Should sulfonylurea be discontinued or maintained at the lowest dose when starting ipragliflozin? A multicenter observational study in Japanese patients with type 2 diabetes

Kiyohiko Takahashi1, Kyu Yong Cho1, Akinobu Nakamura1, Aika Miyazaki2, Arina Miyoshi1, Chiho Yamamoto3, Hiroshi Nomoto1, Hirokatsu Niwa4, Kiyohito Takahashi5, Naoki Manda6, Yoshio Kurihara7, Shin Aoki8, Yoichi Mito9, Tatsuya Atsumi9, Hideaki Miyoshi1,10*

1Department of Rheumatology, Endocrinology and Nephrology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, 2Kushiro Red Cross Hospital, Kushiro, 3Tomakomai City Hospital, Tomakomai, 4NIWA Diabetic Care Clinic, Sapporo, 5Takahashi Kiyohito Clinic, Hakodate, 6Manda Memorial Hospital, 7Kurihara Clinic, 8Aoki Clinic, 9Department of Biostatistics, Hokkaido University Graduate School of Medicine, and 10Division of Diabetes and Obesity, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan

Keywords
Glycated hemoglobin, Sodium–glucose cotransporter 2 inhibitor, Sulfonylurea

*Correspondence
Hideaki Miyoshi
Tel: +81-11-706-5915
Fax: +81-11-706-7710
E-mail address: hmiyoshi@med.hokudai.ac.jp

J Diabetes Investig 2019; 10: 429–438
doi: 10.1111/jdi.12913

Clinical Trial Registry
University Hospital Medical Information Network Center
UMIN000016347

ABSTRACT
Aims/Introduction: We investigated the difference in efficacy and safety between discontinuation and maintaining of sulfonylurea when adding a sodium–glucose cotransporter 2 inhibitor.

Materials and Methods: In the present multicenter, prospective observational study, 200 patients with type 2 diabetes treated with sulfonylurea and with a need to add ipragliflozin were enrolled and divided into two groups: discontinued sulfonylurea (Discontinuation group) or maintained sulfonylurea, but at the lowest dose (Low-dose group) when adding ipragliflozin. We compared the two groups after 24 weeks using propensity score matching to adjust for differences between the groups.

Results: In the matched cohort (58 patients in each group), baseline characteristics of both groups were balanced. The primary outcome of the proportion of patients with non-exacerbation in glycated hemoglobin after 24 weeks was 91.4% in the Low-dose group and 75.9% in the Discontinuation group, a significant difference (P = 0.024). However, bodyweight was significantly decreased in the Discontinuation group compared with the Low-dose group (−4.4 ± 2.1 kg vs −2.9 ± 1.9 kg, P < 0.01). Similarly, liver enzyme improvement was more predominant in the Discontinuation group. A logistic regression analysis showed that high-density lipoprotein cholesterol, age and sulfonylurea dose were independent factors associated with non-exacerbation of glycated hemoglobin in the Discontinuation group.

Conclusions: The purpose of using ipragliflozin should be considered when making the decision to discontinue or maintain sulfonylurea at the lowest dose. Furthermore, low high-density lipoprotein cholesterol level, low dose of sulfonylurea and younger age were possible markers to not show worsening of glycemic control by discontinuing sulfonylurea.

INTRODUCTION
The goal in treating patients with diabetes mellitus is to prevent the development of complications by adequately controlling blood glucose level.

Sodium–glucose cotransporter 2 inhibitors (SGLT2is) improve glucose tolerance by suppressing renal glucose reabsorption without direct pharmacological action on pancreatic β-cells1,2. Several clinical trials have shown that SGLT2is improve not only glycemic control, lowering the risk of hypoglycemia, but also features of metabolic syndrome through the reduction of visceral fat3,4.
Furthermore, it has recently been shown that SGLT2is reduce secondary cardiovascular events and protect kidney damage in patients with type 2 diabetes5,6. Thus, SGLT2i is an established treatment for patients with type 2 diabetes and with established atherosclerotic cardiovascular disease, and their use is recommended in the American Diabetes Association “Standard of Medical Care in Diabetes” due to their effect of reducing major adverse cardiovascular events and of improving mortality7.

Historically, sulfonylureas have been extensively used for the treatment of type 2 diabetes and are considered to exert the strongest glucose-lowering effect among the oral antidiabetic drugs8. Despite their low cost and effective glycem control, they might be associated with weight gain and hypoglycemia9. In addition, the diminution of β-cell function during the course of type 2 diabetes decreases the effectiveness of sulfonylureas10. Thus, patients failing to achieve glycemic control with a sulfonylurea require combination treatment to maintain adequate control of blood glucose levels or should switch to another antidiabetic drug. Previous studies have shown that dapagliflozin is an effective add-on combination treatment with glimepiride, although hypoglycemic events occur more frequently than glimepiride monotherapy11. Furthermore, a head-to-head trial of SGLT2i and sulfonylurea showed that SGLT2i reduced weight loss and hypoglycemia, and improved glycated hemoglobin (HbA1c) to a greater extent than sulfonylurea did4,12. When patients with type 2 diabetes need to improve not only glycemic control, but also body mass, other metabolic parameters, kidney function or cardiovascular risk, SGLT2i is often considered as add-on treatment. However, no study to date has investigated the effect on glycemic control and safety of discontinuing sulfonylurea compared with maintaining low-dose sulfonylurea when adding SGLT2i in patients with type 2 diabetes. Although switching from sulfonylurea to SGLT2i is associated with less frequent hypoglycemia, some patients fail to achieve adequate glycemic control following discontinuation of sulfonylurea. It would therefore be beneficial to identify the patient characteristics that determine the outcome of discontinuing sulfonylurea or adding SGLT2i.

We carried out a multicenter, prospective study among patients with type 2 diabetes who had been treated with sulfonylurea and required SGLT2i to compare the efficacy and safety of discontinuing sulfonylurea or maintaining it at the lowest dose. Furthermore, we sought to determine the patient characteristics associated with maintenance of glycemic control when discontinuing sulfonylurea treatment and adding SGLT2i.

METHODS
Study population
The present study included Japanese patients with type 2 diabetes undergoing outpatient treatment at 14 medical institutions from February 2015 to July 2017. All participants provided written informed consent before study enrolment. The inclusion criteria were as follows: type 2 diabetes and aged between 20 and 75 years, HbA1c level between 6.5% and 8.5%, and receiving sulfonylurea therapy (glimepiride ≥1 mg/day, glinazide ≥40 mg/day or glibenclamide ≥1.25 mg/day) for at least 12 weeks before enrolment. Further criteria included body mass index (BMI) ≥22 kg/m² and estimated glomerular filtration rate ≥45 mL/min/1.73 m². We excluded individuals with unstable diabetic retinopathy, serious liver dysfunction, renal failure and heart complications, and those who were pregnant, lactating or had insufficient endogenous insulin secretion (defined as fasting C-peptide <0.5 ng/mL). The present study was registered with the University Hospital Medical Information Network Center (UMIN000016347) before enrolment, approved by the institutional review board of Hokkaido Hospital and was carried out based on the Declaration of Helsinki.

Protocol
This was a 24-week, multicenter, prospective, parallel-group, observational study. After starting ipragliflozin (50 mg/day), participants either remained on glimepiride or glinazide, but reduced to the lowest dose of 0.5 mg/day or 20 mg/day, respectively (Low-dose group), or discontinued sulfonylurea treatment (Discontinuation group) according to the physician’s decision. Propensity score matching was used to reduce the bias that might result from confounding factors before comparing the groups. Sulfonylurea and any other antidiabetic drugs were continued at a constant dose from enrolment to the end of the treatment period. However, insulin could be reduced where there was a risk of hypoglycemia.

The primary outcome of the present study was the proportion of patients with non-exacerbation of HbA1c, defined as a change in HbA1c ≤0.3% from baseline to week 24 after the addition of ipragliflozin as described in the guidance of the Food and Drug Administration, which specifies a non-inferiority margin for HbA1c of 0.3% or 0.4%13. Secondary end-points were changes in body mass, abdominal circumference, fasting plasma glucose, HbA1c, homeostasis model assessment of insulin resistance, homeostasis model assessment of β-cell function, lipids, liver function and renal function. Data were collected after an overnight fast at baseline and at 24 weeks of observation.

Statistical analysis
The primary and secondary end-points were analyzed based on the intention-to-treat principle. We calculated propensity scores for the likelihood of discontinuing or maintaining sulfonylurea at the lowest dose as add-on to ipragliflozin using baseline covariates in a multivariate logistic regression model. Covariates used in the propensity score included age, BMI, fasting plasma glucose, HbA1c, aspartate aminotransferase, alanine aminotransferase, high-density lipoprotein cholesterol (HDL-C) and sulfonylurea dose (converted glimepiride dose). In calculating the sulfonylurea dose, we considered 1 mg glimepiride to be equivalent to 40 mg glinazide or 1.25 mg glibenclamide, as previously reported14,15. Patients were matched 1:1 within 0.05 caliper widths of the pooled standard deviation of the logit of
propensity scores. Results were expressed as mean ± standard deviation. Differences in baseline characteristics between the groups were compared using a $\chi^2$-test or an unpaired $t$-test. We also used a paired $t$-test or a McNemar test for pre- and post-treatment comparisons. A group comparison of the differences in mean changes was carried out using an unpaired $t$-test. The relationship between change in HDL-C and BMI was assessed using Pearson’s correlation coefficients. Multivariate analyses were carried out using logistic regression to identify factors independently associated with the outcomes. A receiver operating characteristic (ROC) curve analysis was used to define the cut-off values indicative of non-exacerbation of HbA1c in the Discontinuation group. $P$-values <0.05 were considered to denote statistical significance. Statistical analysis was carried out using JMP Pro version 13 (SAS Inc., Cary, NC, USA).

RESULTS
Baseline characteristics of patients
A total of 200 patients (144 men and 56 women) were enrolled in the study and assigned to either the Discontinuation group or the Low-dose group. Two patients were subsequently found not to meet the study criteria, and nine patients withdrew from the study before completion. The reasons for non-completion were withdrawal of consent ($n=5$) and side-effects of test medications, including pruritus, rash, genital infection, palpitation or pollakiuria ($n=4$; Figure 1). A total of 189 patients completed the study (Discontinuation group, 99 patients; Low-dose group, 90 patients). Baseline characteristics of the 200 patients in the Discontinuation and the Low-dose groups are compared in Table 1. In the unmatched cohort, the Discontinuation group showed lower age, and higher estimated glomerular filtration rate and HDL-C compared with the Low-dose group. After 1:1 propensity score matching, 55% and 62% of patients in the Discontinuation and the Low-dose groups, respectively, were retained in the matched cohort (58 patients in each group). After matching, the Discontinuation and the Low-dose groups were adequately balanced in all the clinical characteristics ($P$-value >0.05 for all comparisons). The average age, BMI, HbA1c and sulfonylurea dose of participants were 58.8 years, 27.7 kg/m², 7.57% and 1.4 mg/day, respectively (Table 1).

Outcomes
In the matched cohort, the proportion of patients with non-exacerbation in HbA1c was significantly higher in the Low-dose group (91.4%) compared with the Discontinuation group (75.9%, $P=0.024$; Figure 2). HbA1c levels were significantly decreased in the Low-dose group compared with the Discontinuation group (−0.33 ± 0.51% vs 0.08 ± 0.65%, $P<0.01$, respectively). However, blood pressure was significantly decreased only in the Discontinuation group (Table 2). Bodyweight, BMI, waist circumference, uric acid and liver function parameters significantly decreased in both groups, although the magnitude of

Figure 1 | Study protocol flow diagram. Participants were allocated to one of two groups according to the objective clinical judgment of clinician. All patients added ipragliflozin and either decreased the dose of glimepiride (to 0.5 mg/day) or gliclazide (to 20 mg/day; Low-dose group) or discontinued sulfonylurea (Discontinuation group).
Table 1 | Differences in clinical characteristics between the group that discontinued sulfonylurea and the group that maintained sulfonylurea, but at the lowest dose, before and after propensity matching

|                                | Before propensity matching | P-value | After propensity matching | P-value |
|--------------------------------|---------------------------|---------|---------------------------|---------|
|                                | Discontinuation group     | Low-dose group |                      |         |
|                                | (n = 106)                 | (n = 94)  |                           |         |
| Age (years)                    | 560 ± 9.7                 | 594 ± 8.9 | <0.05                     |         |
| Male/female (n)                | 76/30                     | 68/26    | 0.92                      | 41/17   | 40/18   | 0.84   |
| Duration of diabetes (years)   |                           |          |                           |         |
| 0–4 (%)                        | 11.4                      | 12.2     | 0.49                      | 10.5    | 16.4    | 0.46   |
| 5–9 (%)                        | 31.4                      | 32.3     | <0.01                     | 38.6    | 25.5    |        |
| 10–14 (%)                      | 25.7                      | 34.4     |                           | 19.3    | 20.0    |        |
| 15+ (%)                        | 31.4                      | 30.0     |                           | 31.6    | 38.2    |        |
| Duration of sulfonylurea (years)|                      |          |                           |         |
| 0–4 (%)                        | 33.0                      | 26.3     | 0.38                      | 30.9    | 30.4    | 0.98   |
| 5–9 (%)                        | 27.8                      | 36.8     |                           | 34.6    | 34.8    |        |
| 10–14 (%)                      | 22.7                      | 26.3     |                           | 21.8    | 19.6    |        |
| ≥15 (%)                        | 16.5                      | 10.5     |                           | 12.7    | 15.2    |        |
| Smoking status                 |                           |          |                           |         |
| Never smoked (%)               | 43.4                      | 38.7     | 0.76                      | 44.8    | 40.4    | 0.69   |
| Former smoker (%)              | 24.5                      | 24.7     |                           | 25.9    | 22.8    |        |
| Current smoker (%)             | 32.1                      | 36.6     |                           | 29.3    | 36.8    |        |
| Alcohol drinking status        |                           |          |                           |         |
| Non-current drinker (%)        | 70.8                      | 64.9     | 0.38                      | 52.9    | 47.1    | 0.45   |
| Current drinker (%)            | 29.3                      | 35.1     |                           | 45.7    | 54.4    |        |
| Bodyweight (kg)                | 796 ± 16.4                | 760 ± 14.6 | 0.10                     | 752 ± 12.0 | 755 ± 14.3 | 0.91   |
| BMI (kg/m²)                    | 29.1 ± 5.0                | 27.9 ± 4.5 | 0.08                     | 27.7 ± 4.0 | 27.7 ± 4.3 | 0.98   |
| Waist circumference (cm)       | 97.6 ± 11.0               | 95.1 ± 10.3 | 0.09                     | 94.5 ± 8.0 | 94.5 ± 10.4 | 0.97   |
| SBP (mmHg)                     | 132.6 ± 14.5              | 134.9 ± 15.9 | 0.30                     | 132.5 ± 12.9 | 135.1 ± 17.8 | 0.38   |
| DBP (mmHg)                     | 805 ± 11.6                | 790 ± 10.7 | 0.37                     | 801 ± 9.2  | 79.9 ± 11.7 | 0.91   |
| FPG (mmol/L)                   | 8.2 ± 1.8                 | 8.8 ± 2.3 | 0.06                      | 8.4 ± 1.9  | 8.3 ± 1.9  | 0.87   |
| FPG (mg/dL)                    | 148.4 ± 33.2              | 158.1 ± 41.0 | 0.06                     | 151.1 ± 35.0 | 150.0 ± 35.0 | 0.87   |
| HbA1c (%)                      | 7.51 ± 0.57               | 7.62 ± 0.52 | 0.17                     | 7.60 ± 0.60 | 7.54 ± 0.49 | 0.53   |
| Insulin (µIU/mL)               | 101 ± 10.9                | 125 ± 13.7 | 0.23                     | 103 ± 13.0 | 87 ± 7.8  | 0.48   |
| HOMA-IR                        | 3.8 ± 4.7                 | 5.8 ± 7.7  | 0.06                      | 4.1 ± 5.6  | 3.6 ± 4.6  | 0.67   |
| HOMA-B                         | 481 ± 49.6                | 457 ± 47.3 | 0.77                     | 457 ± 53.3 | 387 ± 36.3 | 0.47   |
| UA (mg/dL)                     | 56.6 ± 13.3               | 54.1 ± 12.2 | 0.23                     | 56.1 ± 13.1 | 53.2 ± 12.1 | 0.15   |
| AST (U/L)                      | 305 ± 14.7                | 309 ± 18.9 | 0.89                     | 296 ± 13.5 | 268 ± 11.7 | 0.25   |
| ALT (U/L)                      | 387 ± 24.9                | 404 ± 30.7 | 0.07                     | 377 ± 22.5 | 345 ± 22.1 | 0.44   |
| γ-GTP (U/L)                    | 67.0 ± 64.9               | 466 ± 37.0 | 0.07                     | 559 ± 58.6 | 498 ± 43.4 | 0.52   |
| Ht (%)                         | 434 ± 4.2                 | 442 ± 4.3  | 0.18                      | 436 ± 4.6  | 438 ± 4.6  | 0.82   |
| ACR (mg/g creatinine)          | 91.7 ± 290.9              | 99.3 ± 247.2 | 0.85                     | 740 ± 170.3 | 1241 ± 305.6 | 0.28   |
| eGFR (mL/min/1.73 m²)          | 808 ± 17.7                | 754 ± 19.1 | <0.05                     | 790 ± 16.4 | 744 ± 17.6 | 0.14   |
| TG (mg/dL)                     | 1398 ± 85.8               | 1523 ± 90.6 | 0.32                     | 1385 ± 86.1 | 1360 ± 80.8 | 0.87   |
| T-Chol (mg/dL)                 | 1803 ± 29.5               | 1795 ± 32.7 | 0.85                     | 1741 ± 24.8 | 1788 ± 29.6 | 0.38   |
| HDL-C (mg/dL)                  | 524 ± 14.9                | 485 ± 11.1 | <0.05                     | 504 ± 13.5 | 519 ± 11.2 | 0.51   |
| LDL (mg/dL)                    | 1001 ± 28.0               | 1011 ± 31.0 | 0.82                     | 962 ± 21.0  | 1004 ± 26.0 | 0.36   |
| Non-HDL-C (mg/dL)              | 1280 ± 29.8               | 1312 ± 31.6 | 0.47                     | 1234 ± 24.9 | 1270 ± 27.2 | 0.48   |
| Sulfonylurea dose (mg/day)      | 1.3 ± 0.5                 | 1.5 ± 0.8  | 0.06                      | 1.3 ± 0.6  | 1.5 ± 0.9  | 0.32   |
| Glimiprid (n)                  | 102                       | 79        |                           | 55       | 49       |        |
| Gliclazide (n)                 | 4                        | 15        |                           | 3        | 9        |        |
| Glimebencamide (n)             | 0                        | 0         |                           | 0        | 0        |        |
| Antidiabetic medicine          |                           |          |                           |         |
| Biguanide (n)                  | 88                       | 77        |                           | 49       | 46       |        |
| DPP-4 inhibitor (n)            | 84                       | 77        |                           | 32       | 47       |        |
| Thiazolidinedione (n)          | 24                       | 14        |                           | 9        | 9        |        |
the effect for bodyweight, BMI and aspartate aminotransferase was significantly greater in the Discontinuation group compared with the Low-dose group (−4.4 ± 2.1 kg vs −2.9 ± 1.9 kg, P < 0.01; −1.6 ± 0.8 kg/m² vs −1.1 ± 0.7 kg/m², P < 0.01; and −7.3 ± 11.7 U/L vs −3.2 ± 6.6 U/L, P < 0.05, respectively; Table 2).

As shown in Table 3, logistic regression analysis identified that low HDL-C, low dose of sulfonylurea and younger age were independent factors associated with the non-exacerbation of HbA1c in the Discontinuation group, after adjustments for age, BMI, HbA1c, HDL-C and sulfonylurea dose. Also, we carried out logistic regression analysis using bodyweight instead of BMI and obtained similar results (data not shown). Using a ROC analysis, the cut-off values for non-exacerbation of HbA1c in the Discontinuation group were 48 mg/dL for HDL-C, 1.0 mg/day for sulfonylurea dose and 62 years-of-age (Table 4). The area under the ROC curve for HDL-C, sulfonylurea dose and age were 0.78, 0.64 and 0.70, respectively (Figures 3a, S1). The cut-off value for HDL-C showed the largest area under the ROC curve among the non-exacerbation factors for change in HbA1c (Figure 3a), and the specificity of the HDL-C cut-off for predicting non-exacerbation of HbA1c in the Discontinuation group was 85.7% (Table 4).

**Adverse events**

In the safety analysis set, 22 events in the Discontinuation group and 20 events in the Low-dose group reported adverse events. No severe adverse events were reported in either group during the present study. The most common adverse event within both groups was hypoglycemia (7 patients [6.6%] in the Discontinuation group and 10 patients [10.6%] in the Low-dose group, respectively; Table 5). The majority of patients who experienced hypoglycemia in both groups had been treated with insulin (three patients [42.9%] in the Discontinuation group and four patients [40.0%] in the Low-dose group, respectively). Furthermore, the incidence of hypoglycemic episodes did not increase in either group during the study period (Figure S2). Other adverse events in both groups included pruritus, pollakiuria, worsening diabetes, rash, hunger sensation, fracture or genital infection (Table 5).

**DISCUSSION**

A distinctive feature of the present study was a lower dropout rate attributed to adverse events (n = 4, 2% of all enrolled patients) compared with previous studies (approximately 12%)\(^\text{16}\), likely because the participating physicians were familiar with the use of SGLT2i, although minor adverse events occurred at a rate of almost 20% in the present study (Table 5).

In the present study, we showed that the proportion of patients with non-exacerbation in HbA1c level was >90% in the Low-dose group and approximately 75% in the Discontinuation group. This indicates that glycemic control did not worsen for almost all patients who remained on the lowest dose of sulfonylurea, but that approximately 25% of patients who discontinued sulfonylurea when adding ipragliflozin failed to achieve glycemic control. As the frequency of hypoglycemia did not increase in either group (Figure S2), adding or switching from sulfonylurea to ipragliflozin can be considered acceptable and effective for the treatment of type 2 diabetes, especially among patients for whom body weight gain and metabolic disorders are factors influencing the choice of treatment. Maintaining sulfonylurea treatment at the lowest dose has been considered more beneficial than discontinuing it for ensuring glycemic control without increasing hypoglycemia when adding a SGLT2i. In previous studies on the addition of various types of glucose-lowering agents to high-dose sulfonylurea, the combination therapy had a beneficial effect on glycemic control with increasing hypoglycemia (~30%)\(^\text{12,17,18}\). As the present study differs from previous reports in the
frequency of hypoglycemia, despite maintaining sulfonylurea treatment in the Low-dose group, our findings show that dose reduction of sulfonylurea is important to avoid hypoglycemia, and that the lowest dose of sulfonylurea is sufficient to avoid worsening of glycemic control when adding SGLT2i to sulfonylurea treatment. Thus, our observations suggest that low-dose sulfonylurea plus iragliblozin is effective for ensuring glycemic control without increasing adverse events, including hypoglycemia.

Decreased visceral fat and improvement in metabolic disorder factors, such as dyslipidemia, hypertension, hyperuricemia and fatty liver associated with the administration of SGLT2i, have been widely recognized in clinical practice. In contrast, sulfonylurea treatment frequently causes weight gain related to mild hypoglycemic symptoms, such as the sensation of hunger. Although bodyweight, BMI and aspartate aminotransferase decreased in both groups in the present study, the magnitude of the effects was significantly larger in the Discontinuation group compared with the Low-dose group. An approximately 1.7-fold reduction in bodyweight was observed in the Discontinuation group compared with the Low-dose group, likely because of the combined effects of iragliblozin initiation and sulfonylurea discontinuation.

We showed in a logistic regression analysis that lower HDL-C was a key characteristic that could predict non-exacerbation of HbA1c when sulfonylurea was discontinued (Table 3). Although the relationship between HDL-C level and the glycemic effect of iragliblozin remains unclear, one possibility might be the observation that HDL-C level is lower in obese patients with type 2 diabetes. In fact, HDL-C is one of the components for classification of metabolic syndrome. In the present study, HDL-C and BMI in the Discontinuation group were significantly negatively correlated ($r = -0.27, P < 0.05$; Figure 3b). Similarly, beneficial effects on glycemic control have been observed with higher BMI compared with lower BMI in Japanese phase III trials of SGLT2is. An additional glucose-lowering effect due to the improvement in insulin resistance or sensitivity is expected to be larger when SGLT2 inhibitors are administered in patients with higher BMI. Taken together, patients with type 2 diabetes who had lower HDL-C ($\leq 48$ mg/dL), lower dose of sulfonylurea ($\leq 1.0$ mg/day) and younger age ($\leq 62$ years) were more likely not to show worsening of glycemic control, and to have reduced bodyweight and improvements in metabolic disorder by switching from sulfonylurea to iragliblozin, although further studies are required to verify this observation.
Table 2 | Comparison of the effects on other parameters evaluated in both groups before and after propensity matching

| Parameter | Before propensity matching | After propensity matching | P-value | P-value |
|-----------|-----------------------------|---------------------------|---------|---------|
|           | Discontinuation group (n=106) | Low-dose group (n=94) |         | Discontinuation group (n=58) | Low-dose group (n=58) |
|           | Baseline | End-point | Baseline | End-point | Baseline | End-point | Baseline | End-point |
| Bodyweight (kg) | 796 ± 164 | 751 ± 164** | 760 ± 146 | 734 ± 142** | <0.01 | 752 ± 120 | 708 ± 122** | 755 ± 143 | 726 ± 140** | <0.01 |
| BMI (kg/m²) | 29 ± 50 | 27 ± 51** | 27 ± 45 | 26 ± 43** | <0.01 | 27 ± 40 | 26 ± 40** | 27 ± 43 | 26 ± 41** | <0.01 |
| Waist circumference (cm) | 976 ± 11.0 | 938 ± 11.1** | 951 ± 103 | 919 ± 100** | 0.24 | 945 ± 80 | 901 ± 78** | 945 ± 104 | 917 ± 101** | 0.63 |
| SBP (mmHg) | 1326 ± 14.5 | 1268 ± 14.3** | 1349 ± 159 | 1309 ± 147** | 0.27 | 1325 ± 129 | 1259 ± 150** | 1351 ± 178 | 1318 ± 144 | 0.25 |
| DBP (mmHg) | 805 ± 11.6 | 758 ± 96** | 790 ± 107 | 780 ± 104 | <0.05 | 801 ± 92 | 752 ± 101** | 799 ± 117 | 779 ± 106 | 0.11 |
| FPG (mmol/L) | 8.2 ± 1.8 | 7.7 ± 1.7** | 8.8 ± 2.3 | 7.6 ± 1.5** | 0.05 | 8.4 ± 1.9 | 8.0 ± 1.9 | 8.3 ± 1.9 | 7.6 ± 1.3** | 0.21 |
| FPG (mg/dL) | 1484 ± 33.2 | 1388 ± 31.2** | 1581 ± 410 | 1375 ± 268** | 0.05 | 1511 ± 350 | 1433 ± 345 | 1504 ± 350 | 1359 ± 228** | 0.21 |
| HbA1c (%) | 7.51 ± 0.57 | 7.55 ± 0.62 | 7.62 ± 0.52 | 7.21 ± 0.59** | <0.01 | 7.60 ± 0.60 | 7.66 ± 0.65 | 7.54 ± 0.49 | 7.21 ± 0.51** | <0.01 |
| Insulin (mU/mL) | 10.1 ± 10.9 | 6.5 ± 49** | 12.5 ± 137 | 7.4 ± 50** | <0.05 | 103 ± 130 | 58 ± 36* | 87 ± 78 | 65 ± 60** | 0.83 |
| HOMA-IR | 38 ± 4.7 | 23 ± 20** | 58 ± 7.7 | 25 ± 2.2** | <0.01 | 41 ± 5.6 | 21 ± 1.9 | 36 ± 4.6 | 23 ± 2.3* | 0.31 |
| HOMA-β | 481 ± 4.96 | 352 ± 32.7** | 457 ± 47.3 | 400 ± 32.2 | 0.63 | 457 ± 53.3 | 282 ± 17.2** | 387 ± 36.3 | 321 ± 24.9 | 0.56 |
| UA (mg/dL) | 56 ± 13 | 51 ± 12** | 54 ± 12 | 51 ± 11** | 0.07 | 56 ± 13 | 52 ± 12** | 53 ± 12 | 50 ± 12** | 0.16 |
| AST (U/L) | 305 ± 14.7 | 240 ± 130** | 309 ± 189 | 258 ± 123** | 0.29 | 296 ± 135 | 223 ± 89** | 268 ± 117 | 237 ± 101** | <0.05 |
| ALT (U/L) | 387 ± 24.9 | 27.4 ± 19.3** | 404 ± 307 | 313 ± 21.4** | 0.48 | 377 ± 22.5 | 260 ± 16.2** | 345 ± 22.1 | 268 ± 16.5** | 0.16 |
| γ-GTP (U/L) | 607 ± 64.9 | 441 ± 44.9** | 466 ± 37.0 | 393 ± 36.0** | <0.05 | 559 ± 58.6 | 386 ± 41.9** | 498 ± 43.4 | 414 ± 41.9** | 0.05 |
| Ht (%) | 434 ± 4.2 | 449 ± 49** | 442 ± 43 | 465 ± 39** | 0.14 | 436 ± 46 | 455 ± 5.4** | 438 ± 46 | 462 ± 4.1** | 0.25 |
| ACR (mg/g creatinine) | 917 ± 290.9 | 830 ± 330.6 | 993 ± 2472 | 697 ± 1323* | 0.46 | 740 ± 170.3 | 450 ± 806 | 1241 ± 305.6 | 738 ± 1481* | 0.50 |
| eGFR (ml/min/1.73 m²) | 808 ± 17.7 | 831 ± 179* | 754 ± 191 | 747 ± 192 | 0.10 | 709 ± 168 | 813 ± 17.7* | 744 ± 176 | 750 ± 180 | 0.27 |
| TG (mg/dL) | 1398 ± 85.8 | 1313 ± 69.3 | 1523 ± 906 | 1425 ± 952 | 0.83 | 1385 ± 81.6 | 1333 ± 68.2 | 1360 ± 808 | 1313 ± 895 | 0.95 |
| T-Chol (mg/dL) | 1803 ± 29.5 | 1844 ± 30.2 | 1795 ± 327 | 1814 ± 342 | 0.74 | 1741 ± 24.8 | 1826 ± 29.3 | 1788 ± 296 | 1825 ± 333 | 0.63 |
| HDL-C (mg/dL) | 524 ± 14.9 | 560 ± 15.0** | 485 ± 11.1 | 529 ± 13.8** | 0.26 | 504 ± 13.5 | 543 ± 14.2** | 519 ± 11.2 | 566 ± 14.4** | 0.54 |
| LDL (mg/dL) | 1001 ± 280 | 1019 ± 263 | 1011 ± 310 | 1002 ± 293 | 0.45 | 962 ± 210 | 1014 ± 238 | 1004 ± 260 | 1001 ± 266 | 0.39 |
| Non-HDL (mg/dL) | 1280 ± 29.8 | 1281 ± 30.3 | 1312 ± 316 | 1289 ± 334 | 0.37 | 1234 ± 249 | 1279 ± 286 | 1270 ± 272 | 1265 ± 325 | 0.35 |

Values are mean ± standard deviation. P-values: mean changes from baseline to the end of the study between the discontinuation group and the low-dose group. *P < 0.05 and **P < 0.01 between baseline and the end of the study. γ-GTP, γ-glutamyl transpeptidase; ACR, albumin/creatinine ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; Discontinuation group, the group that discontinued sulfonylurea; eGFR, estimated glomerular filtration rate; TG, triglyceride; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-β, homeostasis model assessment of beta cell function; HOMA-IR, homeostasis model assessment of insulin resistance; Ht, hematocrit; LDL, low-density lipoprotein cholesterol; Low-dose, the group that maintained sulfonylurea, but at the lowest dose; SBP, systolic blood pressure; T-Chol, total cholesterol; UA, uric acid.
There were several limitations to the current study. First, the number of cases was small and the study duration was relatively short. The purpose of the present study was to explore the potential efficacy and safety of ipragliflozin with decreased versus discontinuation of sulfonylurea. Further studies in a larger sample size are required to confirm our conclusions and extend our current findings. Second, the present study was open-labeled and observational in design, which might have contributed to patient selection bias. Although we used a propensity matching approach to eliminate confounding effects in the study design, a randomized controlled study is required to the present findings. Third, although patients were carefully evaluated to detect episodes of hypoglycemia, some patients might have failed to notice hypoglycemic symptoms, and some episodes of hypoglycemia might have been missed in both groups. Continuous glucose monitoring can be used in future studies to ensure that all hypoglycemic episodes are recorded. Fourth, although sulfonylurea treatment frequently causes weight gain related to mild hypoglycemic symptoms, such as the sensation of hunger, we did not investigate food intake in the present study. Therefore, other findings related to bodyweight or glycemic change might have been affected by the level of food consumption. Finally, the present study was carried out only in Japanese patients. It is unclear whether the present results can be generalized to non-Japanese patients because of differences in bodyweight and insulin secretory capacity between Japanese and Caucasian patients with type 2 diabetes.

In conclusion, when adding ipragliflozin to sulfonylurea in patients with type 2 diabetes, approximately 75% of patients can discontinue sulfonylurea without experiencing a worsening of glycemic control, and with extensive bodyweight

Table 3 | Logistic regression analysis to identify independent factors associated with non-exacerbation of glycated hemoglobin in the group that discontinued sulfonylurea

| Factor                  | OR    | 95% CI       | P-value |
|-------------------------|-------|--------------|---------|
| HDL-C (mg/dL)           | 0.90  | 0.84-0.97    | <0.01   |
| Sulfonylurea dose (mg/day) | 0.09  | 0.01-0.72    | <0.01   |
| Age (years)             | 0.83  | 0.70-0.99    | <0.01   |
| BMI (kg/m²)             | 1.06  | 0.80-1.34    | 0.69    |
| HbA1c (%)               | 1.16  | 0.25-5.35    | 0.85    |

R² = 0.3558. Logistic regression was adjusted for age, body mass index (BMI), glycated hemoglobin (HbA1c), high-density lipoprotein cholesterol (HDL-C) and sulfonylurea dose. 95% CI, 95% confidence interval; OR, odds ratio.

Table 4 | Cut-off values of the independent factors associated with non-exacerbation of glycated hemoglobin in the group that discontinued sulfonylurea

| Factor                  | Cut-off value | AUC  | Sensitivity (%) | Specificity (%) |
|-------------------------|---------------|------|-----------------|-----------------|
| HDL-C (mg/dL)           | 48.0          | 0.78 | 63.6            | 85.7            |
| Sulfonylurea dose (mg/day) | 1.0           | 0.64 | 57.2            | 70.5            |
| Age (years)             | 62.0          | 0.70 | 64.3            | 70.5            |

AUC, area under the receiver operating curve; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol.

Figure 3 | High-density lipoprotein cholesterol (HDL-C) as an independent factor associated with non-exacerbation of glycated hemoglobin in the group that discontinued sulfonylurea. (a) Receiver operating characteristic (ROC) curves for the cut-off value of HDL-C to identify non-exacerbation of glycated hemoglobin. (b) Relationship between HDL-C and body mass index (BMI; r = -0.27, P < 0.05) in the group that discontinued sulfonylurea.
reduction and improvement in metabolic parameters. Maintaining sulfonylurea treatment at the lowest dose, however, can ensure better glycemic control without increasing hypoglycemia, although bodyweight reduction and improvement in metabolic parameters are limited compared with discontinuation of sulfonylurea. Whether sulfonylurea should be discontinued or maintained at the lowest dose should depend on the purpose of initiating SGLT2i therapy. In addition, HDL-C level, sulfonylurea dose and patient age should be considered.

ACKNOWLEDGMENTS
This research was planned and designed by the investigators, and was financially supported by Astellas Pharma, Inc. The sponsor company was not involved in study design, patient enrolment, data aggregation and analysis, data interpretation or manuscript preparation. We thank the participating patients at the Diabetes Outpatient Departments of the Clark Hospital, Hokkaido Spinal Cord Injury Center, Obihir Osei General Hospital, Ogasawara Clinic Sapporo Hospital, Oki Medical Clinic, and Sapporo Diabetes and Thyroid Clinic for their valuable contributions. We also thank Clare Cox, PhD, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

DISCLOSURE
HM has received honoraria for lectures from Astellas Pharma, AstraZeneca, Sumitomo Dainippon Pharma, Eli Lilly, Kissie Pharmaceutical, Mitsubishi Tanabe Pharma, MSD, Novo Nordisk Pharma and Sanofi, and has received research funding from Astellas Pharma, AstraZeneca, Eli Lilly and Mitsubishi Tanabe Pharma. AN has received honoraria for lectures from Sanofi, Mitsubishi Tanabe Pharma, Daiichi Sankyo, Eli Lilly, MSD, Novo Nordisk Pharma, Novartis Pharma, AstraZeneca, Takeda Pharmaceutical, Astellas Pharma, Kowa Pharmaceutical, Ono, Sumitomo Dainippon Pharma, Nippon Boehringer Ingelheim, Kissie Pharmaceutical and Taisho Toyama Pharmaceutical, and has obtained research support from Sanofi, Mitsubishi Tanabe Pharma, MSD, Novo Nordisk Pharma, Novartis Pharma, AstraZeneca, Ono and Taisho Toyama Pharmaceutical. TA has received honoraria for lectures from Mitsubishi Tanabe Pharma, Chugai Pharmaceutical, Astellas Pharma, Takeda Pharmaceutical, Pfizer and AbbVie, and has received research funding from Astellas Pharma, Takeda Pharmaceutical, Mitsubishi Tanabe Pharma, Chugai Pharmaceutical, Daiichi Sankyo and Otsuka Pharmaceutical. The other authors declare no conflict of interest.

REFERENCES
1. Washburn WN. Development of the renal glucose reabsorption inhibitors: a new mechanism for the pharmacotherapy of diabetes mellitus type 2. J Med Chem 2009; 52: 1785–1794.
2. Vallon V. The mechanisms and therapeutic potential of SGLT2 inhibitors in diabetes mellitus. Annu Rev Med 2015; 66: 255–270.
3. Yamamoto C, Miyoshi H, Ono K, et al. Ipragliflozin effectively reduced visceral fat in Japanese patients with type 2 diabetes under adequate diet therapy. Endocr J 2016; 63: 589–596.
4. Nauck MA, Del Prato S, Meier JJ, et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. Diabetes Care 2011; 34: 2015–2022.
5. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015; 373: 2117–2128.
6. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017; 377: 644–657.
7. American Diabetes Association. 8. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes-2018. Diabetes Care 2018; 41(Suppl. 1): S73–S85.
8. United Kingdom Prospective Diabetes Study. (UKPDS). 13: Relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. BMJ 1995; 310: 83–88.
9. UK Prospective Diabetes Study. (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352: 837–853.
10. U.K. Prospective Diabetes Study Group. U.K. prospective diabetes study 16. Overview of 6 years’ therapy of type II diabetes: a progressive disease. *Diabetes* 1995; 44: 1249–1258.

11. Strojek K, Yoon KH, Hruba V, et al. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. *Diabetes Obes Metab* 2011; 13: 928–938.

12. Cefalu WT, Leiter LA, Yoon KH, et al. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. *Lancet* 2013; 382: 941–950.

13. US Food and Drug Administration. Guidance for Industry. *Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention*. Rockville, MD: FDA, 2008.

14. Kamiyama H, Aoki K, Nakajima S, et al. Effect of switching from sulphonylurea to repaglinide twice or three times daily for 4 months on glycemic control in Japanese patients with type 2 diabetes. *Intern Med* 2016; 55: 1697–1703.

15. Basit A, Riaz M, Fawwad A. Glimepiride: evidence-based facts, trends, and observations (GIFTS) [corrected]. *Vasc Health Risk Manag* 2012; 8: 463–472.

16. Yokote K, Terauchi Y, Nakamura I, et al. Real-world evidence for the safety of ipragliflozin in elderly Japanese patients with type 2 diabetes mellitus (STELLA-ELDER): final results of a post-marketing surveillance study. *Expert Opin Pharmacother* 2016; 17: 1995–2003.

17. Barnett AH, Huisman H, Jones R, et al. Linagliptin for patients aged 70 years or older with type 2 diabetes inadequately controlled with common antidiabetes treatments: a randomised, double-blind, placebo-controlled trial. *Lancet* 2013; 382: 1413–1423.

18. Gallwitz B, Rosenstock J, Patel S, et al. Regardless of the degree of glycaemic control, linagliptin has lower hypoglycaemia risk than all doses of glimepiride, at all time points, over the course of a 2-year trial. *Diabetes Obes Metab* 2015; 17: 276–284.

19. Takase T, Nakamura A, Miyoshi H, et al. Amelioration of fatty liver index in patients with type 2 diabetes on ipragliflozin: an association with glucose-lowering effects. *Endocr J* 2017; 64: 363–367.

20. Mitri J, Hamdy O. Diabetes medications and body weight. *Expert Opin Drug Saf* 2009; 8: 573–584.

21. Draeger E. Clinical profile of glimepiride. *Diabetes Res Clin Pract* 1995; 28(Suppl): S139–S146.

22. Tanaka S, Honda M, Wu B, et al. Clinical features of normal weight Japanese patients with type 2 diabetes who had formerly been obese. *J Atheroscler Thromb* 2011; 18: 115–121.

23. Sakai S, Kaku K, Seino Y, et al. Efficacy and safety of the SGLT2 inhibitor luseogliflozin in Japanese patients with type 2 diabetes mellitus stratified according to baseline body mass index: pooled analysis of data from 52-week Phase III trials. *Clin Ther* 2016; 38(843–862): e9.

24. Tobe K, Suganami H, Kaku K. Sodium-glucose cotransporter 2 inhibitor, tofogliflozin, shows better improvements of blood glucose and insulin secretion in patients with high insulin levels at baseline. *J Diabetes Investig* 2018; 9: 862–869.

25. Sone H, Ito H, Ohashi Y, et al. Obesity and type 2 diabetes in Japanese patients. *Lancet* 2003; 361: 85.

26. Kosaka K, Kuzuya T, Hagura R, et al. Insulin response to oral glucose load is consistently decreased in established non-insulin-dependent diabetes mellitus: the usefulness of decreased early insulin response as a predictor of non-insulin-dependent diabetes mellitus. *Diabet Med* 1996; 13(9 Suppl. 6): S109–S119.

**SUPPORTING INFORMATION**

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

**Figure S1** | Receiver operating characteristic for the cut-off value of sulfonylurea dose and age to identify non-exacerbation of glycated hemoglobin in the group that discontinued sulfonylurea.

**Figure S2** | Incidence of hypoglycemic episodes in the group that discontinued sulfonylurea compared with the group that maintained sulfonylurea, but at the lowest dose, during the study period.