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A 52-week randomized controlled trial of ipragliflozin or sitagliptin in type 2 diabetes combined with metformin: The N-ISM study

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Abstract

Aim: To compare the long-term efficacy of sodium-glucose co-transporter-2 inhibitors and dipeptidyl peptidase-4 inhibitors as second-line drugs after metformin for patients not at high risk of atherosclerotic cardiovascular disease (ASCVD).

Materials and methods: In a 52-week randomized open-label trial, we compared ipragliflozin and sitagliptin in Japanese patients diagnosed with type 2 diabetes, without prior ASCVD and treated with metformin. The primary endpoint was a glycated haemoglobin (HbA1c) reduction of ≥0.5% (5.5 mmol/mol) without weight gain at 52 weeks.

Results: Of a total of 111 patients (mean age 59.2 years, mean body mass index [BMI] 26.6 kg/m^2, 61.3% men), 54 patients received ipragliflozin and 57 received sitagliptin. After 52 weeks, achievement of the primary endpoint was not significantly different (37.0% and 40.3%; $P = 0.72$). HbA1c reduction rate at 24 weeks was greater for sitagliptin (56.1%) than for ipragliflozin (31.5%; $P = 0.01$). From 24 to 52 weeks, the HbA1c reduction with sitagliptin was attenuated, with no significant difference in HbA1c reduction after 52 weeks between sitagliptin (54.4%) and ipragliflozin (38.9%; $P = 0.10$). Improvements in BMI, C-peptide and high-density lipoprotein cholesterol were greater with ipragliflozin than with sitagliptin. Adverse events occurred in 17 patients with ipragliflozin and in 10 patients with sitagliptin ($P = 0.11$).

Conclusion: The HbA1c-lowering effect at 24 weeks was greater with sitagliptin than with ipragliflozin, but with no difference in efficacy related to HbA1c and body weight at 52 weeks. However, some ASCVD risk factors improved with ipragliflozin.

KEYWORDS
clinical trial, DPP-4 inhibitor, glycaemic control, randomized trial, SGLT2 inhibitor, sitagliptin

1 | INTRODUCTION

Among the many oral hypoglycaemic agents that are available for treatment of type 2 diabetes, metformin is considered as a first-line drug for pharmacotherapy.[1–3] According to US and European guidelines, sodium-glucose co-transporter-2 (SGLT2) inhibitors are considered second-line drugs after metformin for patients with type 2 diabetes and atherosclerotic cardiovascular disease (ASCVD) or chronic kidney disease.[1] However, appropriate second-line drugs for those with type 2 diabetes and no history of ASCVD, or East Asians who have a lower risk of ASCVD than Westerners, have not yet been determined.

Dipeptidyl peptidase-4 (DPP-4) inhibitors are widely used in the treatment of diabetes because they do not cause weight gain and are associated with a low risk of hypoglycaemia.[4–6] SGLT2 inhibitors are also widely used because of their weight-loss effects and evidence of prevention of ASCVD, chronic kidney disease, and heart failure.[7–9] However, results of studies comparing the efficacy of these drugs as second-line drugs after metformin in patients at low-risk of ASCVD are controversial.[10–13]

Previous studies have been limited to low doses of metformin in conjunction with potential second-line drugs,[10] concomitant use of sulphonylureas,[13] inclusion of study patients with and without ASCVD,[11] and a study period of up to 24 weeks. It was reported that the efficacy of DPP-4 inhibitors[14,15] and SGLT2 inhibitors[16,17] was altered after 24 weeks, depending on lifestyle issues such as diet and insulin clearance. These findings indicate that a 24-week period is not sufficient to evaluate the efficacy of either drug. A long-term randomized controlled trial is needed to produce meaningful results.

We therefore conducted a 52-week, long-term, randomized, open-label, controlled trial in Japanese patients with type 2 diabetes, who had an inadequate response to metformin and no history of ASCVD, to examine the effects of the SGLT2 inhibitor ipragliflozin and the DPP-4 inhibitor sitagliptin on glycated haemoglobin (HbA1c) and weight loss, as well as the degree of adherence to dietary and exercise therapy.

2 | METHODS

2.1 | Study design

The Niigata Ipragliflozin and Sitagliptin with Metformin (N-ISM) study is a prospective, randomized, open-label trial. Participants were assigned to either the SGLT2 inhibitor ipragliflozin group or the DPP-4 inhibitor sitagliptin group. This study was registered in the Japan Registry of Clinical Trials (jRCTs031180205) and approved by the Niigata University Central Review Board of Clinical Research. It was conducted in accordance with the principles of the Declaration of Helsinki (2013 revision) and Clinical Trials Act (2017). Written informed consent was obtained from all participants. The study was conducted as a 22-institution multicentre trial (Table S1 lists the included institutions). The enrolment period was from November 2015 to June 2018 and the study period was from November 2015 to September 2019.

2.2 | Eligibility criteria

To be eligible, patients had to meet the following inclusion criteria after providing written informed consent: type 2 diabetes; insufficient glycaemic control despite being treated with diet and exercise therapy or oral hypoglycaemic drugs, with HbA1c ≥6.5% (47.5 mmol/mol) and < 10.0% (85.8 mmol/mol); and age 20 to 80 years. Additional inclusion criteria to be met at the time of randomization were treatment with metformin therapy (≥500 mg/d) with or without an alpha-glucosidase inhibitor (α-GI) or thiazolidines for at least 8 weeks at the same dose and HbA1c ≥6.5% and < 10.0%.

Exclusion criteria included the following: type 1 diabetes; severe ketosis; diabetic coma or diabetic precoma within the past 6 months; severe infections; being within pre- or postoperative periods, or with a serious traumatic injury; moderate or severe renal dysfunction (serum creatinine level ≥1.3 mg/dL (114.9 μmol/L) in men, ≥ 1.2 mg/dl (106.1 μmol/L) in women; severe hepatic dysfunction; history of stroke, myocardial infarction or other serious vascular complications requiring hospitalization; history of lactic acidosis; consumption of excessive amounts of alcohol; urinary tract infection, genital infection or dehydration at the time of consent to participate; prescription of insulin or glucagon-like peptide-1 receptor agonists within the previous year; pregnancy or lactation; childbearing potential; and history of hypersensitivity to an SGLT2 inhibitor, a DPP-4 inhibitor or a biguanide drug. Patients who were judged to be inappropriate participants by the investigators were also excluded.

2.3 | Study intervention

Each potential participant was screened, and those who met the eligibility criteria and provided informed consent were enrolled in the study by the investigators. After providing consent, participants were treated with metformin therapy for at least 8 weeks. Participants were then assigned to the ipragliflozin 50-mg group or the sitagliptin 50-mg group on a one-to-one basis. Antidiabetic drugs that had been prescribed before assignment to the study drug were continued. The combination treatment was provided for 52 weeks. During the treatment period, no other antidiabetic drug was added, the dose of study drugs was not changed, and drugs were not discontinued unless deemed necessary by clinicians. Diet, exercise therapy and intake of foods for specific health reasons were not newly initiated, discontinued, or altered during the study period. Medications for complications (eg, antiplatelet drugs, antihypertensive drugs, drugs for dyslipidaemia, etc.) as far as possible were not to be changed, discontinued, or newly added during the treatment period. However, if such events occurred, they were recorded.

2.4 | Drug dosage

We compared ipragliflozin 50 mg/d with sitagliptin 50 mg/d for this study. In Japan, the glycaemic effects of 100 mg/d and 50 mg/d of sitagliptin were reported to be equivalent[18] and the 50-mg dosage was set as the usual dose, unlike the 100-mg/d dose in Western

countries. The usual dose of ipragliflozin was set at 50 mg/d, as in Western countries.[19]

We included participants taking a metformin dose of ≥500 mg/d, which would include those taking the normal dose of ≥750 mg/d and the lower-than-usual dose of 500 mg/d. We intended to include what might be a substantial number of participants who could not increase their metformin dose above 500 mg in this clinical trial.

2.5 | Procedures and randomization

Eligible patients were randomly (1:1) assigned to either 52 weeks of treatment with ipragliflozin (50 mg once a day) or sitagliptin (50 mg once a day) on a one-to-one basis by sex, age (under/over 65 years of age), HbA1c prior to assignment (≥8.0% (63.9 mmol/mol) or < 8.0%), and BMI prior to assignment (≥25 kg/m^2 or < 25 kg/m^2) using the minimization method with electronic data capture by a third-party entity (DOT WORLD Co., Ltd., Tokyo, Japan). No blinding was conducted in this study.

2.6 | Data collection

Clinical and biochemical data were collected during outpatient visits at weeks 0, 4, 12, 24, 36 and 52 after randomization with electronic data capture. HbA1c was measured using high-performance liquid chromatography at each institution. Other laboratory analyses were also performed at each institution with the exception of those for insulin, serum C-peptide and urine biochemistry that were performed by a third-party entity (SRL Corp., Tokyo, Japan). Energy intake was assessed by the Food Frequency Questionnaire based on food groups (FFQg)[20] at weeks 0, 24 and 52. We used a standardized software program designed for population-based surveys and nutrition counselling in Japan (Eiyo-kun; Kenpakusha Co., Ltd, Tokyo, Japan) to calculate nutrient and food intake.[21] The amount of physical activity was calculated using the Japanese version of the International Physical Activity Questionnaire (IPAQ) short form[22,23] at weeks 0, 24 and 52. Data collection was conducted by a third-party entity (DOT WORLD Co., Ltd).

2.7 | Study outcomes, statistical analysis and sample design

2.7.1 | Primary endpoint and methods of statistical analysis

The primary endpoint was to compare the proportion of patients in the ipragliflozin 50 mg group versus the sitagliptin 50 mg group who had a reduction in HbA1c of ≥0.5% (5.5 mmol/mol) without weight gain at 52 weeks after randomization. Weight gain is not a major concern with either SGLT2 or DPP-4 inhibitors. However, obesity is associated with an increased risk of cardiovascular disease,[24] and we focused on the benefits of weight loss in the treatment of diabetes and established no weight gain as a composite primary endpoint in addition to a hypoglycaemic effect. The significance level of 0.025 (one-sided) was compared using the chi-squared test. No baseline corrections or model adjustments were performed in this study.

2.7.2 | Secondary endpoints and methods of statistical analysis

The secondary endpoints were to compare the proportion of patients in the ipragliflozin 50-mg group and the sitagliptin 50-mg group at 24 weeks after randomization who achieved an HbA1c reduction of ≥0.5% without weight gain; HbA1c <7.0% (53.0 mmol/mol); systolic blood pressure <130 mmHg and diastolic blood pressure <80 mmHg; and triglycerides <150 mg/dL (1.69 mmol/L), low-density lipoprotein (LDL) cholesterol <120 mg/dL (3.10 mmol/L) and high-density lipoprotein (HDL) cholesterol ≥40 mg/dL (1.03 mmol/L) at 24 weeks after randomization. The significance level of 0.025 (one-sided) was compared using the chi-squared test.

As further secondary endpoints, changes in the following items at 24 weeks and 52 weeks after randomization in the two groups were compared using the Student's *t*-test: body weight, BMI, waist circumference, systolic blood pressure, diastolic blood pressure, insulin, serum C-peptide, red blood cell count, white blood cell count, haemoglobin, haematocrit and platelets, HbA1c, fasting blood glucose, triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, alanine transaminase (ALT), gamma-glutamyl transpeptidase (GGT), creatinine, creatinine kinase, uric acid, Na, K, chlorine, and general urine test results.

For items with non-normal distribution, logarithmic transformation was performed before the Student's *t*-test. Wilcoxon's rank-sum test was used for non-normal distribution, even after logarithmic transformation.

If there were no measured values in a specific participant, values were considered missing and no imputation was performed. In addition, patients without a fasting blood test at weeks 24 and 52 were excluded from the analysis to determine the amount of change in values related to blood testing.

2.7.3 | Other endpoints

Other endpoints included nutrient intake and physical activity obtained from the FFQg and IPAQ at 0, 24, and 52 weeks. Changes from 0 to 24 weeks and from 0 to 52 weeks, respectively, were compared using Student's *t*-test or Wilcoxon's rank-sum test, depending on distribution.

2.7.4 | Safety analysis

Lists and summary tables of adverse events (number of incidents, number of cases and incidence [%]) were prepared for each group. Summary statistics or the frequency distribution for each variable

regarding body weight, BMI, waist circumference, systolic blood pressure, insulin, blood C-peptide, red blood cell count, white blood cell count, haemoglobin, haematocrit, platelets, HbA1c, fasting blood glucose, triglycerides, total, HDL and LDL cholesterol, ALT, GGT, creatinine kinase, uric acid, creatinine, Na, K, and chlorine, as well as results for protein, blood, and ketone bodies in urine, were recorded to confirm the safety of each drug at weeks 0, 4, 12, 24, 36 and 52 after randomization. This safety analysis was not conducted during the metformin therapy period.

2.7.5 | Sample size design

It has been estimated that 66% of patients have a reduction in HbA1c of ≥0.5% after ipragliflozin 50 mg is administered[25,26] and that sitagliptin 50 mg also causes the same hypoglycaemic effect.[15,27] Similarly, the proportion of patients without weight gain was assumed to be 89% for the ipragliflozin 50-mg group and 48% for the sitagliptin 50-mg group. The achievement rate of the primary endpoint was estimated to be 58.7% in the ipragliflozin 50-mg group and 31.7% in the sitagliptin 50-mg group. With a significance level of 0.025 (one-sided) and a power of 90%, the number of participants required to demonstrate the superiority of ipragliflozin 50 mg to sitagliptin 50 mg in the primary endpoint of this study was estimated to be 70 for each group. Taking into account a 15% rate of dropouts, the target number of study participants was set at 166 in total (83 per group).

2.7.6 | Statistical analysis

Analysis of the primary and secondary endpoints was primarily performed on the full analysis set, which included all participants assigned to a study intervention. Analysis of the per-protocol set, which included the participants who completed the combination treatment period, was performed to confirm the stability of the results for the primary and secondary endpoints. In the secondary analysis comparing the changes at 24 and 52 weeks, the full analysis set and per-protocol set comprised the same populations because those who had completed the data collection up to each visit were included in both analyses. The safety analysis set included those who provided informed consent and did not later withdraw that consent. The analysis of the incidence of adverse events was performed on all participants who provided informed consent at the start of the study. All statistical analyses were performed using SPSS (version 19.0, Chicago, Illinois) by an investigator who is a statistics specialist and who was not involved in recruiting participants.

3 | RESULTS

3.1 | Disposition of patients

Final screening was performed in 157 patients, of whom 124 consented to participate in the study. Nine patients discontinued participation in the study during the period of metformin therapy (withdrawal of consent, n = 5; patient's circumstances, n = 2; adverse event, n = 2). Of the 115 patients who completed the metformin therapy period, 57 were assigned to the ipragliflozin group and 58 were assigned to the sitagliptin group. Forty-four of the 57 (77.2%) participants in the ipragliflozin group completed the 52-week study. Of the 13 patients who discontinued participation, three (5.3%) withdrew consent, eight (14.0%) had an adverse event, one (1.8%) violated the protocol at 52 weeks, and one (1.8%) discontinued hospital visits. Fifty-one of the 58 (87.9%) participants in the sitagliptin group remained in the study until week 52. Of seven participants who discontinued the study, one (1.7%) withdrew consent, four (6.9%) had an adverse event, one (1.7%) violated the protocol during the study period, and one (1.7%) violated the protocol at 52 weeks. After assignment, 111 participants, excluding those who withdrew consent after assignment to the study drug, were included in the full analysis set and the 95 participants who completed 52 weeks of the study were included in the per-protocol set. The safety analysis set comprised the 115 participants who did not withdraw consent. All of the 124 participants who had initially provided consent were included in the analysis regarding adverse events. (Figure 1).

3.2 | Baseline characteristics

Baseline values for the entire study population before group assignment were mean age 59.2 years, 38.7% female, mean BMI 26.6 kg/m^2, mean HbA1c 7.54% (58.9 mmol/mol), mean disease duration 9.7 years and mean metformin dose of 1120.5 mg. The baseline characteristics of the ipragliflozin and sitagliptin groups are shown in Table 1, with no differences in the baseline values between the two groups.

3.3 | Primary endpoint

An HbA1c reduction of ≥0.5% at 52 weeks was observed in 21 patients in the ipragliflozin group and 31 in the sitagliptin group (ipragliflozin group 38.9% vs. sitagliptin group 54.4%; $P = 0.10$), while no weight gain was observed in 51 patients and 31 patients, respectively, in the ipragliflozin and sitagliptin groups (ipragliflozin group 94.4% vs. sitagliptin group 54.4%; $P < 0.01$). Twenty patients in the ipragliflozin group and 23 patients in the sitagliptin group achieved the primary endpoint (ipragliflozin group 37.0% vs. sitagliptin group 40.4%; $P = 0.72$). Similar results were obtained in the per-protocol set analysis (ipragliflozin group 43.2% vs. sitagliptin group 43.1%; $P = 0.997$). Details of the primary endpoint are shown in Tables 2 and 3.

3.4 | Secondary endpoints

Reductions in HbA1c of ≥0.5% at 24 weeks were noted in 17 participants in the ipragliflozin group and 32 in the sitagliptin group, with a

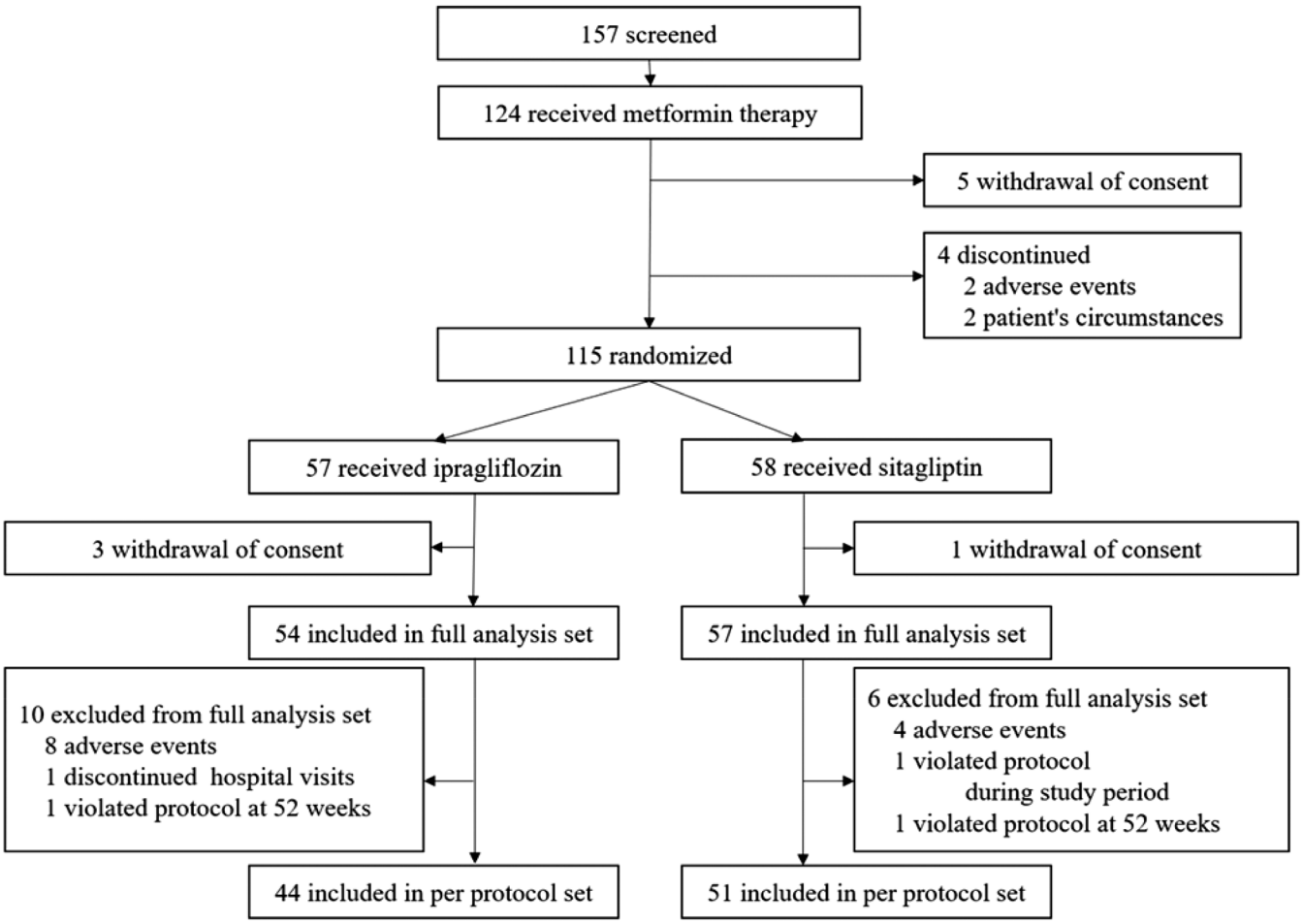

FIGURE 1 Flow chart of participants

significantly higher value in the sitagliptin group (ipragliflozin group 31.5% vs. sitagliptin group 56.1%; $P = 0.01$). The rate of achievement of HbA1c <7.0% at 24 weeks was also significantly greater in the sitagliptin group (ipragliflozin group 35.2% vs. sitagliptin group 61.4%; $P < 0.01$). No weight gain was observed in 42 patients in the ipragliflozin group and 29 patients in the sitagliptin group, with the rate significantly higher in the ipragliflozin group (ipragliflozin group 77.8% vs. sitagliptin group 50.9%; $P < 0.01$). Results of the per-protocol set analysis were similar between the two groups, with the exception that the proportion of patients whose HbA1c reduction of ≥0.5% at 24 weeks was not statistically significant, but tended to be greater in the sitagliptin group (ipragliflozin group 38.6% vs. sitagliptin group 56.9%; $P = 0.08$). Details of the secondary endpoints are also shown in Tables 2 and 3.

Comparisons of changes up to 24 weeks and at 52 weeks were made only in patients who had a fasting blood test at each time point. Changes in each variable from week 0 to week 52 are shown in Table 4. Although there was no significant difference in the change between groups at 52 weeks in HbA1c (−0.51% (5.6 mmol/mol) ipragliflozin group vs. −0.43% (4.7 mmol/mol) sitagliptin group; $P = 0.79$), C-peptide, HDL cholesterol, uric acid, body weight, BMI and waist circumference were significantly and favourably changed in the ipragliflozin group. A decrease in total cholesterol was observed in the sitagliptin group. Haematocrit was elevated and urinary Na was decreased in the ipragliflozin group. As shown in Figure 2, at 24 weeks, the change in HbA1c was −0.33% (3.6 mmol/mol) in the ipragliflozin group and −0.62% (6.8 mmol/mol) in the sitagliptin group, with the change being significantly higher in the sitagliptin group ($P < 0.01$). Although HbA1c was continuously decreased in the ipragliflozin group up to 24 weeks and at 52 weeks, an initial decrease was shown for HbA1c, which was then re-elevated toward week 52 in the sitagliptin group; ($P = 0.01$).

3.5 | Other endpoints

The mean total energy intake at baseline was 1762.6 kcal in the ipragliflozin group and 1803.0 kcal in the sitagliptin group, with no significant difference between groups. Energy intake was significantly greater by week 52 in the ipragliflozin group than in the sitagliptin group (increasing 183.8 kcal in the ipragliflozin group and decreasing

TABLE 1 Baseline characteristics of study participants

	Ipragliflozin (n = 54)	Sitagliptin (n = 57)	*P*
Men, n (%)	33 (61.1)	35 (61.4)	0.98
Age, years	60.0 ± 9.1	58.4 ± 12.5	0.11
Body weight, kg	69.8 ± 10.5	72.0 ± 15.6	0.38
BMI, kg/m^2	26.3 ± 3.1	26.8 ± 4.5	0.77
Systolic blood pressure, mmHg	135.7 ± 12.9	135.4 ± 16.5	0.94
Diastolic blood pressure, mmHg	82.4 ± 10.5	81.4 ± 13.6	0.64
Duration of diabetes, years	10.2 ± 7.6	9.3 ± 6.8	0.67
Alcohol consumption, n (%)	32 (59.3)	25 (43.9)	0.11
Current smoking habit, n (%)	11 (20.4)	10 (17.5)	0.70
HbA1c, % (mmol/mol)	7.54 ± 0.75 (58.9 ± 8.2)	7.53 ± 0.69 (58.8 ± 7.5)	0.89
Fasting blood glucose, mg/dL (mmol/L)	150.4 ± 26.9 (8.36 ± 1.49)	149.4 ± 28.0 (8.30 ± 1.56)	0.91
C-peptide,[a] ng/mL	2.04 ± 0.93	2.13 ± 1.47	0.39
Triglycerides, mg/dL	143.5 (100–206.5)	126.0 (98.5–182)	0.46
Total cholesterol,[b] mg/dL	194.0 (167–223.5)	187.0 (161.5–202.5)	0.13
HDL cholesterol, mg/dL	47.2 (44–56.3)	52.0 (42.3–59.5)	0.60
LDL cholesterol, mg/dL	105 (87.5–129.5)	106 (85.5–127)	0.89
Nephropathy, n (%)	16 (29.6)	11 (19.3)	0.21
Retinopathy, n (%)	9 (16.7)	11 (19.3)	0.72
Neuropathy, n (%)	22 (40.7)	27 (47.4)	0.48
Hypertension	34 (63)	44 (77.2)	0.10
Antihypertension agents, n (%)	24 (44.4)	30 (52.6)	0.39
Dyslipidaemia, n (%)	45 (83.3)	41 (71.9)	0.15
Antidyslipidaemia agents, n (%)	21 (38.9)	25 (43.9)	0.60
Antiplatelet agents, n (%)	1 (1.9)	2 (3.5)	1.00
Metformin dose,[c] mg	1059.9 ± 443.5	1187.5 ± 493.7	0.60
Alpha-glucosidase inhibitors, n (%)	1 (1.9)	2 (3.5)	1.00
Thiazolidines, n (%)	0	1(1.7)	-
Total energy intake,[d] kcal/day	1762.6 ± 408.5	1803.0 ± 479.9	0.87
Physical activity,[a] METs h/week	11.6 (2.8, 41.5)	14.3 (1.7, 39.8)	0.72

Note: Data are presented as mean ± standard deviation, median (25%, 75% percentile), or frequency (percentage). A total of 111 patients in the full analysis set were included in this analysis.
Abbreviations: BMI, body mass index; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; METs, metabolic equivalents.
[a]n = 53 in ipragliflozin group and 54 in sitagliptin group.
[b]n = 53 in ipragliflozin group and 57 in sitagliptin group.
[c]n = 54 in ipragliflozin group and 56 in sitagliptin group.
[d]n = 53 in ipragliflozin group and 55 in sitagliptin group.

TABLE 2 Achievement rates of endpoints (full analysis set)

52 weeks	Ipragliflozin (n = 54)	Sitagliptin (n = 57)	*P*
Composite primary endpoint	20 (37.0)	23 (40.4)	0.72
HbA1c reduction ≥0.5% (5.5 mmol/mol)	21 (38.9)	31 (54.4)	0.10
No body weight increase	51 (94.4)	31 (54.4)	<0.01
24 weeks			
Composite secondary endpoint	14 (25.9)	18 (33.3)	0.51
HbA1c reduction ≥0.5% (5.5 mmol/mol)	17 (31.5)	32 (56.1)	0.01
No body weight increase	42 (77.8)	29 (50.9)	<0.01

Note: Data are presented as frequency (percentage). A total of 111 patients in the full analysis set were included in this analysis.
Abbreviation: HbA1c, glycated haemoglobin.

TABLE 3 Achievement rates of endpoints (per-protocol set)

52 weeks	Ipragliflozin (n = 44)	Sitagliptin (n = 51)	*P*
Composite primary endpoint	19 (43.2)	22 (43.1)	0.997
HbA1c reduction ≥0.5% (5.5 mmol/mol)	20 (45.5)	28 (54.9)	0.36
No body weight increase	42 (95.5)	30 (58.8)	<0.01
24 weeks			
Composite secondary endpoint	14 (31.8)	16 (31.4)	0.96
HbA1c reduction ≥0.5% (5.5 mmol/mol)	17 (38.6)	29 (56.9)	0.08
No body weight increase	37 (84.1)	27 (52.9)	<0.01

Note: Data are presented as frequency (percentage). A total of 95 patients in the per-protocol set were included in this analysis.
Abbreviation: HbA1c, glycated haemoglobin.

TABLE 4 Changes in each variable from week 0 to week 52

	Ipragliflozin (n = 44)	Sitagliptin (n = 48)	*P*
ΔBody weight, kg	−2.9 ± 2.0	−0.5 ± 2.1	<0.01
ΔBMI, kg/m^2	−1.1 ± 0.8	−0.2 ± 0.8	<0.01
ΔWaist circumference,[a] cm	−2.1 ± 4.2	−0.2 ± 4.0	0.04
ΔSystolic blood pressure, mmHg	−6.7 ± 14.6	−2.5 ± 14.4	0.17
ΔDiastolic blood pressure, mmHg	−3.1 ± 9.4	−0.4 ± 12.6	0.25
ΔHbA1c, % (mmol/mol)	−0.51 ± 0.61 (−5.6 ± 6.7)	−0.43 ± 0.76 (−4.7 ± 8.3)	0.79
ΔFasting blood glucose, mg/dl (mmol/L)	−19.8 ± 19.9 (−1.10 ± 1.11)	−7.9 ± 26.1 (−0.44 ± 1.45)	0.02
ΔC-peptide,[b] ng/mL	−0.33 ± 0.66	−0.02 ± 0.67	<0.01
ΔTriglycerides, mg/dl	−16.3 ± 54.4	−6.5 ± 59.2	0.41
ΔTotal cholesterol,[c] mg/dl	4.6 ± 20.0	−0.8 ± 22.1	0.02
ΔHDL cholesterol, mg/dl	4.6 ± 5.7	−1.4 ± 6.2	<0.01
ΔLDL cholesterol, mg/dl	4.6 ± 17.6	2.6 ± 20.0	0.27
ΔeGFR, ml/min/1.73 m^2	−2.9 ± 10.7	−2.3 ± 7.9	0.91
ΔUric acid,[d] mg/dl	−0.6 ± 0.7	0.1 ± 0.9	<0.01
ΔHaematocrit, %	2.5 ± 2.2	0 ± 1.8	<0.01
ΔUrinary albumin,[e] mg/g creatinine	−0.51 ± 0.61	−0.43 ± 0.76	0.46
ΔUrinary Na,[e] mEq/L	−25.1 ± 50.0	2.1 ± 52.9	0.02
ΔTotal energy intake,[f] kcal/d	183.8 ± 468.7	−4.8 ± 436.7	0.02
ΔPhysical activity,[g] METs h/week	1.6 (−3.0, 16.0)	−1.7 (−18.0, 1.70)	0.02

Note: Data are presented as mean ± standard deviation or median (25%, 75% percentile). A total of 92 patients in the full analysis set with fasting biochemical data at 52 weeks were included in this analysis; this was the same population as that with fasting biochemical data in the per-protocol set.
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; METs, metabolic equivalents.
[a]n = 43 in ipragliflozin group and 45 in sitagliptin group.
[b]n = 43 in ipragliflozin group and 47 in sitagliptin group.
[c]n = 43 in ipragliflozin group and 48 in sitagliptin group.
[d]n = 44 in ipragliflozin group and 47 in sitagliptin group.
[e]n = 40 in ipragliflozin group and 47 in sitagliptin group.
[f]n = 44 in ipragliflozin group and 45 in sitagliptin group.
[g]n = 44 in ipragliflozin group and 43 in ipragliflozin group.

4.8 kcal in the sitagliptin group; $P < 0.02$). The median level of physical activity was 11.6 metabolic equivalents (METs) h/week in the ipragliflozin group and 14.3 METS h/week in the sitagliptin group, values that were not significantly different. Physical activity also increased in the ipragliflozin group compared with the sitagliptin group (increasing 1.6 METS h/week in the ipragliflozin group and decreasing 1.7 METS h/week in the sitagliptin group; $P < 0.02$).

3.6 | Safety analysis

During the metformin therapy, we observed two patients (1.6%) with an adverse event. One (0.8%) was a severe adverse event that was not related to metformin and the other (0.8%) was a non-severe adverse event related to metformin. During the ipragliflozin and sitagliptin therapy, 29 adverse events were observed in 27 patients, with 17 patients in the ipragliflozin group and 10 patients in the sitagliptin group (ipragliflozin group 29.8% vs. sitagliptin group 17.2%; P = 0.11). Serious adverse events occurred in two patients in the ipragliflozin group and in three patients in the sitagliptin group (ipragliflozin group 3.5% vs. sitagliptin group 5.2%; P = 1.00). Adverse events related to study drugs were observed in seven patients in the ipragliflozin group and in one patient in the sitagliptin group (ipragliflozin group 12.3% vs. sitagliptin group 1.7%; P = 0.03). There were no symptoms of hypoglycaemia or hypoglycaemia below 70 mg/dL (3.9 mmol/L) or below 54 mg/dL (3.0 mmol/L) during the study period. None of the patients died. Table S2 provides details of adverse events.

Safety analysis of clinical and biochemical data was performed at each visit, with 111 participants at 0 weeks, 108 at 4 weeks, 108 at 12 weeks, 103 at 24 weeks, 100 at 36 weeks, and 97 at 52 weeks. We did not observe significant safety-related abnormalities in this analysis. Details are shown in Table S5.

4 | DISCUSSION

This is the first study to evaluate the long-term efficacy of ipragliflozin or sitagliptin given in combination with metformin for 52 weeks in actual clinical practice. There was a greater HbA1c-lowering effect in the sitagliptin group at 24 weeks, but there was no difference in the primary endpoints (proportion of patients without weight gain and a ≥0.5% HbA1c decrease) between the two groups at 52 weeks. However, the metabolic status in the ipragliflozin group showed improvements, including in HDL cholesterol, C-peptide, BMI and waist circumference, compared to the sitagliptin group. In the ipragliflozin group, total energy intake increased, but HbA1c and body weight decreased.

Because a 24-week period is short and was considered insufficient to compare the efficacy of these drugs,[14,16,17] this study was conducted over a longer period of 52 weeks, which was sufficient to show the effects of the drugs. Although the differences in the composite endpoints of HbA1c and body weight were not significant between the two drugs, ipragliflozin was effective in improving some metabolic factors. The results of this study provided useful information for drug selection in conjunction with metformin in patients with low ASCVD risk in daily clinical practice.

The primary endpoint was not met in this clinical trial. Although the proportion of participants without weight gain was almost the same as we expected, the rate of those with a reduction in HbA1c ≥0.5% was lower than we had estimated. Generally, the HbA1c-lowering effect of both drugs was shown to be greater in those with

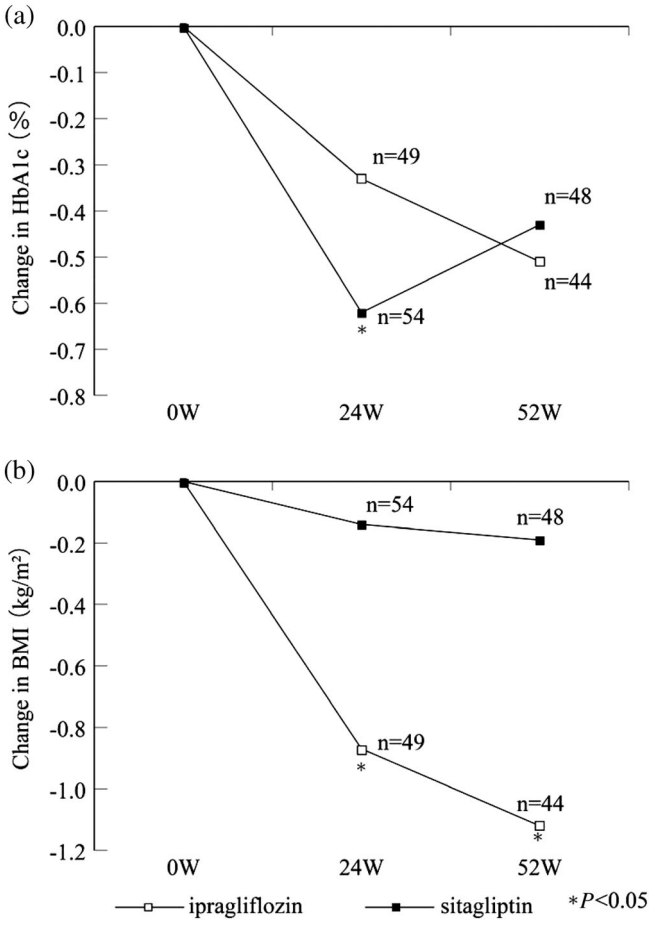

FIGURE 2 Changes in glycated haemoglobin (HbA1c) and body mass index (BMI) at 24 weeks and 52 weeks. Patients with fasting biochemical data at each time point were included in the analysis

higher HbA1c values before treatment.[28,29] Compared with HbA1c values of 8% (63.9 mmol/mol) or more in previous studies,[25–27] HbA1c values at the start of the present study were 7.5% (58.5 mmol/mol) and were considerably lower, resulting in the lower achievement rate of an HbA1c reduction ≥0.5%. On the other hand, unlike the effect on HbA1c, the effect on body weight of SGLT2 inhibitors was independent of HbA1c values before treatment,[28] and the percentage of patients without weight gain with ipragliflozin was similar to that shown in previous studies.

In our clinical trial, the mean change in HbA1c at week 52 from baseline was greater in the ipragliflozin group than in the sitagliptin group (−0.51% and −0.43%, −5.6 mmol/mol and −4.7 mmol/mol; P = 0.79). Conversely, the proportion of patients who had HbA1c reductions ≥0.5% at week 52 was lower in the ipragliflozin group than in the sitagliptin group (38.9% and 54.4%; P = 0.10). The difference in the distribution of changes in HbA1c between the two groups might account for what could be considered conflicting results, although the differences were not statistically significant.

As shown in Table S4, among patients who had HbA1c reductions of ≥0.5% at week 52, more participants in the ipragliflozin group had large improvements in HbA1c than in the sitagliptin group. As a result, contrary to the proportion of the participants who reached HbA1c

reductions of ≥0.5%, the mean decrease in HbA1c was greater in the ipragliflozin group than in the sitagliptin group (−1.00% vs. −0.88%, −10.9 mmol/mol vs −9.6 mmol/mol ; P = 0.44). Among patients without HbA1c reductions of ≥0.5%, some participants in the sitagliptin group had a large HbA1c increase while none did in the ipragliflozin group. As a result, the mean decrease in HbA1c was greater in the ipragliflozin group than in the sitagliptin group (−0.10% vs. +0.09%, −1.1 mmol/mol vs +1.0 mmol/mol; P = 0.57). In other words, more ipragliflozin group participants than sitagliptin group participants had a large HbA1c decrease, while more sitagliptin group participants than ipragliflozin group participants had a large HbA1c increase.

We cannot fully explain these tendencies leading to apparently conflicting results because the number of participants with significant changes in HbA1c was not sufficient for a meaningful interpretation. These results may represent the characteristics of SGLT2 inhibitors and DPP-4 inhibitors.

In our long-term comparison of the SGLT2 inhibitor ipragliflozin with the DPP-4 inhibitor sitagliptin, weight loss was consistently significantly greater with ipragliflozin throughout 52 weeks, similar to previous studies.[7–13,25] However, HbA1c was significantly reduced in those in the sitagliptin group at 24 weeks. This finding is supported by recent systematic reviews showing that the glucose-lowering effects of DPP-4 inhibitors up to 24 weeks were more effective in East Asians than in non-Asians,[30] whereas the effects of SGLT2 inhibitors were not different between Asians and non-Asians.[31]

In previous studies,[10–13] the HbA1c-lowering effect of both drugs by 24 weeks varied. Scott et al[13] reported that the HbA1c-lowering effect at 24 weeks was −0.36% (−3.9 mmol/mol) for a SGLT2 inhibitor and −0.51% (−5.6 mmol/mol) for the DPP-4 inhibitor, indicating the effectiveness of the latter agent. Halvorsen et al[11] reported that the lowering effect of the SGLT2 inhibitor was −0.74% (−8.1 mmol/mol) and that for the DPP-4 inhibitor was −0.82% (−9.0 mmol/mol), indicating that SGLT2 inhibitors were not inferior, while Fuchigami et al[10] reported that the HbA1c-lowering effect was −0.9% (−9.8 mmol/mol) in both treatment groups.

In the sitagliptin group, HbA1c initially decreased up to 24 weeks and then increased again toward week 52. It has been reported that the HbA1c-lowering effect of sitagliptin may be attenuated over the long term.[32] Tajiri et al[15] reported that with DPP-4 inhibitors, a longer duration of diabetes, weight gain up to 24 weeks, worsening lifestyle, and switching from α-GI drugs have been reported to be associated with re-elevation of HbA1c after 24 weeks. However, in this study, there were no significant differences in the duration of diabetes, changes in energy intake, or changes in physical activity between patients whose HbA1c increased at weeks 24 to 52 and those whose HbA1c decreased. Overall, in this study, sitagliptin had a greater HbA1c-lowering effect at 24 weeks than ipragliflozin, but at 52 weeks, the HbA1c-lowering effect was comparable to that of ipragliflozin, indicating no difference in the long-term efficacy of these drugs. It did become evident that a 24-week period is insufficient to compare the two drugs. A longer study period is required for meaningful results.

We observed that in the ipragliflozin group, total energy intake increased but HbA1c and body weight decreased. Other studies have similarly reported increases in energy intake with SGLT2 inhibitors,[33,34] but they did not include a control group and did not compare changes in HbA1c with or without increased energy intake. In the ipragliflozin group, those with increased energy intake had a smaller HbA1c reduction, although not statistically significant, compared to those with no increase in energy intake (−0.39% vs.−0.68%, −4.3 mmol/mol vs −7.4 mmol/mol; P = 0.06). In the sitagliptin group, the effect of changes in energy intake on HbA1c was smaller than the effect in the ipragliflozin group (−0.41% vs. −0.48%, −4.5 mmol/mol vs −5.2 mmol/mol; P = 0.65). It is possible that assignment to an SGLT2 inhibitor may have altered dietary behaviour and influenced the effect of lowering HbA1c.

We also observed that the change in physical activity differed between the two groups. It is known that SGLT2 inhibitors decrease skeletal muscle mass and may be related to the incidence of sarcopenia.[35] The present study was an open-label trial, and it is possible that participants in the SGLT2 inhibitor group took measures to avoid the risk of muscle weakness and, as a result, increased physical activity.

Adverse events were observed in 17 patients in the ipragliflozin group and 10 patients in the sitagliptin group, but there was no significant difference in incidence. However, adverse events related to the drug occurred more often in the ipragliflozin group than in the sitagliptin group (12.3% vs. 1.7%; P = 0.03). Most of the adverse events related to ipragliflozin, such as urinary tract infection, genital infection, genital pruritus, thirst, and urinary frequency might have been related to the pharmacological effect of the SGLT2 inhibitor itself. Although both drugs were well tolerated, we need to take into account adverse events considering the characteristics of each drug, especially with ipragliflozin.

The strengths of this study are as follows. The study was conducted in a population that was taking approximately 1000 mg of metformin, which is equivalent to the average dose in Japan.[36] In addition, the study followed a 52-week course based on the consideration that this was sufficiently long to reveal the long-term course of the drug. In fact, results of the evaluation differed between 24 and 52 weeks.

We are aware of several limitations. First, we included four participants taking an α-GI or a thiazolidine in this trial. Their inclusion would seem to have a limited impact on the interpretation of the efficacy of SGLT2 and DPP-4 inhibitors. Second, the target number of patients was not reached. The reason was that few patients were included who remained inadequately controlled on metformin alone in the 22 institutions taking part in this study. We also had financial reasons not to extend the study period. Third, the efficacy of both drugs, especially the DPP-4 inhibitor,[30] might vary between White and Japanese cohorts. Generalization to non-Japanese cohorts might not be possible. Fourth, as we discussed above, we cannot fully interpret the effect of changes in energy intake and physical activity on HbA1c and body weight.

In conclusion, this was the first study to evaluate the 52-week efficacy of ipragliflozin and sitagliptin in actual clinical practice. There was no difference in the composite primary endpoints related to HbA1c and body weight between the two groups. We found a greater HbA1c-lowering effect in the sitagliptin group at 24 weeks. At 52 weeks, compared with the sitagliptin group, the ipragliflozin group showed improvement in metabolic status such as HDL cholesterol, C-peptide, BMI and waist circumference. Because the 24-week period that has been studied previously appears to be insufficient to compare the efficacy of these drugs, this study was conducted over a longer period of 52 weeks. Differences shown between the two time periods indicate the value of this longer period and provided useful information in drug selection in daily clinical practice.

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CONFLICT OF INTEREST

H. Sone has received research funds from Kyowa Hakko Kirin Co., Ltd., Novartis AG, Ono Pharmaceutical Co., Ltd., Taisho Pharmaceutical Co., Ltd. and Takeda Pharmaceutical Co. The remaining authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

M.K., K. Fujihara, S.T. and H. Sone made substantial contributions to the conception and design of the study. M.K., T.K., H.Suzuki, S.M., M.Y., T.I., M.Y., K. Furukawa, M.I., K. Fujihara, T.Y. and H. Sone substantially contributed to the acquisition of data; M.K., K.Fujihara, S.T. and H. Sone made substantial contributions to analysis and interpretation of data; and M.K., K. Fujihara and H. Sone were involved in drafting the manuscript or revising it critically for important intellectual content. All authors gave final approval of the version to be published. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14288.

DATA AVAILABILITY STATEMENT

Date availability The datasets that were analyzed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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