

# Efficacy and safety of sodium–glucose cotransporter 2 inhibitor ipragliflozin on glycemic control and cardiovascular parameters in Japanese patients with type 2 diabetes mellitus; Fukuoka Study of Ipragliflozin (FUSION)

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**Abstract.** Sodium–glucose co-transporter-2 inhibitors are newly established anti-diabetic agents with a unique glucose-lowering mechanism. In the present study, we investigated the efficacy and safety of the sodium–glucose co-transporter-2 inhibitor ipragliflozin (Ipra) for metabolic markers and cardiovascular parameters in Japanese patients with type 2 diabetes mellitus (T2DM). This study was an investigator-initiated, open-label, single-arm, multicenter prospective study. Patients with T2DM were treated with 50 mg Ipra for 24 and 52 weeks. The primary outcome investigated was the reduction of glycated hemoglobin (HbA1c) level. The secondary outcome was the change in other metabolic and cardiovascular parameters by 24 weeks. Before and after 52 weeks of treatment, carotid intima-media thickening (IMT) was measured by echography. A total of 134 patients were recruited in the study. A 24-week treatment with 50 mg Ipra daily significantly reduced HbA1c level ( $-0.6\%$ ,  $p < 0.01$ ). Body mass index (BMI), blood pressure and serum C-peptide were reduced significantly ( $p < 0.05$ ), while serum glucagon level was unchanged. Interestingly, the serum adiponectin and high-density lipoprotein (HDL) cholesterol levels were significantly increased by Ipra. However, 52 weeks of Ipra treatment did not change carotid IMT. Multiple regression analysis revealed that the only significant contributing factor for HbA1c reduction by Ipra was baseline HbA1c level. These data suggest that Ipra decreased not only glucose level but also BMI, blood pressure and serum C-peptide, and the contributing factor for HbA1c reduction by Ipra was baseline HbA1c level. Further, Ipra improved serum adiponectin and HDL cholesterol levels.

**Key words:** Sodium–glucose co-transporter-2 inhibitor, Baseline hemoglobin A1c, Adiponectin, C-peptide, High-density lipoprotein cholesterol

**RECENTLY**, a wide variety of oral anti-diabetic agents have been investigated and used clinically. Following the appearance of new and unique anti-diabetic agents, their prescription for glycemic control in patients with

type 2 diabetes mellitus (T2DM) has changed in Japan, as we previously reported [1]. Sodium–glucose co-transporter-2 inhibitors (SGLT2I) are among the most recently established oral anti-diabetic agents. The mechanism by which SGLT2I reduce blood glucose levels is by disposing of glucose into the urea by inhibiting renal glucose reuptake, mainly through SGLT2 [2]. Because this mechanism is unique, independent of insulin action and different from other anti-diabetic agents, it is reported that SGLT2I have beneficial side effects, such as body weight loss and reduction of blood pressure. Accord-

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ingly, the cardiovascular protective effects of SGLT2I have been reported not only in patients in Western countries [3] but also in Asian patients with T2DM [4].

Ipragliflozin (Ipra) is an SGLT2I that is made in Japan [5] and was the first SGLT2I to enter clinical use in Japan. In clinical trials conducted before it was made available, the efficacy and safety of Ipra for its glucose-lowering effect was established in a phase 3, randomized, placebo-controlled trial [6]. However, the actual clinical efficacy and safety of Ipra has not been well examined, and the effect of Ipra on cardiovascular parameters is still being elucidated. In the present study, we examined the efficacy and safety of Ipra for glycemic control in an actual clinical situation and the effects of Ipra on cardiovascular parameters in Japanese patients with T2DM.

## Materials and Methods

### Study design

This study was an investigator-initiated open-label single-arm multicenter prospective study conducted at Fukuoka University Hospital; Futata Tetsuhiro Clinic, Arase Naika Clinic, Diabetes Center Murakamkarindoh Hospital Karinkai Incorporate Shinyukuhashi Hospital, Muta Hospital, UMEI Clinic, Saiseikai Ohmuta Hospital, Hattanaikaiai; Kitajima Internal Medicine Clinic, Yagi Hospital, Imamura Clinic, Internal Medicine and Cardiology, Fukuseikai Hospital, Fukuoka Teishin Hospital, Yatabe Naika Clinic, Med. Co. LTA, PS Clinic and Fukuda Internal Medicine as an association for the Fukuoka Study of Ipragliflozin (FUSION) trial. The patients included in this study were treated once daily with 50 mg Ipra for 52 weeks. The study protocol was approved by the ethics committees of Fukuoka University Hospital and the participating hospitals and was designed in compliance with the principles embodied by the Declaration of Helsinki (2013). All patients in this study provided written informed consent prior to all procedures related to this study. This study was registered with UMIN-CTR (UMIN000014797).

### Patients

The inclusion criteria were Japanese patients with T2DM aged  $\geq 20$  years and  $\leq 75$  years at the time of consent, with glycated hemoglobin (HbA1c) level  $\geq 6.5\%$  under diet and exercise therapy with or without other anti-diabetic agents, including insulin therapy, and without any exclusion criteria below. The exclusion criteria

were as follows: patients with type 1 diabetes mellitus or an insulin-dependent state, severe renal dysfunction,  $\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$ , or liver dysfunction, AST or ALT  $> 100 \text{ U/L}$ , severe diabetic ketosis or coma and precoma, hypersensitivity to Ipra, severe infectious disease and injury, a perioperative state; or patients considered otherwise inappropriate for this study by their attending physicians.

### Efficacy and safety outcomes

The primary outcome investigated at 0, 4, 12, and 24 weeks was the change in HbA1c from its baseline value. At the same points in the treatment course, changes in body mass index (BMI), serum C-peptide immunoreactivity (S-CPR), and serum glucagon levels were examined. Before and 24 weeks after treatment, the change in body weight (BW), blood pressure (BP), fasting blood glucose (FBG), total-cholesterol (T-Cho), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), high molecular weight (HMW) adiponectin, leptin, plasma renin activity (PRA), and aldosterone were examined. All adverse events were reported as soon as possible during the study period. Depending on the patients' attending physician, Ipra treatment and the study were discontinued.

### Measurement of carotid artery intima-media thickening

Ultrasonographic scans of the carotid artery were performed by well-trained doctors or sonographers using echography with a Toshiba SSA-780A (Toshiba Memory Corporation, Tokyo, Japan) or Hitachi EUB-7500 (Hitachi Medical Corporation, Tokyo, Japan). To avoid inter-clinic variability, intima-media thickening (IMT) was measured using the same equipment (high-resolution B-mode ultrasound scanner equipped with a high-frequency ( $>7.5 \text{ MHz}$ ) linear transducer, with a limit of detection of  $<0.1 \text{ mm}$ ) at the baseline and after 52 weeks of treatment. Scanning of the extracranial common carotid artery (CCA) in the neck were performed bilaterally in at least three different longitudinal projections (anterior, lateral and posterior, which approximately correspond to 60, 90 and 150 degrees for the right carotid artery, and 210, 270 and 300 degrees for the left carotid artery, marked on the Meijer's Arc) as well as transverse projections, and the site of the greatest thickness, including plaque lesion, was sought along the arterial walls. The IMT was measured as the distance between two parallel echogenic lines corresponding to the vascular lumen

and the adventitial layer.

To avoid inter-clinic variability, all scans were electronically stored and sent to Fukuoka University and then read by experienced readers unaware of the clinical characteristics of the subjects and treatment status using an automated digital edge-detection software program (Intimascope; Media Cross, Tokyo, Japan) as we previously reported [7]. The software system averaged 240 points of IMT values in the 2-cm segment proximal to the dilation of the carotid bulb (mean IMT), and the highest thickness of IMT, including plaque lesions in the CCA, was measured as the max IMT.

### *Assessment of arterial stiffness*

The brachial–ankle pulse wave velocity (baPWV) and ankle–brachial index (ABI) were examined at the baseline and after 52 weeks of treatment. The automatic pulse wave analyzer (Omron Colin, Tokyo, Japan) was recruited to measure baPWV and ABI, as described previously [8]. Briefly, patients were guided into the supine position on a bed and allowed to rest for at least 5 min before examination. Occlusion and monitoring cuffs were placed snugly around sites in the upper and lower extremities. Pressure waveforms were then recorded simultaneously from the brachial arteries with an oscillographic method. The ABI was calculated as follows: ABI = ankle systolic BP/brachial systolic BP.

### *Statistical analysis*

All statistical analyses were independently carried out at DOT WORLD Co., Ltd. using SAS version 9.4 (SAS Institute, Cary, NC, USA). All efficacy analyses were conducted using data from all patients who had received at least one dose of Ipra.

Baseline values were summarized using frequencies for categorical variables and means and standard deviations for continuous variables. Changes from the baseline in primary and secondary endpoints were assessed using a linear mixed-effects model. In the model, time was included as a fixed effect and subject as a random effect. The covariance structure was assumed to be “unstructured,” and the compound symmetry was used if the model did not converge. Stepwise multiple regression analysis was performed with selection criteria of 0.15. A significant level of 0.05 was used for all tests. Although the multiplicity of longitudinal data analysis for the primary endpoint was adjusted using the Tukey–Kramer method, tests for multiple endpoints were performed with no adjustment of multiplicity because this is not a

confirmatory study.

## **Results**

Patients' characteristics at the baseline before Ipra treatment are shown in Table 1. A total of 134 patients, 70 male and 64 female, were recruited for the study. Finally, 101 patients were able to complete 52 weeks of Ipra treatment, and 33 patients dropped out (11 patients had adverse effects, 9 patients chose not to participate in the study, 3 patients had inadequate glycemic control, and 10 patients dropped out for other reasons). The overall average age was 53.9 years, with a maximum of 75 years, and the average duration of T2DM diagnosis was 8.2 years. The average BMI was 29.6 kg/m<sup>2</sup>, suggesting that mainly obese Japanese patients with T2DM were recruited. Interestingly, 79.1% of the patients were being treated with dipeptidyl peptidase 4 inhibitors (DPP-4I) and 63.4% of the patients were being treated with biguanides at the baseline, reflecting the current prescription of anti-diabetic agents in Japan [1].

The changes in HbA1c levels are shown in Fig. 1A. During the 24-week Ipra treatment period, HbA1c significantly and continuously reduced from 8.02 ± 1.16% to 7.76 ± 0.92% (4 weeks), 7.46 ± 0.88% (12 weeks) and 7.44 ± 0.91% (24 weeks), and finally a −0.6% reduction in HbA1c was observed. As shown in Fig. 1B, there was a statistically significant reduction in BMI; however, this was just −0.4 kg/m<sup>2</sup> and a very small reduction volume, from 29.6 ± 4.9 kg/m<sup>2</sup> to 29.1 ± 5.0 kg/m<sup>2</sup> (24 weeks). Interestingly, S-CPR was significantly decreased by Ipra from 2.69 ± 1.41 ng/mL to 2.42 ± 1.47 ng/mL (24 weeks) as shown in Fig. 1C, even though HbA1c was significantly reduced (Fig. 1A). However, the serum glucagon level was not increased by Ipra treatment (Fig. 1D).

The changes in metabolic parameters are shown in Table 2. BW was slightly but significantly decreased by Ipra. Both systolic and diastolic blood pressures were significantly decreased by almost −5 mmHg. FBG was significantly decreased consistent with HbA1c reduction. Although T-Chol, LDL-C and TG levels were not changed by Ipra treatment, HDL-C was significantly increased. Further, HMW adiponectin, tissue-protective adipokine, was significantly increased by Ipra treatment, although there was no change in leptin levels. In addition, PRA was slightly increased and the serum aldosterone level was significantly increased by Ipra treatment.

To examine the most important contributing factor for

**Table 1** Patients' characteristics at baseline

	<i>n</i> = 134
Sex (Male : Female) ( <i>n</i> )	70 : 64
Age (years)	53.9 ± 10.5 (20–75)
Duration of T2DM (years)	8.2 ± 7.9 (0–44)
Body weight (kg)	79.0 ± 16.9 (50–159)
BMI (kg/m <sup>2</sup> )	29.6 ± 4.9 (20.8–48.7)
Nephropathy (stage 1/2/3) (%)	59.7/18.5/13.0
Retinopathy (none/simple/ preproliferative/proliferative) (%)	68.5/18.5/2.2/7.6
Neuropathy (–/+) (%)	55.4/43.5
Macroangiopathy (–/+) (%)	71.2/27.2
Anti-hypertensive drugs (%)	50.8
Anti-hyperlipidemic drugs (%)	72.4
Concomitant anti-diabetic agents (%)	Mono 6.7 SU 15.7 a-GI 8.2 Biguanides 63.4 DPP-4I 79.1 GLP-1RA 0.7 TZD 14.2 Insulin 25.4

Data are expressed as the mean ± SD (min-max)

Mono, monotherapy; SU, sulfonyl ureas; a-GI, a-glucosidase inhibitors; DPP-4I, dipeptidyl peptidase-4 inhibitors; TZD, thiazolidinediones

HbA1c reduction by Ipra, we next performed stepwise multiple regression analysis. As shown in Table 3, baseline HbA1c level was only one significant contributor for the HbA1c reduction value by Ipra.

We next examined the effect of Ipra on the cardiovascular system (Table 4A). Max and mean IMT were not changed by 52 weeks of Ipra treatment. Although the change was within the normal range, bilateral ABI was decreased significantly. To perform separate analyses depending on the patients' basal status, such as peripheral vascular disease or calcification of medial arteries, we categorized patients into three groups depending on the basal ABI (group I: <0.9, group II: ≥0.9 and <1.3, group III: ≥1.3). As shown in Table 4B, most patients were categorized in group II, and statistical analysis of the change of ABI in group I and II could not be performed, because the number was too small. However, Ipra did not worsen ABI in group I, at least. In group II, Rt. ABI was significantly decreased within the normal range. Further, Lt. PWV was significantly decreased by

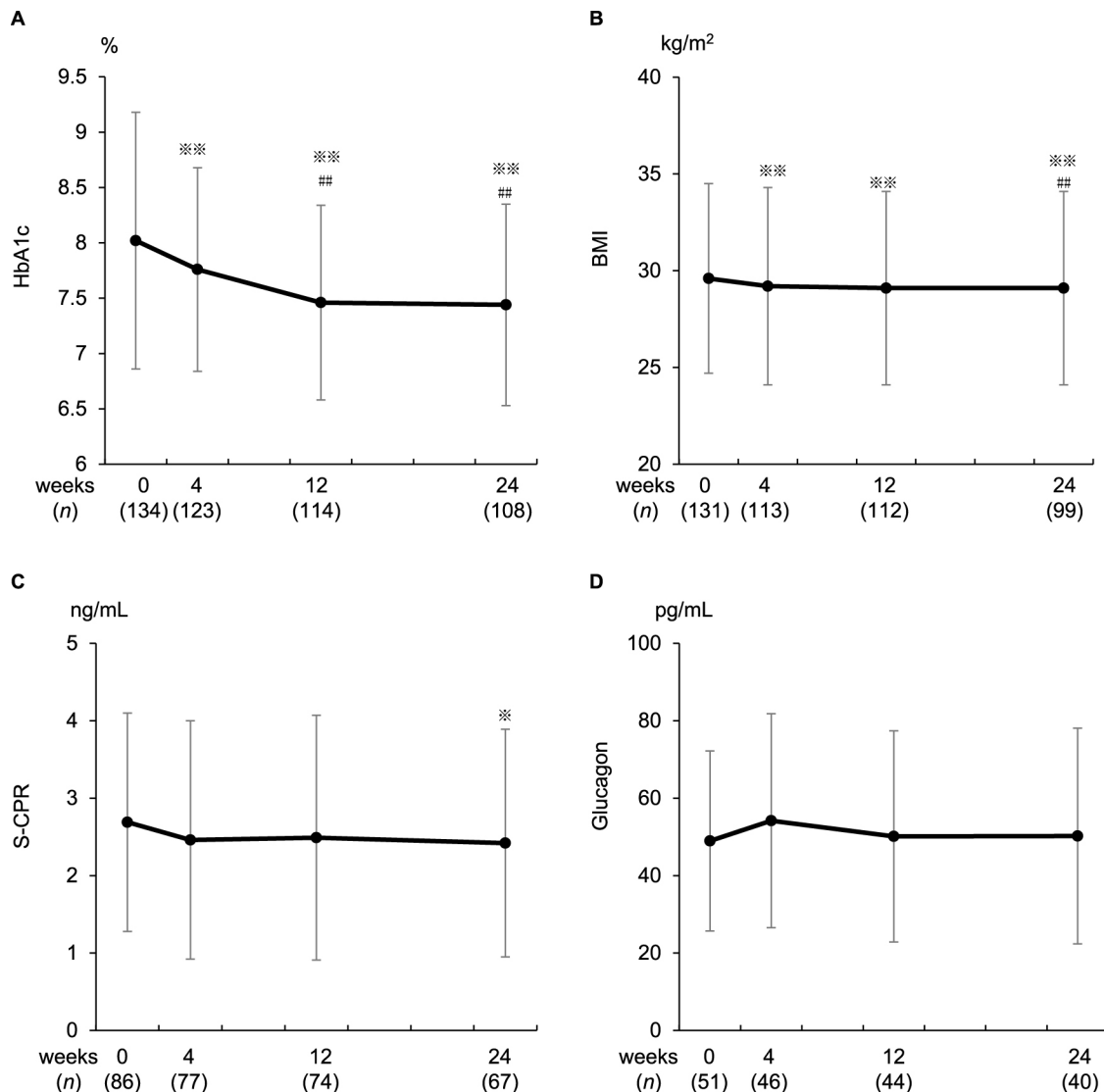
Ipra.

All adverse events are listed in Table 5. Overall 42 events in 32 patients (23.9%) were observed during the study period. The most frequently experienced adverse event was thirst (3.7%), followed by hypoglycemia, genital itching and constipation (3.0%). The most severe adverse event was thalamic hemorrhage in one patient. However, the causal relationship between Ipra treatment and thalamic hemorrhage was unclear because the patient had severe obesity (BMI 35.2 kg/m<sup>2</sup>) and inadequately controlled hypertension (154/99 mmHg) at baseline. To elucidate the risk of ketosis induced by Ipra treatment, we measured serum ketone body levels 4 weeks after Ipra treatment. Fortunately, there was no significant increase in ketone body levels (total ketone body: 177.1 ± 196.4 to 2,333.3 ± 217.9 μmol/L, *p* = 0.35).

## Discussion

In the present study, we investigated the efficacy and safety of Ipra in Japanese patients with T2DM. A total of 134 patients with T2DM were recruited. Although 11 patients discontinued the study because of adverse events, 101 patients (75.4%) completed 52 weeks of treatment without severe adverse events. One case of thalamic hemorrhage was observed during the study period. However, a causal relation was not detected between Ipra and the hemorrhage; the patient was at high risk for cerebral hemorrhage because of severe obesity and inadequately controlled BP. Further, there is no report suggesting a relationship between SGLT2I and cerebral hemorrhage in previous studies. However, because of this event, cerebral hemorrhage should be considered a potential risk during SGLT2I treatment.

In the present study, we observed a –0.6% reduction in HbA1c level after 24 weeks of treatment with 50 mg Ipra. This is nearly compatible with phase 3 data among Asian patients with T2DM [6] and a previous report on Japanese patients with T2DM [9], suggesting that Ipra decreases HbA1c effectively in clinical situations as well. In the present study, older adult Japanese patients with T2DM were also included (40 patients were at least 60 years old), and Ipra reduced HbA1c in these patients effectively and safely, suggesting that Ipra could be used in older adult patients with T2DM, as a previous report indicated [10]. Significant reductions in BMI (–0.4 kg/m<sup>2</sup>) and BW (–1.0 kg) were observed in the present study; however, they were small (Fig. 1B) compared



**Fig. 1** Effect of ipragliflozin during the time course. A. Changes in HbA1c; B. Changes in BMI; C. Changes in S-CPR; D. Changes in serum glucagon. \*  $p < 0.05$  vs. 0 week, \*\*  $p < 0.01$  vs. 0 week, ##  $p < 0.01$  vs. 4 weeks.

with those previously reported [11]. In a previous report, Yamamoto *et al.* suggested that adequate education regarding diet therapy was an important factor for reducing visceral fat obesity during Ipra treatment, resulting in a  $-2.49$ -kg BW reduction [11]. We recognize the need for stricter dietary therapy in our hospital and clinic than is currently available; however, at least patients in the present study did not experience increased BW. This confirmed that Ipra could decrease HbA1c without weight gain. To identify the factors contributing to HbA1c reduction by Ipra, we performed stepwise multiple regression analysis. Consequently, the baseline HbA1c level was the only significant contributing factor

(Table 3). In fact, a higher baseline HbA1c is a common contributing factor for HbA1c reduction by any class of anti-diabetic agents, as we have previously reported using DPP-4I sitagliptin [12]. The present result suggested that Ipra did not have a specific contributing factor for HbA1c reduction in Japanese patients with T2DM. However, patients recruited into the present study were patients with some limitations, such as higher BMI, younger age and shorter duration compared with the general population of patients with T2DM. Further investigation with a larger number of patients with diverse backgrounds is required.

Interestingly, S-CPR was significantly reduced in the

**Table 2** Changes in metabolic parameters and serum data

	0 weeks	24 weeks	<i>p</i> value
BW (kg)	79.0 ± 16.9 (134)	78.0 ± 18.0 (102)	<0.01
Systolic BP (mmHg)	133.5 ± 15.9 (130)	127.9 ± 13.3 (98)	<0.05
Diastolic BP (mmHg)	79.3 ± 11.8 (130)	74.6 ± 9.8 (98)	<0.01
FBG (mg/dL)	162.3 ± 46.8 (129)	139.1 ± 38.4 (105)	<0.01
T-Cho (mg/dL)	187.1 ± 29.5 (130)	193.7 ± 30.3 (109)	0.13
LDL-C (mg/dL)	109.7 ± 24.3 (131)	113.0 ± 24.8 (109)	0.67
TG (mg/dL)	163.7 ± 95.5 (131)	150.9 ± 101.2 (109)	0.51
HDL-C (mg/dL)	50.4 ± 12.6 (131)	54.1 ± 16.0 (109)	<0.01
HMW adiponectin (mg/mL)	2.84 ± 2.4 (80)	2.99 ± 2.51 (109)	<0.01
Leptin (mg/mL)	16.6 ± 11.1 (80)	15.4 ± 11.2 (59)	0.64
PRA (ng/mL/hr)	1.91 ± 2.93 (56)	3.04 ± 4.70 (40)	0.08
Aldosterone (pg/mL)	127.8 ± 63.0 (56)	162.9 ± 96.4 (41)	<0.05

Data are expressed as the mean ± SD (*n*).

present study, compatible with a previous report by another group [13]. These data suggest that Ipra decreased HbA1c, reducing the overload on pancreatic  $\beta$  cells. As a previous report suggested, reduction of the pancreatic  $\beta$  cell load could result in improved pancreatic  $\beta$  cell function by Ipra [14]. Further, it was recently reported that too much insulin injection and consequent hyperinsulinemia might be a risk of cardiovascular events and cancer [15]. Reduction of S-CPR and serum insulin concentration could be beneficial not only for pancreatic  $\beta$  cell protection but also for preventing cardiovascular events and cancer. Recently, SGLT2I have been reported to increase serum glucagon level [16], but this increase did not occur in the present study, probably because of combination therapy with other anti-diabetic agents. As shown in Table 1, 79.1% of the patients in the present study were being treated with DPP-4I at the baseline and 63.4% with biguanides (metformin). A recent study suggested that the DPP-4I sitagliptin ameliorates paradoxical glucagon secretion after a glucose load in Japanese patients with impaired glucose tolerance [17]. Further, metformin is reported to inhibit the glucagon signal in the liver [18]. This collaboration in combination therapy might inhibit glucagon secretion and achieve good glycemic control.

In the present study, BP was significantly decreased by Ipra, similar to a previous study [3]. Reduction of BP by the SGLT2I Ipra should be a crucial mechanism in cardiovascular protection [19]. Although T-Cho, LDL-C

**Table 3** Stepwise multiple regression analysis of clinical factors associated with HbA1c reduction

Variables	Estimated value	<i>t</i> value	<i>p</i> value
Intercept	4.92246	7.95	<0.01
Male/female	-0.24801	-1.51	0.134
Baseline HbA1c	-0.67838	-8.91	<0.01
Retinopathy	0.38855	1.88	0.063

and TG level were not changed, HDL-C was significantly increased by Ipra (Table 2). In a previous report, Hayashi *et al.* suggested that the SGLT2I dapagliflozin also increased HDL-C levels in Japanese patients with T2DM [20]. In fact, HDL-C is the second most important factor for coronary artery disease in patients with type 2 diabetes, as the United Kingdom Prospective Diabetes Study (UKPDS: 23) suggested [21]. Increasing HDL-C could contribute to cardiovascular protection by Ipra. Very interestingly, the HMW adiponectin level was significantly increased by Ipra (Table 2), which supports a previous report by another group [13]. Although we did not measure waist circumference, abdominal fat might be decreased by Ipra because the adiponectin level was increased. Adiponectin is one of the most important adipokines for protecting the cardiovascular system [22]. Accordingly, induction of HMW adiponectin could be an important pleiotropic effect of SGLT2I Ipra. In addition, PRA and serum aldosterone level were increased in the

**Table 4A** Changes in cardiovascular examinations

	0 weeks	52 weeks	<i>p</i> value
Rt. Max IMT (mm)	0.96 ± 0.21 (70)	0.99 ± 0.24 (60)	0.36
Lt. Max IMT (mm)	0.99 ± 0.25 (70)	1.01 ± 0.24 (60)	0.70
Rt. Mean IMT (mm)	0.76 ± 0.16 (70)	0.75 ± 0.15 (60)	0.40
Lt. Mean IMT (mm)	0.75 ± 0.18 (70)	0.76 ± 0.17 (60)	0.41
Rt. ABI	1.15 ± 0.08 (104)	1.12 ± 0.08 (67)	<0.01
Lt. ABI	1.14 ± 0.09 (104)	1.11 ± 0.10 (67)	<0.05
Rt. PWV (cm/sec)	1,639.0 ± 347.0 (95)	1,605.8 ± 329.0 (61)	0.17
Lt. PWV (cm/sec)	1,632.8 ± 368.5 (95)	1,572.6 ± 325.4 (61)	<0.05

Data are expressed as the mean ± SD (*n*).

**Table 4B** Change of ABI in three groups categorized by basal ABI (I: <0.9, II: ≥0.9 and <1.3, III: ≥1.3)

Group		0 weeks	52 weeks	<i>p</i> value
I	Rt. ABI	0.88 (1)	0.95 (1)	ND
	Lt. ABI	0.89 (1)	— (0)	ND
II	Rt. ABI	1.14 ± 0.07 (101)	1.11 ± 0.08 (59)	<0.01
	Lt. ABI	1.13 ± 0.08 (100)	1.10 ± 0.10 (61)	0.14
III	Rt. ABI	1.32 ± 0.01 (2)	1.19 ± 0.03 (2)	ND
	Lt. ABI	1.35 ± 0.06 (3)	1.19 (2)	ND

Data are expressed as the mean ± SD (*n*).

present study, probably to compensate for dehydration caused by Ipra. However, it is still unclear whether this reflection is a pathological reaction.

Carotid IMT was not changed by Ipra (Table 4A). Further longer elucidation may be needed for IMT change by SGLT2I. Further, PWV was significantly decreased on the left side, probably reflecting vascular relaxation from decreased BP. Right PWV was also decreased, however a statistical significance was not achieved. Probably, it may due to low power of statistical analysis, such as small sample size. Unfortunately, bilateral ABI was significantly decreased (Table 4A). In the present study, the change was within the normal range, and Ipra did not worsen ABI in a patient with suspected peripheral vascular disease at baseline (Table 4B). Thus, the observed ABI reduction might not be a pathophysiological change. However, the SGLT2I canagliflozin increased the risk of amputation 2-fold in a previous large-scale study [23]. Thus, care needs to be taken when treating patients with lower limb lesions with SGLT2I, and further examination is required.

In the present study, we recognize several limitations. First, the present study is a non-randomized single-arm study without placebo control, and the attending physicians and doctors or lab technicians who performed the vascular examinations were not blinded. Second, the present study was performed in a specific location, Fukuoka city, during a relatively short time period. Further, patients recruited in the present study were relatively young, more obese and with a shorter duration of T2DM compared with the general population of Japanese patients with T2DM. In addition, this study is an explanatory study without preliminary calculation of sample size. Unfortunately, the present study had a high dropout rate, at 24.6%, because of fear of adverse effects from SGLT2I before the clinical application began. However, its tolerability has now been confirmed, even in older patients with T2DM [10]. To investigate the precise efficacy and safety of Ipra in Japanese patients with T2DM, a large-scale, long-term, randomized-control trial should be conducted.

In conclusion, Ipra decreased not only the glucose

**Table 5** Summary of adverse events

Events	Number of events (n)	Number of patients (n) (%)
All adverse events	42	32 (23.9)
Thirstiness	5	5 (3.7)
Hypoglycemia	6	4 (3.0)
Genital itching	6	4 (3.0)
Constipation	5	4 (3.0)
Frequent urination	3	3 (2.2)
Rash	3	3 (2.2)
Vaginal candidiasis	2	2 (1.5)
Folliculitis	2	2 (1.5)
Abdominal distension	1	1 (0.7)
Vulvar burning sensation	1	1 (0.7)
Cystitis	1	1 (0.7)
Low blood pressure	1	1 (0.7)
Arrhythmia	1	1 (0.7)
Thalamic hemorrhage	1	1 (0.7)
Dizziness	1	1 (0.7)
Dysuria	1	1 (0.7)
Vulvar erosion	1	1 (0.7)
Pruritus	1	1 (0.7)
Eczema	1	1 (0.7)
Alopecia	1	1 (0.7)
Hives	1	1 (0.7)

level but also BMI, blood pressure and serum C-peptide level. The contributing factor for the level of HbA1c reduction by Ipra was baseline HbA1c level. Further, Ipra improved serum adiponectin and HDL cholesterol levels in Japanese patients with T2DM.

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T.N. performed data analysis, wrote the manuscript and conceived the research hypothesis and design. T.Y. conceived the research design and reviewed the manuscript. D.S., Y.T., T.F., R.M. and M.T. reviewed the manuscript. All authors and collaborators for the FUSION trial assisted in patient recruitment.

## Disclosure

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