Endocrine Journal 2018, **65** (7), 693-705

ORIGINAL

Improved cardiometabolic risk factors in Japanese patients with type 2 diabetes treated with ipragliflozin: a pooled analysis of six randomized, placebo-controlled trials

Atsunori Kashiwagi[1)], Taishi Sakatani[2)], Ichiro Nakamura[2)], Noriko Akiyama[2)], Kenichi Kazuta[2)], Eiji Ueyama[2)], Hideyuki Takahashi[2)] and Yoshinori Kosakai[2)]

[1)] *Kusatsu General Hospital, Kusatsu, Shiga 525-8585, Japan*
[2)] *Astellas Pharma Inc., Chuo-ku, Tokyo 103-8411, Japan*

Abstract. To examine differential improvements among cardiovascular risk factors in response to treatment with ipragliflozin in Japanese type 2 diabetes mellitus (T2DM) patients, we conducted a pooled analysis of six randomized, double-blind trials of Japanese T2DM patients who received ipragliflozin 50 mg/day or placebo and had patient-level data for cardiometabolic risk parameters. Risk factors included glycated hemoglobin (HbA1c), body weight, homeostatic model assessment for insulin resistance and beta-cell function (HOMA-R and HOMA-beta, respectively), systolic blood pressure, fasting serum insulin concentrations, and the concentration of uric acid, lipids, and liver enzymes from baseline to end of treatment (EOT; 12–24 weeks). The primary endpoint of each trial was the change in HbA1c from baseline to EOT. Changes in risk factors from baseline to EOT were compared between ipragliflozin-treated and placebo groups, and between two subgroups (high- and low-risk groups for each parameter). All parameters, except low-density lipoprotein cholesterol (LDL-C) and non high-density lipoprotein cholesterol (non HDL-C), improved significantly in the ipragliflozin group. Subgroup analysis revealed a significantly greater improvement in the high-risk group *versus* low-risk group in HbA1c, HOMA-R, HOMA-beta, aspartate transaminase, alanine transaminase, and gamma-glutamyltransferase, but not in any of the lipid parameters or blood pressure. Liver function improvement in the ipragliflozin group was significantly correlated with changes in body weight, HbA1c, HOMA-beta, and HOMA-R. This analysis demonstrated that, in Japanese T2DM patients, ipragliflozin 50 mg/day was associated with improvements in cardiometabolic risk factors, except for LDL-C and non HDL-C.

Key words: Ipragliflozin, Cardiometabolic risk factors, Type 2 diabetes mellitus, Pooled analysis, Liver function

DIABETES MELLITUS is generally accepted as a major risk factor for cardiovascular disease (CVD), and patients with type 2 diabetes mellitus (T2DM) have a higher frequency of cardiovascular morbidity and mortality compared with non-diabetics [1]. Moreover, the risk of cardiovascular disease in diabetes patients is reported to be higher in Asia than in Europe [2].

Patients with T2DM also have an increased risk of liver function abnormalities, such as those seen in non-alcoholic fatty liver disease (NAFLD), because of the high prevalence of obesity and increased insulin resistance, which are closely associated with the progression of fatty liver disease [3]. Furthermore, NAFLD is associated with an increased risk of mortality from CVD [4]. Therefore, effective treatment of T2DM is important to reduce the risk factors for cardiovascular morbidity and mortality and the risk of liver function abnormalities as a marker for risk reduction in this patient population.

Sodium–glucose co-transporter 2 (SGLT2) inhibitors reduce the plasma glucose concentration by increasing renal glucose elimination and inhibiting renal glucose reabsorption [5, 6], as SGLT2 is predominantly distributed on the luminal surface of cells in the S1 segment of the renal proximal tubules [6]. Many clinical trials have shown that SGLT2 inhibitors improve glycemic control

Submitted Nov. 16, 2017; Accepted Mar. 29, 2018 as EJ17-0491
Released online in J-STAGE as advance publication May 29, 2018
Correspondence to: Atsunori Kashiwagi, MD, PhD, Kusatsu General Hospital, 1660 Yabase-cho, Kusatsu, Shiga 525-8585, Japan.
E-mail: kashiwagi@kusatsu-gh.or.jp

while avoiding hypoglycemia and promoting weight loss and blood pressure reduction [7, 8].

Empagliflozin, a selective SGLT2 inhibitor, was reported to reduce the risk of cardiovascular outcomes and mortality in a randomized, double-blind, placebo-controlled trial conducted in T2DM patients with a high cardiovascular risk from 42 countries [9] as well as in a sub-analysis of Asian patients [10]. Similarly, in the CANVAS and CANVAS-R trials, patients treated with canagliflozin, another SGLT2 inhibitor, had a lower risk of cardiovascular events than those who received placebo [11]. The CVD-REAL study showed that T2DM patients who received SGLT2 inhibitors had a lower risk of heart failure and death compared with those who received other glucose-lowering drugs [12]. Therefore, improvement in cardiovascular risk may be expected in patients treated with SGLT2 inhibitors.

Ipragliflozin is an orally bioavailable and selective SGLT2 inhibitor that was approved for the treatment of T2DM in Japan in 2014 [13]. However, limited and fragmentary evidence is available regarding the effects of ipragliflozin on cardiometabolic risk factors [14, 15]. Thus, the objective of this pooled analysis was to examine the impact of ipragliflozin treatment on the improvement of cardiometabolic risk factors in Japanese patients with T2DM, and to determine whether high-risk patients had greater risk reductions compared with low-risk patients.

Materials and Methods

Study design

We performed a pooled analysis of six Japanese phase II and III randomized controlled trials in which patients with T2DM received ipragliflozin or placebo. The trials were identified *via* a search of previously conducted clinical trials of ipragliflozin in Japanese patients with T2DM that had patient-level data on cardiometabolic parameters. The six trials identified and included in this pooled analysis were as follows (details given as trial reference number, Clinical Trials.gov identifier): a phase II dose-finding trial (CL0103, NCT00621868) [16]; a phase III trial in patients with renal impairment (CL0072, NCT01316094) [17]; a phase III monotherapy trial (CL0105, NCT01057628) [18]; a phase III trial in combination with metformin (CL0106, NCT01135433) [19]; a phase III trial in combination with pioglitazone (CL0107, NCT01225081) [20]; and a phase III trial in combination with a sulfonylurea (CL0109, NCT01242215) [21]. Details of the six studies included in the present pooled analysis have been described previously [14, 15].

All the clinical trials included a 4-week screening period, a 2-week placebo run-in period, a specified treatment phase that ranged between 12 and 24 weeks, and a follow-up phase of 4–6 weeks after completing treatment. Study CL0106 included a 6-week washout period, and studies CL0107 and CL0109 included a 4-week washout period in which previously used antidiabetic drugs were washed out, except for the specified combination drug, before the screening period. In studies CL0103 and CL0105, previously used antidiabetic drugs were eliminated in the screening period. In study CL0072, patients who had used α-glucosidase inhibitor, sulfonylurea, or pioglitazone for ≥12 weeks before enrolment could continue using it throughout the treatment period; changes in the regimen or switching to an alternative drug were prohibited. The primary endpoint of each trial was the change in glycated hemoglobin (HbA1c) from baseline to the end of treatment (EOT). HbA1c was measured according to the requirements of the Japan Diabetes Society, and units were converted to National Glycohemoglobin Standardization Program values [22]. Only randomized, double-blind, placebo-controlled trials in which ipragliflozin was administered at a dose of 50 mg/day were included in this pooled analysis.

Patients

Patients aged ≥20 years who were diagnosed with T2DM ≥12 weeks before screening/washout, and who had an HbA1c ≥7.4% (57 mmol/mol), a body mass index (BMI) ≥20 kg/m^2, creatinine levels within the normal range, and a urinary microalbumin/urinary creatinine ratio <300 mg/g were eligible for the trials. For study CL0072, patients had to have an HbA1c ≥6.9% to be eligible, and additional criteria included the presence of mild (estimated glomerular filtration rate [eGFR] ≥60 to <90 mL/min/1.73 m^2) or moderate (eGFR ≥30 to <60 mL/min/1.73 m^2) renal impairment.

All trials were performed in accordance with Good Clinical Practice, International Conference on Harmonisation guidelines, applicable laws and regulations, and with the approval of the institutional review boards of the participating institutions. All included studies required participants to provide written informed consent before enrolment.

Procedures

For the pooled analysis, patients were divided into two subgroups according to the median value of their cardiometabolic risk factors (high- and low-risk groups for each parameter). The changes in variables from baseline to EOT in the double-blind period of the clinical trials were compared between the ipragliflozin and placebo groups in each subgroup. Comparisons were made between the ipragliflozin and placebo groups in each low- and high-risk subgroup, and an interaction test was performed to show if there was any difference in treatment effect between high- and low-risk groups. Additionally, analyses were performed to identify correlations among parameters.

Statistical analysis

For the present pooled analysis, the change from baseline to EOT values was compared between the ipragliflozin and placebo groups. The pooled analyses were conducted using patient-level cardiometabolic data from the full analysis set (efficacy parameters: HbA1c, body weight, fasting serum insulin [FSI], homeostatic model assessment for insulin resistance [HOMA-R], and homeostatic model assessment for beta-cell function [HOMA-beta]), and from the safety analysis set (safety parameters: systolic blood pressure [SBP] and the serum concentrations of uric acid, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], non HDL-C, triglycerides [TG], aspartate transaminase [AST], alanine transaminase [ALT], and gamma-glutamyltransferase [gamma-GTP]).

The full analysis set consisted of all patients who received at least one dose of ipragliflozin/placebo and had at least one efficacy variable measured after dosing in each trial. The safety analysis set consisted of all patients who received at least one dose of ipragliflozin/placebo in each trial.

Subgroup analyses were conducted by dividing patients into low- and high-risk groups according to the values of each of the following parameters: HbA1c (<8% *versus* ≥8%), body weight (<70 kg *versus* ≥70 kg), FSI (<6 uU/mL *versus* ≥6 uU/mL), HOMA-R (<2.5 *versus* ≥2.5), HOMA-beta (<20% *versus* ≥20%), and SBP (<130 mmHg *versus* ≥130 mmHg), and the serum concentrations of uric acid (<5 mg/dL *versus* ≥5 mg/dL), LDL-C (<120 mg/dL *versus* ≥120 mg/dL), HDL-C (≥50 mg/dL *versus* <50 mg/dL), TG (<120 mg/dL *versus* ≥120 mg/dL), non HDL-C (<140 mg/dL *versus* ≥140 mg/dL), AST (<25 IU/L *versus* ≥25 IU/L), ALT (<25 IU/L *versus* ≥25 IU/L), and gamma-GTP (<30 IU/L *versus* ≥30 IU/L). The cut-off values for all parameters were selected as values close to the median value for each variable.

Descriptive statistics (mean ± standard deviation [SD], and number [proportion, %]) were calculated for the baseline characteristics of all patients combined. The changes from baseline to EOT were assessed overall and for each subgroup by analysis of covariance in which the treatment group and clinical trial were included as fixed effects and the baseline value was included as a covariate. The results are presented as the placebo-adjusted mean difference with 95% confidence intervals (CI). A p-value <0.05 was considered statistically significant.

The differences in treatment effect between high- and low-risk groups were also assessed by the interaction test with analysis of variance in which the treatment group, clinical trial, and the interaction between the treatment group and clinical trial were included as fixed effects. When evaluating changes in ALT from baseline to EOT according to high- and low-HOMA-R and HOMA-beta groups, the following analysis of covariance (ANCOVA) models were used: an ANCOVA model with treatment group and study as fixed effects and baseline ALT value as a covariate in each subgroup, and an ANCOVA model with treatment group, study, baseline HOMA-R/HOMA-beta category, and treatment group × baseline HOMA-R/HOMA-beta category as fixed effects, and baseline ALT value as a covariate.

The correlation between liver function and other parameters was assessed using a partial correlation coefficient adjusted for study and its p-value. All statistical analyses were performed using SAS Drug Development (version 3.4 or 4.5; SAS Institute Inc., Cary, NC, USA) and PC-SAS (version 9.1.3 or 9.4; SAS Institute Inc.).

Results

Among the clinical trials included in the pooled analysis, 628 and 368 patients were treated with ipragliflozin 50 mg/day or placebo, respectively. A summary of the characteristics of the patients in each group is shown in Table 1. The mean age of the patients in the ipragliflozin and placebo groups was 59.0 and 58.5 years, respectively. There were no clinically significant differences in baseline characteristics between the two groups, although BMI (p = 0.007), eGFR (p = 0.009), FSI (p = 0.024), AST (p = 0.004), ALT (p = 0.031), and uric acid (p = 0.018) were significantly different between the two groups.

Table 1 Patient characteristics

	Placebo (n = 368)	Ipragliflozin 50 mg (n = 628)	p-value[a]
Sex			0.833
Male	250 (67.9)	431 (68.6)	
Female	118 (32.1)	197 (31.4)	
Age (at consent), years	58.5 ± 10.1	59.0 ± 10.1	0.486
BMI, kg/m^2	25.33 ± 3.60	25.98 ± 3.73	0.007*
Diabetes duration, months	95.7 ± 73.5 (363)	100.0 ± 80.8 (621)	0.403
eGFR (at baseline), mL/min/1.73 m^2	86.50 ± 19.47	83.01 ± 20.86	0.009*
HbA1c, %	8.24 ± 0.75 (367)	8.17 ± 0.75 (626)	0.157
Body weight (at baseline), kg	67.6 ± 12.4 (367)	69.0 ± 12.6 (626)	0.082
FSI, uU/mL	6.90 ± 5.06 (367)	7.64 ± 4.98 (626)	0.024*
HOMA-R	2.93 ± 2.20 (367)	3.18 ± 2.28 (626)	0.086
HOMA-beta, %	25.9 ± 28.5 (367)	29.1 ± 24.3 (626)	0.056
SBP, mmHg	128.7 ± 13.6	130.0 ± 13.7	0.158
Uric acid, mg/dL	4.77 ± 1.29	4.97 ± 1.32	0.018*
LDL-C, mg/dL	123.1 ± 32.1	119.3 ± 31.5	0.067
HDL-C, mg/dL	56.5 ± 14.0	56.8 ± 16.4	0.736
TG, mg/dL	145.6 ± 107.6	153.8 ± 108.6	0.244
Non HDL-C, mg/dL	145.4 ± 34.3	141.8 ± 34.7	0.114
AST, IU/L	24.1 ± 8.9	25.9 ± 10.2	0.004*
ALT, IU/L	26.4 ± 13.9	28.6 ± 16.2	0.031*
gamma-GTP, IU/L	45.5 ± 46.1	49.2 ± 50.1	0.239

Values are presented as n (%) or the mean ± standard deviation. Where the number of patients differed from the number of patients in the full analysis set, the number is given in parentheses.

[a] Values were compared between the ipragliflozin and placebo groups using Fisher's exact test for categorical variables or independent-samples t-tests for continuous variables.

* $p < 0.05$

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; eGFR, estimated glomerular filtration rate; FSI, fasting serum insulin; gamma-GTP, gamma-glutamyltransferase; HDL-C, high-density lipoprotein cholesterol; HbA1c, glycated hemoglobin; HOMA-beta, homeostatic model assessment for beta-cell function; HOMA-R, homeostatic model assessment for insulin resistance; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides.

A comparison of the change in various cardiometabolic parameters in the overall population is shown in Table 2. In general, all parameters except for LDL-C and non HDL-C improved significantly in the ipragliflozin group *versus* the placebo group. The adjusted mean difference in HbA1c between patients receiving placebo and ipragliflozin was –1.04% (95% CI, –1.133% to –0.941%, $p < 0.001$).

A comparison of the change in various cardiometabolic parameters stratified by low- and high-risk group is shown in Table 3. When comparing placebo and ipragliflozin groups in each low- and high-risk group, a significant improvement was found in HbA1c, body weight, FSI, HOMA-R, HOMA-beta, SBP, uric acid, HDL-C, AST, and ALT with ipragliflozin treatment *versus* placebo. However, LDL-C (in both risk groups), non HDL-C (in both risk groups), gamma-GTP (in the low-risk group), and TG (in the high-risk group) were not significantly improved with ipragliflozin treatment *versus* placebo. The results of the interaction test between the

Table 2 Changes in all parameters from baseline to end of treatment in all patients

	Placebo (n = 368)	Ipragliflozin (n = 628)
HbA1c (%)		
Baseline/EOT	8.24 ± 0.747 (367) / 8.56 ± 1.206 (367)	8.17 ± 0.755 (626) / 7.45 ± 0.740 (625)
Change	0.33 ± 0.898 (367)	–0.72 ± 0.654 (625)
AMD (95% CI)	–1.04 (–1.133, –0.941), $p < 0.001$	
Body weight (kg)		
Baseline/EOT	67.56 ± 12.35 (367) / 67.10 ± 12.46 (367)	68.99 ± 12.64 (626) / 66.82 ± 12.47 (626)
Change	–0.46 ± 1.84 (367)	–2.17 ± 1.87 (626)
AMD (95% CI)	–1.70 (–1.944, –1.463), $p < 0.001$	
FSI (uU/mL)		
Baseline/EOT	6.90 ± 5.059 (367) / 6.44 ± 4.151 (367)	7.64 ± 4.977 (626) / 6.21 ± 4.417 (626)
Change	–0.46 ± 3.914 (367)	–1.43 ± 3.438 (626)
AMD (95% CI)	–0.63 (–1.032, –0.230), $p = 0.002$	
HOMA-R		
Baseline/EOT	2.93 ± 2.198 (367) / 2.85 ± 2.176 (366)	3.18 ± 2.280 (626) / 2.12 ± 1.617 (626)
Change	–0.08 ± 2.067 (366)	–1.06 ± 1.871 (626)
AMD (95% CI)	–0.82 (–1.020, –0.619), $p < 0.001$	
HOMA-beta (%)		
Baseline/EOT	25.9 ± 28.47 (367) / 23.5 ± 25.92 (366)	29.1 ± 24.28 (626) / 32.7 ± 26.35 (626)
Change	–2.4 ± 14.32 (366)	3.6 ± 13.87 (626)
AMD (95% CI)	6.7 (4.90, 8.45), $p < 0.001$	
SBP (mmHg)		
Baseline/EOT	128.7 ± 13.6 / 128.1 ± 13.3 (367)	130.0 ± 13.7 / 125.8 ± 13.7 (626)
Change	–0.7 ± 12.8 (367)	–4.1 ± 13.8 (626)
AMD (95% CI)	–2.8 (–4.4, –1.3), $p < 0.001$	
Uric acid (mg/dL)		
Baseline/EOT	4.77 ± 1.286 / 4.76 ± 1.373 (367)	4.97 ± 1.317 / 4.75 ± 1.285 (626)
Change	–0.01 ± 0.697 (367)	–0.23 ± 0.818 (626)
AMD (95% CI)	–0.19 (–0.28, –0.09), $p < 0.001$	
LDL-C (mg/dL)		
Baseline/EOT	123.1 ± 32.05 / 121.7 ± 31.23 (367)	119.3 ± 31.49 / 118.8 ± 30.45 (626)
Change	–1.4 ± 21.79 (367)	–0.5 ± 24.00 (626)
AMD (95% CI)	0.4 (–2.4, 3.1), $p = 0.799$	
HDL-C (mg/dL)		
Baseline/EOT	56.5 ± 13.97 / 57.3 ± 15.06 (367)	56.8 ± 16.39 / 61.0 ± 17.40 (626)
Change	0.8 ± 8.15 (367)	4.1 ± 8.84 (626)
AMD (95% CI)	3.1 (2.0, 4.2), $p < 0.001$	
TG (mg/dL)		
Baseline/EOT	145.6 ± 107.57 / 146.9 ± 131.30 (367)	153.8 ± 108.55 / 135.0 ± 99.73 (626)
Change	1.2 ± 105.74 (367)	–18.9 ± 96.92 (626)
AMD (95% CI)	–15.2 (–27.1, –3.3), $p = 0.013$	

Table 2 Cont.

	Placebo (n = 368)	Ipragliflozin (n = 628)
Non HDL-C (mg/dL)		
Baseline/EOT	145.4 ± 34.34 / 142.9 ± 34.13 (367)	141.8 ± 34.72 / 138.2 ± 33.90 (626)
Change	–2.5 ± 22.14 (367)	–3.6 ± 25.06 (626)
AMD (95% CI)	–1.2 (–4.1, 1.6), p = 0.398	
AST (IU/L)		
Baseline/EOT	24.1 ± 8.94 / 25.7 ± 12.73 (367)	25.9 ± 10.21 / 23.9 ± 8.40 (626)
Change	1.6 ± 9.03 (367)	–2.1 ± 7.92 (626)
AMD (95% CI)	–3.2 (–4.2, –2.2), p < 0.001	
ALT (IU/L)		
Baseline/EOT	26.4 ± 13.91 / 27.4 ± 16.34 (367)	28.6 ± 16.19 / 23.4 ± 11.48 (626)
Change	0.9 ± 9.35 (367)	–5.2 ± 11.20 (626)
AMD (95% CI)	–5.5 (–6.6, –4.3), p < 0.001	
gamma-GTP (IU/L)		
Baseline/EOT	45.5 ± 46.08 / 45.6 ± 43.93 (367)	49.2 ± 50.06 / 39.6 ± 38.09 (626)
Change	0.1 ± 22.78 (367)	–9.7 ± 25.19 (626)
AMD (95% CI)	–8.9 (–11.5, –6.3), p < 0.001	

Values are presented as the mean ± standard deviation. Where the number of patients differed from the number of patients in the full analysis set, the number is given in parentheses.

Abbreviations: ALT, alanine transaminase; AMD, adjusted mean difference; AST, aspartate transaminase; CI, confidence interval; EOT, end of treatment; FSI, fasting serum insulin; gamma-GTP, gamma-glutamyltransferase; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-beta, homeostatic model assessment for beta-cell function; HOMA-R, homeostatic model assessment for insulin resistance; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides.

low- and high-risk groups for each parameter showed significant improvements in HbA1c (p < 0.0001), HOMA-R (p = 0.0003), HOMA-beta (p = 0.0159), AST (p < 0.0001), ALT (p < 0.0001), and gamma-GTP (p < 0.0001) in the high-risk group compared with the low-risk group. However, there were no significant differences in the changes in body weight, FSI, SBP, uric acid, LDL-C, HDL-C, TG, or non HDL-C between the high- and low-risk groups.

To identify the factors associated with improvement in liver function, we analyzed the association of changes in HbA1c, body weight, HOMA-R, and HOMA-beta with changes in liver function (ALT). The changes in HbA1c (r = 0.178, p < 0.001), body weight (r = 0.127, p = 0.001), HOMA-R (r = 0.096, p = 0.017), and HOMA-beta (r = –0.207, p < 0.001) were significantly correlated with the changes in liver function (ALT) among patients in the ipragliflozin group (Fig. 1A–D). For baseline ALT, a significant negative correlation (r = –0.699, p < 0.001) was observed between baseline ALT and the changes in ALT from baseline to EOT in the ipragliflozin group (Fig. 2). In the placebo group, no correlations were observed except for that between body weight and changes in liver function (ALT) (r = 0.144, p = 0.006) (Figs. 1A–D and 2). Furthermore, when comparing the change in ALT from baseline to EOT between placebo and ipragliflozin-treated patients according to low-HOMA-R and high-HOMA-R groups, a significant improvement (p < 0.001) was found among ipragliflozin-treated patients in both the low-HOMA-R and high-HOMA-R groups (Table 4). The interaction test of change in ALT with ipragliflozin treatment in the low- and high-HOMA-R groups showed a significantly greater improvement (p < 0.001) in the high HOMA-R group compared with the low-HOMA-R-group (Table 4). Similarly, changes in AST (r = 0.131, p = 0.001) and gamma-GTP (r = 0.149, p < 0.001) also correlated with a decrease in HbA1c in the ipragliflozin group. Changes in TG levels were also weakly associated with ALT (r = 0.091, p = 0.023), AST (r = 0.098, p = 0.014), and gamma-GTP (r = 0.125, p = 0.002) in the ipragliflozin group.

Table 3 Changes in all parameters from baseline to end of treatment according to risk group (low- and high-risk groups)

	Low-risk		High-risk	
HbA1c (%)	<8%		≥8%	
	Placebo (*n* = 152)	Ipragliflozin (*n* = 270)	Placebo (*n* = 215)	Ipragliflozin (*n* = 356)
Baseline/EOT	7.56 ± 0.259 / 7.81 ± 0.765	7.51 ± 0.305 / 7.06 ± 0.477	8.72 ± 0.586 / 9.10 ± 1.176	8.67 ± 0.591 / 7.75 ± 0.766
Change	0.25 ± 0.666	–0.45 ± 0.457	0.38 ± 1.030	–0.92 ± 0.705
AMD (95% CI)	–0.71 (–0.815, –0.597), $p < 0.001$		–1.28 (–1.425, –1.139), $p < 0.001$	
Interaction test	$p < 0.0001$			
Body weight (kg)	<70 kg		≥70 kg	
	Placebo (*n* = 234)	Ipragliflozin (*n* = 362)	Placebo (*n* = 133)	Ipragliflozin (*n* = 264)
Baseline/EOT	60.18 ± 6.39 / 59.77 ± 6.70	60.50 ± 6.39 / 58.52 ± 6.51	80.56 ± 9.15 / 79.99 ± 9.40	80.65 ± 9.38 / 78.21 ± 9.27
Change	–0.40 ± 1.67	–1.98 ± 1.65	–0.57 ± 2.11	–2.43 ± 2.12
AMD (95% CI)	–1.56 (–1.835, –1.288), $p < 0.001$		–2.00 (–2.454, –1.552), $p < 0.001$	
Interaction test	$p = 0.1812$			
FSI (uU/mL)	<6 uU/mL		≥6 uU/mL	
	Placebo (*n* = 185)	Ipragliflozin (*n* = 288)	Placebo (*n* = 182)	Ipragliflozin (*n* = 338)
Baseline/EOT	3.76 ± 1.230 / 3.94 ± 1.728	3.98 ± 1.249 / 3.70 ± 1.787	10.09 ± 5.468 / 8.98 ± 4.356	10.76 ± 4.834 / 8.35 ± 4.843
Change	0.19 ± 1.427	–0.28 ± 1.487	–1.11 ± 5.297	–2.41 ± 4.236
AMD (95% CI)	–0.40 (–0.676, –0.128), $p = 0.004$		–0.90 (–1.612, –0.183), $p = 0.014$	
Interaction test	$p = 0.0641$			
HOMA-R	<2.5		≥2.5	
	Placebo (*n* = 196)	Ipragliflozin (*n* = 301)	Placebo (*n* = 171)	Ipragliflozin (*n* = 325)
Baseline/EOT	1.60 ± 0.549 / 1.80 ± 1.008	1.61 ± 0.551 / 1.33 ± 0.807	4.46 ± 2.377 / 4.05 ± 2.514	4.64 ± 2.311 / 2.86 ± 1.822
Change	0.20 ± 0.853	–0.28 ± 0.722	–0.40 ± 2.861	–1.78 ± 2.276
AMD (95% CI)	–0.47 (–0.611, –0.329), $p < 0.001$		–1.22 (–1.585, –0.850), $p < 0.001$	
Interaction test	$p = 0.0003$			
HOMA-beta (%)	<20%		≥20%	
	Placebo (*n* = 182)	Ipragliflozin (*n* = 244)	Placebo (*n* = 185)	Ipragliflozin (*n* = 382)
Baseline/EOT	12.3 ± 4.32 / 12.7 ± 6.45	12.5 ± 4.17 / 16.9 ± 9.02	39.3 ± 35.06 / 34.1 ± 32.61	39.7 ± 25.83 / 42.8 ± 28.71
Change	0.4 ± 5.34	4.4 ± 7.78	–5.2 ± 19.06	3.1 ± 16.62
AMD (95% CI)	4.0 (2.69, 5.37), $p < 0.001$		8.7 (5.67, 11.66), $p < 0.001$	
Interaction test	$p = 0.0159$			
SBP (mmHg)	<130 mmHg		≥130 mmHg	
	Placebo (*n* = 186)	Ipragliflozin (*n* = 288)	Placebo (*n* = 182)	Ipragliflozin (*n* = 340)
Baseline/EOT	118.0 ± 7.7 / 122.2 ± 12.2	118.3 ± 7.6 / 119.9 ± 11.7	139.7 ± 8.7 / 134.0 ± 11.6	139.9 ± 8.9 / 130.8 ± 13.4
Change	4.1 ± 12.2	1.7 ± 11.0	–5.7 ± 11.5	–9.1 ± 14.0
AMD (95% CI)	–2.6 (–4.7, –0.5), $p = 0.013$		–3.2 (–5.4, –0.9), $p = 0.006$	
Interaction test	$p = 0.5095$			
Uric acid (mg/dL)	<5 mg/dL		≥5 mg/dL	
	Placebo (*n* = 209)	Ipragliflozin (*n* = 326)	Placebo (*n* = 159)	Ipragliflozin (*n* = 302)
Baseline/EOT	3.87 ± 0.76 / 3.94 ± 0.97	3.97 ± 0.70 / 3.92 ± 0.84	5.95 ± 0.77 / 5.84 ± 1.04	6.05 ± 0.91 / 5.64 ± 1.06
Change	0.07 ± 0.60	–0.05 ± 0.64	–0.12 ± 0.80	–0.42 ± 0.94
AMD (95% CI)	–0.12 (–0.23, –0.01), $p = 0.036$		–0.29 (–0.45, –0.12), $p < 0.001$	
Interaction test	$p = 0.0619$			

Table 3 Cont.

	Low-risk		High-risk	
LDL-C (mg/dL)	<120 mg/dL		≥120 mg/dL	
	Placebo (*n* = 174)	Ipragliflozin (*n* = 315)	Placebo (*n* = 194)	Ipragliflozin (*n* = 313)
Baseline/EOT	97.2 ± 17.69 / 102.6 ± 24.59	95.1 ± 17.73 / 102.2 ± 25.11	146.3 ± 22.97 / 139.0 ± 26.16	143.7 ± 22.11 / 135.6 ± 25.89
Change	5.4 ± 18.41	7.1 ± 20.69	–7.5 ± 22.84	–8.2 ± 24.68
AMD (95% CI)	1.7 (–2.0, 5.4), *p* = 0.364		–0.9 (–4.9, 3.1), *p* = 0.663	
Interaction test	*p* = 0.5011			
HDL-C (mg/dL)	≥50 mg/dL		<50 mg/dL	
	Placebo (*n* = 256)	Ipragliflozin (*n* = 390)	Placebo (*n* = 112)	Ipragliflozin (*n* = 238)
Baseline/EOT	62.5 ± 12.1 / 63.0 ± 14.1	65.9 ± 14.0 / 69.4 ± 16.0	42.6 ± 5.1 / 44.3 ± 6.9	42.0 ± 5.8 / 47.1 ± 8.4
Change	0.4 ± 9.0	3.5 ± 9.8	1.8 ± 5.5	5.1 ± 6.9
AMD (95% CI)	3.2 (1.8, 4.7), *p* < 0.001		3.0 (1.5, 4.4), *p* < 0.001	
Interaction test	*p* = 0.8041			
TG (mg/dL)	<120 mg/dL		≥120 mg/dL	
	Placebo (*n* = 184)	Ipragliflozin (*n* = 297)	Placebo (*n* = 184)	Ipragliflozin (*n* = 331)
Baseline/EOT	85.5 ± 22.4 / 100.2 ± 50.2	84.2 ± 21.0 / 86.7 ± 37.9	205.6 ± 124.3 / 193.4 ± 166.2	216.3 ± 117.1 / 178.4 ± 116.7
Change	14.8 ± 45.0	2.7 ± 32.7	–12.3 ± 141.3	–38.2 ± 126.9
AMD (95% CI)	–11.4 (–18.6, –4.3), *p* = 0.002		–18.1 (–40.1, 4.0), *p* = 0.108	
Interaction test	*p* = 0.2867			
Non HDL-C (mg/dL)	<140 mg/dL		≥140 mg/dL	
	Placebo (*n* = 163)	Ipragliflozin (*n* = 305)	Placebo (*n* = 205)	Ipragliflozin (*n* = 323)
Baseline/EOT	116.1 ± 18.2 / 119.4 ± 24.3	114.0 ± 18.5 / 118.1 ± 26.4	168.7 ± 25.1 / 161.6 ± 28.8	168.0 ± 24.6 / 157.3 ± 28.8
Change	3.3 ± 18.8	4.1 ± 20.9	–7.1 ± 23.5	–10.8 ± 26.5
AMD (95% CI)	0.9 (–2.9, 4.8), *p* = 0.628		–2.8 (–7.0, 1.4), *p* = 0.185	
Interaction test	*p* = 0.1472			
AST (IU/L)	<25 IU/L		≥25 IU/L	
	Placebo (*n* = 240)	Ipragliflozin (*n* = 362)	Placebo (*n* = 128)	Ipragliflozin (*n* = 266)
Baseline/EOT	19.5 ± 2.83 / 21.2 ± 7.94	19.6 ± 2.95 / 20.4 ± 4.14	32.8 ± 9.97 / 34.3 ± 15.36	34.6 ± 10.25 / 28.6 ± 10.24
Change	1.7 ± 7.44	0.8 ± 3.59	1.5 ± 11.46	–6.0 ± 10.22
AMD (95% CI)	–0.9 (–1.8, 0.0), *p* = 0.048		–7.0 (–9.2, –4.8), *p* < 0.001	
Interaction test	*p* < 0.0001			
ALT (IU/L)	<25 IU/L		≥25 IU/L	
	Placebo (*n* = 207)	Ipragliflozin (*n* = 339)	Placebo (*n* = 161)	Ipragliflozin (*n* = 289)
Baseline/EOT	17.7 ± 3.91 / 18.6 ± 6.17	17.8 ± 3.84 / 17.1 ± 4.94	37.6 ± 14.13 / 38.6 ± 18.28	41.3 ± 16.01 / 30.7 ± 12.60
Change	0.8 ± 5.16	–0.7 ± 4.49	1.0 ± 12.88	–10.5 ± 14.05
AMD (95% CI)	–1.6 (–2.4, –0.8), *p* < 0.001		–10.0 (–12.5, –7.6), *p* < 0.001	
Interaction test	*p* < 0.0001			
gamma-GTP (IU/L)	<30 IU/L		≥30 IU/L	
	Placebo (*n* = 175)	Ipragliflozin (*n* = 266)	Placebo (*n* = 193)	Ipragliflozin (*n* = 362)
Baseline/EOT	21.0 ± 5.23 / 22.0 ± 8.10	20.6 ± 5.50 / 19.9 ± 11.28	67.6 ± 54.73 / 67.0 ± 51.51	70.3 ± 57.26 / 54.0 ± 43.95
Change	0.9 ± 6.20	–0.7 ± 9.79	–0.6 ± 30.87	–16.4 ± 30.45
AMD (95% CI)	–1.5 (–3.2, 0.1), *p* = 0.072		–15.6 (–20.0, –11.1), *p* < 0.001	
Interaction test	*p* < 0.0001			

Values are presented as the mean ± standard deviation.

Abbreviations: ALT, alanine transaminase; AMD, adjusted mean difference; AST, aspartate transaminase; CI, confidence interval; EOT, end of treatment; FSI, fasting serum insulin; gamma-GTP, gamma-glutamyltransferase; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-beta, homeostatic model assessment for beta-cell function; HOMA-R, homeostatic model assessment for insulin resistance; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides.

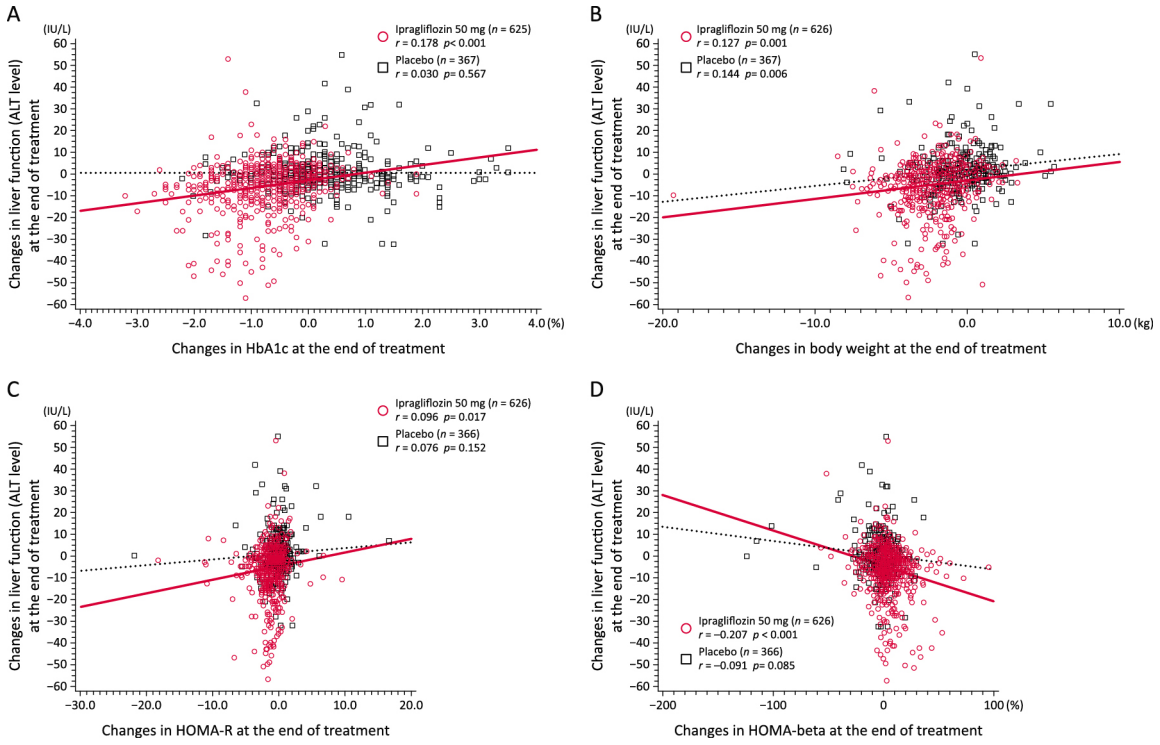

Fig. 1 Correlations between various parameters and ALT level.

A. Correlation between HbA1c reduction and changes in ALT level.

B. Correlation between body weight reduction and changes in ALT level.

C. Correlation between changes in HOMA-R and ALT level.

D. Correlation between changes in HOMA-beta and ALT level.

Abbreviations: ALT, alanine transaminase; HbA1c, glycated hemoglobin; HOMA-R, homeostatic model assessment for insulin resistance; HOMA-beta, homeostatic model assessment for beta-cell function.

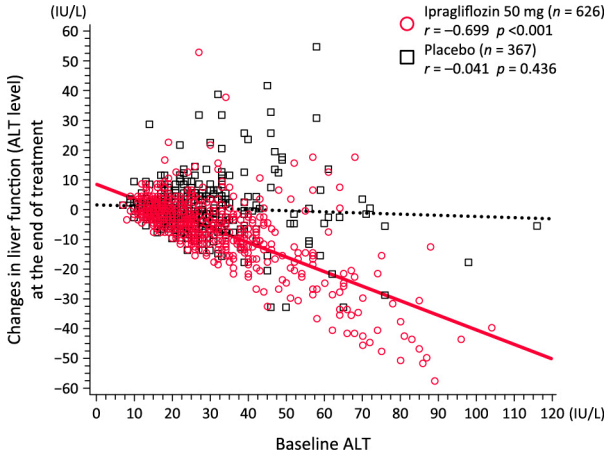

Fig. 2 Correlation between baseline ALT level and changes in ALT level at the end of treatment.

Abbreviation: ALT, alanine transaminase.

Discussion

In this pooled analysis, we examined the impact of ipragliflozin treatment on the cardiometabolic risk reduction in Japanese patients with T2DM, comparing patients with low and high basal levels of cardiometabolic risk factors. Overall, we observed a significant improvement in each parameter in the ipragliflozin group compared with the placebo group, except for LDL-C and non HDL-C. The results of the interaction test demonstrated that the improvements in HbA1c, HOMA-R, HOMA-beta, and liver function were significantly greater in high-risk groups than low-risk groups.

In the present analysis, the adjusted mean difference in HbA1c between patients receiving placebo and ipragliflozin was –1.04% (95% CI, –1.133% to –0.941%) ($p <$ 0.001). This difference is slightly higher than that reported in the study population including Asian patients with T2DM who were treated with 10 mg and 25 mg of empa-

Table 4 Changes in ALT from baseline to end of treatment according to low- and high-HOMA-R and HOMA-beta groups

ALT	HOMA-R < 2.5		HOMA-R ≥ 2.5		HOMA-beta < 20		HOMA-beta ≥ 20	
	Placebo (*n* = 197)	Ipragliflozin (*n* = 302)	Placebo (*n* = 171)	Ipragliflozin (*n* = 326)	Placebo (*n* = 183)	Ipragliflozin (*n* = 245)	Placebo (*n* = 185)	Ipragliflozin (*n* = 383)
Baseline/EOT	22.0 ± 9.2 / 22.1 ± 10.7	23.0 ± 11.4 / 20.3 ± 9.6	31.6 ± 16.4 / 33.4 ± 19.4	33.8 ± 18.1 / 26.2 ± 12.3	22.7 ± 11.7 / 21.7 ± 10.5	23.5 ± 11.7 / 20.1 ± 9.7	30.1 ± 14.9 / 32.9 ± 19.0	31.9 ± 17.7 / 25.4 ± 12.1
Change	0.2 ± 6.9	–2.7 ± 8.1	1.8 ± 11.5	–7.5 ± 13.0	–1.1 ± 7.1	–3.2 ± 8.6	2.8 ± 10.8	–6.5 ± 12.4
AMD (95% CI)[a]	–2.6 (–3.9, –1.3), $p < 0.001$		–8.6 (–10.6, –6.6), $p < 0.001$		–2.0 (–3.3, –0.6), $p = 0.004$		–8.7 (–10.5, –6.9), $p < 0.001$	
Interaction test[b]	$p < 0.0001$				$p < 0.0001$			

The low- and high-HOMA-R and HOMA-beta groups were determined based on HOMA-R and HOMA-beta levels at baseline.

[a] ANCOVA model with treatment group and study as fixed effects, and baseline ALT value as a covariate in each subgroup.

[b] ANCOVA model with treatment group, study, baseline HOMA-R/HOMA-beta category, and treatment group × baseline HOMA-R/HOMA-beta category as fixed effects, and baseline ALT value as a covariate.

Abbreviations: ALT, alanine transaminase; AMD, adjusted mean difference; ANCOVA, analysis of covariance; CI, confidence interval; EOT, end of treatment; HOMA-beta, homeostatic model assessment for beta-cell function; HOMA-R, homeostatic model assessment for insulin resistance.

gliflozin at 24 weeks (–0.74% and –0.85%, respectively) [23]. However, future work should evaluate ethnic differences in the effectiveness of SGLT2 inhibitors for the reduction of HbA1c, adjusting for patient and drug characteristics.

The improvements in body weight, SBP, FSI, HOMA-R and HOMA-beta, liver function parameters, TG, and HDL-C shown in the present analysis are consistent with those previously reported in Japanese patients with T2DM receiving ipragliflozin [8, 14-21, 24]. Further, the improvement in serum uric acid concentration with ipragliflozin treatment in the present study is consistent with the results of a previous pooled analysis of the effect of canagliflozin, another SGLT2 inhibitor, on serum uric acid levels [25], and those of the study of empagliflozin use in Asian patients with T2DM [10].

The improvement in liver function by SGLT2 inhibitors has been discussed in recent published reports, of which the majority are pre-clinical studies [26-34]. Among these, Nishimura *et al*. reported that insulin resistance plays a role in the progression of fatty liver disease to liver fibrosis [26]. Therefore, treatment with ipragliflozin likely leads to improved liver function by possibly ameliorating insulin resistance. In a recent clinical study, ipragliflozin was found to have a beneficial effect on NAFLD (improvement in the liver-to-spleen attenuation ratio) and glycemic control in Japanese T2DM patients [35]. In the present analysis, a significant correlation was found between the improvement in ALT levels and changes in HOMA-R as well as reductions in body weight, HbA1c, and HOMA-beta. These results suggest that ipragliflozin causes a reduction of hepatic lipogenesis through both reductions of plasma glucose and insulin concentrations and the upregulation of hepatic gluconeogenesis, which enhances beta-oxidation in hepatic cells, thereby ameliorating hepatic steatosis [24]. However, a reduction in fatty liver index was not found to be correlated with changes in body weight or visceral and subcutaneous adipose tissue mass [24]. Thus, the present analysis suggests that body weight reduction with both glycemic control and improvement in insulin resistance might be associated with improved liver function. Consistently, it has also been reported that canagliflozin improves liver function through reductions in both HbA1c and body weight [36, 37].

Although the pathogenesis of fatty liver is multifactorial, the accumulation of fat in the liver secondary to obesity, along with subsequent inflammation, plays a central role in its development [38, 39]. The body weight reductions in patients treated with ipragliflozin are not only related to urinary glucose excretion and mild osmotic diuresis, but also to a reduction in body fat mass [40], which may be associated with improved liver function. In the present pooled analysis, ipragliflozin improved the reduction of both fasting glucose and insulin levels, resulting in an improvement of HOMA-R as well as HOMA-beta. Furthermore, there was a significant correlation between the reduction of HOMA-R or increased HOMA-beta and the improvement in liver function, suggesting that improved insulin secretory activity and insulin sensitivity might be associated with an improvement in liver function. Improvements in beta-

cell function with ipragliflozin treatment have already been reported in Japanese patients with T2DM [41, 42]. Similarly, ipragliflozin treatment improved hepatic steatosis and insulin resistance in diabetic model mice [29].

Hyperuricemia in the presence of T2DM is associated with metabolic syndrome and cardiovascular disease. The present results showed that serum uric acid levels were reduced after ipragliflozin treatment compared with the placebo group. Our pooled analysis revealed a negative correlation between eGFR and serum uric acid in both placebo and ipragliflozin treatment groups, involving a greater reduction in eGFR and a smaller change in serum uric acid. In addition, on any level of change in eGFR levels, the reduction in serum uric acid levels was always greater in the ipragliflozin treatment group compared with the placebo treatment group. This indicates that the change in eGFR was unlikely to have caused the reduction in serum uric acid levels after ipragliflozin treatment. In addition, it has previously been reported that SGLT2 inhibitors lower serum uric acid levels *via* alterations in uric acid transport caused by changes in urinary glucose levels [43].

In the present analysis, LDL-C remained unchanged after ipragliflozin treatment. This finding is inconsistent with the results of a post-marketing surveillance study [44] and a comparative study of ipragliflozin *versus* continued treatment [45] in Japanese patients with T2DM, which demonstrated significant improvements in LDL-C with ipragliflozin. However, it has been reported that both canagliflozin 100 and 300 mg, once daily, were associated with increases in LDL-C and HDL-C resulting in no change in the LDL-C/HDL-C ratio, relative to placebo [46]. A study of empagliflozin use in Asian patients with T2DM also showed small increases in LDL-C [10]. Furthermore, a similar increase in LDL-C was reported in studies with another SGLT2 inhibitor [47]. Therefore, the effect of SGLT2 inhibitors on LDL-C differs depending on the clinical trial.

In the present analysis, we determined whether the high-risk group had a greater cardiometabolic risk reduction following ipragliflozin treatment compared with the low-risk group. The subgroup analysis revealed a significantly greater improvement in the high-risk group *versus* the low-risk group in HbA1c, HOMA-R, HOMA-beta, AST, ALT, and gamma-GTP, but not in body weight, blood pressure, TG, HDL-C, uric acid, or LDL-C.

The present pooled analysis had several limitations; for instance, the included studies differed in terms of treatment modality and duration of treatment, which may be a source of bias. Additionally, the treatment period was limited to 24 weeks. The impact of co-administration of other oral antidiabetic drugs with ipragliflozin on cardiometabolic parameters could not be evaluated because of the slight differences in baseline characteristics of the study patients in the six studies. The use of concomitant drugs other than antidiabetic drugs in both the ipragliflozin group and the placebo group during the study were changed at the discretion of the attending physician and were not recorded. Thus, other concomitant drugs might have an effect on the parameters evaluated. The patients were divided into two groups based on their cardiometabolic risk factors, but patients in the high-risk group could still have had risk factors outside the normal range for many of the parameters. In addition, it is possible that the significant improvements in cardiometabolic risk factors with ipragliflozin treatment might have been affected by the small, but significant, difference in basal risk factor levels. Finally, although it is generally accepted that both HOMA-beta and HOMA-R should be carefully evaluated in patients with a higher fasting plasma glucose, the present changes in both parameters were consistent with the previously reported results on the effects of ipragliflozin on insulin secretion and action [41, 42].

In conclusion, the present pooled analysis of six clinical randomized trials suggests that ipragliflozin 50 mg/day is associated with improvements in various cardiometabolic risk factors, except for LDL-C and non HDL-C, in Japanese patients with T2DM. In addition, greater improvements in the placebo-adjusted mean change from baseline in HbA1c, HOMA-R, HOMA-beta, and liver function were found in the high-risk group compared with the low-risk group among patients treated with ipragliflozin 50 mg/day.

Acknowledgements

The authors wish to thank all of the investigators involved in each trial. This study was sponsored by Astellas Pharma Inc. Medical writing and editorial support was funded by Astellas Pharma Inc. and provided by Michelle Belanger, MD, of Edanz Medical Writing.

Disclosure

AK has acted as a consultant for Astellas Pharma Inc. and has received consulting fees/honoraria from Astellas Pharma Inc. The other authors are employees of Astellas Pharma Inc., Japan.

References

1. Martín-Timón I, Sevillano-Collantes C, Segura-Galindo A, Del Cañizo-Gómez FJ (2014) Type 2 diabetes and cardiovascular disease: have all risk factors the same strength? *World J Diabetes* 5: 444–470.
2. Tillin T, Hughes AD, Mayet J, Whincup P, Sattar N, *et al.* (2013) The relationship between metabolic risk factors and incident cardiovascular disease in Europeans, South Asians, and African Caribbeans: SABRE (Southall and Brent Revisited)—a prospective population-based study. *J Am Coll Cardiol* 61: 1777–1786.
3. Bhatt HB, Smith RJ (2015) Fatty liver disease in diabetes mellitus. *Hepatobiliary Surg Nutr* 4: 101–108.
4. Adams LA, Lymp JF, Sauver JS, Sanderson SO, Lindor KD, *et al.* (2005) The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology* 129: 113–121.
5. Abdul-Ghani MA, Norton L, DeFronzo RA (2011) Role of sodium-glucose cotransporter 2 (SGLT 2) inhibitors in the treatment of type 2 diabetes. *Endocr Rev* 32: 515–531.
6. Isaji M (2011) SGLT2 inhibitors: molecular design and potential differences in effect. *Kidney Int Suppl* 120: S14–S19.
7. Abdul-Ghani MA, Norton L, DeFronzo RA (2012) Efficacy and safety of SGLT2 inhibitors in the treatment of type 2 diabetes mellitus. *Curr Diab Rep* 12: 230–238.
8. Kashiwagi A, Maegawa H (2017) Metabolic and hemodynamic effects of sodium-dependent glucose cotransporter 2 inhibitors on cardio-renal protection in the treatment of patients with type 2 diabetes mellitus. *J Diabetes Investig* 8: 416–427.
9. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, *et al.* (2015) Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 373: 2117–2128.
10. Kaku K, Lee J, Mattheus M, Kaspers S, George J, *et al.* (2017) Empagliflozin and cardiovascular outcomes in Asian patients with type 2 diabetes and established cardiovascular disease: results from EMPA-REG OUTCOME. *Circ J* 81: 227–234.
11. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, *et al.* (2017) Canagliflozin and cardiovascular and renal events in type 2 diabetes. *New Engl J Med* 377: 644–657.
12. Kosiborod M, Cavender MA, Fu AZ, Wilding JP, Khunti K, *et al.* (2017) Lower risk of heart failure and death in patients initiated on SGLT-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL study (Comparative effectiveness of cardiovascular outcomes in new users of sodium-glucose cotransporter-2 inhibitors). *Circulation* 136: 249–259.
13. Poole RM, Dungo RT (2014) Ipragliflozin: first global approval. *Drugs* 74: 611–617.
14. Kashiwagi A, Yoshida S, Nakamura I, Kazuta K, Ueyama E, *et al.* (2016) Efficacy and safety of ipragliflozin in Japanese patients with type 2 diabetes stratified by body mass index: a subgroup analysis of five randomized clinical trials. *J Diabetes Investig* 7: 544–554.
15. Kashiwagi A, Yoshida S, Kawamuki K, Nakamura I, Kazuta K, *et al.* (2016) Effects of ipragliflozin, a selective sodium-glucose co-transporter 2 inhibitor, on blood pressure in Japanese patients with type 2 diabetes mellitus: a pooled analysis of six randomized, placebo-controlled clinical trials. *Diabetol Int* 8: 76–86.
16. Kashiwagi A, Kazuta K, Yoshida S, Nagase I (2014) Randomized, placebo-controlled, double-blind glycemic control trial of novel sodium-dependent glucose cotransporter 2 inhibitor ipragliflozin in Japanese patients with type 2 diabetes mellitus. *J Diabetes Investig* 5: 382–391.
17. Kashiwagi A, Takahashi H, Ishikawa H, Yoshida S, Kazuta K, *et al.* (2015) A randomized, double-blind, placebo-controlled study on long-term efficacy and safety of ipragliflozin treatment in patients with type 2 diabetes mellitus and renal impairment: results of the long-term ASP1941 safety evaluation in patients with type 2 diabetes with renal impairment (LANTERN) study. *Diabetes Obes Metab* 17: 152–160.
18. Kashiwagi A, Kazuta K, Takinami Y, Yoshida S, Utsuno A, *et al.* (2015) Ipragliflozin improves glycemic control in Japanese patients with type 2 diabetes mellitus: the BRIGHTEN study. *Diabetol Int* 6: 8–18.
19. Kashiwagi A, Kazuta K, Goto K, Yoshida S, Ueyama E, *et al.* (2015) Ipragliflozin in combination with metformin for the treatment of Japanese patients with type 2 diabetes: ILLUMINATE, a randomized, double-blind, placebo-controlled study. *Diabetes Obes Metab* 17: 304–308.
20. Kashiwagi A, Shiga T, Akiyama N, Kazuta K, Utsuno A, *et al.* (2015) Efficacy and safety of ipragliflozin as an add-on to pioglitazone in Japanese patients with inadequately controlled type 2 diabetes: a randomized, double-blind, placebo-controlled study (the SPOTLIGHT study). *Diabetol Int* 6: 104–116.
21. Kashiwagi A, Akiyama N, Shiga T, Kazuta K, Utsuno A, *et al.* (2015) Efficacy and safety of ipragliflozin as an add-on to a sulfonylurea in Japanese patients with inadequately controlled type 2 diabetes: results of the randomized, placebo-controlled, double-blind, phase III EMIT study. *Diabetol Int* 6: 125–138.
22. Kashiwagi A, Kasuga M, Araki E, Oka Y, Hanafusa T, *et al.* (2012) International clinical harmonization of glycated hemoglobin in Japan: from Japan Diabetes Society to National Glycohemoglobin Standardization Program values. *J Diabetes Investig* 3: 39–40.
23. Roden M, Weng J, Eilbracht J, Delafont B, Kim G, *et al.* (2013) Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Diabetes Endocrinol* 1: 208–219.

24. Takase T, Nakamura A, Miyoshi H, Yamamoto C, Atsumi T (2017) Amelioration of fatty liver index in patients with type 2 diabetes on ipragliflozin: an association with glucose-lowering effects. *Endocr J* 64: 363–367.
25. Davies MJ, Trujillo A, Vijapurkar U, Damaraju CV, Meininger G (2015) Effect of canagliflozin on serum uric acid in patients with type 2 diabetes mellitus. *Diabetes Obes Metab* 17: 426–429.
26. Nishimura N, Kitade M, Noguchi R, Namisaki T, Moriya K, *et al.* (2016) Ipragliflozin, a sodium-glucose cotransporter 2 inhibitor, ameliorates the development of liver fibrosis in diabetic Otsuka Long-Evans Tokushima fatty rats. *J Gastroenterol* 51: 1141–1149.
27. Honda Y, Imajo K, Kato T, Kessoku T, Ogawa Y, *et al.* (2016) The selective SGLT2 inhibitor ipragliflozin has a therapeutic effect on nonalcoholic steatohepatitis in mice. *PLoS One* 11: e0146337.
28. Jojima T, Tomotsune T, Iijima T, Akimoto K, Suzuki K, *et al.* (2016) Empagliflozin (an SGLT2 inhibitor), alone or in combination with linagliptin (a DPP-4 inhibitor), prevents steatohepatitis in a novel mouse model of non-alcoholic steatohepatitis and diabetes. *Diabetol Metab Syndr* 8: 45.
29. Komiya C, Tsuchiya K, Shiba K, Miyachi Y, Furuke S, *et al.* (2016) Ipragliflozin improves hepatic steatosis in obese mice and liver dysfunction in type 2 diabetic patients irrespective of body weight reduction. *PLoS One* 11: e0151511.
30. Hayashizaki-Someya Y, Kurosaki E, Takasu T, Mitori H, Yamazaki S, *et al.* (2015) Ipragliflozin, an SGLT2 inhibitor, exhibits a prophylactic effect on hepatic steatosis and fibrosis induced by choline-deficient l-amino acid-defined diet in rats. *Eur J Pharmacol* 754: 19–24.
31. Qiang S, Nakatsu Y, Seno Y, Fujishiro M, Sakoda H, *et al.* (2015) Treatment with the SGLT2 inhibitor luseogliflozin improves nonalcoholic steatohepatitis in a rodent model with diabetes mellitus. *Diabetol Metab Syndr* 7: 104.
32. Yokono M, Takasu T, Hayashizaki Y, Mitsuoka K, Kihara R, *et al.* (2014) SGLT2 selective inhibitor ipragliflozin reduces body fat mass by increasing fatty acid oxidation in high-fat diet-induced obese rats. *Eur J Pharmacol* 727: 66–74.
33. Suzuki M, Takeda M, Kito A, Fukazawa M, Yata T, *et al.* (2014) Tofogliflozin, a sodium/glucose cotransporter 2 inhibitor, attenuates body weight gain and fat accumulation in diabetic and obese animal models. *Nutr Diabetes* 4: e125.
34. Tahara A, Kurosaki E, Yokono M, Yamajuku D, Kihara R, *et al.* (2013) Effects of SGLT2 selective inhibitor ipragliflozin on hyperglycemia, hyperlipidemia, hepatic steatosis, oxidative stress, inflammation, and obesity in type 2 diabetic mice. *Eur J Pharmacol* 715: 246–255.
35. Ito D, Shimizu S, Inoue K, Saito D, Yanagisawa M, *et al.* (2017) Comparison of ipragliflozin and pioglitazone effects on nonalcoholic fatty liver disease in patients with type 2 diabetes: a randomized, 24-week, open-label, active-controlled trial. *Diabetes Care* 40: 1364–1372.
36. Leiter LA, Forst T, Polidori D, Balis DA, Xie J, *et al.* (2016) Effect of canagliflozin on liver function tests in patients with type 2 diabetes. *Diabetes Metab* 42: 25–32.
37. Seko Y, Sumida Y, Sasaki K, Itoh Y, Iijima H, *et al.* (2018) Effects of canagliflozin, an SGLT2 inhibitor, on hepatic function in Japanese patients with type 2 diabetes mellitus: pooled and subgroup analyses of clinical trials. *J Gastroenterol* 53: 140–151.
38. Than NN, Newsome PN (2015) A concise review of non-alcoholic fatty liver disease. *Atherosclerosis* 239: 192–202.
39. Yki-Järvinen H (2014) Non-alcoholic fatty liver disease as a cause and a consequence of metabolic syndrome. *Lancet Diabetes Endocrinol* 2: 901–910.
40. Trujillo JM, Nuffer WA (2017) Impact of sodium-glucose cotransporter 2 inhibitors on nonglycemic outcomes in patients with type 2 diabetes. *Pharmacotherapy* 37: 481–491.
41. Takahara M, Shiraiwa T, Matsuoka TA, Katakami N, Shimomura I (2015) Ameliorated pancreatic beta cell dysfunction in type 2 diabetic patients treated with a sodium-glucose cotransporter 2 inhibitor ipragliflozin. *Endocr J* 62: 77–86.
42. Nagai Y, Ohta A, Sada Y, Kato H, Tanaka Y (2017) Effect of 24-week treatment with ipragliflozin on proinsulin/C-peptide ratio in Japanese patients with type 2 diabetes. *Expert Opin Pharmacother* 18: 13–17.
43. Chino Y, Samukawa Y, Sakai S, Nakai Y, Yamaguchi J, *et al.* (2014) SGLT2 inhibitor lowers serum uric acid through alteration of uric acid transport activity in renal tubule by increased glycosuria. *Biopharm Drug Dispos* 35: 391–404.
44. Maegawa H, Tobe K, Tabuchi H, Nakamura I (2016) Baseline characteristics and interim (3-month) efficacy and safety data from STELLA-LONG TERM, a long-term post-marketing surveillance study of ipragliflozin in Japanese patients with type 2 diabetes in real-world clinical practice. *Expert Opin Pharmacother* 17: 1985–1994.
45. Bando Y, Tohyama H, Aoki K, Kanehara H, Hisada A, *et al.* (2016) Ipragliflozin lowers small, dense low-density lipoprotein cholesterol levels in Japanese patients with type 2 diabetes mellitus. *J Clin Transl Endocrinol* 6: 1–7.
46. Sinclair A, Bode B, Harris S, Vijapurkar U, Mayer C, *et al.* (2014) Efficacy and safety of canagliflozin compared with placebo in older patients with type 2 diabetes: a pooled analysis of clinical studies. *BMC Endocr Disord* 14: 37.
47. Bristol-Myers Squibb/AstraZeneca FEIG (2012) Summary of product characteristics: Foxiga 3 mg and 10 mg film-coated tablets. Middlesex, United Kingdom.