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ORIGINAL RESEARCH ARTICLE

Canagliflozin as an Initial Therapy in Drug-Naïve Subjects with Type 2 Diabetes Mellitus: A Potential Involvement of Atherogenic Lipids in its Glycemic Efficacy

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Abstract

Background and Objectives The aim of this study is to investigate canagliflozin as an initial therapy in type 2 diabetes mellitus and to explore the effects on metabolic parameters in relation to effects on glycemic control.

Subjects and Methods Treatment-naïve subjects with type 2 diabetes mellitus received canagliflozin 50–100 mg/day monotherapy. At 3 months, levels of glycemic and non-glycemic parameters were compared with those at baseline ($n = 39$). As a comparator, our previous data of baseline glycosylated hemoglobin (HbA_{1c})-matched treatment-naïve subjects with ipragliflozin 25–50 mg monotherapy ($n = 27$) were employed.

Results Significant reductions in HbA_{1c} (from 9.96 to 8.33%), fasting blood glucose (−23.9%), homeostasis model assessment-R (HOMA-R, −33.5%), body mass index (−1.8%), and uric acid (UA, −5.2%) levels and significant increases in homeostasis model assessment-B (HOMA-B, 30.1%) levels were observed. Approximately one third of the subjects experienced certain adverse events. Similar results were obtained with ipragliflozin. Baseline levels of HbA_{1c}, triglycerides, non-high-density lipoprotein-cholesterol (HDL-C), and low-density lipoprotein-cholesterol (LDL-C) were chosen as significant contributing factors for the changes in HbA_{1c} levels with canagliflzoin, while only baseline HbA_{1c} levels were selected as such a factor with ipragliflozin. Significant positive correlations between the changes in HbA_{1c} and changes in non-HDL-C ($R = 0.3954$) or between changes in HbA_{1c} and changes in LDL-C ($R = 0.4317$) were observed with canagliflozin. With ipragliflozin, no such correlations were noted. No correlations between the changes in HbA_{1c} and changes in body mass index were seen with both drugs.

Conclusions These results suggest that (1) canagliflozin appears to offer clinically beneficial outcomes as an initial therapy in subjects with type 2 diabetes mellitus, although with certain adverse events. (2) Atherogenic cholesterols including non-HDL-C and LDL-C could be involved in the glycemic efficacy of canagliflozin. This was not the case with ipragliflozin. (3) Unexpectedly, weight reductions with canagliflozin are not associated with its glycemic efficacy.

Key Points

Canagliflozin as a first-line drug fpr patients with type 2 diabetes mellitus appears to be beneficial in many aspects including glycemic control, body weight, uric acid (UA), insulin sensitivity, and beta-cell function, though certain precautions are required regarding its adverse events.

Atherogenic cholesterols including non-high-density lipoprotein-cholesterol and low-density lipoprotein-cholesterol may be involved in the glycemic efficacy of canagliflozin.

Some differences may exist between canagliflozin and ipragliflozin regarding their effect on metabolic markers in relation to their glycemic efficacies.

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1 Introduction

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors are new glucose-lowering agents that exert their therapeutic effects by inhibiting glucose reabsorption in the proximal tubule of the kidneys [1–3]. This pharmacologically induced glycosuria causes physiological and adaptive responses in glucose homeostasis and other metabolic parameters. For example, SGLT-2 inhibitors have also been shown to possess some non-glycemic benefits such as weight reduction, blood pressure control, diuretic action, and renal protection [4, 5]. Canagliflozin is one of the SGLT-2 inhibitors and is available in many countries including Japan, USA, and Europe [6–8]. Similar glycemic and non-glycemic efficacies were reported with other SGLT-2 inhibitors [6–8]. With the simple mechanism of discarding glucose into the urine, SGLT-2 inhibitors including canagliflozin were shown to ameliorate beta-cell function and insulin resistance [1–3, 6–9]. However, consistent with their mechanisms of action, they are associated with a higher incidence of certain adverse events including genital mycotic infections, urinary tract infections, osmotic diuretic-related adverse events, and volume depletion-related adverse events [10].

Metformin is regarded as the initial drug for patients with type 2 diabetes mellitus (T2DM) in many countries [11]. Sodium-glucose co-transporter 2 inhibitors including canagliflozin are currently used as add-on therapy to metformin or other drugs as part of dual or triple therapy [11]. However, they could also be used as alternative first-line options in patients with contraindications/intolerance to metformin or in other situations [9, 12].

To date, limited clinical data are available on whether canagliflozin could be used as an initial drug in patients with T2DM in an actual clinical setting. This project was initiated to investigate this question. It makes sense to perform this type of study with drug-naïve subjects using monotherapy to eliminate the influences of other drugs as much as possible. As an initial step towards investigating this question, canaglflozin 50–100 mg/day monotherapy was performed with drug-naïve subjects with T2DM and effects on some glycemic and non-glycemic parameters were measured. As a comparator, our previous study performed with ipragliflozin 25–50 mg/day monotherapy in drug-naïve subjects was employed [9].

2 Subjects and Methods

2.1 Subjects

Inclusion criteria were subjects who were newly diagnosed with T2DM or who were previously diagnosed but were untreated. The diagnosis was made according to the criteria of the Japan Diabetes Society [13]. No subjects had received any regularly prescribed drugs in the 6 months prior to the study. Exclusion criteria were subjects with clinically significant impaired renal function (creatinine >1.5 mg/dL), hepatic function [glutamic oxaloacetic transaminases/glutamic pyruvic transaminases (aspartate transaminase and alanine transaminase) >70/70 IU/L], history of heart disorders, severe hypertension (blood pressure above 160/100 mmHg), type 1 diabetes mellitus, and pregnancy. These subjects were recruited from the outpatient department of the Division of Diabetes and Endocrinology, Gyoda General Hospital (Saitama, Japan) and other related hospitals. Initially, 53 subjects were enrolled in this study. Nine subjects had stopped visiting the hospitals without any reasons. Five subjects dropped out because of tolerability problems and/or adverse events. These drop-out subjects were excluded from data analysis. Final analysis was performed with 39 subjects (female/male = 10/29); these patients received canagliflozin 50–100 mg/day monotherapy. Female subjects took 50 mg/day owing to frequent female adverse events (e.g., urogenital infections, ten), while male subjects took 100 mg/day. The subjects were encouraged to follow the exercise and diet regimen suggested by the American Diabetes Association [14]. The protocol was approved by the Investigational Review Board of Gyoda General Hospital, informed consent was obtained from the subjects who participated, and the study was conducted in accordance with principles of Good Clinical Practice. As a control, our previous data from baseline HbA_{1c}-matched drug-naïve subjects treated with ipragliflozin 25–50 mg monotherapy were employed [9].

2.2 Laboratory Measurements

The primary endpoint was the changes in HbA_{1c} levels from baseline to 3 months. The HbA_{1c} values are shown with National Glycoprotein Standardization Program standardization [15, 16] throughout this article. The secondary endpoints included fasting blood glucose (FBG), insulin, body mass index (BMI), HOMA-R, HOMA-B, triglycerides (TG), high-density lipoprotein-cholesterol (HDL-C), non-HDL-C, and UA. Blood was collected at the fasting state before breakfast and standard techniques were used to measure these parameters as described previously [9]. Measurements of HbA_{1c} and FBG were performed once a month. Insulin levels were measured at the start (baseline) and at the end (3 months) of the study (Abbott Japan, Tokyo, Japan). Anti-glutamic acid decarboxylase antibody levels were measured in some suspected patients to exclude those with type 1 diabetes mellitus (Mitsubishi BML, Tokyo, Japan). HOMA-R and HOMA-B were

calculated as described [17]; HOMA-R = insulin × FBG/405, HOMA-B = insulin × 360/(FBG-63). Hepatic [aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT)] and renal (blood urea nitrogen and creatinine) functions were also monitored 1 month after administration of canagliflozin. In the case of any significant increases of these parameters, administration of canagliflozin was to be discontinued. Responders of canagliflozin were defined as reductions in HbA_{1c} levels of $\geq$1% [18].

2.3 Data Analyses

Change was calculated as the values at 3 months (post-therapy) minus those at baseline (pre-therapy). When the data were normally distributed, the paired Student's *t* test was used to analyze the changes in each group (intra-group differences). When the data were not normally distributed, the Wilcoxon signed-rank test was employed. The unpaired Student's *t* test was used to compare baseline values in these two drug groups. Simple regression analysis was performed to analyze the correlations of measured parameters.

In an effort to identify any contributing factors for the changes in HbA_{1c} levels, multiple regression analysis was performed using HbA_{1c} as a dependent variable and other glycemic and non-glycemic parameters including age, HbA_{1c}, FBG, insulin, BMI, HOMA-R, HOMA-B, TG, HDL-C, non-HDL-C, and UA as independent variables. The results were expressed as the mean plus standard deviation. Throughout the statistical analysis, values of $p < 0.05$ were considered significant.

3 Results

3.1 Safety and Tolerability of Canagliflozin Monotherapy as an Initial Therapy in Drug-Naïve Subjects with T2DM

Two out of 44 subjects reported a mild hypoglycemic event, which could be easily managed by ingesting glucose drinks. Ten subjects experienced pollakiuria and three subjects reported skin rashes (eczema). Three women complained of itching around the genital area (potential genital mycotic infection and/or lower urinary tract infection). Five subjects (two for pollakisuria and three for potential urinary tract infections) discontinued canagliflozin therapy because of intolerance or adverse events. The final analysis was performed with 39 subjects (29 for men and ten for women). These potential adverse events occurred in the first 6 weeks of the initiation of the drug. Otherwise, no subjects had any clinically significant elevations of renal or hepatic enzymes. As for ipragliflozin, similar tolerability problems and adverse events were noted in our previous study [9].

3.2 Effect of Canagliflozin Monotherapy on Glycemic Parameters in Drug-Naïve Subjects with T2DM

Baseline characteristics of glycemic and non-glycemic parameters were similar and no statistically significant differences were observed between canagliflozin and ipragliflozin subjects (results not shown, see baseline values of Table 1 and reference [9]). At 3 months, effective

Table 1 Changes in glycemic and non-glycemic parameters with 3 months' treatment with canagliflozin monotherapy in drug-naïve subjects with type 2 diabetes mellitus

	Baseline	3 months	*p* values	% changes
Age	53.1 ± 14.0			
F/M	10/29			
HbA1c (%)	9.96 ± 2.52	8.33 ± 1.66	<0.00001	−16.3
FBG (mg/dL)	193.4 ± 66.7	147.1 ± 32.4	<0.00001	−23.9
Insulin (μU/mL)	9.45 ± 7.17	8.42 ± 6.26	0.077	−10.8
HOMA-R	4.50 ± 9.15	2.99 ± 2.17	<0.00001	−33.5
HOMA-B	31.91 ± 30.12	41.52 ± 38.20	<0.03	30.1
BMI	26.84 ± 5.56	26.34 ± 5.50	<0.00001	−1.8
UA (mg/dL)	5.35 ± 1.21	5.07 ± 1.19	<0.05	−5.2
T-C (mg/dL)	219.1 ± 38.7	215.1 ± 39.1	n.s.	−1.8
TG (mg/dL)	187.2 ± 134.8	165.6 ± 95.8	0.057	−11.5
HDL-C (mg/dL)	52.4 ± 13.3	54.4 ± 12.2	n.s.	3.8
Non-HDL-C (mg/dL)	166.6 ± 38.3	160.7 ± 39.6	n.s.	−3.5
LDL-C (mg/dL)	140.2 ± 37.8	137.1 ± 34.6	n.s.	−2.2

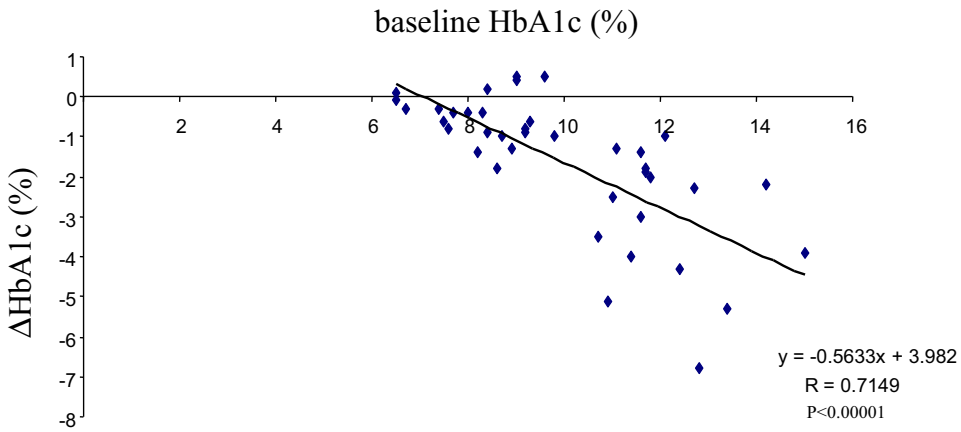

Fig. 1 Baseline-dependent reductions in glycosylated hemoglobin (HbA_{1c}) levels of canagliflozin. Simple regression analysis was performed between baseline HbA_{1c} and changes (Δ) in HbA_{1c} levels

significant reductions in FBG and HbA_{1c} levels were observed with canagliflozin 50–100 mg monotherapy (for each value and statistical significance, see Table 1). Significant negative correlations were observed between the changes in HbA_{1c} and baseline HbA_{1c} levels (Fig. 1). Seventeen out of 39 subjects were non-responders whose HbA_{1c} levels had <1% reductions from baseline [18]. Nine out of 39 subjects achieved HbA_{1c} <7% in 3 months' treatment with canagliflozin (results not shown). Similar results regarding the glycemic efficacy were obtained with ipragliflozin in our previous study [9]. Multiple regression analysis was performed to identify potential contributing factors for the changes (reductions) in HbA_{1c} levels with canagligliflozin or ipragliflozin as described in Sect. 2. Among the parameters tested, baseline levels of HbA_{1c}, TG, non-HDL-C, and LDL-C were selected as the significant contributing factors for the changes in HbA_{1c} levels (Table 2A). As for ipragliflozin, only baseline levels of HbA_{1c} were selected as such a factor (Table 2B). To assess the effect of canagliflozin on insulin resistance and beta-cell function, changes in HOMA-R and HOMA-B levels were evaluated. At 3 months, significant reductions in HOMA-R levels and increases in HOMA-B levels were observed (Table 1). Similar results were obtained with ipragliflozin [9].

3.3 Effect of Canagliflozin on Non-Glycemic Parameters in Drug-Naïve Subjects with T2DM

Effects of canagliflozin on non-glycemic parameters including body weight, lipids, and serum UA were investigated. Among the parameters tested, significant reductions in BMI and serum UA levels were seen (Table 1). No significant changes were noted in lipid levels, though TG levels had a tendency to decrease (Table 1). Blood pressure was also monitored. Reduced levels of blood pressure were observed with canagliflozin; however, the variations were so large and therefore no solid data were established regarding the effect of canagliflozin on blood pressure (results not shown). Similar results were obtained with ipragliflozin [9].

3.4 Link Between the Changes in Metabolic Parameters

As shown in Table 2A, baseline levels of TG, non-HDL-C, and LDL-C were chosen as significant contributing factors for the changes in HbA_{1c} levels with canagliflozin. However, only baseline HbA_{1c} levels were selected as such a factor with ipragliflozin (Table 2B). Simple regression analysis was performed to identify any correlations between the changes in HbA_{1c} and those of glycemic and non-glycemic parameters with canagliflozin or ipragliflozin. As shown in Table 3A, significant positive correlations between HbA1c and non-HDL-C or between HbA_{1c} and LDL-C were observed with canagliflozin. By contrast, with ipragliflozin, significant positive correlations between HbA1c and TG and negative correlations between HbA_{1c} and UA were seen (Table 3B). With both drugs, significant positive correlations between HbA_{1c} and FBG and negative correlations between HbA_{1c} and insulin or between HbA_{1c} and HOMA-B were observed (Table 3A and B). Unexpectedly, no correlations were noted between the changes of BMI and those of glycemic parameters (Table 3A and B).

4 Discussion

4.1 Glycemic Efficacy and Safety of Canagliflozin as an Initial Therapy with T2DM

Canagliflozin monotherapy as an initial option in drug-naïve subjects with T2DM was shown to be rather effective and to have beneficial effects on beta-cell function, insulin sensitivity, and body weight (Table 1). Our group has been

Table 2 Multiple regression analysis with the factors associated with the changes in glycosylated hemoglobin (HbA_{1c}) levels with canagliflozin

0	Coefficient	SE	*t* value	*p* value	R^2
(A) Canagliflozin					
Constant	−1.374	3.7421	−0.36717	0.71658	0
Age	0.024168	0.018375	1.3152	2.00E−01	0.024128
HbA1c	−0.83641	0.18562	−4.506	0.000134	0.46652
FBG	0.017085	0.009091	1.8794	0.071895	0.20613
Insulin	0.047408	0.29753	0.15934	0.87468	0.053026
BMI	0.028767	0.072687	0.39576	0.69564	0.020409
HOMA-R	−0.02944	0.45409	−0.06483	0.94882	0.00085
HOMA-B	0.005526	0.033547	0.16473	0.87048	0.15989
TG	−0.00905	0.003648	−2.4803	0.020214	0.006131
HDL-C	0.022281	0.018685	1.1925	0.24427	0.023862
Non-HDL-C	0.058565	0.02184	2.6815	0.012794	0.00772
LDL-C	−0.05288	0.021241	−2.4895	0.019805	9.82E−05
UA	0.063483	0.22951	0.2766	0.78436	0.01183
(B) Ipragliflozin					
Constant	5.0469	4.2932	1.1756	0.25509	0
Age	0.019515	0.022548	0.86548	0.39816	0.15101
HbA1c	−0.48812	0.23057	−2.117	0.048445	0.43358
FBG	−0.01283	0.009475	−1.3542	0.19243	0.20424
Insulin	−0.21354	0.35315	−0.60469	0.55293	0.011142
BMI	−0.09143	0.06348	−1.4403	0.16696	0.066983
HOMA-R	0.77484	0.58649	1.3212	0.203	0.010184
HOMA-B	−0.01357	0.03741	−0.36264	0.7211	0.089243
TG	−0.00114	0.002732	−0.4171	0.68154	0.091779
HDL-C	0.002301	0.023205	0.099156	0.92211	0.050386
Non-HDL-C	0.005596	0.01869	0.2994	0.76807	0.16314
LDL-C	−0.0071	0.018719	−0.3794	0.70883	0.028367
UA	0.19859	0.22846	0.86926	0.39615	0.070164

Dependent variables: changes (Δ) in HbA_{1c} levels, independent variables: age, baseline levels of HbA_{1c}, fasting blood glucose (FBG), insulin, body mass index (BMI), homeostasis model assessment-R (HOMA-R), homeostasis model assessment-B (HOMA-B), triglycerides (TG), high-density lipoprotein-cholesterol (HDL-C), non-HDL-C, and uric acid (UA)

studying the effect of oral hypoglycemic drugs in drug-naïve subjects with T2DM in the past years. The glycemic efficacy of canagliflozin is comparable to other drugs including ipragliflozin [9], pioglitazone [19], alogliptin [20], or teneligliptin [21]. However, certain proportions of the drug-naïve subjects with T2DM were non-responders to canagliflozin (17 out of 39 subjects, reductions in HbA_{1c} of <1%). Currently, we are investigating whether any differences exist in metabolic parameters between responders and non-responders treated with canagliflozin monotherapy. Analogous to other oral hypoglycemic drugs (e.g., another SGLT-2 inhibitor ipragliflozin) [9], the glycemic efficacy of canagliflozin is baseline HbA_{1c} dependent (Fig. 1).

Further, it was shown that the glycemic efficacies of canagliflozin were linked to improved beta-cell function, but not to decreased insulin resistance (Table 3A). It remains to be investigated whether the above observations also occur in subjects treated with multiple drugs or insulin. There are at least six SGLT-2 inhibitors on the market. It is of interest to investigate whether any differences exist in glycemic and non-glycemic efficacies among these different SGLT-2 inhibitors. Because canagliflozin is widely marketed worldwide, efficacy across different ethnicities will be of great interest.

Multiple regression analysis revealed that baseline levels of HbA_{1c}, and atherogenic lipids including TG, non-HDL-C, and LDL-C were selected as the significant confounding factors for the changes in the glycemic efficacy of canagliflozin (Table 2A). However, only baseline HbA_{1c} levels were selected as such a factor with ipragliflozin (Table 2B). Although canagliflozin appears to have no effect on these atherogenic lipids in subjects overall (Table 1A), changes in HbA_{1c} levels had significant

Table 3 Correlations between the changes in glycosylated hemoglobin (ΔHbA_{1c}) and those of other parameters

	R	*p* values
(A) Canagliflozin		
ΔHbA1c vs. ΔFBG	0.7443	<0.00001
vs. Δinsulin	−0.3888	<0.002
vs. ΔBMI	0.2402	n.s.
vs. ΔHOMA-R	0.0665	n.s.
vs. ΔHOMA-B	−0.6328	<0.00001
vs. ΔTG	0.0982	n.s.
vs. ΔHDL-C	−0.1198	n.s.
vs. Δnon-HDL-C	0.3954	<0.002
vs. ΔLDL-C	0.4317	<0.01
vs. ΔUA	−0.227	n.s.
(B) Ipragliflozin		
ΔHbA1c vs. ΔFBG	0.5524	<0.001
vs. Δinsulin	−0.4864	<0.005
vs. ΔBMI	0.1836	n.s.
vs. ΔHOMA-R	−0.0342	n.s.
vs. ΔHOMA-B	−0.5813	<0.0005
vs. ΔTG	0.3978	<0.05
vs. ΔHDL-C	−0.1665	n.s.
vs. Δnon-HDL-C	0.1723	n.s.
vs. ΔLDL-C	−0.1091	n.s.
vs. ΔUA	−0.4309	<0.02

Simple regression analysis was performed between the changes of indicated parameters

correlations with those with atherogenic cholesterols including non-HDL-C and LDL-C (Table 3A). The underlying mechanism responsible for this phenomenon remains to be investigated. One potential explanation is that glucose lowering per se with canagliflozin is associated with a reduced influx of glucose to the liver and reduced very low-density lipoprotein/apoliprotein E production, thereby causing reductions in atherogenic lipids. In fact, we are currently working on responders and non-responders with canagliflozin. Indeed, atherogenic cholesterols including non-HDL-C and LDL-C were differentially regulated between these two groups (more reductions were observed in responders vs. non-responders; E. Kutoh, personal communication). However, ipragliflozin had different profiles. Significant positive correlations between HbA_{1c} and TG and negative correlations between HbA_{1c} and UA were seen with ipragliflozin (Table 3B). These results imply that these two drugs differ in the effects on metabolic parameters in relation to their glycemic efficacies. It is also possible that the differences in lipid regulation with these two drugs were a result of the distinct backgrounds of the subjects between these two groups.

Safety and tolerability could be of concern. Five out of 44 subjects discontinued therapy because of intolerance or adverse events. Potential canagliflozin-induced adverse events occurred in approximately one third of subjects (e.g., pollakiuria, genital and/or lower urinary tract infection). Although no robust statistical analysis has been performed, rates of adverse events, intolerance, or discontinuation with canagliflozin appear to be higher than other drugs but similar to ipragliflozin [9]. The duration of this study is only 3 months with relatively young subjects. A long-term follow-up of safety issues in elderly patients is required to have a better understanding of the safety profiles of canagliflozin.

4.2 Non-Glycemic Efficacy of Ipragiflozin

One of the most notable non-glycemic efficacies of canagliflozin is the reduction in body weight (Table 1). This is similar to other SGLT-2 inhibitors [1–3, 9]. Many diabetes drugs such as insulin, sulfonylureas, and thiazolidinediones cause weight gain. Therefore, drugs that have reducing effects on body weight are particularly important. To date, few studies report the relationship between body weight reductions with canagliflozin and its effects on glycemic control. Our investigation on this issue unexpectedly revealed that the glycemic efficacies of canagliflozin were not associated with the degrees of body weight reductions (Table 3A). Recently, we reported two distinct glucose-lowering mechanisms may exist depending on body weight changes with ipragliflozin [22]. Currently, we are investigating whether similar results would be obtained with canagliflozin.

Significant reductions in serum UA levels were observed (Table 1). This is most probably owing to the increased UA levels in the urine, possibly through the urate transporter [23]. However, a possibility that canagliflozin reduces hepatic UA productions cannot be ruled out. Elevated UA levels are a risk factor for cardiovascular disorder as well as gout [24]. No significant effects on lipid parameters were noted with canagliflozin in overall subjects, though TG levels had a tendency to decrease (Table 1). Effects on lipid metabolism with SGLT-2 inhibitors in general are inconsistent and non-significant [1–3]. Sodium-glucose co-transporter 2 inhibitors were shown to reduce blood pressure, probably as a result of weight loss and diuretic action [4, 5]. Sodium-glucose co-transporter 2 inhibitors induce beneficial changes in these above-mentioned cardiovascular risk factors in addition to improved glycemic control. It was recently reported that empagliflozin had favorable cardiovascular outcomes in patients with T2DM at high risk for cardiovascular events [25]. As shown in this work, canagliflozin appears to have favorable metabolic profiles (e.g., reducing UA or body weight) other

than its glycemic efficacy, although it remains to be investigated whether canagliflozin has similar outcomes on cardiovascular events. Results from large clinical studies of SGLT-2 inhibitors including canagliflozin (CANVAS, [26]) will answer this question.

4.3 Limitations and Strengths of the Study

There are a number of limitations with this study. It is an observational (though prospective) study with small numbers of subjects and a short study duration. Further, male subjects took 100 mg/day while female subjects received 50 mg/day; this can result in an inaccurate evaluation of the efficacy of a drug efficacy. However, one can assume that the observed changes were caused exclusively by canagliflozin based on the design of the study (monotherapy with drug-naïve patients). Further randomized double-blind placebo-controlled studies of longer duration and with an increased number of subjects are required to strengthen the findings of this study.

5 Conclusions

The results of this study add the following novel information to our current knowledge. [1] Canagliflozin is a candidate for one of the first-line drugs in patients with T2DM. It has beneficial effects on some parameters including UA, body weight, insulin sensitivity, and beta-cell function, though certain precautions are required regarding its tolerability and adverse events. [2] Atherogenic cholesterols including non-HDL-C and LDL-C appear to be involved in the glycemic efficacy of canagliflozin, while TG and UA could be selected as such factors with ipragliflozin. Thus, these two drugs may differ in their effects on metabolic markers in relation to their glycemic efficacies. It remains to be investigated whether other SGLT-2 inhibitors (e.g., dapagliflozin, empagliflozin) have similar or distinct regulatory patters.

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Authors' contributions EK participated in the design of the study, acquisition of the data, performed the statistical analysis, and drafted the manuscript. AW, TM, MK, and TY made substantial contributions to the conception and design of the study and helped draft the manuscript. All authors read and approved the final manuscript.

Compliance with Ethical Standards

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Conflict of interest Eiji Kutoh, Asuka Wada, Teruma Murayama, and Yui Takizawa have no conflicts of interest directly relevant to the content of this study.

Ethics approval The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines.

Consent to participate All subjects provided informed consent.

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