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ORIGINAL ARTICLE

Safety and effectiveness of tofogliflozin in Japanese patients with type 2 diabetes mellitus in real-world practice: Results of 12-month interim analysis of a long-term post-marketing surveillance study (J-STEP/LT)

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Keywords
Post-marketing study, Tofogliflozin, Type 2 diabetes mellitus

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ABSTRACT

Aims/Introduction: Due to the paucity of tofogliflozin data, we assessed the safety and effectiveness of tofogliflozin among Japanese patients with type 2 diabetes mellitus in the clinical setting, stratifying the patients by age, sex, estimated glomerular filtration (eGFR) rate and body mass index. We report the results of a 12-month interim analysis.

Materials and Methods: This was a 3-year prospective, observational and multicenter post-marketing study (Japanese Study of tofogliflozin with type 2 diabetes mellitus Patients/Long Term).

Results: Out of 6,897 patients enrolled, the safety and effectiveness analysis populations consisted of 6,712 and 6,449 patients, respectively. During 12 months, adverse drug reactions and their incidence were 9.12 and 0.88%, respectively. The incidence of hypoglycemia was 0.67%. Polyuria/pollakiuria occurred more frequently in patients aged ≥65 years than in patients aged <65 years. Women experienced higher rates of urinary tract and genital infection than men. The lowest eGFR subgroup experienced maximum volume depletion-related events. Cardiovascular and cerebrovascular disorders occurred in 0.55% of the patients. Glycated hemoglobin (HbA1c) and bodyweight significantly decreased by −0.76% and −2.73 kg, respectively, from baseline to the last observation carried forward ($P < 0.0001$). Except for the lowest eGFR subgroup, other eGFR subgroups showed significantly decreased HbA1c values. All eGFR subgroups showed significantly decreased bodyweight, and all body mass index subgroups showed significantly decreased HbA1c and bodyweight.

Conclusions: Our interim 12-month data suggest that tofogliflozin could be used safely and effectively in Japanese patients with type 2 diabetes mellitus, as tofogliflozin was well tolerated with low hypoglycemia risk, and significantly improved HbA1c and bodyweight.

INTRODUCTION

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are a new class of oral antidiabetic drugs (OADs) that contribute to lowering glycated hemoglobin (HbA1c) levels and bodyweight, accompanied by the low risk of hypoglycemia[1–3]. Unique adverse events (AEs) of SGLT2 inhibitors include urinary tract infections and genital infections[1,2,4,5], which are also highlighted in the recommendations for appropriate SGLT2 inhibitor use issued by Japanese clinical experts[6].

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Comprehensive consideration of patient characteristics, such as age, sex, estimated glomerular filtration rate (eGFR) and obesity, is necessary while administering SGLT2 inhibitors for safety and efficacy concerns, in line with general management of type 2 diabetes mellitus. For example, the aforementioned recommendation also calls for careful attention to SGLT2 inhibitor administration, particularly for older adults aged ≥75 years and patients aged 65–74 years with geriatric syndrome[6]. It is also well known that women are more likely to experience urinary tract and genital infections[1,7]. Furthermore, because SGLT2 inhibitors increase the urinary glucose excretion[8,9], eGFR, which is indicative of renal function, is one of the important parameters to take into account for type 2 diabetes mellitus management. SGLT2 inhibitors might be less efficacious for glycemic control, in particular among patients with low eGFR (indicative of compromised renal function), as HbA1c improvement was compromised or not confirmed with SGLT2 inhibitor treatment in patients with type 2 diabetes mellitus and moderate renal impairment[10,11]. Additionally, SGLT2 inhibitors might be a beneficial treatment option, particularly for overweight/obese patients, given their effect on bodyweight reduction.

Tofogliflozin hydrate, an SGLT2 inhibitor, was approved in Japan in 2014 for type 2 diabetes mellitus treatment[12,13] under the commercial name of Apleway® (Sanofi K.K., Tokyo, Japan) and Deberza® (Kowa Company, Ltd., Nagoya, Japan). The efficacy and safety of tofogliflozin have been shown in mono- and combination therapies with other OADs and/or insulin in clinical trials[14–17], and among the elderly in a real-world study[18]. However, those findings are mainly based on clinical trials with a limited number and range of patients and study durations. Thus, to date, long-term data on tofogliflozin in a large number of Japanese patients with type 2 diabetes mellitus in a real-world setting are scarce.

We carried out a 3-year post-marketing study of tofogliflozin among Japanese patients with type 2 diabetes mellitus in a real-world setting (Japanese Study of tofogliflozin with type 2 diabetes mellitus Patients/Long Term [J-STEP/LT]), which is ongoing as of 2018. We have previously reported the 3-month results of this study, which showed a well-tolerated profile, and HbA1c and bodyweight reducing effects of tofogliflozin[19]. We, here report the 12-month results of the interim analysis to assess the safety and effectiveness of tofogliflozin, stratifying the patients according to age, sex and eGFR for safety, and eGFR and body mass index (BMI) for effectiveness.

METHODS

Study design

Details of the present study are available elsewhere[19]. In brief, the J-STEP/LT is a prospective, observational and multicenter post-marketing study that was co-sponsored by the manufacturers, Sanofi K.K. and Kowa Company, Ltd. We carried out this study in accordance with the ethical principles of the Declaration of Helsinki and the Japanese authorized standards for post-marketing surveillance, and Good Post-marketing Study Practice without intervening in the dosage and administration of tofogliflozin. As Good Post-marketing Study Practice does not require the patients' consent and approval of study protocol by the institutional review board of each participating center, we did not obtain patients' consent.

Patients and data collection

Tofogliflozin-naïve patients with type 2 diabetes mellitus were enrolled in the present study. We set no other specific restrictions for patients' inclusion; for example, age, HbA1c, concomitant medications or pre-existing diseases. The patients were instructed to use tofogliflozin 20 mg once daily, according to the package insert before or after breakfast. Patients were enrolled by a central registration system, and patients' data were recorded in electronic case report forms. Investigation parameters included demographic and baseline characteristics, AEs, adverse drug reactions (ADRs), HbA1c and bodyweight. AEs were recorded on their occurrence after tofogliflozin initiation for 12 months.

Assessment and definition

Safety was assessed by the incidence of ADRs and ADRs of special interest, and cardiovascular and cerebrovascular disorders. ADRs of special interest were stratified by age (<65 or ≥65 years), sex (male or female) and baseline eGFR (30 to <45, 45 to <60, 60 to <90 or ≥90 mL/min/1.73 m^2). ADRs were defined as the AEs that were considered to be related to tofogliflozin administration. ADRs of special interest were defined as polyuria/pollakiuria, volume depletion-related events, urinary tract infection, genital infection, hypoglycemia and skin disorders. ADRs were categorized according to the Medical Dictionary for Regulatory Activities/Japanese edition version 20.1, and classified according to System Organ Class and Preferred Term.

Effectiveness was assessed by mean changes in HbA1c levels and bodyweight. The changes in HbA1c levels and bodyweight were further stratified by baseline eGFR (<30, 30 to <45, 45 to <60, 60 to <90 or ≥90 mL/min/1.73 m^2) and BMI (<22, 22 to <25, 25 to <30 or ≥30 kg/m^2). Vital signs and clinical laboratory tests were also assessed and are summarized in the Supporting Information.

Statistical analysis

Patient characteristics and safety were analyzed descriptively for the population, and were defined for all patients for whom the electronic case report forms were collected, excluding those with no visits after the first tofogliflozin administration. The vital signs and clinical laboratory tests were analyzed for effectiveness of tofogliflozin in the population, which was defined as all patients in the safety analysis population excluding those with no effectiveness data. The mean values of HbA1c levels, bodyweight, clinical laboratory tests and vital signs were descriptively summarized. Missing data at 12 months were

imputed with the last observation carried forward (LOCF) method. The change was calculated from baseline to LOCF data and tested by one-sample *t*-test. No intergroup comparisons were carried out.

This analysis included patients who discontinued tofogliflozin during the 12-month safety and effectiveness analysis in populations; we used the available data at discontinuation or the latest available data as the data of their last observation during 12 months.

The statistical significance level was set at 5%. All analyses were carried out using statistical analysis software (SAS) release 9.3 (SAS Institute Japan Ltd., Tokyo, Japan).

RESULTS

Patients

Patient disposition and the reasons for patient exclusion from the safety and effectiveness analysis populations are shown in Figure 1. Of 6,897 patients enrolled from 1,258 institutions, electronic case report forms of 6,818 patients were collected. Safety analysis of the population consisted of 6,712 patients, and the effectiveness analysis consisted of 6,449 patients.

The mean ± SD duration of the patient observation was 320.3 ± 112.4 days. Among 6,712 patients in the safety analysis population, 1,620 patients (24.1%) discontinued the study. The percentage of patients who dropped out of the study included patients who discontinued visits (509 patients, 7.6%), showed AEs (358 patients, 5.3%), had patient requests (275 patients, 4.1%), insufficient or no response (230 patients, 3.4%), circumstances of institutions or physicians (109 patients, 1.6%), improvement in diabetes (72 patients, 1.1%) and others (67 patients, 1.0%).

Table 1 summarizes the patient characteristics at baseline. Men comprised 60.8% of the study population; and mean ± standard deviation (SD) age, duration of diabetes, BMI, eGFR and HbA1c levels at baseline were 56.9 ± 12.2 years, 8.2 ± 6.4 years, 28.7 ± 5.0 kg/m^2, 82.5 ± 22.5 mL/min/1.73 m^2 and 8.0 ± 1.5%, respectively. Diabetic complications were reported in approximately 28.0% of the patients, with diabetic nephropathy being the most commonly reported diabetic complication (21.0%).

A total of 79.7% of the patients concomitantly received antidiabetic treatment, and 77.4% of the patients concomitantly received OADs. The mean ± SD for concomitant OAD use was 2.0 ± 1.0. Dipeptidyl peptidase-4 inhibitors were the most commonly used OAD (58.1%), followed by biguanides (43.6%) and sulfonylureas (27.6%). Insulin was concomitantly used in 11.5% of the patients.

Safety

Overall, ADRs occurred in 612 patients (9.12%), and serious ADRs were observed in 59 patients (0.88%) in the safety analysis of the population (6,712 patients) during 12 months. Incidence of ADRs summarized by System Organ Class and Preferred Term are provided in Table S1. The most frequently occurring serious ADRs observed by System Organ Class were nervous system disorders and cardiac disorders (0.18% for both), followed by infections and infestations (0.16%). Seven patients died (suicide and pancreatic cancer for two patients each; aspiration pneumonia, accidental death and lung cancer for one patient each). Of these, one male patient aged 63 years with a history of smoking was diagnosed with lung cancer and discontinued tofogliflozin treatment after 11 months of

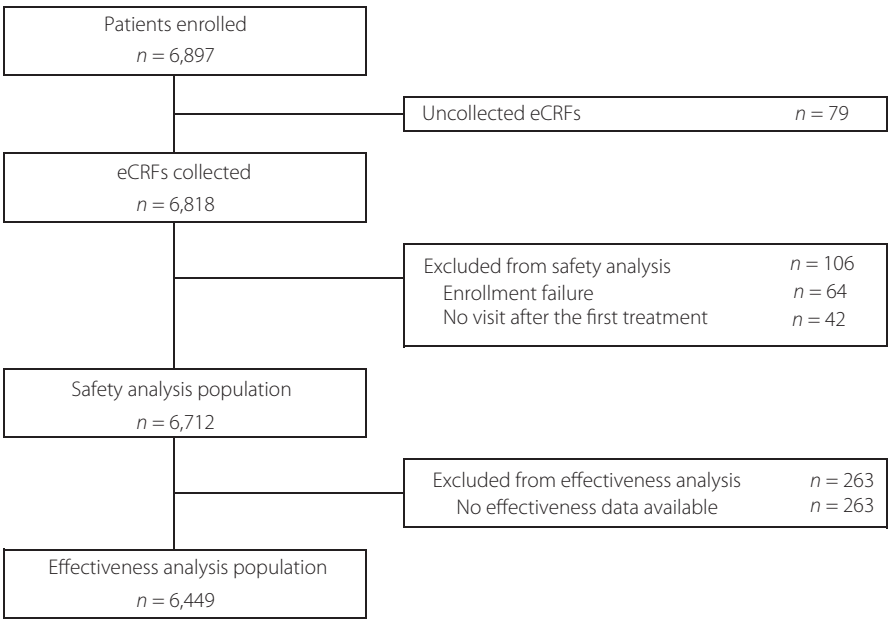


Figure 1 | Patient disposition. eCRF, electronic case report form.

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

	n	(%) or mean ± SD
No. patients	6,712	(100.0)
Sex		
Male	4,083	(60.8)
Female	2,629	(39.2)
Age (years)	6,712	56.9 ± 12.2
Duration of diabetes (years)	3,968	8.2 ± 6.4
Bodyweight (kg)	5,980	77.5 ± 16.8
BMI at baseline (kg/m^2)	5,538	28.7 ± 5.0
eGFR level at baseline (mL/min/1.73 m^2)	4,949	82.5 ± 22.5
HbA1c at baseline (%)	6,411	8.0 ± 1.5
Complications		
Diabetic complications		
Yes	1,879	(28.0)
Diabetes retinopathy	535	(8.0)
Diabetic nephropathy	1,410	(21.0)
Diabetic neuropathy	620	(9.2)
Other	11	(0.2)
Cardiovascular and cerebrovascular complications		
Yes	690	(10.3)
Cardiovascular diseases	553	(8.2)
Cerebrovascular diseases	124	(1.9)
Cardiac failures	157	(2.3)
Concomitant antidiabetic treatment		
Yes	5,349	(79.7)
Unknown	71	(1.1)
OADs		
Yes	5,197	(77.4)
Biguanide	2,925	(43.6)
Sulfonylurea	1,851	(27.6)
DPP-4 inhibitor	3,899	(58.1)
SGLT2 inhibitor	1	(0.0)
Rapid-acting insulin secretagogues	374	(5.6)
α-Glucosidase inhibitor	808	(12.0)
Thiazolidinediones	918	(13.7)
Unknown	71	(1.06)
Insulin products		
Yes	774	(11.5)
GLP-1 receptor agonists		
Yes	261	(3.9)
Concomitant use of diuretics		
Yes	433	(6.5)

BMI, body mass index; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; OADs, oral antidiabetic drugs; SD, standard deviation; SGLT2, sodium–glucose cotransporter 2.

tofogliflozin initiation. Approximately a month later, the patient died of lung cancer, which was considered by the study investigator to be related to tofogliflozin treatment.

Table 2 summarizes the incidence of ADRs of special interest. Hypoglycemia occurred in 45 patients (0.67%). Genital infection was the most common ADR of special interest (90 patients, 1.37%), followed by volume depletion-related events (80 patients, 1.19%) and polyuria/pollakiuria (73 patients, 1.09%). However, no serious events of polyuria/pollakiuria and genital infection were observed.

Incidences of ADRs of special interest were stratified by age, sex and eGFR at baseline, as shown in Figure 2. In the age subgroups, the incidence of polyuria/pollakiuria was higher in the patients aged ≥65 years (1.53%) than those aged <65 years (0.91%; Figure 2a). In the sex subgroups, urinary tract infection and genital infection were more apparent in female patients than in the male patients (urinary tract infection 2.17 vs 0.22%, genital infection 2.85 vs 0.42% for females vs males, respectively; Figure 2b). In eGFR subgroups, polyuria/pollakiuria incidence was 1.35, 2.42, 1.14 and 0.70% for eGFR of 30 to <45, 45 to <60, 60 to <90 and ≥90 mL/min/1.73 m^2, respectively (Figure 2c). Hypoglycemia and volume depletion-related events occurred most frequently in the lowest eGFR subgroup (30 to <45 mL/min/1.73 m^2; Figure 2c).

From the safety analysis population (6,712 patients), 37 patients (0.55%) reported cardiovascular and cerebrovascular disorders. Cardiovascular disorders occurred in 24 patients (0.36%), and included acute myocardial infarction (seven patients, 0.10%), angina pectoris (one patient, 0.01%), heart failure (two patients, 0.03%), cardiac failure congestive (one patient, 0.01%) and myocardial infarction (three patients, 0.04%). By age, cardiovascular disorders were reported in 20 (0.42%) patients aged <65 years, and in four (0.21%) patients aged ≥65 years. Cerebrovascular disorders were noted in 13 patients (0.19%), such as brainstem infarction (one patient, 0.01%), cerebral hemorrhage (two patients, 0.03%), cerebral infarction (five patients, 0.07%) and lacunar infarction (three patients, 0.04%). By age, cerebrovascular disorders were reported in nine (0.19%) patients aged <65 years, and in four (0.21%) patients aged ≥65 years.

Effectiveness

The mean ± SD HbA1c levels significantly decreased from 8.00 ± 1.48% (6,232 patients) at baseline to 7.24 ± 1.18% (6,354 patients) at LOCF, by −0.76 ± 1.25% (6,160 patients, $P < 0.0001$) from baseline to LOCF. The mean ± SD bodyweight also decreased significantly from 77.85 ± 16.71 kg (5,385 patients) at baseline to 75.15 ± 16.49 kg (5,532 patients) at LOCF, by −2.73 ± 3.97 kg (5,190 patients, $P < 0.0001$) from baseline to LOCF.

Figure 3 shows the results of HbA1c levels and bodyweight stratified by eGFR and BMI at baseline. Except for the lowest eGFR subgroup (<30 mL/min/1.73 m^2), the other eGFR subgroups showed significantly decreased HbA1c levels, with the reduction ranging by −0.40 ± 1.17% to −1.05 ± 1.39% ($P < 0.0001$; Figure 3a). All eGFR subgroups showed significantly decreased bodyweight ($P = 0.0209$ to $P < 0.0001$; Figure 3b). Irrespective of BMI, HbA1c levels and bodyweight decreased significantly ($P < 0.0001$ for all; Figure 3c,d).

Table 2 | Incidence of adverse drug reactions of special interest (safety analysis population)

	Incidence of ADRs of special interest, *n* (%)	
	Non-serious and serious	Serious
No. patients	6,712	
Hypoglycemia	45 (0.67)	
Hypoglycemia	45 (0.67)	4 (0.06)
Polyuria/pollakiuria	73 (1.09)	
Nocturia	12 (0.18)	–
Pollakiuria	53 (0.79)	–
Polyuria	6 (0.09)	–
Urine output increased	2 (0.03)	–
Volume depletion-related events	80 (1.19)	
Blood urea increased	14 (0.21)	–
Cerebral infarction	5 (0.07)	4 (0.06)
Constipation	19 (0.28)	–
Dehydration	26 (0.39)	3 (0.04)
Depressed level of consciousness	1 (0.01)	1 (0.01)
Dry mouth	1 (0.01)	–
Myocardial infarction	3 (0.04)	2 (0.03)
Polycythemia	2 (0.03)	–
Thirst	8 (0.12)	–
Lacunar infarction	3 (0.04)	3 (0.04)
Heat illness	2 (0.03)	1 (0.01)
Acute kidney injury	1 (0.01)	1 (0.01)
Urinary tract infection	66 (0.98)	
Bacteriuria	1 (0.01)	–
Cystitis	30 (0.45)	1 (0.01)
Pyelonephritis	1 (0.01)	–
Pyelonephritis acute	3 (0.04)	3 (0.04)
Sepsis	1 (0.01)	1 (0.01)
Sepsis shock	2 (0.03)	2 (0.03)
Urethritis	5 (0.07)	–
Urinary tract infection	23 (0.34)	3 (0.04)
Cystitis-like symptoms	2 (0.03)	–
Cystitis bacterial	1 (0.01)	–
Genital infection	92 (1.37)	
Balanitis candida	1 (0.01)	–
Balanoposthitis	8 (0.12)	–
Genital candidiasis	3 (0.04)	–
Genital herpes	1 (0.01)	–
Penile pain	1 (0.01)	–
Prostatitis	1 (0.01)	–
Pruritus genital	30 (0.45)	–
Vaginal infection	3 (0.04)	–
Vulvitis	3 (0.04)	–
Vulvovaginal candidiasis	14 (0.21)	–
Genital infection	18 (0.27)	–
Vulvovaginal pruritus	3 (0.04)	–
Genital infection female	1 (0.01)	–
Vulvar erosion	5 (0.07)	–
Candida infection	3 (0.04)	–
Skin disorders	45 (0.67)	
Cellulitis	1 (0.01)	1 (0.01)
Dermatitis	2 (0.03)	–
Drug eruption	1 (0.01)	–
Eczema	7 (0.10)	–
Erythema	1 (0.01)	–
Herpes zoster	1 (0.01)	–
Pruritus	7 (0.10)	–
Rash	11 (0.16)	–
Rash erythematous	2 (0.03)	–
Rash generalised	2 (0.03)	–
Rash pruritic	2 (0.03)	–
Seborrhoeic dermatitis	1 (0.01)	–
Skin disorder	1 (0.01)	–
Skin erosion	1 (0.01)	–
Skin infection	1 (0.01)	–
Skin ulcer	1 (0.01)	1 (0.01)
Tinea pedis	1 (0.01)	–
Urticaria	1 (0.01)	–
Pruritus generalised	2 (0.03)	–

Individual adverse drug reactions (ADRs) were coded according to Medical Dictionary for Regulatory Activities/Japanese edition version 20.1 classified according to Preferred Term.

Vital signs and clinical laboratory tests

The vital signs and clinical laboratory tests are shown in Table S2. From baseline to LOCF, the mean ± SD reduction in statistical significance ($P < 0.0001$) included fasting plasma glucose (−33.19 ± 60.50 mg/dL), BMI (−1.02 ± 1.46 kg/m^2), systolic blood pressure (−3.9 ± 15.4 mmHg) and diastolic blood pressure (−2.5 ± 10.3 mmHg). The mean ± SD eGFR also decreased significantly ($P < 0.0001$), from 82.46 ± 22.45 mL/min/1.73 m^2 (4,815 patients) at baseline to 80.57 ± 22.66 mL/min/1.73 m^2 (5,312 patients) at LOCF, by −1.92 ± 12.64 mL/min/1.73 m^2 (4,521 patients).

DISCUSSION

We carried out the present 12-month interim analysis to assess the safety and effectiveness of tofogliflozin in the real-world clinical setting in Japanese patients with type 2 diabetes mellitus. During the 12 months, ADRs and serious ADRs occurred in 9.12 and 0.88% of the patients, respectively. The incidence of hypoglycemia, ADRs of special interest, was low (0.67%). No new safety concerns were found, and the HbA1c levels and bodyweight decreased significantly by −0.76% and −2.73 kg, respectively, from baseline to LOCF.

The incidence of ADRs and serious ADRs increased slightly from the 3 months[19] to 12 months (ADRs 5.14–9.12%, and serious ADRs 0.45–0.88% from 3 months[19] to 12 months, respectively); however, they remained relatively low. A similar ADR incidence was reported in a previous ipragliflozin study

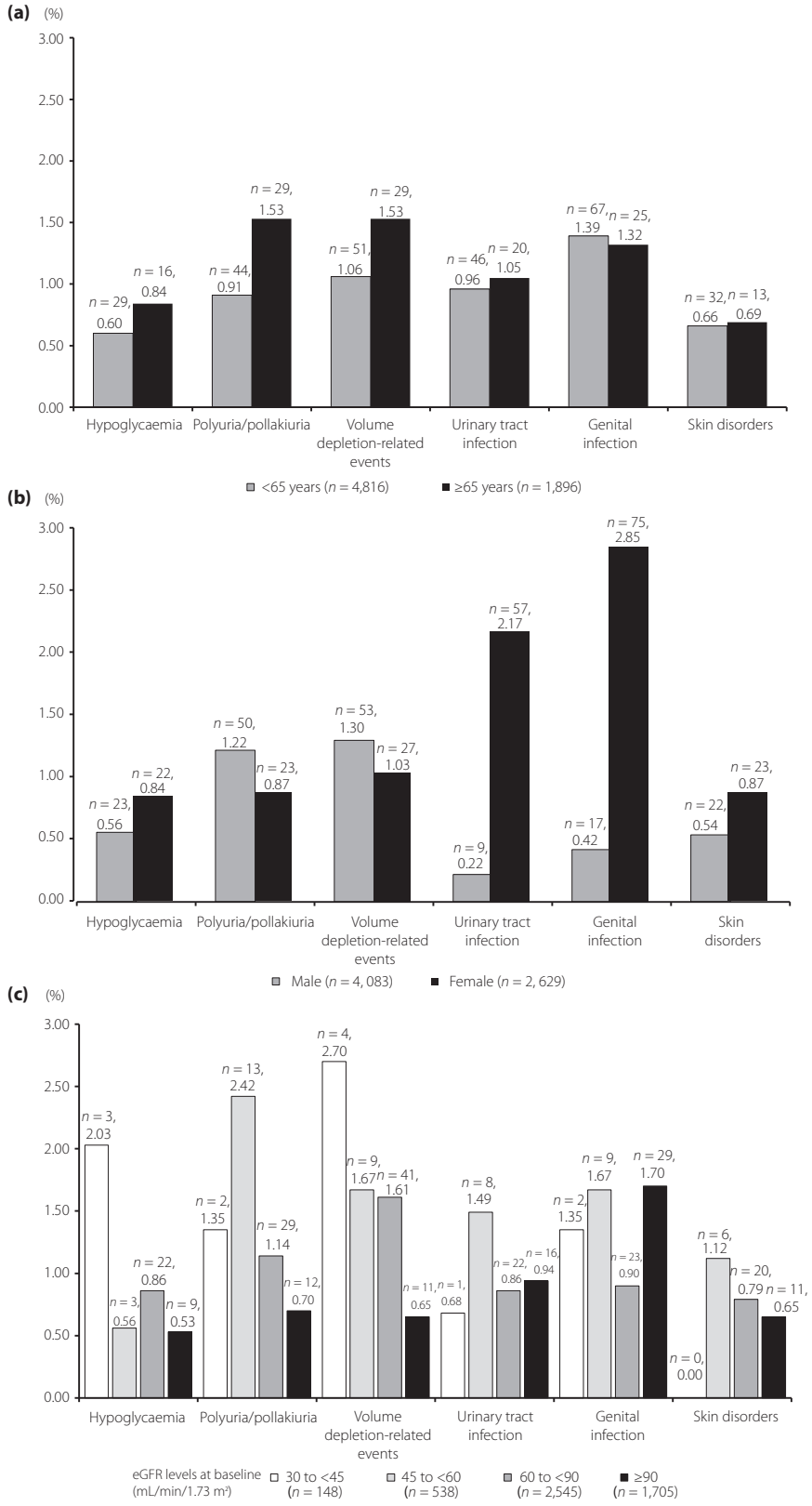
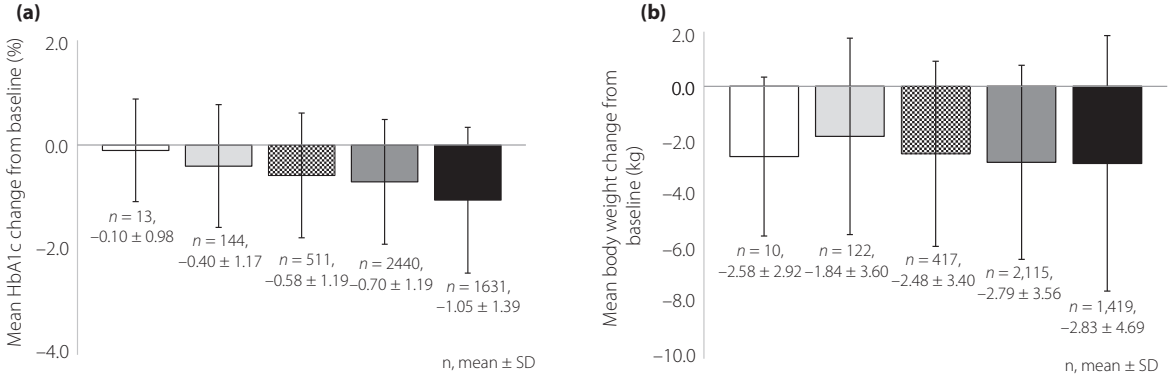


Figure 2 | Incidence of adverse drug reactions of special interest stratified by patient characteristics. (a) Age subgroups. (b) Sex subgroups. (c) Estimated glomerular filtration rate level subgroups. No adverse drug reactions of special interest occurred at estimated glomerular filtration rate levels <30.

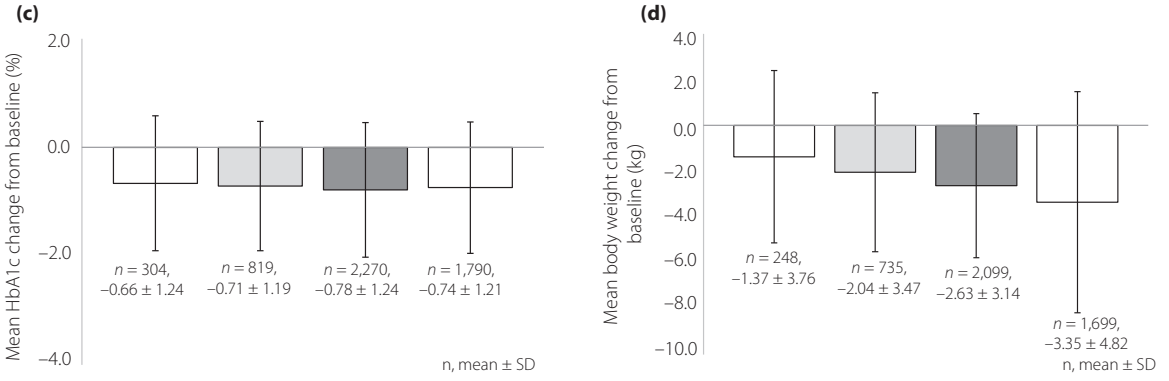
1) eGFR subgroup



eGFR levels at baseline (mL/min/1.73 m²) □ <30 □ 30 to <45 ▩ 45 to <60 ■ 60 to <90 ■ ≥90

eGFR levels at baseline	HbA1c (%), mean ± SD(n)				Body weight (kg), mean ± SD (n)			
	Baseline	LOCF	Change	*P*-value†	Baseline	LOCF	Change	*P*-value†
<30	7.18 ± 0.89 (13)	7.08 ± 0.93 (13)	−0.10 ± 0.98 (13)	*P* = 0.7204	77.51 ± 30.51 (12)	75.89 ± 32.79 (11)	−2.58 ± 2.92 (10)	*P* = 0.0209
30 to <45	7.72 ± 1.46 (145)	7.33 ± 1.25 (145)	−0.40 ± 1.17 (144)	*P* < 0.0001	71.66 ± 15.04 (125)	69.40 ± 15.50 (131)	−1.84 ± 3.60 (122)	*P* < 0.0001
45 to <60	7.76 ± 1.29 (521)	7.20 ± 1.02 (517)	−0.58 ± 1.19 (511)	*P* < 0.0001	74.46 ± 15.54 (447)	72.23 ± 14.92 (438)	−2.48 ± 3.40 (417)	*P* < 0.0001
60 to <90	7.83 ± 1.38 (2,459)	7.13 ± 1.09 (2,450)	−0.70 ± 1.19 (2,440)	*P* < 0.0001	77.04 ± 16.03 (2,182)	74.19 ± 15.66 (2,209)	−2.79 ± 3.56 (2,115)	*P* < 0.0001
≥90	8.39 ± 1.65 (1,651)	7.34 ± 1.31 (1,635)	−1.05 ± 1.39 (1,631)	*P* < 0.0001	80.27 ± 17.59 (1,461)	77.49 ± 17.57 (1,474)	−2.83 ± 4.69 (1,419)	*P* < 0.0001

2) BMI subgroup



BMI at baseline (kgn/m²) □ <22.0 □ 22.0 to <25.0 ■ 25.0 to <30.0 ■ ≥30.0

BMI at baseline	HbA1c (%), mean ± SD(n)				Body weight (kg), mean ± SD (n)			
	Baseline	LOCF	Change	*P*-value†	Baseline	LOCF	Change	*P*-value†
<22.0	7.94 ± 1.48 (307)	7.28 ± 1.29 (313)	−0.66 ± 1.24 (304)	*P* < 0.0001	53.59 ± 7.47 (266)	52.54 ± 8.24 (271)	−1.37 ± 3.76 (248)	*P* < 0.0001
22.0 to <25.0	7.87 ± 1.42 (828)	7.16 ± 1.09 (839)	−0.71 ± 1.19 (819)	*P* < 0.0001	63.50 ± 7.72 (775)	61.52 ± 7.97 (768)	−2.04 ± 3.47 (735)	*P* < 0.0001
25.0 to <30.0	8.01 ± 1.46 (2,297)	7.23 ± 1.14 (2,320)	−0.78 ± 1.24 (2,270)	*P* < 0.0001	74.10 ± 9.26 (2,174)	71.49 ± 9.49 (2,188)	−2.63 ± 3.14 (2,099)	*P* < 0.0001
≥30.0	8.02 ± 1.47 (1,808)	7.29 ± 1.22 (1,842)	−0.74 ± 1.21 (1,790)	*P* < 0.0001	92.59 ± 14.76 (1,737)	89.26 ± 15.05 (1,769)	−3.35 ± 4.82 (1,699)	*P* < 0.0001

Figure 3 | Results of glycated hemoglobin (HbA1c) and bodyweight stratified by estimated glomerular filtration rate (eGFR) and body mass index (BMI). (a,b) HbA1c and bodyweight changes in eGFR subgroups. (c,d) HbA1c and bodyweight changes in BMI subgroups. †One-sample *t*-test. LOCF, last observation carried forward; SD, standard deviation.

in the clinical setting (10.71% during 24 months); although the direct comparison with that study is limited by the differences in study design, such as the study duration[20]. Similarly, the incidence of ADRs of special interest during 12 months increased slightly, but was not considerably different from the 3-month results (hypoglycemia 0.37–0.67%, polyuria/pollakiuria 0.74–1.09%, volume depletion-related events 0.36–1.19%, urinary tract infection 0.60–0.98%, genital infection 0.83–1.37% and skin disorders 0.48–0.67% from 3 months[19] to 12 months). Consistent with the 3-month results, tofogliflozin was generally well tolerated, given the relatively low incidence of ADRs, including the serious events and ADRs of special interest, and no new safety concerns were observed during the 12 months of clinical administration.

Owing to the insulin-independent mechanism of action of SGLT2 inhibitors, the risk of hypoglycemia is low with SGLT2 inhibitors[1,3,8]. In the present study, the overall hypoglycemia incidence was low (0.67%), and did not differ notably in any of the subgroups (0.60–0.84% for age subgroups, 0.56–0.84% for sex subgroups and 0.53–2.03% for eGFR subgroups). The above-mentioned ipragliflozin study reported a similar hypoglycemia incidence (0.22% during 24-months), despite the differences in study design[20]. In a previous 1-year tofogliflozin study among the elderly in clinical settings, hypoglycemia (as ADRs) occurred in 1.06% of the patients aged ≥65 years[18]. A pooled luseogliflozin analysis of clinical trials reported that hypoglycemia as an AE occurred in 3.3–5.4% of the patients with eGFR 30 to <45, 45 to <60, 60 to <90 and ≥90 mL/min/1.73 m^2 [11]. The present findings suggest that tofogliflozin also presents a low risk of hypoglycemia in a range of patients, because hypoglycemia incidence remained low irrespective of age, sex or eGFR among patients with various characteristics in the clinical settings included in the present study.

Because SGLT2 inhibitors stimulate glycosuria[8], ADRs, such as polyuria/pollakiuria and volume depletion-related events, might be induced[1,3,21]. In the present study, polyuria/pollakiuria occurred at a slightly higher rate among the elderly (1.53 vs 0.91% for ≥65 vs <65 years, respectively), and occurred in 0.70–2.42% of eGFR subgroups of 30–≥90 mL/min/1.73 m^2. In the above-mentioned tofogliflozin study among the elderly, 2.92% of the patients aged ≥65 years reported polyuria/pollakiuria as ADRs[18]. The luseogliflozin study reported that 1.7–4.7% of the patients with eGFR 30 to ≥90 mL/min/1.73 m^2 experienced AEs related to pollakiuria[11]. As for volume depletion-related events during 12 months, the lowest eGFR subgroup (30 to <45 mL/min/1.73 m^2) experienced the most volume depletion (2.70%). This was also observed in the aforementioned luseogliflozin study among Japanese patients with the same eGFR (30 to <45 mL/min/1.73 m^2), indicating moderate-to-severe renal impairment, which was reported in 11.1% of the patients experiencing AEs related to volume depletion, the highest among the eGFR groups[11]. Taken together, the physicians should provide thorough instructions for sufficient fluid intake, particularly for the elderly and patients with comparatively low eGFR while administering tofogliflozin.

Urinary tract infections and genital infections are more likely to occur among female patients[1,7]. Consistent with these observations, the incidence was higher in the female patients in the present study (urinary tract infection 2.17 vs 0.22%, genital infection 2.85 vs 0.42% for women vs men, respectively), although these incidences remained low, and serious events were rare or none. Urinary tract and genital infections should be borne in mind when administering tofogliflozin to female patients in particular, although these events are generally rare and mild.

During the 12 months, the cerebrovascular disorders occurred rarely (0.19% in total). The package insert of tofogliflozin calls attention to events such as thrombosis and embolism, including cerebral infarction, particularly for patients who are likely to experience volume depletion. As we also confirmed the cerebrovascular events in the present study, we suggest that physicians should pay careful attention when administering tofogliflozin, especially for patients with volume depletion risk, especially for elderly patients and patients using diuretics. However, the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients trial showed that combined use of diuretics and empagliflozin was not associated with an increased risk of stroke[22,23]. Indeed, further studies are required before drawing any conclusions.

As for effectiveness, tofogliflozin significantly reduced HbA1c levels by −0.76%, and bodyweight by −2.73 kg from baseline to 12-month LOCF. All BMI subgroups showed reduced HbA1c levels and bodyweight. All eGFR subgroups also showed reduced HbA1c and bodyweight, however, HbA1c reduction was higher in higher eGFR subgroups, whereas bodyweight reduction did not largely differ among groups. Patients with moderate renal impairment (eGFR 30 to <60 mL/min/1.73 m^2) are less likely to respond to SGLT2 inhibitors to cause HbA1c reduction in particular[10,11]. Diminished efficacy among patients with renal impairment might again be explained by the mechanism of action of SGLT2 inhibitors. As the amount of glucose excreted depends on the glomerular filtration rate, low eGFR might result in lesser urinary glucose excretion, thereby leading to reduced efficacy among the patients with renal impairment[8,9].It should also be noted that SGLT2 inhibitors might reduce eGFR, as has been observed in the present study, although the reduction generally continues only for short period, and can be reversed and stabilized over time[20,24,25]. Hence, for patients with low eGFR, physicians should initiate tofogliflozin administration after careful risk–benefit consideration of its use, or should continuously monitor eGFR, given the modest HbA1c reduction and already impaired renal function. However, because the bodyweight-reducing effect of tofogliflozin was less likely to be diminished regardless of the eGFR when compared with the HbA1c-lowering effect, tofogliflozin might be a treatment option for overweight patients with relatively low eGFR and generally controlled HbA1c.

The results of the present study should be interpreted with care. First, the results of this interim analysis are not solely attributable to tofogliflozin, as this study was carried out in a clinical setting. For example, the effects of other factors, such as concomitant pharmacological therapies and comorbidities among the patients, might have affected the study results to some extent. Second, owing to the lack of comparator, we cannot determine the effect of tofogliflozin. Finally, a comparatively small number of the patients with low eGFR (<30, and 30 to <45 mL/min/1.73 m^2) were included in this interim analysis, which might partially limit the interpretation of the results for those with low eGFR. However, SGLT2 inhibitors, including tofogliflozin, are not recommended for patients with severe renal impairment, and administration should be carefully considered for patients with moderate renal impairment. Hence, the small number of patients with low eGFR included in this analysis is reasonable, assuming that the study investigators administered tofogliflozin properly, as indicated.

In conclusion, our interim 12-month data suggest that tofogliflozin could be used safely and effectively for Japanese patients with type 2 diabetes mellitus and a wide range of patient characteristics, was generally well-tolerated with a low risk of hypoglycemia, and also significantly improved both HbA1c and bodyweight in the clinical setting. Owing to the paucity of information on long-term safety and effectiveness of tofogliflozin in clinical settings, the present study and further studies are expected to contribute to the literature, enhancing the management of type 2 diabetes mellitus.

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SUPPORTING INFORMATION

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

Table S1 | Overall summary of the incidences of adverse drug reactions (safety analysis population).
Table S2 | Results of vital signs and clinical laboratory tests.