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ORIGINAL ARTICLE

Impact of body mass index on the efficacy and safety of ipragliflozin in Japanese patients with type 2 diabetes mellitus: A subgroup analysis of 3-month interim results from the Specified Drug Use Results Survey of Ipragliflozin Treatment in Type 2 Diabetic Patients: Long-term Use study

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Keywords
Body mass index, Ipragliflozin, Postmarketing product surveillance

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ABSTRACT

Aims/Introduction: Specified Drug Use Results Survey of Ipragliflozin Treatment in Type 2 Diabetic Patients: Long-term Use is an ongoing postmarketing study of ipragliflozin for long-term use in Japanese patients with type 2 diabetes mellitus. A subgroup analysis of data from the study was carried out to investigate the impact of obesity on the efficacy and safety of ipragliflozin in this population.

Materials and Methods: Patients were divided into the following subgroups according to their body mass index (BMI): <22.0, 22.0 to <25.0, 25.0 to <30.0 and ≥30.0 kg/m^2. Changes in bodyweight and glycemic parameters up to 3 months were evaluated, as well as adverse drug reactions (ADRs) that occurred during ipragliflozin treatment.

Results: In the efficacy analysis set (8,633 patients), glycemic control and bodyweight statistically significantly improved from baseline to 3 months in all BMI subgroups (all $P < 0.05$). No strong correlations were identified between changes in bodyweight and changes in hemoglobin A1c, waist circumference or BMI in any of the subgroups. The incidence of adverse drug reactions was 6.29, 8.44, 11.18 and 11.74% in the <22.0, 22.0 to <25.0, 25.0 to <30.0 and ≥30.0 kg/m^2 groups, respectively ($P = 0.001$), in the safety analysis set ($n = 11,053$ patients).

Conclusions: In Japanese patients with type 2 diabetes mellitus, ipragliflozin improved glycemic control and reduced bodyweight, regardless of BMI. Adverse drug reactions were more common in patients with higher BMI than in those with lower BMI.

INTRODUCTION

Overweight or obesity (body mass index [BMI] >25 or >30 kg/m^2, respectively) is associated with increased risk of type 2 diabetes mellitus[1–3]. The exact mechanisms underlying this association are unclear. However, the increased risk of type 2 diabetes mellitus might be due to obesity-associated insulin resistance, progressive β-cell dysfunction or genetic factors[4].

Interethnic differences mean that East Asians with increased BMI are particularly susceptible to developing type 2 diabetes mellitus and certain complications of type 2 diabetes mellitus. Compared with people of European ethnic origin, they develop

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type 2 diabetes mellitus at a lower mean BMI, and are at increased risk of developing renal complications and strokes as a result of type 2 diabetes mellitus[5]. A pooled cross-sectional analysis of >900,000 Asian (including East Asian) participants confirmed a strong association between BMI and diabetes risk in this population; compared with individuals with a BMI of 22.5–24.9 kg/m^2, those with BMI ≥35.0 kg/m^2 had an odds ratio for diabetes of 2.23 (95% confidence interval 1.86–2.67)[6]. Furthermore, BMI has been found to be an independent predictor of mortality in a large group of Japanese patients with diabetes[7].

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are oral antihyperglycemic drugs that inhibit renal reabsorption of glucose and promote glycosuria, thereby effecting an insulin-independent reduction in blood glucose concentration[8,9]. Their specific mechanism of action enables improved glycemic control without the risk of hypoglycemia, and additionally, through their glycosuric effect, promotion of weight loss[9].

The results of several randomized controlled trials have shown the SGLT2 inhibitor, ipragliflozin, to be well tolerated and efficacious in reducing glycated hemoglobin (HbA1c), fasting plasma glucose and bodyweight in Japanese patients with type 2 diabetes mellitus[9–16]. In the most recent of these trials (the ASSIGN-K study), 12 weeks of ipragliflozin treatment reduced mean bodyweight and body fat by 1.82 and 1.46 kg, respectively ($P < 0.001$)[16]. Furthermore, an analysis of data pooled from five randomized controlled trials, in which 508 patients received ipragliflozin, showed that it was efficacious and well tolerated in Japanese type 2 diabetes mellitus patients, regardless of their BMI[17].

The Specified Drug Use Results Survey of Ipragliflozin Treatment in Type 2 Diabetic Patients: Long-term Use (STELLA-LONG TERM) study is being carried out to evaluate the long-term efficacy and safety of ipragliflozin in Japanese patients with type 2 diabetes mellitus under real-world conditions of use, in accordance with national requirements for post-marketing surveillance. The study is currently ongoing; patients will be observed for a total of 3 years. The baseline characteristics of the patients have been reported previously; notably, the proportion of overweight or obese patients registered for the study is unexpectedly large compared with the general Japanese population[18]. Here, we describe a subgroup analysis of the 3-month interim results from STELLA-LONG TERM[19], in which

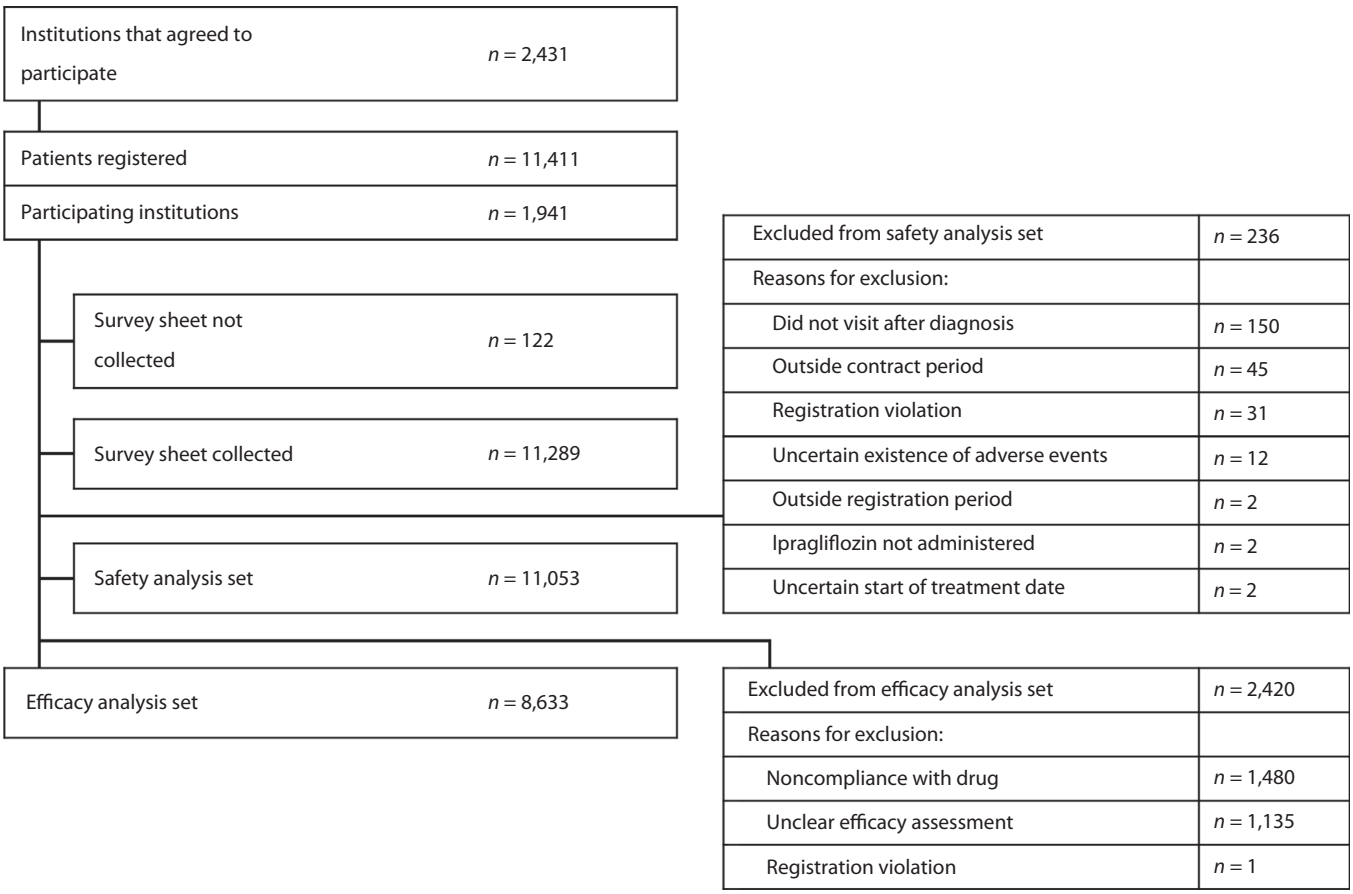


Figure 1 | Patient disposition. Patients might have been excluded for multiple reasons; therefore, the numbers do not necessarily add up to the total number of patients included in the study.

Table 1 | Patient characteristics at baseline (safety analysis set)

	<22.0 kg/m^2 *n* (%)	22.0 to <25.0 kg/m^2 *n* (%)	25.0 to <30.0 kg/m^2 *n* (%)	≥30.0 kg/m^2 *n* (%)	*P*-value[†]	Unknown *n* (%)
Total (safety analysis set)						
–	302 (100.0)	1,125 (100.0)	3,015 (100.0)	2,589 (100.0)	–	4,022 (100.0)
Sex						
Male	188 (62.3)	700 (62.2)	1,903 (63.1)	1,503 (58.1)	(1) 0.001	2,420 (60.2)
Female	114 (37.7)	425 (37.8)	1,112 (36.9)	1,086 (41.9)		1,602 (39.8)
Age (years)						
n	302	1,125	3,015	2,589	(2) <0.001	4,022
Mean ± SD	63.9 ± 11.2	61.4 ± 10.7	57.2 ± 11.4	51.3 ± 11.3		58.5 ± 12.5
Age (category)						
<65 years	149 (49.3)	659 (58.6)	2,188 (72.6)	2,249 (86.9)	(1) <0.001	2,651 (65.9)
≥65 years	153 (50.7)	466 (41.4)	827 (27.4)	340 (13.1)		1,371 (34.1)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)
Bodyweight (kg)						
n	302	1,125	3,015	2,589	–	628
Mean ± SD	54.08 ± 7.25	63.09 ± 7.34	73.90 ± 9.34	93.59 ± 16.28		75.68 ± 16.28
Duration of diabetes (years)						
n	184	766	2,184	2,025	(2) <0.001	2,089
Mean ± SD	10.086 ± 8.056	9.373 ± 6.861	8.251 ± 6.510	7.467 ± 5.951		7.441 ± 6.410
Complications						
No	53 (17.5)	163 (14.5)	371 (12.3)	208 (8.0)	(1) <0.001	915 (22.7)
Yes	246 (81.5)	957 (85.1)	2,642 (87.6)	2,380 (91.9)		3,021 (75.1)
Unknown	3 (1.0)	5 (0.4)	2 (0.1)	1 (0.0)		86 (2.1)
Type of complication[‡]						
Diabetic neuropathy	26 (8.6)	106 (9.4)	289 (9.6)	280 (10.8)	–	249 (6.2)
Diabetic nephropathy	46 (15.2)	185 (16.4)	571 (18.9)	589 (22.8)		402 (10.0)
Diabetic retinopathy	21 (7.0)	102 (9.1)	305 (10.1)	269 (10.4)		187 (4.6)
Cardiovascular disease, cerebrovascular disease	36 (11.9)	113 (10.0)	287 (9.5)	190 (7.3)		390 (9.7)
Myocardial infarction	6 (2.0)	18 (1.6)	43 (1.4)	29 (1.1)		47 (1.2)
Angina pectoris	12 (4.0)	58 (5.2)	134 (4.4)	81 (3.1)		177 (4.4)
Heart failure	9 (3.0)	19 (1.7)	61 (2.0)	56 (2.2)		77 (1.9)
Arteriosclerosis obliterans	8 (2.6)	15 (1.3)	35 (1.2)	27 (1.0)		51 (1.3)
Cerebrovascular disease	11 (3.6)	26 (2.3)	70 (2.3)	42 (1.6)		113 (2.8)
Hypertension	125 (41.4)	539 (47.9)	1,723 (57.1)	1,717 (66.3)		2,037 (50.6)
Dyslipidemia (hyperlipidemia)	153 (50.7)	746 (66.3)	2,132 (70.7)	1,873 (72.3)		2,060 (51.2)
Osteoporosis	10 (3.3)	26 (2.3)	44 (1.5)	26 (1.0)		73 (1.8)
Hyperuricemia	16 (5.3)	67 (6.0)	286 (9.5)	384 (14.8)		278 (6.9)
Urinary tract infection	0 (0.0)	2 (0.2)	3 (0.1)	7 (0.3)		6 (0.1)
Genital infection	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.2)		3 (0.1)
Malignant tumor	0 (0.0)	11 (1.0)	21 (0.7)	13 (0.5)		25 (0.6)
Others	116 (38.4)	393 (34.9)	1,084 (36.0)	1,164 (45.0)		1,127 (28.0)

Table 1 (*Continued*)

	<22.0 kg/m^2 *n* (%)	22.0 to <25.0 kg/m^2 *n* (%)	25.0 to <30.0 kg/m^2 *n* (%)	≥30.0 kg/m^2 *n* (%)	*P*-value[†]	Unknown *n* (%)
eGFR (mL/min/1.73 m²)						
n	206	777	2,053	1,812	(2) <0.001	1,266
Mean ± SD	81.45 ± 22.08	80.86 ± 20.41	81.02 ± 21.31	85.09 ± 22.67		79.68 ± 21.41
HbA1c						
<8.0%	178 (58.9)	648 (57.6)	1,651 (54.8)	1,339 (51.7)	(1) <0.001	1,812 (45.1)
≥8.0%	114 (37.7)	437 (38.8)	1,272 (42.2)	1,178 (45.5)		1,353 (33.6)
Unknown	10 (3.3)	40 (3.6)	92 (3.1)	72 (2.8)		857 (21.3)
SBP (mmHg)						
n	282	1,048	2,809	2,359	(2) <0.001	1,676
Mean ± SD	127.8 ± 15.0	131.8 ± 14.8	132.5 ± 14.8	135.6 ± 15.4		132.9 ± 15.4
DBP (mmHg)						
n	282	1,047	2,809	2,358	(2) <0.001	1,673
Mean ± SD	72.7 ± 10.2	76.3 ± 10.4	78.1 ± 10.6	81.0 ± 11.1		76.7 ± 11.2
LDL-C (mg/dL)						
n	196	731	1,899	1,675	(2) 0.037	1,174
Mean ± SD	108.5 ± 32.4	112.3 ± 30.9	113.8 ± 31.8	114.7 ± 31.6		115.4 ± 32.3
HDL-C (mg/dL)						
n	201	745	2,011	1,821	(2) <0.001	1,201
Mean ± SD	56.6 ± 16.6	53.6 ± 14.5	50.5 ± 13.0	48.6 ± 12.6		52.1 ± 14.0
Non-HDL-C (mg/dL)						
n	117	437	1,194	1,122	(2) <0.001	785
Mean ± SD	132.2 ± 44.9	140.2 ± 49.9	144.9 ± 37.2	146.4 ± 38.7		146.8 ± 39.9
Triglycerides (mg/dL)						
n	205	777	2,094	1,875	(2) <0.001	1,323
Mean ± SD	149.7 ± 130.4	177.4 ± 204.1	198.6 ± 161.4	206.7 ± 185.4		195.9 ± 199.1
Uric acid (mg/dL)						
n	180	689	1,822	1,648	(2) <0.001	1,123
Mean ± SD	4.82 ± 1.28	5.00 ± 1.28	5.32 ± 1.26	5.62 ± 1.36		5.30 ± 1.38
Hematocrit (%)						
n	200	719	1,804	1,565	(2) <0.001	1,105
Mean ± SD	41.73 ± 4.56	42.45 ± 4.24	43.16 ± 4.05	43.50 ± 4.34		42.80 ± 4.45
AST (U/L)						
n	205	783	2,072	1,851	(2) <0.001	1,318
Mean ± SD	26.3 ± 18.8	24.7 ± 14.4	27.8 ± 16.4	35.2 ± 21.9		30.2 ± 21.6
ALT (U/L)						
n	206	785	2,105	1,878	(2) <0.001	1,334
Mean ± SD	25.2 ± 17.9	26.9 ± 19.8	35.4 ± 25.9	47.7 ± 34.6		36.4 ± 27.9
γ-GTP, male (U/L)						
n	125	456	1,213	991	(2) <0.001	727
Mean ± SD	66.6 ± 131.5	53.4 ± 60.6	63.7 ± 75.5	74.9 ± 81.3		69.6 ± 86.4

Table 1 (*Continued*)

	<22.0 kg/m^2 *n* (%)	22.0 to <25.0 kg/m^2 *n* (%)	25.0 to <30.0 kg/m^2 *n* (%)	≥30.0 kg/m^2 *n* (%)	*P*-value†	Unknown *n* (%)
γ-GTP, female (U/L)						
n	56	253	695	741	(2) <0.001	469
Mean ± SD	37.2 ± 37.6	36.0 ± 36.3	45.2 ± 45.8	49.2 ± 42.3		46.3 ± 69.0

γ-GTP, gamma-glutamyl transferase; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SD, standard deviation. †(1) χ^2-test and (2) one-way analysis of variance. ‡Some patients had more than one complication.

patients were stratified by BMI to investigate the impact of obesity on the efficacy and safety of ipragliflozin.

METHODS

A detailed description of the STELLA-LONG TERM study is available in the previous interim report[19]. In summary, the study population comprised all Japanese type 2 diabetes mellitus patients who were first prescribed ipragliflozin between 17 July 2014 and 16 October 2015 at any of the participating medical centers in Japan.

Ipragliflozin was prescribed and taken according to the specifications in the package insert. Thus, patients received a once-daily oral 50-mg dose before or after the first meal of the day. Attending physicians were free, after careful consideration, to prescribe lower doses for patients with severe hepatic impairment. They were also allowed to increase the dose (up to a maximum of 100 mg/day) if they deemed the treatment to be insufficiently effective. However, such cases necessitated careful monitoring of the clinical course of the individual patient.

Study design

The study was carried out in accordance with national guidelines for Good Post-marketing Study Practice. A full description of the study design is provided in the previous report[19]. The report also includes details of the data collected, including demographic and clinical characteristics, information on the use of other medications, laboratory test results, vital signs (i.e., blood pressure and heart rate) and safety data (i.e., adverse events). In this subgroup analysis, the efficacy and safety data at 3 months were analyzed according to the following BMI categories: <22.0, 22.0 to <25.0, 25.0 to <30.0 and ≥30.0 kg/m^2. These categories are based on the Japanese guidelines for the management of obesity, in which obesity is defined as having a BMI of 25.0 kg/m^2 or higher[20].

Efficacy outcome measures included changes in glycemic control (reflected by changes in HbA1c) and bodyweight from baseline to 3 months. The safety outcome was incidence of adverse drug reactions (ADRs). ADRs were coded and classified according to System Organ Class and Preferred Terms, as defined by the Medical Dictionary for Regulatory Activities (Japanese version; MedDRA/J), v19.1.

Statistical analysis

The initial report describes in detail the way in which the minimum sample size was calculated and the rationale for the duration of the study[18]. Of note, no sample size calculation was considered regarding the subgroup comparisons. Means ± standard deviations are presented for the efficacy variables, vital signs and laboratory test results. Categorical variables, such as baseline characteristics and ADRs, are presented in terms of the number and proportion of patients. Paired *t*-tests were used to determine the statistical significance of changes from baseline. Patient and treatment characteristics in different groups were compared by using the χ^2-test and the

one-way analysis of variance. The χ^2-test was used for comparisons of the incidence of ADRs in different groups. Additionally, Pearson's correlation coefficients were calculated to investigate relationships between changes in bodyweight and changes in HbA1c, waist circumference and BMI by BMI subgroup. No adjustments were carried out for type I error based on multiple hypothesis testing. SAS statistical software v9.2 (SAS Institute Inc., Cary, NC, USA) was used for the statistical analyses.

RESULTS

Patient disposition

Patient disposition is summarized in Figure 1. A total of 11,411 patients were initially registered in the STELLA-LONG TERM study, from 1,941 of the 2,431 institutions that had agreed to participate. By 3 months, report forms for 11,289 patients had been collected. Locked data for these patients were available for analysis, with the safety and efficacy analysis sets at 3 months comprising data from 11,053 and 8,633 patients, respectively. Figure 1 shows the reasons patients were excluded from each analysis set.

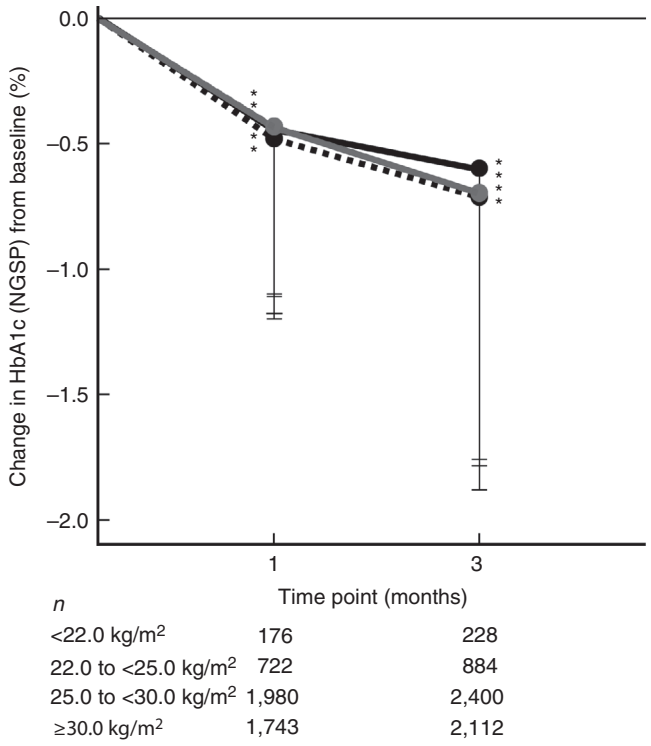
Patient characteristics

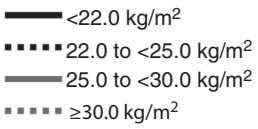
The general characteristics of patients in the safety and efficacy analysis sets are summarized in Tables 1 and S1, respectively. BMI data were missing for 4,022 of the 11,053 patients (36.4%) in the safety analysis set, and for 2,606 of the 8,633 patients (30.2%) in the efficacy analysis set.

Patients in the highest BMI subgroup (≥30.0 kg/m^2) were more likely than those in the other BMI subgroups (<30.0 kg/m^2) to be female (<22.0 kg/m^2, 37.7%; 22.0 to <25.0 kg/m^2, 37.8%; 25.0 to <30.0 kg/m^2, 36.9%; ≥30.0 kg/m^2, 41.9%), to be aged <65 years (49.3, 58.6, 72.6 and 86.9%, respectively), to have HbA1c ≥8% (37.7, 38.8, 42.2 and 45.5%, respectively) and to have a shorter duration of diabetes (10.086 ± 8.056, 9.373 ± 6.861, 8.251 ± 6.510 and 7.467 ± 5.951 years, respectively). Patients in the BMI subgroups ≥25.0 kg/m^2 were found to suffer more frequently from diabetic nephropathy, hypertension, dyslipidemia and hepatic impairment than those in the lower BMI subgroups (<25.0 kg/m^2).

Treatment characteristics

The treatments received at baseline and at 3 months by patients whose data comprised the safety and efficacy analysis sets are summarized in Tables S2 and S3, respectively. A higher numerical percentage of patients in the highest BMI subgroup (≥30.0 kg/m^2) than those in the other BMI subgroups (<30.0 kg/m^2) received concomitant antidiabetic drugs, although the difference was not statistically significant (<22.0 kg/m^2, 84.1%; 22.0 to <25.0 kg/m^2, 83.1%; 25.0 to <30.0 kg/m^2, 83.2%; ≥30.0 kg/m^2,





	1 month	3 months
<22.0 kg/m^2	−0.44 ± 0.76 (176)	−0.60 ± 1.18 (228)
22.0 to <25.0 kg/m^2	−0.46 ± 0.72 (722)	−0.72 ± 1.18 (884)
25.0 to <30.0 kg/m^2	−0.42 ± 0.69 (1,980)	−0.69 ± 1.09 (2,400)
≥30.0 kg/m^2	−0.42 ± 0.71 (1,743)	−0.69 ± 1.09 (2,112)

Mean ± SD (*n*)

Efficacy analysis set (*n* = 8,633)

Figure 2 | Changes in glycated hemoglobin (HbA1c) from baseline; National Glycohemoglobin Standardization Program (NGSP) units. Results are presented as the mean and the error bars indicate standard deviation. *$P < 0.05$ versus baseline (paired *t*-test).

85.2%). However, a statistically higher percentage ($P < 0.001$) of patients in the higher BMI subgroup (≥30.0 kg/m^2) received other concomitant drugs (excluding antidiabetics and diuretics; 66.9, 69.2, 72.6 and 76.5%, respectively).

Regarding the daily dose of ipragliflozin received by patients in each BMI subgroup, most patients (>80%) received a daily dose of 50 to <75 mg, approximately 9–17% of patients received <50 mg and <1% received 75 to ≤100 mg. Across all the BMI subgroups, the most frequently used concomitant drugs, other than antidiabetic and diuretic drugs, were statins and antihypertensive drugs.

Efficacy

The efficacy analysis set at 3 months comprised data from 8,633 patients. Significant improvements in glycemic control were apparent at 1 and 3 months of treatment in each of the BMI subgroups (all $P < 0.05$ by paired *t*-test; Figure 2). Bodyweight decreased significantly from baseline to 1 and 3 months of treatment in all BMI subgroups (all $P < 0.05$ by paired *t*-test; Figure S1). The percentage changes in bodyweight from baseline to 3 months were similar across the three higher BMI subgroups (−2.69% to −2.85% in the 22.0 to <25.0, 25.0 to <30.0 and ≥30.0 kg/m^2 subgroups), whereas it was smaller in the <22.0 kg/m^2 group (−1.69%; Figure 3). No strong correlations were identified between changes in bodyweight and changes in HbA1c, waist circumference, or BMI in any of the BMI subgroups (Table S4).

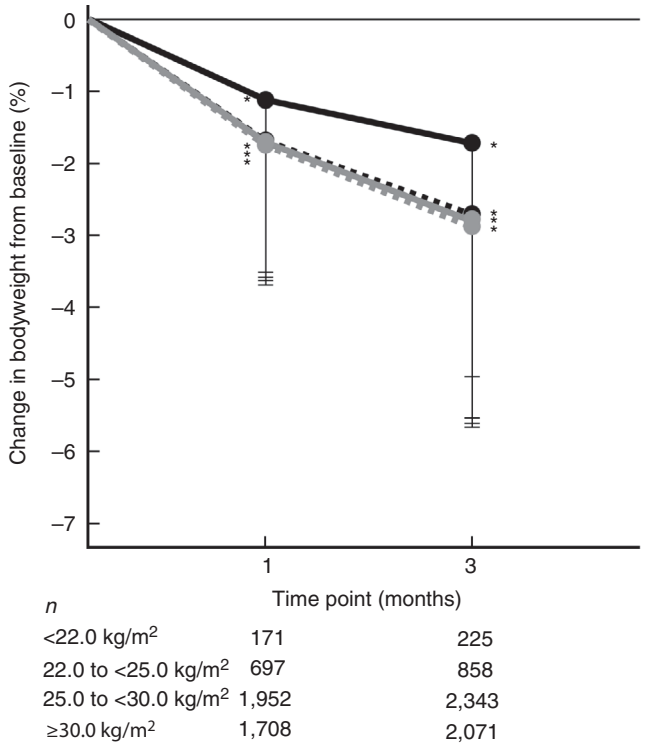
Safety

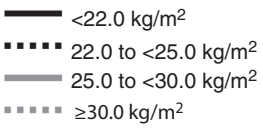
The incidence of ADRs in the 11,053 patients whose data were used in the safety analysis set is presented in Table 2. Incidence of ADRs increased with BMI (<22.0 kg/m^2, 6.29%; 22.0 to <25.0 kg/m^2, 8.44%; 25.0 to <30.0 kg/m^2, 11.18%; ≥30.0 kg/m^2, 11.74%; $P = 0.001$). The incidence of serious ADRs was low in all BMI subgroups (<1%).

Polyuria/pollakiuria was the most common ADR in all BMI subgroups (<22.0 kg/m^2, 2.65%; 22.0 to <25.0 kg/m^2, 3.64%; 25.0 to <30.0 kg/m^2, 5.37%; ≥30.0 kg/m^2, 6.33%). Genital and urinary tract infections, and volume depletion tended to be more frequent in the highest BMI subgroups (25.0 to <30.0 and ≥30.0 kg/m^2).

DISCUSSION

This subgroup analysis of data from the STELLA-LONG TERM study[19] was carried out to evaluate the impact of BMI on the efficacy and safety of ipragliflozin in Japanese type 2 diabetes mellitus patients under real-world conditions. The results pertaining to patient background characteristics showed that patients with higher BMI had less favorable glycemic control and lipid profile, as well as higher blood pressure, estimated





	1 month	3 months
<22.0 kg/m^2	−1.10 ± 2.39 (171)	−1.69 ± 3.26 (225)
22.0 to <25.0 kg/m^2	−1.66 ± 2.02 (697)	−2.69 ± 2.84 (858)
25.0 to <30.0 kg/m^2	−1.70 ± 1.94 (1,952)	−2.75 ± 2.86 (2,343)
≥30.0 kg/m^2	−1.71 ± 1.86 (1,708)	−2.85 ± 2.82 (2,071)

Mean ± SD (*n*)

Efficacy analysis set (*n* = 8,633)

Figure 3 | Percent change in bodyweight from baseline. Results are presented as the mean and the error bars indicate standard deviation. *$P < 0.05$ versus baseline (paired *t*-test).

Table 2 | Adverse drug reactions, serious adverse drug reactions and adverse drug reactions of special interest

	All (3 months)	<22.0 kg/m^2	22.0 to <25.0 kg/m^2	25.0 to <30.0 kg/m^2	≥30.0 kg/m^2	*P*-value (χ^2-test)	Unknown
Total (safety analysis set)	11,053 (100.0)	302 (100.0)	1,125 (100.0)	3,015 (100.0)	2,589 (100.0)	–	4,022 (100.0)
ADRs	1,074 (9.72)	19 (6.29)	95 (8.44)	337 (11.18)	304 (11.74)	0.001	319 (7.93)
Serious ADRs	47 (0.43)	2 (0.66)	5 (0.44)	10 (0.33)	7 (0.27)	–	23 (0.57)
ADRs of special interest							
Hypoglycemia	23 (0.21)	0 (0.00)	6 (0.53)	9 (0.30)	3 (0.12)	–	5 (0.12)
Genital infection	98 (0.89)	1 (0.33)	6 (0.53)	29 (0.96)	30 (1.16)	–	32 (0.80)
Urinary tract infection	67 (0.61)	0 (0.00)	5 (0.44)	16 (0.53)	21 (0.81)	–	25 (0.62)
Polyuria/pollakiuria	484 (4.38)	8 (2.65)	41 (3.64)	162 (5.37)	164 (6.33)	–	109 (2.71)
Volume depletion	125 (1.13)	1 (0.33)	10 (0.89)	47 (1.56)	34 (1.31)	–	33 (0.82)
Renal disorder	63 (0.57)	0 (0.00)	5 (0.44)	24 (0.80)	15 (0.58)	–	19 (0.47)
Hepatic disorder	38 (0.34)	1 (0.33)	5 (0.44)	12 (0.40)	13 (0.50)	–	7 (0.17)
Fracture	1 (0.01)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.04)	–	0 (0.00)
Malignant tumor	2 (0.02)	0 (0.00)	0 (0.00)	1 (0.03)	0 (0.00)	–	1 (0.02)
Cardiovascular disease	9 (0.08)	0 (0.00)	0 (0.00)	6 (0.20)	3 (0.12)	–	0 (0.00)
Cerebrovascular disease	11 (0.10)	0 (0.00)	3 (0.27)	5 (0.17)	0 (0.00)	–	3 (0.07)
Skin complications	115 (1.04)	0 (0.00)	8 (0.71)	28 (0.93)	18 (0.70)	–	61 (1.52)
Ketone body-related events	3 (0.03)	0 (0.00)	1 (0.09)	2 (0.07)	0 (0.00)	–	0 (0.00)

Data are presented as *n* (%). ADRs, adverse drug reactions.

glomerular filtration rate, hematocrit and uric acid, than patients with lower BMI, although the clinical significance of differences in the latter three factors remains unclear. Notably, patients with a higher BMI tended to be younger, female and have shorter disease duration than patients with lower BMI. Patients with a higher BMI were receiving a higher dose of ipragliflozin than patients with lower BMI.

In terms of efficacy, HbA1c and bodyweight significantly decreased with ipragliflozin treatment ($P < 0.05$) in all BMI subgroups. The percentage change in bodyweight was similar in the three higher BMI subgroups, whereas it was slightly smaller in the lowest BMI subgroup. Furthermore, there was no obvious correlation between the changes in bodyweight and the changes in HbA1c in all BMI subgroups. Ferrannini *et al.* reported that a lower bodyweight reduction, in terms of percentage change, was observed in patients with lower BMI. They suggested that patients with lower BMI increase their food intake to make up for the loss of bodyweight induced by diet or bariatric surgery[21]. In real-world clinical practice, type 2 diabetes mellitus patients with BMI ≥30 kg/m^2 tend to have increased appetite and experience relatively small reductions in body weight; however, these patients still show a decrease in HbA1c as a result of pharmacotherapy. The results of the present subgroup analysis are consistent with what is observed in clinical practice, in that a significant reduction in HbA1c was shown with ipragliflozin treatment in patients with BMI ≥30 kg/m^2. Although we did not identify a strong correlation between bodyweight reduction and improvement in HbA1c in the present study, such a correlation has been reported previously for another SGLT2 inhibitor, tofogliflozin[22]. In that study, patients were divided into tertiles according to baseline insulin levels, and a correlation between improvement in glucose control and reduction in bodyweight was observed, but only in the tertile with the highest fasting insulin level. As the current study did not stratify patients according to baseline insulin levels, it is difficult to make a definitive conclusion on the relationship between bodyweight reduction and improvements in HbA1c in the case of ipragliflozin.

In terms of safety, the overall incidence of ADRs increased as BMI increased. The most frequent ADR was polyuria/pollakiuria, with a higher incidence in the higher BMI subgroups compared with the lower BMI subgroups. A possible reason for this finding might be an association with age, because those with higher BMI tended to be younger than those with lower BMI in the present subgroup analysis. In another subgroup analysis of elderly versus non-elderly patients[23], polyuria/pollakiuria was more frequently observed in non-elderly versus elderly patients. This might have been due to reduced water intake in the elderly patients[24].

Genital and urinary tract infection also tended to be more frequent in the higher BMI subgroups than in the lower BMI subgroups. A clear relationship between obesity and immune response to infections has not been established. Nassaji *et al.*[25] found no association between BMI and urinary tract infection

in adult patients, including those with diabetes mellitus. However, further studies are warranted to elucidate the relationship between BMI and different types of infection.

The present study had several limitations. First, incorrect completion of report forms might have introduced bias. Second, BMI data were unavailable for 4,022 patients in the safety analysis set and 2,606 patients in the efficacy analysis set. Third, the lack of a control group precludes comparisons with placebo or comparator. Fourth, only data up to 3 months were included in the present analysis. In the future, we plan to carry out further analyses to obtain a clearer picture of long-term effectiveness and safety of ipragliflozin according to BMI. Finally, the present study population was limited to Japanese patients, which limits the generalizability of the results. Although there are limited data for ipragliflozin outside of Asia, the effects of other SGLT2 inhibitors (e.g., canagliflozin) have been studied in detail. For example, a recent review by Inagaki *et al.*[26] concluded that canagliflozin had similar efficacy and safety profiles in Japanese and non-Japanese patients. The international comparative effectiveness of cardiovascular outcomes in new users of sodium-glucose cotransporter-2 inhibitors (CVD-REAL) 2 Study focused on cardiovascular risk associated with SGLT2 inhibitors and found no differences in cardiovascular risk according to patient ethnic or racial background, suggesting a possible class effect[27].

In conclusion, patients with higher BMI had less favorable baseline characteristics, including in terms of HbA1c, lipid profile and blood pressure, compared with patients with lower BMI. The overall incidence of ADRs was higher in patients with higher BMI than in those with lower BMI. Ipragliflozin was effective in Japanese patients with type 2 diabetes mellitus in terms of glycemic control and bodyweight reduction, regardless of their BMI.

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SUPPORTING INFORMATION

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

Figure S1 | Changes in bodyweight (kg) from baseline.
Table S1 | Patient characteristics at baseline (efficacy analysis set).
Table S2 | Treatments used at baseline and/or during the 3-month survey period (safety analysis set).
Table S3 | Treatments used at baseline and/or during the 3-month survey period (efficacy analysis set).
Table S4 | Correlation between changes in bodyweight and changes in glycated hemoglobin, waist circumference and body mass index at 3 months.