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Comparison of efficacy between dipeptidyl peptidase-4 inhibitor and sodium–glucose cotransporter 2 inhibitor on metabolic risk factors in Japanese patients with type 2 diabetes mellitus: Results from the CANTABILE study

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ABSTRACT

Aims: The aim of this study was to compare the effectiveness of teneligliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and canagliflozin, a sodium–glucose cotransporter 2 (SGLT2) inhibitor, at reducing a composite outcome of three metabolic risk factors (obesity, hypertension, and dyslipidemia) in Japanese patients with type 2 diabetes mellitus (T2DM) and metabolic risks.

Methods: In this prospective, multicenter, open-label, randomized, parallel-group comparison study, 162 patients with T2DM and one or more metabolic risk factors were randomized into a teneligliptin or canagliflozin group and treated for 24 weeks. The primary endpoint was the composite percentage of subjects who experienced an improvement in at least one metabolic risk after 24 weeks of treatment.

Results: The primary endpoint was achieved significantly by more patients in the canagliflozin group than in the teneligliptin group (62.2% vs. 31.3%, $p = 0.0004$). A $\geq$ 3% body weight loss was also achieved by significantly more participants in the canagliflozin group than in the teneligliptin group (55.9% vs. 10.5%, $p < 0.0001$).

Conclusions: This study showed canagliflozin to be more effective at reducing metabolic risks than teneligliptin. In Japanese patients with T2DM and metabolic risk factors, SGLT2 inhibitors may be superior to DPP-4 inhibitors at controlling multiple metabolic risk.

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1. Introduction

There has been a growth in the number of people affected by diabetes mellitus worldwide over recent years. Type 2 diabetes mellitus (T2DM) is associated with multiple vascular complications, increased mortality, and decreased quality of life [1]. However, while many studies have shown that reducing glycated hemoglobin (HbA1c) levels effectively prevents microvascular events, most have failed to prove that this approach can decrease the risk of cardiovascular events [2–5].

In contrast to studies focusing on intensive glycemic control in isolation, trials of multifactorial interventions based on glycemic, blood pressure, and lipid control have indicated the potential to reduce cardiovascular complications and mortality in patients with T2DM [6,7]. Obesity, hypertension, and dyslipidemia are all independent risk factors for T2DM. When these metabolic risk factors are present in a single patient, which is often the case, the risk of cardiovascular events is enhanced synergistically rather than additively [8]. It is also known that there is a higher prevalence of hypertension, obesity, low high-density lipoprotein cholesterol (HDL-C), and hypertriglyceridemia in patients with T2DM and no previous cardiovascular disease (CVD) [9–12]. Therefore, controlling metabolic risk while treating T2DM is plausible.

The development of new classes of antidiabetic drugs has provided ever more options for the pharmacotherapy of diabetes mellitus. However, the optimal antidiabetic drug choice to achieve the greatest control of multiple cardiometabolic risks has yet to be elucidated. Sodium–glucose cotransporter 2 (SGLT2) inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors are widely used antidiabetic drugs. Recent prospective large-scale clinical trials have showed the beneficial effects of SGLT2 inhibitors on cardiovascular events [13–15], but these trials primarily enrolled patients taking multiple T2DM medications, including metformin, sulfonylureas, and insulin. Therefore, the isolated effects of SGLT2 inhibitors on the reduction in cardiovascular events, especially in patients with early-stage T2DM who are drug-naive or receiving metformin monotherapy, remain unclear. DPP-4 inhibitors have also been reported to have beneficial effects on preventing the progression of atherosclerotic lesions [16,17], but they are generally thought to have neutral effects on cardiovascular events [18]. Finally, several studies have compared SGLT2 inhibitors and DPP-4 inhibitors, mainly in terms of glycemic control (e.g., reducing HbA1c or preventing hypoglycemia), and, therefore, the subjects of these studies were not T2DM patients with metabolic risk factors [19–21]. In another direct comparison study of SGLT2 inhibitors and DPP-4 inhibitors that evaluated cardiometabolic parameters as the primary outcome, the study subjects were T2DM patients with established coronary artery disease [22]. Thus, the effects of SGLT2 inhibitors and DPP-4 inhibitors on metabolic risk factors in early-stage T2DM patients with metabolic risk factors have not yet been fully validated.

Based on this background, the CANTABILE (Comparison of Canagliflozin versus Teneligliptin against Basic Metabolic Risks in Patients with T2DM) study aimed to compare canagliflozin, an SGLT2 inhibitor, with teneligliptin, a DPP-4 inhibitor, in terms of their effects on reducing a composite of metabolic risk factors as the primary outcome in Japanese patients with early-stage T2DM and metabolic risk factors.

2. Material and methods

2.1. Study design

The rationale, design, and methods of the CANTABILE prospective, multicenter, open-label, randomized, parallel-group comparison study have been reported elsewhere [23]. It was conducted at 38 institutions in Japan, and it complied with the articles of the Declaration of Helsinki (as revised in October 2013) and the Ethical Guidelines for Medical and Health Research Involving Human Subjects established by the Ministry of Health, Labor, and Welfare in Japan. The study protocol was approved by the Nara Medical University Certified Review Board (approval number: nara0002) in accordance with the law on clinical research in Japan.

2.2. Study participants

Patients were included if they gave their written informed consent to take part in the study, were aged $\geq$ 20 and < 85 years (regardless of sex), and had an HbA1c $\geq$ 7.0% (52 mmol/mol) but < 10.0% (86 mmol/mol). We also included patients who did not change their antidiabetic therapy for at least 8 weeks before granting informed consent if they received diet and/or exercise therapy with either metformin alone or no antidiabetic medications. To assess the composite risk factors, participants were required to have at least one of three metabolic risk factors: (1) body mass index (BMI) $\geq$ 25 kg/m^2; (2) systolic blood pressure (SBP) $\geq$ 130 mmHg or diastolic blood pressure (DBP) $\geq$ 85 mmHg; and (3) triglycerides (TG) $\geq$ 150 mg/dL or HDL-C < 40 mg/dL.

Patients were excluded if they met any of the following criteria: type 1 diabetes mellitus; a BMI < 22 kg/m^2; hypersensitivity to teneligliptin or canagliflozin; required insulin therapy for blood glucose management; congestive heart failure (New York Heart Association functional class of III or IV); were pregnant, breast feeding, or potentially pregnant; diagnosed or suspected malignant tumor; or, in the preceding 8 weeks, received medications or therapy disallowed by the study protocol.

2.3. Randomization and study interventions

After being confirmed eligible, participants were dynamically randomized to either the teneligliptin group or the canagliflozin group based on the following assignment factors: HbA1c on the date of consent, fasting TG, BMI, SBP, and whether metformin was administered. Participants in the canagliflozin group received 100 mg canagliflozin (CANAGLU®; Mitsubishi Tanabe Pharma Corporation, Osaka, Japan) orally with their usual diabetic treatment. By contrast, those in

the teneligliptin group received 20 mg teneligliptin (TENELIA®; Mitsubishi Tanabe Pharma Corporation, Osaka, Japan) orally with their usual diabetic treatment, titrated as necessary, to 40 mg per day. Diet (total caloric intake of 25 kcal/kg ideal body weight/day with 40%–60% of calories coming from carbohydrates, up to 20% from protein, and the rest from fat) and exercise therapies started at least 8 weeks before the date of informed consent were continued without modification until week 24 of treatment.

2.4. Primary and secondary endpoints

The primary endpoint was the percentage of subjects who improved in one or more of three metabolic risk factors: obesity, hypertension, and dyslipidemia. The following definitions and changes were used to assess these endpoints.

(1) Obesity: BMI $\geq$ 25 kg/m^2 at week 0 and a $\geq$ 3% weight loss at week 24. The Japanese cutoff for obesity (BMI > 25) was used, which is different from the WHO cutoff [30]. The Japan Society for the Study of Obesity has selected this lower threshold for obesity because of the high prevalence of obesity-related complications in Japanese populations above this cutoff.
(2) Hypertension: SBP $\geq$ 130 mmHg or DBP $\geq$ 85 mmHg at week 0 and SBP < 130 mmHg or DBP < 85 mmHg at week 24.
(3) Dyslipidemia: fasting TG $\geq$ 150 mg/dL ($\geq$1.69 mmol/L) or HDL-C < 40 mg/dL (<1.03 mmol/L) at week 0 and fasting TG of < 150 mg/dL (<1.69 mmol/L) or HDL-C $\geq$ 40 mg/dL ($\geq$1.03 mmol/L) at week 24.

Eight secondary endpoints were also considered, as follows: (1) the percentages of participants meeting each of the primary criteria; (2) the change in HbA1c from baseline; (3) the change in fasting blood glucose from baseline; (4) the percentages achieving HbA1c values < 6.0% (41 mmol/mol) and < 7.0% (52 mmol/mol); (5) the percentages achieving $\geq$ 3% and $\geq$ 5% weight loss; (6) the changes in BMI, waist circumference, and body weight from baseline; (7) the changes in HDL-C and fasting TG from baseline; and (8) the changes in SBP and DBP levels.

2.5. Measurement

Data were collected every 6 weeks. Although the CANTABILE Study considered a much wider range of variables [22], blood tests for the present analysis focused on HbA1c, fasting TG, HDL-C, and fasting blood glucose. Vital parameters, such as height, body weight, abdominal circumference, BMI, SBP, and DBP, were collected by standard methods. Questionnaires were also administered on drinking, smoking, implementation status of diet and exercise therapies, and adherence to the study medicine.

2.6. Safety assessments

Safety was assessed at each visit based on clinical investigation results, vital sign measurements, and adverse events. The severity, causal relationship to the study drug, and outcomes of all adverse events were documented. Adverse events with a clear and plausible causal relationship are reported.

2.7. Sample size and statistical analyses

The sample size was calculated using data from clinical trials of the study drugs. Assuming the primary endpoint would be achieved for canagliflozin and teneligliptin in 65%–70% and 40%–45%, respectively [24–26], it was estimated that 81–82 cases per group were needed to detect a difference using the chi-square test ($1 - \beta = 0.9$, $\alpha = 0.05$ two-sided). The percentage of patients who achieved the endpoint in this study was obtained by extracting unpublished individual patient data of those who were eligible for this study from cited trials. Thus, we planned to include 200 patients in consideration of the expected drop-out.

Descriptive data are presented as numbers (percentages) for discrete variables and as means ± standard deviations for continuous variables. Comparisons of the baseline data were by the Fisher exact test or Wilcoxon signed-rank test, as appropriate. The primary and secondary endpoints were analyzed on the full analysis set, defined as the patient population that had the value of each endpoint measured at baseline and at least one assessment point during treatment. Outcomes are reported as percentages with 95% confidence intervals (95 %CIs), and p-values for between-group comparisons were obtained using Fisher's exact test. For the secondary outcomes, data are presented as numbers (percentages) of achievers or as means ± standard deviations for the change in values (Δ) from week 0 to week 24, with comparisons assessed by analysis of covariance. All statistical analyses were performed using SAS® software (SAS Institute Inc., Cary, NC, USA) and p-values < 0.05 were considered significant.

3. Results

3.1. Patient characteristics

Written informed consent was obtained from 187 patients. However, the calculated sample size was 162 patients as 25 patients did not meet the study criteria and were excluded before randomization. It was necessary to obtain informed consent from these patients in order to check their laboratory results. After assessing their eligibility, 162 patients were randomized to the teneligliptin group (n = 80) or canagliflozin group (n = 82). After randomization, 17 participants (10.5%) dropped out. Thus, a total of 145 patients were included in the full analysis with 70 in the teneligliptin group and 75 in the canagliflozin group (Fig. 1). Table 1 shows that patient characteristics were comparable between the two groups at week 0. Participants were middle-aged (average age, 56 years), obese (average BMI, 29 kg/m^2), and had an average HbA1c of 7.8% (61 mmol/mol). Furthermore, 60% of patients received metformin monotherapy.

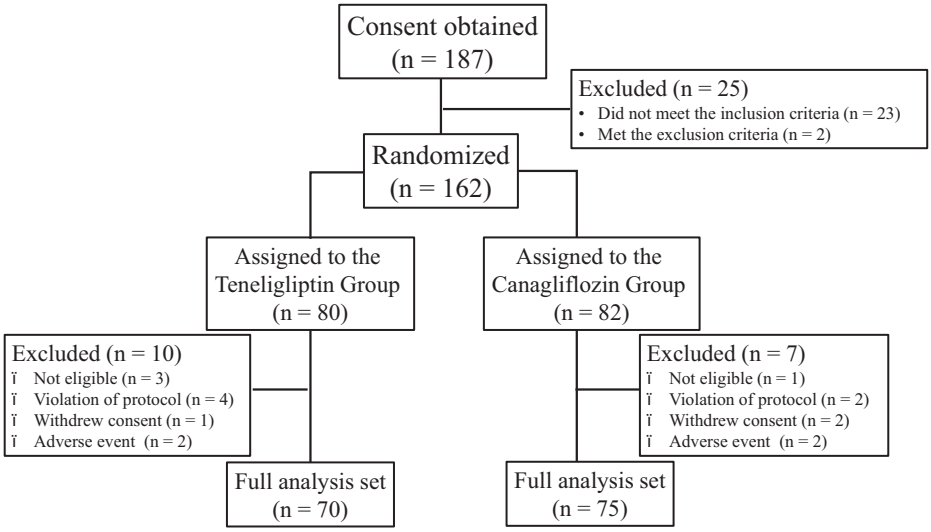

Fig. 1 – Enrollment and randomization In total, 162 were randomized to the teneligliptin group (n = 80) and canagliflozin group (n = 82); of these, 145 patients were included in the full analysis set (70 and 75 patients in each group, respectively).

Table 1 – Patient characteristics.

	Teneligliptin group(n = 70)	Canagliflozin group(n = 75)	p-value
Male	47 (67.1)	51 (68)	1.0000
Female	23 (32.9)	24 (32.0)	
Age	55.2 ± 11.4	57.2 ± 11.5	0.5277
Height (cm)	165.5 ± 9.5	165.5 ± 9.2	0.9984
Body weight (kg)	79.2 ± 16.7	79.0 ± 15.2	0.7848
BMI	28.8 ± 4.8	28.7 ± 4.7	0.8540
HbA1c (%(mmol/mol))	7.8 ± 0.8 (61 ± 9)	7.7 ± 0.6 (60 ± 7)	0.3706
HDL-C (mg/dL)	53.6 ± 11.4	52.1 ± 12.1	0.3532
Triglyceride (mg/dL)	169.7 ± 115.5	202.1 ± 195.0	0.5336
SBP (mmHg)	137.8 ± 14.7	140.7 ± 19.0	0.4580
DBP (mmHg)	82.7 ± 9.9	83.4 ± 10.5	0.7454
BMI > 25	57 (81.4)	59 (78.7)	0.8357
Dyslipidemia	31 (44.39)	34 (45.3)	1.0000
Hypertension	50 (71.4)	55 (73.3)	0.8536
Duration of DM (years)	6.7 ± 6.3	5.9 ± 4.9	0.7889
Metformin treatment	44 (62.9)	44 (58.7)	0.6148

Data are presented as number (percentage) for discrete variables and as mean ± standard deviation for continuous variables. P-values for between-group comparisons were obtained using Fisher's exact test or Wilcoxon signed-rank test, as appropriate.

Abbreviations: BMI,body mass index, DBP, diastolic blood pressure, DM, diabetes mellitus, HbA1c,glycated haemoglobin, HDL-C,high-density lipoprotein cholesterol, SBP, systolic blood pressure

3.2. *Primary and secondary endpoint*

As shown in Fig. 2, the primary endpoint was achieved significantly by more patients in the canagliflozin group (62.2%, 95 %CI 50.1%–73.2%) than in the teneligliptin group (31.3%, 95 %CI 20.6%–43.8%; p = 0.004). The rate of primary endpoint achievement was significantly higher in the canagliflozin group in patients with BMI ≥ 25; by contrast, there was no difference in the rate of primary endpoint achievement between the teneligliptin and canagliflozin groups in patients with BMI < 25 (Table 2). Metformin use did not change the result of this study: the rate of primary endpoint achievement was higher in the canagliflozin group (Table 2).

The secondary endpoints are summarized in Table 3. Significantly more patients achieved ≥ 3% body weight loss in the canagliflozin group (55.9%, 95 %CI 42.4%–68.6%) than in the teneligliptin group (10.5%, 95 %CI 4.0%–21.5%; p < 0.0001). By contrast, the percentages meeting the criteria for changes in blood pressure and dyslipidemia did not differ between the two groups.

Regarding the other secondary endpoints (Table 3), there were no significant differences in the changes in fasting blood glucose, HbA1c, TG, and blood pressure between the groups. However, differences favoring the canagliflozin group were observed in metrics related to weight loss. For example, there was a significantly higher percentage of patients who

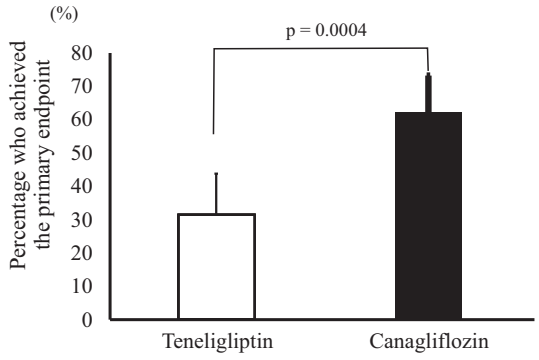

Fig. 2 – Results of the primary endpoint at Week 24 of treatment The primary endpoint was the percentage of subjects who improved in one or more of three metabolic risk factors: obesity, hypertension, and dyslipidemia. The error bars represent the 95% confidence intervals, and the p-value for the between-group comparison was obtained using Fisher's exact test.

achieved ≥ 3.0% weight loss in the canagliflozin group compared with the teneligliptin group (55.9% vs. 10.5%, p < 0.0001). The canagliflozin group also achieved larger reductions in abdominal circumference (–2.4 ± 0.5 cm vs. 0.3 ± 0.5 cm), body weight (–2.6 ± 0.3 kg vs. 0.3 ± 0.3 kg), and BMI (–0.9 ± 0.1 kg/m^2 vs. 0.1 ± 0.1 kg/m^2).

3.3. *Safety endpoints*

In the present study, the total number of adverse events in the canagliflozin group (64 adverse events reported by 44 patients) was significantly higher than that in the teneligliptin group (44 adverse events reported by 27 patients; Supplementary Table 1). None of the adverse events was severe in either group. The adverse events in the canagliflozin group included glucosuria (n = 6), pollakiuria or polyuria (n = 7), and thirst (n = 4). No CVD events occurred in either group.

4. Discussion

There have been few direct comparison studies of SGLT2 inhibitors and DPP-4 inhibitors. To the best of our knowledge, this is the first study to have compared the effects of canagliflozin and teneligliptin on improvement of metabolic risks other than glycemic indices (obesity, hypertension, and dyslipidemia) as a primary composite outcome in Japanese patients with early-stage T2DM and metabolic risk factors. The BMI of our patients was higher than that of the general Asian population [27] because these metabolic risk factors are caused by

Table 2 – Subgroup analysis of achievement of the primary endpoint.

	BMI		Metformin use	
	< 25	≥ 25	no	yes
Teneligliptin group	4/10 (40.0%)	17/57 (29.8%)	6/25 (24.0%)	15/42 (35.7%)
Canagliflozin group	6/15 (40.0%)	40/59 (67.8%)	21/30 (70.0%)	25/44 (56.8%)
p-value between groups	1.0000	< 0.0001	0.0011	0.0558

Table 3 – Summary of the secondary endpoints.

	Teneligliptin group	Canagliflozin group	p-value
Endpoint			
≥3% body weight loss	6/57 (10.5%)	33/59 (55.9%)	< 0.0001
BP < 130/85 mmHg	16/50 (32.0%)	18/55 (32.7%)	1.0000
HDL-C < 40 mg/dL & TG < 150 mg/dL	3/31 (9.7%)	7/34 (20.6%)	0.3088
HbA1c < 7% (52 mmol/mol)	31/70 (44.3%)	35/75 (46.7%)	0.8677
HbA1c < 6% (41 mmol/mol)	1/70 (1.4%)	2/75 (2.7%)	1.0000
Weight loss > 5%	1/57 (1.8%)	13/59 (22.0%)	0.0010
Changes in variables			
Δ HbA1c (%)	−0.65 ± 0.06	−0.67 ± 0.06	0.7500
Δ Fasting plasma glucose (mg/dL)	−13.5 ± 3.7	−21.3 ± 3.6	0.1300
Δ Abdominal circumference (cm)	0.3 ± 0.5	−2.4 ± 0.5	0.0006
Δ Body weight (kg)	0.3 ± 0.3	−2.6 ± 0.3	< 0.0001
Δ BMI (kg/m^2)	0.1 ± 0.1	−0.9 ± 0.1	< 0.0001
Δ HDL-C (mg/dL)	−0.8 ± 0.8	4.8 ± 0.7	< 0.0001
Δ TG (mg/dL)	−16.4 ± 9.5	−28.5 ± 9.3	0.3677
Δ SBP (mmHg)	−5.9 ± 1.4	−7.9 ± 1.4	0.3037
Δ DBP (mmHg)	−2.5 ± 1.0	−4.3 ± 1.0	0.1873

Data are presented as the number (percentage) of patients achieving an endpoint or as the mean ± standard deviation for the change in values (Δ) from 0 to 24 weeks. P-values for between-group comparisons were obtained by analysis of covariance.
Abbreviations: BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglyceride.

weight gain [28]. Our study results demonstrated that canagliflozin improved composite metabolic risk compared with teneligliptin in Japanese patients with T2DM receiving either metformin monotherapy or no antidiabetic agent. By contrast, the decrease in HbA1c level was similar in both groups. These results indicate that both canagliflozin and teneligliptin improved glycemic control, but that canagliflozin independently improved the metabolic risk factors.

Concerning the three components of the composite primary endpoint, only obesity improved significantly, with dyslipidemia only tending to improve more in the canagliflozin group, and there being no difference in blood pressure improvement. Thus, the superiority of canagliflozin in these primary endpoints seems related to the effect of the drug in reducing body weight.

The ratio of patients who achieved a $\geq$ 3% weight loss after 24 weeks of treatment was significantly larger in the canagliflozin group than in the teneligliptin group. Obesity is an established risk factor for CVD, with its management recommended in the guidelines for T2DM of the American Diabetes Association and the European Society of Endocrinology [29,30]. Post-hoc analysis of the Look AHEAD study, which was a large randomized trial on intensive lifestyle-based weight loss intervention in people with T2DM, suggested that well-achieved weight loss might decrease the risk for CVDs in patients with T2DM, regardless of the intervention method, although there was no significant reduction in CVD incidence between the intensive lifestyle intervention and control groups [31,32]. Therefore, the results of this study suggest that compared with DPP-4 inhibitors, SGLT2 inhibitors may be the more optimal choice for the simultaneous control of comorbid obesity and T2DM.

Blood pressure decreased in both group after 24 weeks. The change in blood pressure in the canagliflozin group was greater than that in the teneligliptin group, although this difference was not statistically significant. A previous *meta*-analysis reported that, compared with other antidiabetic drugs, SGLT2 inhibitors significantly lowered blood pressure [33,34]. A previous *meta*-analysis showed that DPP-4 inhibitors achieved greater reduction in blood pressure compared with placebo or nontreatment, although there was no significant difference in blood pressure reduction between DPP-4 inhibitors and other antidiabetic drugs except for SGLT2 inhibitors [35]. The subjects in our study may likely show a decrease in blood pressure by DPP-4 inhibitor because they were drug-naive or had a history of only metformin use. Indeed, consistent with our results, a recent study reported no significant difference in blood pressure changes between dapagliflozin and sitagliptin [21].

Dyslipidemia improved by similar percentages in the canagliflozin and teneligliptin groups, albeit with a significantly larger increase in HDL-C in the canagliflozin group. Earlier research has shown that SGLT2 inhibitors, such as canagliflozin, modestly increased HDL-C levels compared with placebo [36]. This is important because low HDL-C levels have been reported to be an independent risk factor for CVD in patients with T2DM [37,38]. Therefore, canagliflozin may be more suitable for patients with T2DM and low HDL-C. In our study, serum triglyceride levels in both groups decreased. Changes in triglyceride levels in the canagliflozin group were greater than those in the teneligliptin group, although the difference was not statistically significant. A previous *meta*-analysis showed that triglyceride levels decreased due to SGLT2 inhibitor treatment [39]. DPP-4 inhibitors have also been reported to decrease triglyceride levels in diabetes patients in a *meta*-analysis [34]. Thus, DPP-4 inhibitors as well as SGLT2 inhibitors may have an effect on reducing triglyceride levels.

In the present study, the achievement rate of the primary outcome in the canagliflozin group was significantly higher than that in the teneligliptin group, only in patients with BMI > 25. By contrast, there was no difference in achievement of the primary outcome between the canagliflozin and teneligliptin groups in patients with BMI < 25. These results suggest that SGLT2 inhibitors may be especially preferable to DPP4 inhibitors in Japanese T2DM patients with obesity,

Recent clinical trials have showed that SGLT2 inhibitors decrease cardiovascular events in patients with T2DM taking multiple diabetic medications. However, these trials mainly enrolled patients with previous cardiovascular events (100% in the EMPA-REG OUTCOME study; 70% in the CANVAS study; and 40% in the DECLARE-TIMI 58 study) [13–15], making their populations different to ours. In those trials, atherosclerotic cardiovascular events were not reduced, but there was a reduction in the deterioration of heart failure over follow-up periods of 3–4 years. A *meta*-analysis also indicated that SGLT2 inhibitors reduced the risk of nonfatal myocardial infarction, cardiovascular death, and heart failure [40]. Our results add to these data by showing that SGLT2 inhibitors reduce metabolic risks in T2DM patients with metabolic risk factors. Therefore, studies with long-term follow-up periods may be needed to provide the necessary evidence of reduced atherosclerotic events when using SGLT2 inhibitors in diabetes patients with metabolic risks, who are at a very high risk of CVDs.

In the present study, the total number of adverse events in the canagliflozin group was significantly higher than that in the teneligliptin group. However, glucosuria, pollakiuria or polyuria, and thirst were included among the adverse events. These are expected effects because SGLT2 inhibitors mainly act on renal proximal tubule cells and inhibit SGLT2-dependent glucose reabsorption, leading to osmotic diuresis due to glucose loss in the urine.

This study has several limitations that should be mentioned. First, we did not achieve the planned number of participants. Case accruals was slower than expected, and we were only able to collect 145 patients. Even if we extended the enrollment period, we could not expect any additional enrollment and the novelty of the study would be lost. However, even in this case, the post power was calculated as 0.86 (65% vs. 40%) and 0.87 (70% vs. 45%), so we judged that the sample size was large enough for analysis, although it was less than the planned power, and, as a result, this study may have failed to detect differences in the effects between canagliflozin and teneligliptin on blood pressure and lipid metabolism. Second, this study had an open-label design, a small sample limited to Japanese patients, and a short observation period. Therefore, we failed to examine the occurrence of CVDs and, as such, it remains unclear whether improvement in metabolic risk factors induced by canagliflozin reduces CVD events. To overcome these limitations, further

study is necessary with a larger sample and longer follow-up period. Third, systemic blood pressure level, which was one of the primary endpoints, was evaluated as the blood pressure at an office because many of the small clinics that participated in this study could not perform ambulatory blood pressure monitoring (ABPM). For more accurate measurement of blood pressure, ABPM is preferred.

5. Conclusion

This study provides evidence that canagliflozin is more effective than teneligliptin in reducing metabolic risks in obese patients, whereas there was no difference in reduction of metabolic risks between teneligliptin and canagliflozin in non-obese patients. These results suggest that SGLT2 inhibitors may be especially preferable to DPP4 inhibitors in Japanese early-stage T2DM patients with obesity.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [CS received grants and personal fees from MSD, grants and personal fees, from Mitsubishi Tanabe Pharma Corporation, grants from Sanofi K.K., grants from Eli Lilly Japan K.K., grants from Novartis Pharma K.K., grants and personal fees from Takeda Pharmaceutical, personal fees from Taisho Toyama Pharmaceutical Co, personal fees from Fujifilm Pharma, and personal fees from Sumitomo Dainippon Pharma. MK received compensation as an advisor of the medical consulting firm Reason Why, Inc.; payments for lectures from Fuji Yakuhin, Pfizer, Daiichi Sankyo Co., Teijin, Fuji Film, Baxter, and Otsuka Pharmaceutical; and grants from Mitsubishi Tanabe Pharma Corporation, Daiichi Sankyo Co., and Fuji Yakuhin. TT has stocks in Sumitomo Dainippon Pharma Co., Astellas Pharma Inc.; received payment for lectures from Taisho Toyama Pharmaceutical Co., Daiichi Sankyo Co., Mitsubishi Tanabe Pharma Corporation, AstraZeneca, EA Pharma Co., Kissei Pharmaceutical Co., Novartis Pharma, Takeda Pharmaceutical Co., Boehringer Ingelheim Japan, Kowa Pharmaceutical Co., MSD K.K., Astellas Pharma Inc., Ono Pharmaceutical Co., Amgen Astellas BioPharma K.K., Medtronic company, Novo Nordisk Pharma, Sanwa Kagaku Kenkyusho, Co., Eli Lilly Japan K.K., the Japanese Society of Internal Medicine, Covidien Japan K.K., MMS Communications K.K. and Aichi Prefecture Insurance Medical Association; received honoraria for manuscript from Taisho Toyama Pharmaceutical Co., Nippon Rinsho Sha Co., Yodosha Co., Hokuryukan & NEW SCIENCE Co., SHINDAN TO CHIRYO SHA, Inc., and Kyoto University Press; and received grants from Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical Co., Kamitsure Laboratory Co., Smoking Research Foundation, Japan Society for the Promotion of Science, Kowa Pharmaceutical Co., Eli Lilly Japan K.K., MSD K.K., Ono Pharmaceutical Co., Novo Nordisk Pharma, Taisho Toyama Pharmaceutical Co., Novartis Pharma, and Sanofi K.K. KN received grants from Philips Japan Co., Terumo Co., and Daiichi Sankyo Co. ST received payment for lectures from Novo Nordisk Pharma and Takeda Pharmaceutical. SK received grants from Mitsubishi Tanabe Pharma Corporation. YO received grants and personal fees from Mitsubishi Tanabe Pharma Corporation, Ono Pharmaceutical Co., and Astellas Pharma Inc., grants from AstraZeneca, Kyowa Hakko Kirin, Taisho Pharmaceutical, Mochida Pharmaceutical, Cosmic Co., Miyarisan Pharmaceutical, Kissei Pharmaceutical, Kowa Pharmaceutical, Roche DC Japan, Boehringer Ingelheim Japan, Novo Nordisk Pharma, Sanwa Kagaku Kenkyusho, Co., Sumitomo Dainippon Pharma, Sanofi K.K., Pfizer, Takeda Pharmaceutical. K.H. received grants, personal fees, and non-financial support from Mitsubishi Tanabe Pharma Co., personal fees from MSD, Sanofi, Eli Lilly, Novartis, Takeda, Astellas, Daiichi Sankyo, Amgen, Novo Nordisk Pharma, Kyowa Hakko Kirin, Ono, Sumitomo Dainippon, AstraZeneca, Taisho Pharma, Boehringer Ingelheim, and OMRON HEALTHCARE; grants from MSD, Sanofi, Eli Lilly, and Takeda. TN and YM declare no competing interests.].

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Appendix A. Supplementary material

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