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Safety and effectiveness of tofogliflozin in Japanese people with type 2 diabetes: A multicenter prospective observational study in routine clinical practice

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ABSTRACT

Aims/Introduction: Sodium–glucose cotransporter 2 (SGLT2) inhibitors effectively and safely reduce fasting and postprandial hyperglycemia while promoting weight loss. However, their unique mechanism of action contributes to concerns regarding their safety. We therefore carried out a large-scale, non-commercial, investigator-initiated study on the safety and effectiveness of the SGLT2 inhibitor tofogliflozin.

Materials and Methods: This multicenter, open-label, uncontrolled, prospective observational study was carried out at hospitals and clinics across Japan in participants aged ≥20 years who were SGLT2 inhibitor-naïve and had an established diagnosis of type 2 diabetes. The primary endpoint was adverse drug reactions (ADRs) of special interest. Secondary endpoints included all other ADRs and adverse events, glycated hemoglobin (HbA1c), and weight loss.

Results: The study, carried out from June 2014 through February 2020, enrolled 11,480 participants from 1,103 medical institutions; 6,967 participants completed the 104-week follow up. The most common ADRs of special interest were urinary and genital tract infections (1.53%), followed by volume depletion (1.25%). Hypoglycemia occurred in 27 participants (0.24%), adverse events in 1,054 (9.18%) and ADRs in 645 (5.62%). HbA1c decreased by 0.85% (95% confidence interval 0.82%–0.88%) and bodyweight decreased by 3.05 kg (95% confidence interval 2.94–3.17 kg). The HbA1c target was achieved by 51.70% of participants for target HbA1c <7.0%, 85.3% for <8.0% and 5.4% for <6.0% at week 104.

Conclusions: Tofogliflozin was associated with only mild or moderate ADRs characteristic of SGLT2 inhibitors, with no unpredictable, new, serious, or high-incidence adverse events or ADRs. This independent study confirmed the safety and effectiveness of tofogliflozin in adult type 2 diabetes patients.

INTRODUCTION

A wide range of glucose-lowering agents are available for glycemic management in people with type 2 diabetes, including both oral and parenteral drugs for use singly or in combination. However, despite the large number of treatment options, existing therapies are often unable to adequately manage blood glucose levels[1]. In addition, each of these drugs has been linked to specific adverse drug reactions (ADRs), such as hypoglycemia

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and weight gain[2], that are associated with their respective mechanisms of action, making avoidance of ADRs a major challenge in diabetes treatment.

Sodium–glucose cotransporter 2 (SGLT2) inhibitors first became available for clinical use in Japan in 2014, and are currently recommended in international and Japanese guidelines as a useful option for the treatment of type 2 diabetes[3,4]. SGLT2 inhibitors inhibit glucose reabsorption in the proximal renal tubules, increasing the excretion of glucose and thereby decreasing total blood glucose. Because of their mechanism of action, the SGLT2 inhibitors carry a low risk of hypoglycemia and are also associated with weight loss[5]. Thus, SGLT2 inhibitors are expected to have a lower incidence of the various ADRs associated with other oral glucose-lowering agents[6].

However, SGLT2 inhibitors are relatively new, and their mechanism of action has been associated with ADRs, including urinary tract infection (UTI), genital tract infection (GTI) and loss of body fluids[7–10]. Concerns have also been raised regarding increased risk of ketoacidosis and possible bone resorption and fracture[11,12]. These questions signal the need to investigate the safety and effectiveness of SGLT2 inhibitors in a large number of people with type 2 diabetes in routine clinical practice.

Tofogliflozin, the drug under investigation in the present study, is an SGLT2 inhibitor that was approved in Japan in 2014. Clinical trials have shown substantial glucose-lowering effects in combination with other oral glucose-lowering agents and insulin, and the drug has been well tolerated without serious adverse events (AEs)[13,14]. A recently reported 3-year post-marketing surveillance (PMS) study in Japan confirmed the safety and effectiveness of tofogliflozin in clinical use[15], but that study was carried out by a drug development company as an extension of their clinical trial. A large-scale, non-commercial, investigator-initiated study is needed to explore safety and effectiveness from the perspectives of physicians and patients with diabetes involved in diabetes treatment.

The Japan Association for Diabetes Education and Care (JADEC) is a public interest organization comprising people with diabetes, medical professionals, other citizens and companies involved in diabetes care. In the present study, JADEC conducted a large-scale prospective observational study to examine the safety and effectiveness of tofogliflozin in more than 10,000 people with type 2 diabetes in routine clinical practice in hospitals and clinics across Japan.

MATERIALS AND METHODS

Study design

This multicenter, open-label, uncontrolled, prospective observational study was designed by JADEC to collect information on the safety and effectiveness of SGLT2 inhibitors for people with type 2 diabetes in routine clinical practice. Companies that had SGLT2 inhibitors on the market were notified, and then JADEC carried out a public call for sponsors of the study on its website from 8 January to 31 January 2014. After assessing the responses to that call, we decided to select Kowa Company, Ltd., as the study sponsor and to use tofogliflozin as the study drug. The enrollment period was planned for 208 weeks, from June 2014 to May 2018, with early termination of enrollment to be considered if the target number of participants was reached before the end of the period. Maximum follow up was 104 weeks. The study planned to enroll 10,000 participants in 1,000–2,000 prospective medical institutions nationwide that agreed with the purpose of this study, including university hospitals, flagship hospitals and independent general practitioners. The protocol for the research project was approved by a suitably constituted Ethics Committee of the institutions within which the work was undertaken. Registration No. UMIN000014129.

Participants

The participants were SGLT2 inhibitor-naïve participants aged ≥20 years with an established type 2 diabetes diagnosis when the tofogliflozin prescription was initiated. They had received their tofogliflozin prescription within the previous 8 weeks and in the context of routine clinical practice as described in the package insert. Participants were excluded from participation if they had a history of sensitivity to the ingredients of tofogliflozin or a history of severe ketosis, diabetic coma or precoma, had severe infections, were pre- or post-surgery, were recovering from severe trauma, were in end-stage renal failure requiring dialysis, or were considered by the principal investigator or subinvestigator to be otherwise unsuited to participate in the study.

Outcomes

The primary endpoint was safety, including the occurrence, severity and incidence proportion of ADRs of special interest; that is, hypoglycemia, UTI and GTI (UTI/GTI), fluid volume depletion through dehydration, polyuria/pollakiuria or hypotension, diabetic ketoacidosis, renal dysfunction, liver dysfunction, bone fractures, malignancy, cardiovascular or cerebrovascular events, or skin symptoms. Secondary safety endpoints were all other ADRs and AEs. Secondary endpoints related to effectiveness included amount of change from before administration of tofogliflozin in glycated hemoglobin (HbA1c), blood glucose, total cholesterol, low-density lipoprotein cholesterol (calculated), high-density lipoprotein cholesterol, triglycerides, uric acid, weight and blood pressure, and proportion of patients achieving each targeted value of HbA1c (<6.0%, <7.0% and <8.0%). Additionally, post-hoc analysis was carried out in subgroups for AEs and ADRs stratified by participant characteristics of sex, age and body mass index (BMI).

ADRs were defined as "AEs that occurred after administration of tofogliflozin and for which, in the judgment of the primary physician, a causal relationship to tofogliflozin could not be ruled out;" AEs were defined as "undesirable symptoms or signs that occurred in study participants." An AE was considered serious if it was fatal or life-threatening, required hospitalization or prolongation of hospitalization for treatment, resulted in permanent or marked disability or dysfunction, or resulted

in other events or reactions that were considered medically significant.

Data collection

Principal investigators and subinvestigators confirmed that participants met the inclusion criteria and did not meet the exclusion criteria, enrolled those participants into the electronic data capture system (Viedoc Technologies, Uppsala, Sweden) on the study website, and entered survey item data into that system.

Tofogliflozin treatment was started after participant enrollment at a dose of 20 mg orally once daily before or after breakfast. Data were entered into the electronic data capture system at 12, 24, 52 and 104 weeks after the start of treatment, using the pre-tofogliflozin data as the baseline. The survey ended after 104 weeks of data entry. If the survey was discontinued before 104 weeks, data at the time of discontinuation were entered. AEs were entered at the time of occurrence.

Statistical analysis

The Japanese "Guideline for Clinical Evaluation of Oral Hypoglycemic Agents"[16] recommends that investigatory drugs be evaluated in combination with all groups of drugs that might be used concomitantly. Therefore, when this study was planned, the need for a sufficiently large sample size to enable evaluation of the concomitant use of tofogliflozin with the least prescribed supplementary glucose-lowering drug was taken into consideration to more accurately reflect clinical conditions. According to basic aggregated data from the Japan Diabetes Clinical Data Management Study Group, glucagon-like peptide-1 receptor agonists represent the smallest proportion of supplementary prescriptions for SGLT inhibitors in people with type 2 diabetes, which is estimated at 2.0%; the proportion receiving concomitant oral glucose-lowering agents was estimated at 60%. For additional context, findings from a questionnaire completed by members of JADEC (2007)[17] showed that 13% of people with type 2 diabetes had discontinued diabetes treatment. Thus, to collect data on the concomitant use of glucagon-like peptide-1 receptor agonists with tofogliflozin in 100 participants, the study would need to enroll approximately 10,000 participants: $100 / (0.02 \times 0.6 \times [1 - 0.13]) = 9{,}578$.

Safety was evaluated from the safety analysis set, consisting of participants enrolled in the study who had taken the study drug at least once. Primary effectiveness analysis was performed on the full analysis set, which was the population of all participants enrolled in the study who received at least one dose of the study drug after enrollment, who visited the study site at least once during the treatment period and for whom effectiveness data were available. Participants for whom baseline data were unavailable and participants with serious protocol violations were excluded from the full analysis set.

For participant characteristics in the analysis set, the incidence and proportion of each category were calculated for nominal variables; summary statistics were calculated for continuous variables. For analysis of the primary endpoint, the incidence and proportion of predefined ADRs and serious ADRs were calculated for each category based on the classifications of the Common Terminology Criteria for Adverse Events, version 4.0. Incidence and proportion were also calculated for analyzing secondary safety endpoints. For the safety subgroup analyses, the incidence and proportion of AEs and ADRs were classed by sex, age (<65, 65–75 and ≥75 years) and BMI at baseline (stratified by median BMI). A χ^2-test was used for between-group comparisons, stipulating a two-sided significance level of 5%. Summary statistics were used for changes over time in parameters of the secondary effectiveness endpoints, and incidence and proportion of achieving the HbA1c target were estimated. All statistical analyses were carried out using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Participants

Enrollment was from June 2014 to the end of February 2018, and the study period was from June 2014 to the end of February 2020. A total of 1,103 medical institutions (223 hospitals and 880 clinics) across Japan participated in the study.

The study had 12,816 participant candidates, enrolled 11,972 and excluded 492 who had no record of tofogliflozin administration at baseline, leaving 11,480 participants in the safety analysis population and the full analysis set. A total of 6,967 participants completed the 104-week follow up (Figure 1).

Men comprised 62.7% of the participants, whose mean age was 59.5 ± 13.1 years, BMI 27.8 ± 5.1 kg/m^2, mean HbA1c 8.0 ± 1.5% and mean duration of diabetes 7.5 ± 7.2 years (Table 1).

Safety

Of the 10 predefined ADRs, UTI/GTIs were the most common (1.53% of participants), followed by fluid volume depletion (1.25%). Hypoglycemia occurred in 27 participants (0.24%). Very few serious ADRs were observed, the most common being cardiovascular and cerebrovascular events in 0.15% of the participants (Table 2).

Among the 11,480 participants, AEs occurred in 1,054 (9.18%) and ADRs in 645 (5.62%). Serious events and reactions occurred in 198 (1.72%) and 48 participants (0.42%), respectively. Other than the 10 events included in the primary endpoint, gastrointestinal disorders accounted for both the most commonly occurring AEs and the most commonly occurring ADRs (0.97% and 0.40%, respectively; Table 3).

In subgroup analysis, significant differences were noted for some categories of AEs and ADRs. Among AEs, UTI/GTIs were more common in women than men, and were also more common in participants with BMI ≥27.0 kg/m^2 (the median BMI in this study) than those with BMI <27.0 kg/m^2. Greater volume depletion was noted in participants with BMI ≥27.0 kg/m^2 than in those with BMI <27.0 kg/m^2. Bone fractures and skin symptoms were more common in women than in men, malignancies were more common in the older age groups, and

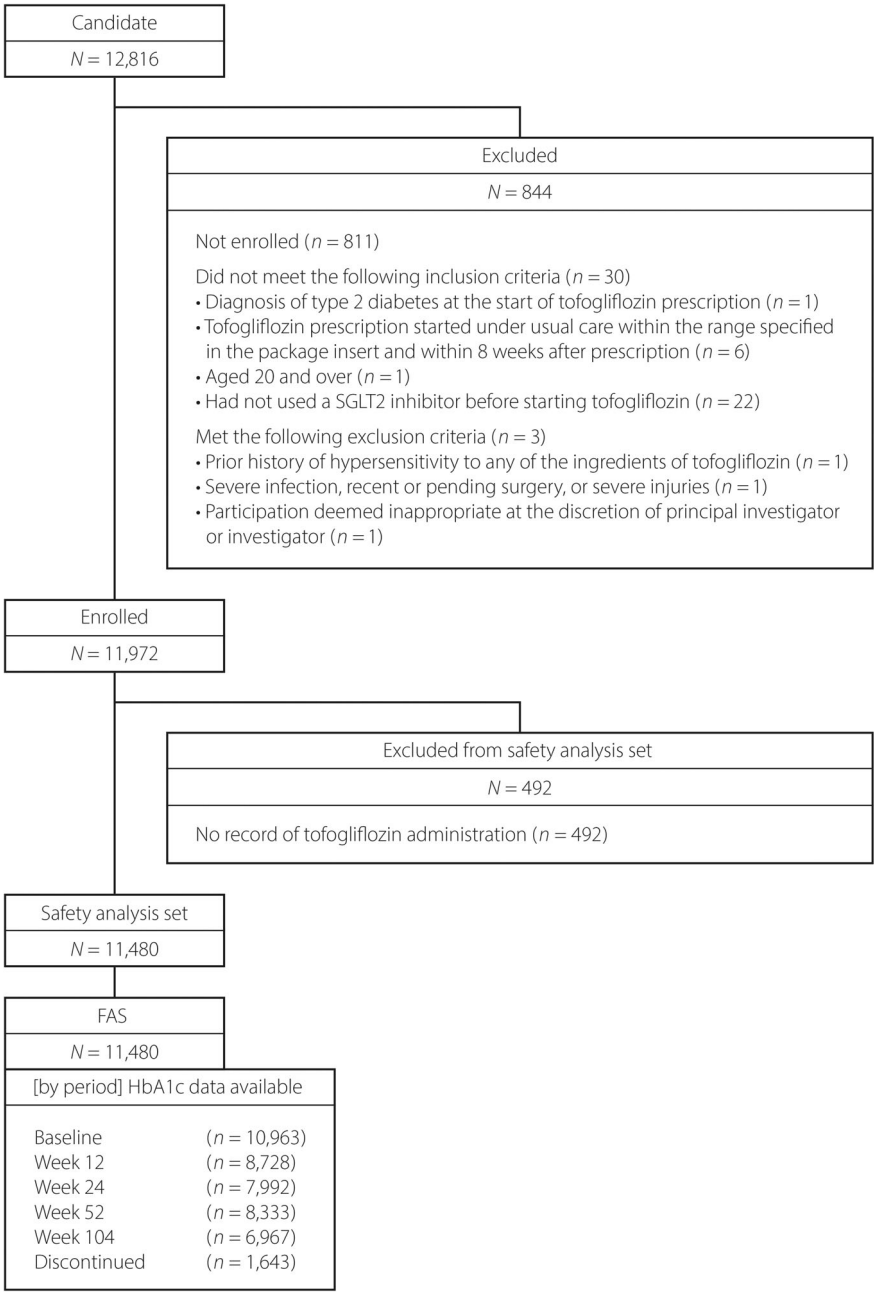

Figure 1 | Participant disposition. FAS, full analysis set; HbA1c, glycated hemoglobin; SGLT2, sodium–glucose cotransporter 2.

cardiovascular and cerebrovascular events were more common in men than in women and in older age groups. Among ADRs, UTI/GTIs were more common in younger age groups in addition to the differences noted above between sexes and BMI categories. Differences in volume depletion in different BMI categories were similar to those seen with AEs. Renal dysfunction and skin symptoms were more common in women than in men. Cardiovascular and cerebrovascular events were more common in participants with BMI <27.0 kg/m^2 than in those with BMI ≥27.0 kg/m^2. Unlike the situation with AEs, there were no age-related differences in malignancies or cardiovascular and cerebrovascular events related to ADRs (Table 4).

Effectiveness

Although all parameters improved significantly at each time point, their patterns of change over time differed slightly, depending on the parameter. HbA1c and blood glucose decreased by 0.85% (95% confidence interval 0.82%–0.88%)

Table 1 | Participant characteristics

	N	*n* (%) or mean ± SD
Sex		
Female	11,480	4,281 (37.3)
Male		7,199 (62.7)
Age (years)	11,480	59.5 ± 13.1
20–29		105 (0.9)
30–39		651 (5.7)
40–49		2,018 (17.6)
50–59		2,726 (23.8)
60–69		3,353 (29.2)
70–79		1,965 (17.1)
80–89		624 (5.4)
90–99		38 (0.3)
Body height (cm)	10,140	163.4 ± 9.5
Bodyweight (kg)	10,301	74.6 ± 16.5
BMI (kg/m^2)	9,752	27.8 ± 5.1
<20		258 (2.7)
20–24.9		2,780 (28.5)
25–29.9		4,057 (41.6)
≥30		2,657 (27.3)
HbA1c (%)	10,963	8.0 ± 1.5
Diabetes duration (years)	11,259	7.5 ± 7.2
Concomitant disease	11,443	7,754 (67.8)
Past medical history	11,443	2,830 (24.7)
Pretreatment for diabetes		
Diet therapy	11,471	8,041 (70.1)
Exercise therapy	11,471	6,775 (59.1)
Drug therapy	7,759	6,034 (77.8)
Concomitant drugs other than antidiabetic drugs		
Antihypertensive drugs	11,443	5,945 (52.0)
Lipid-lowering drugs		5,564 (48.6)
Antiplatelet drugs		1,238 (10.8)
Drinking history	11,442	3,150 (27.5)
Smoking history	11,440	3,213 (28.1)
Family history of diabetes	11,437	4,110 (35.9)

BMI, body mass index; HbA1c, glycated hemoglobin; SD, standard deviation.

and 36.25 mg/dL (95% confidence interval 34.50–38.01 mg/dL) at 104 weeks, respectively. Those values decreased notably by 12 weeks after the start of treatment, and the decreases were sustained throughout the rest of the treatment period. Systolic and diastolic blood pressure, triglycerides, and uric acid also improved in the same manner. Bodyweight decreased by 3.05 kg (95% confidence interval 2.94–3.17 kg) at 104 weeks, improving notably by 12 weeks after the start of treatment, and tending to improve further over time. Total cholesterol, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol improved over time (Figure 2 and Table S1).

The proportion of participants achieving their HbA1c target increased over time, but it was not a marked increase when that target was <7.0% (42.1% of participants at Week 12, 51.7% at Week 104). The proportion was 85.3% for HbA1c <8.0% and 5.4% for <6.0% at Week 104 (Figure 3).

Table 2 | Primary endpoint: Incidence of adverse drug reactions and adverse events of special interest

N = 11,480	ADRs		AEs	
	All *n* (%)	Serious *n* (%)	All *n* (%)	Serious *n* (%)
Hypoglycemia	27 (0.24)	2 (0.02)	31 (0.27)	2 (0.02)
UTI and genital tract infection	176 (1.53)	2 (0.02)	183 (1.59)	2 (0.02)
Volume depletion (dehydration, polyuria/ pollakiuria, hypotension)	144 (1.25)	1 (0.01)	153 (1.33)	2 (0.02)
Diabetic ketoacidosis	5 (0.04)	1 (0.01)	6 (0.05)	1 (0.01)
Renal dysfunction	31 (0.27)	6 (0.05)	45 (0.39)	8 (0.07)
Liver dysfunction	8 (0.07)		39 (0.34)	1 (0.01)
Bone fracture	1 (0.01)	1 (0.01)	16 (0.14)	8 (0.07)
Malignancy	6 (0.05)	5 (0.04)	52 (0.45)	44 (0.38)
Cardiovascular and cerebrovascular events	31 (0.27)	17 (0.15)	100 (0.87)	64 (0.56)
Skin symptoms	55 (0.48)	2 (0.02)	87 (0.76)	7 (0.06)

ADR, adverse drug reaction; AE, adverse event; UTI, urinary tract infection.

DISCUSSION

The present study evaluated the safety and effectiveness of tofogliflozin, an SGLT2 inhibitor, in 11,480 Japanese with type 2 diabetes over a 2-year period under routine clinical practice. The results show that tofogliflozin has a favorable safety profile. The most common ADRs of special interest were UTI/GTIs, followed by fluid volume depletion. The majority of ADRs were of mild or moderate severity. An analysis of AEs and ADRs in subgroups of sex, age, and BMI showed intersubgroup differences in UTI/GTIs, volume depletion, renal dysfunction, bone fractures, malignancies, and cardiovascular and cerebrovascular events. All effectiveness parameters improved significantly at each time point, with slight differences in parametric trends over time. Almost half of the participants achieved the HbA1c target of <7.0% at Week 104.

Participant characteristics in this study showed that tofogliflozin is presently prescribed to relatively younger and more obese people with type 2 diabetes in Japan. The mean age was 59.5 years and mean BMI was 27.8 kg/m^2 in this study, compared with 67.53 years and 24.8 kg/m^2 in the largest previous cohort of Japanese with type 2 diabetes (approximately 55,000 people in 2011)[1]. The difference in age might reflect early concerns about safety, especially in the elderly, when SGLT2 inhibitors first became available for clinical use in Japan. The difference in BMI might reflect expectations for weight loss based on the mechanism of action of the SGLT2 inhibitors.

When the data on ADRs for each category in the 3-year-long PMS study of tofogliflozin[15] were adjusted to allow comparison with the present study, the incidence of ADRs in all categories during the PMS study appeared to be considerably higher than

Table 3 | Secondary endpoint: Incidence of other adverse events

N = 11,480	ADRs		AEs	
	All *n* (%)	Serious *n* (%)	All *n* (%)	Serious *n* (%)
All events	645 (5.62)	48 (0.42)	1,054 (9.18)	198 (1.72)
Gastrointestinal disorders	46 (0.40)	1 (0.01)	111 (0.97)	10 (0.09)
General disorders and administration site conditions	28 (0.24)	1 (0.01)	40 (0.35)	6 (0.05)
Surgical and medical procedures	1 (0.01)		3 (0.03)	
Infections and infestations	5 (0.04)	1 (0.01)	88 (0.77)	13 (0.11)
Hepatobiliary disorders	1 (0.01)	1 (0.01)	7 (0.06)	5 (0.04)
Eye disorders	2 (0.02)		16 (0.14)	5 (0.04)
Musculoskeletal and connective tissue disorders	8 (0.07)	1 (0.01)	45 (0.39)	8 (0.07)
Blood and lymphatic system disorders	6 (0.05)		11 (0.10)	1 (0.01)
Vascular disorders	7 (0.06)	2 (0.02)	19 (0.17)	6 (0.05)
Respiratory, thoracic and mediastinal disorders	5 (0.04)		33 (0.29)	5 (0.04)
Ear and labyrinth disorders	3 (0.03)		7 (0.06)	1 (0.01)
Social circumstances			1 (0.01)	
Injury, poisoning and procedural complications	3 (0.03)	1 (0.01)	15 (0.13)	4 (0.03)
Cardiac disorders	4 (0.03)		5 (0.04)	1 (0.01)
Nervous system disorders	40 (0.35)	2 (0.02)	70 (0.61)	2 (0.02)
Renal and urinary disorders	15 (0.13)		19 (0.17)	
Reproductive system and breast disorders	2 (0.02)		5 (0.04)	
Psychiatric disorders	1 (0.01)		11 (0.10)	1 (0.01)
Metabolism and nutrition disorders	10 (0.09)	1 (0.01)	27 (0.24)	6 (0.05)
Endocrine disorders			1 (0.01)	
Skin and subcutaneous tissue disorders	4 (0.03)		6 (0.05)	
Immune system disorders			1 (0.01)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.01)		4 (0.03)	1 (0.01)
Investigations	10 (0.09)	1 (0.01)	22 (0.19)	1 (0.01)

ADR, adverse drug reaction; AE, adverse event.

that during the 2 years of the present study; the overall incidence of ADRs was 6.61% for 2 years in this study, and 12.61% for 3 years in the PMS. However, this difference might be due to the difference in dropout rate in the two studies. In the present study, 39.3% of the participants (4,513/11,480) dropped out during the 2-year period, compared with 41.0% of participants (2,753/6,711) during the 3-year period of the PMS study. Per year, our study had a higher number of dropouts than the PMS study, which means that we also had a higher number of dropouts in the early stages of treatment. Because most ADRs occur during the early stage of treatment, this high number of early dropouts might have lowered the rate of ADR detection during the study, which could be one reason for the much lower incidence of ADRs in the present study than in the PMS study.

When compared with the incidence of AEs in a meta-analysis of clinical trials of SGLT2 inhibitors overseas[18], the values for all categories of AEs were considerably lower in the present study. In contrast, the overall incidence of AEs in the Japanese phase III studies of tofogliflozin[13–15] were almost the same as those in the overseas studies, suggesting important differences between clinical trials and routine clinical practice. Such differences could include more careful selection of people with type 2 diabetes for treatment with SGLT2 inhibitors in routine clinical practice and more attention to warnings from academic societies[11].

In the present study, UTI/GTIs occurred more frequently in women and participants with higher BMI. In addition, higher BMI was associated with a greater incidence of fluid volume depletion. Furthermore, the PMS study showed similar results of AEs for tofogliflozin[15] as for other SGLT2 inhibitors[7–10], which suggests that these effects might be typical of the SGLT2 inhibitors based on their pharmaceutical characteristics, and confirms the importance of increased attention to safety when using the drugs in certain populations. In contrast, the increase in fluid volume depletion in participants aged ≥65 years that was reported in the PMS with tofogliflozin[15] was not observed in the present study. Participants aged ≥65 years accounted for 38.5% of the total in this study, compared with 28.3% in the PMS. Thus, physicians prescribing tofogliflozin to elderly participants might well have become more vigilant in monitoring body fluid loss in routine clinical practice. Our finding that malignancy and cardiovascular and cerebrovascular events were more common in the elderly reflects a generally accepted risk in this age group[19,20].

Table 4 | Subgroup analysis by participant characteristics

	N	ADRs		AEs	
		n (%)	*P*-value	*n* (%)	*P*-value
Sex (*N* = 11,480)					
Hypoglycemia					
Female	4,281	15 (0.35)	0.0707	17 (0.40)	0.0610
Male	7,199	12 (0.17)		14 (0.19)	
UTI and genital tract infection					
Female	4,281	133 (3.11)	<0.0001	139 (3.25)	<0.0001
Male	7,199	43 (0.60)		44 (0.61)	
Volume depletion (dehydration, polyuria/pollakiuria, hypotension)					
Female	4,281	45 (1.05)	0.1408	48 (1.12)	0.1307
Male	7,199	99 (1.38)		105 (1.46)	
Diabetic ketoacidosis					
Female	4,281	1 (0.02)	0.6570	1 (0.02)	0.4215
Male	7,199	4 (0.06)		5 (0.07)	
Renal dysfunction					
Female	4,281	19 (0.44)	0.0083	23 (0.54)	0.0636
Male	7,199	12 (0.17)		22 (0.31)	
Liver dysfunction					
Female	4,281	4 (0.09)	0.4815	16 (0.37)	0.6226
Male	7,199	4 (0.06)		23 (0.32)	
Bone fracture					
Female	4,281	1 (0.02)	0.3729	12 (0.28)	0.0030
Male	7,199			4 (0.06)	
Malignancy					
Female	4,281		0.0906	17 (0.40)	0.5664
Male	7,199	6 (0.08)		35 (0.49)	
Cardiovascular and cerebrovascular events					
Female	4,281	9 (0.21)	0.4573	26 (0.61)	0.0218
Male	7,199	22 (0.31)		74 (1.03)	
Skin symptoms					
Female	4,281	29 (0.68)	0.0244	44 (1.03)	0.0139
Male	7,199	26 (0.36)		43 (0.60)	
Age (*N* = 11,480)					
Hypoglycemia					
<65 years	7,062	18 (0.25)	0.8146	19 (0.27)	0.8083
65–75 years	2,915	7 (0.24)		7 (0.24)	
≥75 years	1,503	2 (0.13)		5 (0.33)	
UTI and genital tract infection					
<65 years	7,062	122 (1.73)	0.0497	126 (1.78)	0.1086
65–75 years	2,915	40 (1.37)		40 (1.37)	
≥75 years	1,503	14 (0.93)		17 (1.13)	
Volume depletion (dehydration, polyuria/pollakiuria, hypotension)					
<65 years	7,062	93 (1.32)	0.7371	95 (1.35)	0.9854
65–75 years	2,915	35 (1.20)		39 (1.34)	
≥75 years	1,503	16 (1.06)		19 (1.26)	
Diabetic ketoacidosis					
<65 years	7,062	5 (0.07)	0.3236	6 (0.08)	0.2602
65–75 years	2,915				
≥75 years	1,503				

Table 4. (*Continued*)

	N	ADRs		AEs	
		n (%)	*P*-value	*n* (%)	*P*-value
Age (*N* = 11,480)					
Renal dysfunction					
<65 years	7,062	21 (0.30)	0.7514	30 (0.42)	0.8837
65–75 years	2,915	6 (0.21)		10 (0.34)	
≥75 years	1,503	4 (0.27)		5 (0.33)	
Liver dysfunction					
<65 years	7,062	4 (0.06)	0.6762	23 (0.33)	0.7321
65–75 years	2,915	3 (0.10)		12 (0.41)	
≥75 years	1,503	1 (0.07)		4 (0.27)	
Bone fracture					
<65 years	7,062		0.1309	8 (0.11)	0.1312
65–75 years	2,915			3 (0.10)	
≥75 years	1,503	1 (0.07)		5 (0.33)	
Malignancy					
<65 years	7,062	3 (0.04)	0.3211	16 (0.23)	<0.0001
65–75 years	2,915	1 (0.03)		23 (0.79)	
≥75 years	1,503	2 (0.13)		13 (0.86)	
Cardiovascular and cerebrovascular events					
<65 years	7,062	16 (0.23)	0.3630	45 (0.64)	0.0001
65–75 years	2,915	9 (0.31)		27 (0.93)	
≥75 years	1,503	6 (0.40)		28 (1.86)	
Skin symptoms					
<65 years	7,062	27 (0.38)	0.1011	46 (0.65)	0.2125
65–75 years	2,915	21 (0.72)		26 (0.89)	
≥75 years	1,503	7 (0.47)		15 (1.00)	
BMI (*N* = 9,752)					
Hypoglycemia					
<27.0 kg/m^2	4,877	6 (0.12)	0.0522	8 (0.16)	0.1073
≥27.0 kg/m^2	4,875	15 (0.31)		16 (0.33)	
UTI and genital tract infection					
<27.0 kg/m^2	4,877	58 (1.19)	0.0001	59 (1.21)	0.0001
≥27.0 kg/m^2	4,875	107 (2.19)		111 (2.28)	
Volume depletion (dehydration, polyuria/pollakiuria, hypotension)					
<27.0 kg/m^2	4,877	49 (1.00)	0.0060	56 (1.15)	0.0260
≥27.0 kg/m^2	4,875	80 (1.64)		82 (1.68)	
Diabetic ketoacidosis					
<27.0 kg/m^2	4,877	2 (0.04)	0.6874	2 (0.04)	0.4529
≥27.0 kg/m^2	4,875	3 (0.06)		4 (0.08)	
Renal dysfunction					
<27.0 kg/m^2	4,877	11 (0.23)	0.4414	16 (0.33)	0.2100
≥27.0 kg/m^2	4,875	15 (0.31)		24 (0.49)	
Liver dysfunction					
<27.0 kg/m^2	4,877	2 (0.04)	0.2888	16 (0.33)	0.5105
≥27.0 kg/m^2	4,875	5 (0.10)		20 (0.41)	
Bone fracture					
<27.0 kg/m^2	4,877	1 (0.02)	1.000	7 (0.14)	0.7743
≥27.0 kg/m^2	4,875			5 (0.10)	

Table 4. (*Continued*)

BMI (N = 9,752)					
	N	ADRs		AEs	
		n (%)	P-value	n (%)	P-value
Malignancy					
<27.0 kg/m^2	4,877	4 (0.08)	0.6874	25 (0.51)	0.4504
≥27.0 kg/m^2	4,875	2 (0.04)		19 (0.39)	
Cardiovascular and cerebrovascular events					
<27.0 kg/m^2	4,877	17 (0.35)	0.2471	50 (1.03)	0.2869
≥27.0 kg/m^2	4,875	10 (0.21)		39 (0.80)	
Skin symptoms					
<27.0 kg/m^2	4,877	21 (0.43)	0.2611	38 (0.78)	0.5795
≥27.0 kg/m^2	4,875	29 (0.59)		43 (0.88)	

P-values are two-sided and were calculated using a Fisher's exact test.
ADR, adverse drug reaction; AE, adverse event; BMI, body mass index; UTI, urinary tract infection.

The improvements in the effectiveness parameters disclose not only early reductions in blood glucose and HbA1c, as reported previously[13–15], but also early and continuous reduction of bodyweight. A pooled analysis of two phase III studies of tofogliflozin reported that participants experienced significant weight loss of almost 3 kg on average in 52 weeks[21]. The present study showed a similar benefit; that is, decreases of 2.80 kg at 52 weeks and 3.05 kg at 104 weeks. Favorable changes in blood pressure and lipids were also observed. These findings might well be associated with the mechanism of action of SGLT2 inhibitors.

A total of 51.7% of the participants achieved the HbA1c target of <7.0% by Week 104, which is similar to the 50.5% noted for oral medication in the Japan Diabetes Clinical Data Management Study Group (2021)[1]. However, both studies found that only a little more than half of the participants achieved this goal. In the present study, baseline HbA1c was 8.0%, and HbA1c at 104 weeks decreased by 0.85%, showing that treatment with an SGLT inhibitor alone is insufficient for many people with type 2 diabetes. However, the use of SGLT inhibitors with other glucose-lowering agents in appropriately selected people with type 2 diabetes should permit aggressive glycemic management in routine clinical practice.

The present study had limitations. As it was an investigation of drug use in routine clinical practice, there was no control group. In addition, the lengthy 104-weeks follow-up period resulted in only about half of the approximately 10,000 enrolled participants being able to complete the entire study. Furthermore, because the occurrence of hypoglycemia and some other AEs were based on participant reports, the decrease in the number of participants might have reduced the detection rate. Finally, the current study did not address a possible association between use of tofogliflozin and sarcopenia or frailty in older people with type 2 diabetes, although muscle mass and strength are rarely investigated in routine clinical practice. Particularly careful observations are needed in the presence of chronic kidney disease and/or heart failure, known to be critical risk factors for sarcopenia and frailty[22,23].

In conclusion, the present physician-initiated, open-label, uncontrolled, prospective observational study of >10,000 participants with type 2 diabetes in routine clinical practice found that tofogliflozin was associated with only mild or moderate ADRs characteristic of SGLT2 inhibitors, with no unpredictable, new, serious, or high-incidence AEs or ADRs. This independent study confirmed the safety and effectiveness of tofogliflozin in adult type 2 diabetes patients.

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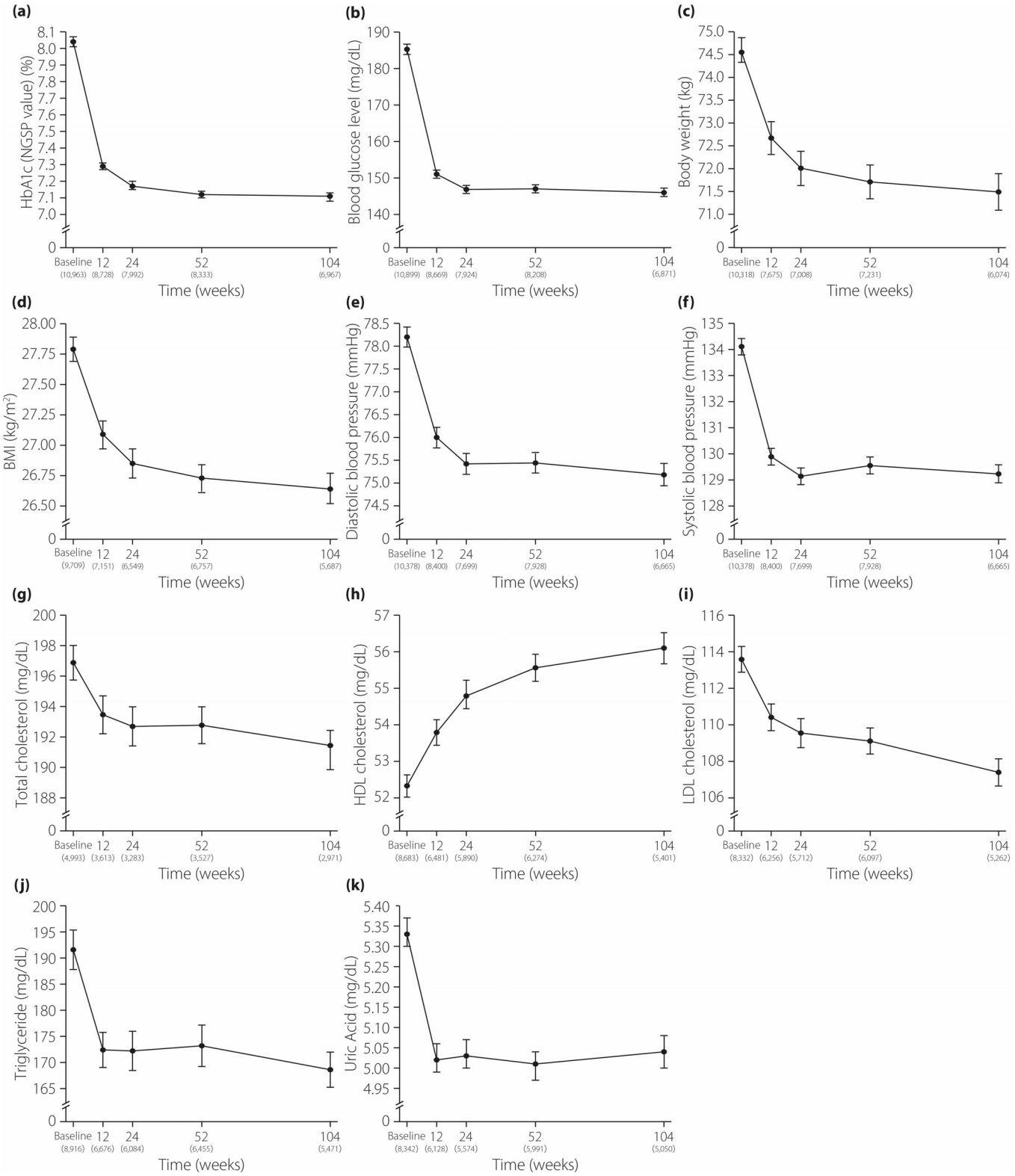

Figure 2 | Trends in measured values of efficacy parameters. Error bar, 95% confidence interval. (), *n*. BMI, body mass index; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NGSP, National Glycohemoglobin Standardization Program.

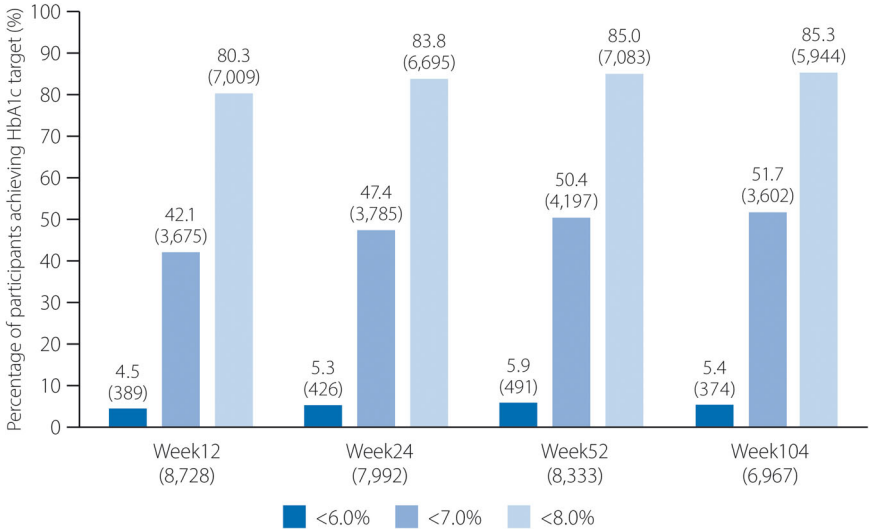

Figure 3 | Proportion of participants achieving HbA1c targets. (), *n*. HbA1c, glycated hemoglobin.

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Informed consent: Opt-out.

Approval date of registry and the registration no. of the study/trial: 2014/05/31 UMIN000014129.

Animal studies: N/A.

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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. Trends in efficacy parameter changes.