β-cell function, HOMA-IR: homeostasis model assessment of insulin resistance.

Table 4. Comparison of improvement ratio (values of improvement/values of basement) between canagliflozin and ipragliflozin, upon each parameter

	Canagliflozin (n = 10)	Ipragliflozin (n = 15)	p
Body weight	0.0512	0.0376	0.3161
Fasting plasma glucose	0.0770	0.0713	0.9186
Glycated hemoglobin	0.0925	0.0534	0.2205
HOMA-β	0.0956	0.3133	0.1170
HOMA-IR	0.1032	- 0.0985	0.3554
Low-density lipoprotein-cholesterol	0.0563	0.0920	0.5541
High-density lipoprotein-cholesterol	0.0735	0.0176	0.4800
Triglyceride	0.1147	0.0022	0.4741
Aspartate transaminase	0.1539	0.0750	0.3750
Alanine transaminase	0.1775	0.0378	0.1823
γ-glutamyl transferase	0.0476	0.1236	0.1825
Urinary albumin	0.0115	0.0330	0.9443
Estimated glomerular filtration rate	0.0016	0.0036	0.9567
Brain natriuretic peptide	0.4404	0.0970	0.0275*
Systolic blood pressure	0.0775	0.0906	0.7703
Diastolic blood pressure	0.1179	0.0264	0.1547

Data are shown as means ± standard deviation (SD). The significance of differences between means was estimated by unpaired t-test. $p < 0.05$ were considered to indicate statistical significance (*). HOMA-β: homeostasis model assessment of β-cell function, HOMA-IR: homeostasis model assessment of insulin resistance.

conditions in addition to high blood glucose levels. It was reported that SGLT2is decrease body weight and fat mass, and improve concomitant insulin resistance (*5,6*). Meanwhile, it was reported that SGLT2is could improve insulin secretion of beta cells in the pancreas (*23,24*). They were also reported to improve metabolic disorders, such as hyperlipidemia, fatty liver, albuminuria (*7-9*). Furthermore, several previous studies demonstrated that the SGLT2is lowers the prevalence of death from cardiovascular causes and hospitalization for heart failure (*11-13*). Thus, SGLT2is have various advantages besides their occasional side effects. These adverse events: infection of urinary or genital tracts; dehydration; and diabetic ketosis/ketoacidosis may sometimes lead to unwelcomed results (*14,15*). We hypothesized low-dose administration of SGLT2is might be useful for prevention of such serious adverse effects. Indeed, we previously investigated several patients with low-dose ipraglifozin and showed that adverse events did not occur (*25*). In the present study, all patients completed the study without complications such as infection of urinary or genital tracts, diabetic ketosis/ketoacidosis. Moreover, there were no changes in eGFR between baseline and 24 weeks after administration of SGLT2is. In previous studies, it was reported that the recommended dose of SGLT2is cause decrease of eGFR at 24-48 weeks after administration (*11-13*). Considering eGFR did not change, low-dose of SGLT2is could carry a low risk of severe dehydration. Hence, patients with low-dose SGLT2is could avoid the adverse effects of SGLT2is that have been reported to be problematic.

In terms of efficacy of SGLT2is, our investigations demonstrated that the levels of HbA_{1c}, FPG, and HOMA-β improved significantly. Considering that levels of BW was reduced significantly, we think that levels of HOMA-IR would improve if we continued to use low-dose of SGLT2is over a long period. With regard to metabolic parameters, levels of LDL-C, AST, γ-GTP, and U-Alb as well as those of BW, decreased significantly. In addition, levels of circulatory parameters, such as BNP, SBP, and DBP, improved significantly. These data suggest that low-dose SGLT2is could have adequate efficacy despite of less adverse events.

On the other hand, we also investigated the differences between two SGLT2is, canagliflozin and ipragliflozin. Our study indicated canagliflozin significantly improved BNP, more than that of ipraglifozin. Decreased BNP could indicate the improvement in cardiovascular function (*26*). Actually, SGLT2is were reported to have the efficacy for heart failure mainly by diuretic effects of the inhibition of SGLT2. Whereas, SGLT2is could inhibit SGLT1 as well as SGLT2 (*18,19*). Recently, several reports demonstrated the inhibition of SGLT1 could have diuretic effects (*16,17*). Actually, canagliflozin was reported to be more effective for SGLT1 among the available SGLT2is (*24*). The difference between two different SGLT2is, canagliflozin and ipraglifozin, in the present study, can be found in previous reports. Our results indicate that canagliflozin, which has more potency for SGLT1 inhibition than ipragliflozin, might be suitable for patients with disorders of cardiovascular function, such as heart failure.

In summary, our study revealed that low-dose SGLT2is were useful for hyperglycemia in T2DM patients but also their metabolic and circulatory disorders without eliciting adverse events. Furthermore, in regard of the efficacy for cardiovascular function, canagliflozin could be more promising than ipragliflozin. However, our study has limitations. The present study is a nonrandomized study with a small number of cases and short duration. Thus, randomized control studies with larger cohorts and longer terms are required to confirm our results in the future.

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