

Safety and effectiveness of tofogliflozin in Japanese patients with type 2 diabetes mellitus treated in real-world clinical practice: Results of a 36-month post-marketing surveillance study (J-STEP/LT)

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Keywords

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ABSTRACT

Aims/Introduction: Tofogliflozin is a sodium–glucose cotransporter 2 (SGLT2) inhibitor that lowers plasma glucose levels by enhancing urinary glucose excretion. After its approval in Japan in 2014 for the treatment of type 2 diabetes mellitus, we carried out a 3-year prospective observational post-marketing surveillance study in Japanese patients (Japanese Study of Tofogliflozin with Type 2 Diabetes Mellitus Patients/Long Term [J-STEP/LT]).

Materials and Methods: This surveillance was carried out between September 2014 and February 2019, and recorded safety in terms of adverse drug reactions (ADRs) and ADRs of special interest, and effectiveness in terms of changes in glycated hemoglobin and bodyweight from baseline to last observation carried forward.

Results: Of 6,897 patients with type 2 diabetes mellitus registered, 6,711 and 6,451 were analyzed for safety and effectiveness, respectively. ADRs were reported in 846 patients (12.61%), with serious ADRs in 101 patients (1.5%). ADRs of special interest included hypoglycemia (62 patients [0.9%]), polyuria/pollakiuria (90 [1.3%]), volume depletion-related disorders (135 [2.0%]), urinary tract infections (91 [1.4%]), genital infections (117 [1.7%]) and skin diseases (53 [0.8%]). One case of diabetic ketoacidosis was reported. The mean \pm standard deviation changes from baseline to last observation carried forward in glycated hemoglobin and bodyweight were $-0.68 \pm 1.34\%$ ($n = 6,158, P < 0.0001$) and -3.13 ± 4.67 kg ($n = 5,213, P < 0.0001$), respectively.

Conclusions: J-STEP/LT, a 3-year, prospective, observational, post-marketing study in Japan, found no unprecedented ADRs, and consistent reductions from baseline in glycated hemoglobin and bodyweight over the observation period. The present results provide further evidence regarding the safety and tolerability of tofogliflozin in Japanese patients with type 2 diabetes mellitus.

Prior publication: Interim results (at 3, 12 and 24 months) of J-STEP/LT were previously published as: Utsunomiya K, Senda M, Kakiuchi S, *et al.* Safety and efficacy of tofogliflozin in Japanese patients with type 2 diabetes mellitus in real-world clinical practice: Results of 3-month interim analysis of a long-term post-marketing surveillance study (J-STEP/LT). *J Diabetes Investig* 2019; 10: 1272–1283; Utsunomiya K, Senda M, Kakiuchi S, *et al.* 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 Diabetes Investig* 2020; 11: 132–142; and Utsunomiya K, Kakiuchi S, Senda M, *et al.* Safety and effectiveness of tofogliflozin in Japanese patients with type 2 diabetes mellitus: Results of 24-month interim analysis of a long-term post-marketing study (J-STEP/LT). *J Diabetes Investig* 2020; doi: 10.1111/jdi.13233. Final results of the study were accepted for presentation as an abstract and oral presentation at the Japan Diabetes Society annual congress, May 2020 (abstract a90566).

[Correction added on 14 October 2020, after first online publication: '3.13 \pm 4.67 kg' under 'Results' in the abstract has been amended as '-3.13 \pm 4.67 kg']

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INTRODUCTION

Sodium–glucose cotransporter 2 (SGLT2) inhibitors comprise one of the newest classes of oral antidiabetic drugs to have been approved for the treatment of diabetes mellitus¹. These drugs block glucose reuptake in the proximal tubule, which promotes urinary glucose excretion to lower blood glucose levels. SGLT2 inhibitors are characterized by an insulin-independent mechanism of action, low rate of hypoglycemia and reductions in bodyweight. Several recent cardiovascular outcome trials also showed the potential for SGLT2 inhibitors to lower the risk of cardiovascular events^{2–5} and delay the progression of renal dysfunction in patients with type 2 diabetes mellitus^{6,7}.

SGLT2 inhibitors are recommended in the American Diabetes Association/European Association for the Study of Diabetes consensus statement, especially for patients with established arteriosclerotic cardiovascular disease, heart failure or chronic kidney disease if glycated hemoglobin (HbA1c) remains above the target range with metformin and lifestyle modifications⁸. SGLT2 inhibitors are also recommended for those without arteriosclerotic cardiovascular disease, heart failure or chronic kidney disease if hypoglycemia is a concern. In the Japan Diabetes Society treatment guidelines, the type of pharmacotherapy should be selected according to the patient's clinical status, and treatment options include SGLT2 inhibitors⁹.

Despite these recommendations, some possible concerns of SGLT2 inhibitors have been identified, including the risk of genital/urinary infections and fluid loss as a result of osmotic diuresis with potential for renal failure, that are related to the mechanism of SGLT2 inhibitors^{10,11}, and euglycemic diabetic ketoacidosis^{2,12–16}. Increased risks of fracture⁴ and lower limb amputation^{4,16} have also been reported in some patients, although these findings are not universal, and no increase in risk was noted in other studies^{17–20}.

Tofogliflozin (Apleway[®], Deberza[®]) is a SGLT2 inhibitor that was approved in Japan in 2014. Clinical trials showed its effectiveness when used in combination with other oral drugs or insulin, and that it was well tolerated with few serious adverse events (AEs)^{21–24}. After its approval in Japan, several post-marketing surveillance studies were implemented, including the J-STEP/EL²⁵, which monitored the safety and effectiveness of tofogliflozin in elderly patients treated for up to 1 year in clinical practice. However, the clinical trials and J-STEP/EL were limited to 1 year of duration and included relatively small sample sizes. Therefore, a larger post-marketing surveillance, Japanese Study of Tofogliflozin with Type 2 Diabetes Mellitus Patients/Long Term (J-STEP/LT), was carried out, and collected safety and effectiveness data for 36 months, with interim analyses at 3, 12 and 24 months^{26–28}. Here, we report the final analyses of J-STEP/LT of patients treated with tofogliflozin for up to 36 months in actual clinical practice.

METHODS

Ethics

This surveillance adhered with the Declaration of Helsinki, Japanese authorized standards for post-marketing surveillance and Good Post-marketing Study Practice. Patient consent or approval of the study protocol by institutional review boards at participating sites was not necessary, in accordance with the mandates of Good Post-Marketing Study Practice.

Patients and data collection

Tofogliflozin-naïve patients who started treatment with tofogliflozin for the treatment of type 2 diabetes mellitus were to be registered in the surveillance, with no specific restrictions on patient eligibility. The package insert for tofogliflozin recommends that tofogliflozin should be administered once daily at a dose of 20 mg, either before or after breakfast. All treatment decisions were at the prescribing physician's discretion. Data were to be collected using electronic case report forms, which recorded baseline demographics/characteristics, AEs, adverse drug reactions (ADRs), HbA1c, bodyweight, vital signs and laboratory tests.

Assessments and definitions

AEs and ADRs were recorded and categorized according to the Medical Dictionary for Regulatory Activities/Japanese edition, version 22.0. ADRs were defined as the AEs that were considered by the physician or the sponsor to be related to tofogliflozin administration. The following ADRs were considered of special interest: polyuria/pollakiuria, volume depletion-related disorders, urinary tract infection, genital infection, hypoglycemia, skin disorders, renal disorders, liver disorders, lower limb-related disorders, cardiac or cerebrovascular disorders, weight loss-related disorders, ketoacidosis (including diabetic ketoacidosis), malignant tumors and fracture/bone-related disorders. Major adverse cardiovascular events (MACE)²⁹ were evaluated as AEs by an adjudication committee consisting of a cardiologist and a neurosurgeon using four sets of preferred terms. The standardized MedDRA queries (SMQ) for MACE include the preferred terms for “Myocardial Infarction” and “Central Nervous System Hemorrhages and Cerebrovascular Accidents”³⁰, and are further classified into “broad” and “narrow” sets³¹. We also used the “FDA custom MACE” term, a subset of SMQ MACE with greater specificity for myocardial infarction and ischemic stroke³², and the “Company custom MACE”, which was defined by the adjudication committee to specifically evaluate three-point MACE (cardiac death, non-fatal myocardial infarction, stroke), and includes heart failure, unstable angina, coronary revascularization and transient ischemic attack. The effectiveness of tofogliflozin was evaluated in terms of the changes in HbA1c and bodyweight. Vital signs and clinical laboratory tests were also recorded.

Statistical analysis

Adverse drug reactions were assessed in all patients combined and in patients stratified by age (<65 or ≥65 years), sex, body mass index (BMI; <22, 22 to <25, 25 to <30, ≥30 kg/m²) and baseline estimated glomerular filtration rate (eGFR; <30, ≥30 to <45, 45 to <60, 60 to <90, ≥90 mL/min/1.73 m²). Effectiveness was assessed in terms of the mean changes in HbA1c and bodyweight (absolute change and percent change) in all patients combined and in patients stratified by baseline eGFR or BMI (as per safety analyses). Baseline characteristics and safety were analyzed descriptively for all patients for whom electronic case report forms were collected, after excluding patients who did not return to their clinic after the first tofogliflozin administration (safety population). Vital signs and clinical laboratory tests were analyzed descriptively in the safety population after excluding patients with no

effectiveness data. Missing data for HbA1c, bodyweight, clinical laboratory tests and vital signs were imputed using the last observation carried forward (LOCF). Changes from baseline to 36 months were analyzed using one-sample *t*-tests, without intergroup comparisons. Statistical significance level was set at 5%. SAS version 9.3 (SAS Institute Japan Ltd., Tokyo, Japan) was used for all analyses.

RESULTS

Patients

A total of 6,897 patients were initially registered across 1,258 sites (Figure 1). The electronic case report forms were collected for 6,818 patients (1,234 sites), of whom 6,711 and 6,451 patients were included in the safety and effectiveness analyses, respectively. A total of 2,753 patients discontinued treatment with tofogliflozin for various reasons, including stopping clinic visits (965; 14.38%), development of AEs (487; 7.26%) and at

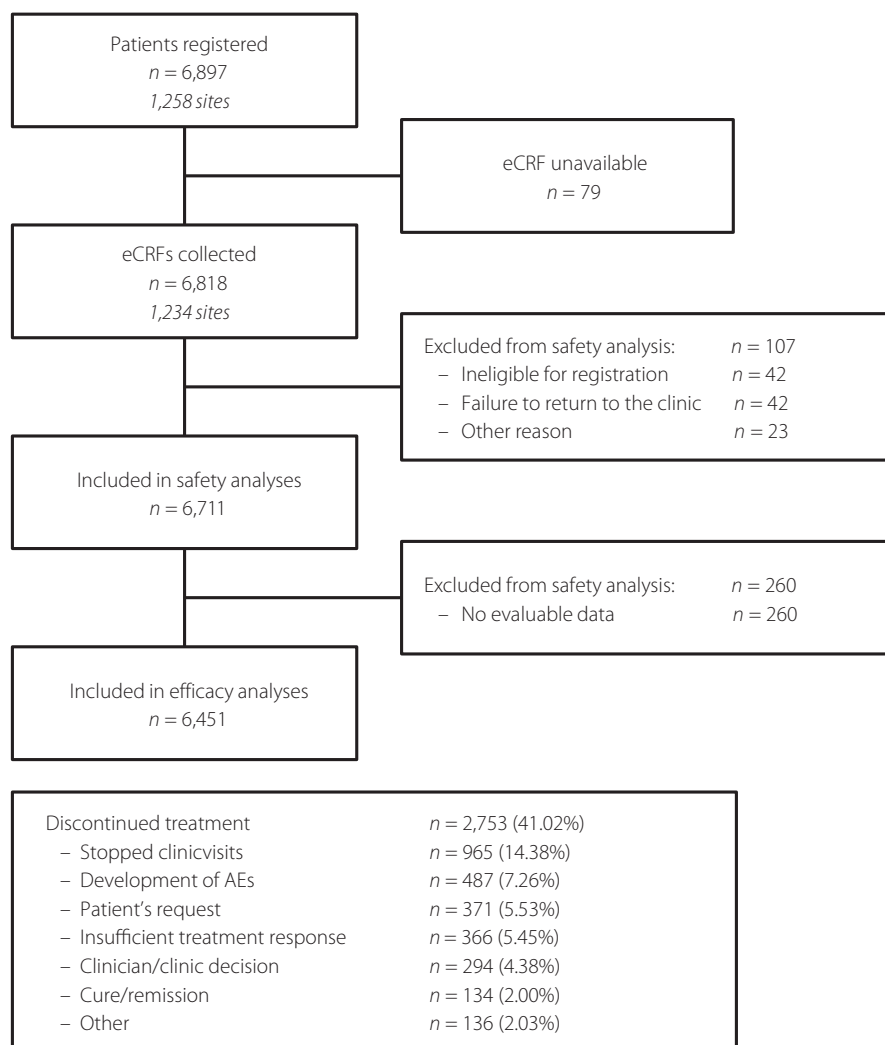


Figure 1 | Patient disposition. AE, adverse event; eCRF, electronic case report form.

Table 1 | Patient characteristics

Characteristic	n	% or mean ± SD
Total	6,711	
Age (years)	6,711	56.9 ± 12.2
Sex		
Male	4,082	(60.83%)
Female	2,629	(39.17%)
BMI (kg/m ²)	5,538	28.74 ± 5.02
Disease duration (years)	3,966	8.20 ± 6.40
HbA1c (%)	6,411	8.00 ± 1.48
eGFR (mL/min/1.73 m ²)	4,951	82.53 ± 22.46
Diabetic complications		
Any	1,882	(28.04%)
Retinopathy	534	(7.96%)
Nephropathy	1,414	(21.07%)
Neuropathy	622	(9.27%)
Other	8	(0.12%)
Cardiac and cerebrovascular diseases		
Any	690	(10.28%)
Cardiovascular disease	557	(8.30%)
Cerebrovascular disease	159	(2.37%)
Heart failure	159	(2.37%)
Prior antidiabetic therapy		
Yes	5,434	(80.97%)
Unknown	72	(1.07%)
Oral hypoglycemic drugs		
Yes	5,300	(78.97%)
Unknown	72	(1.07%)
Biguanides		
Yes	3,154	(47.00%)
Sulfonylureas		
Yes	1,929	(28.74%)
DPP-4 inhibitors		
Yes	4,051	(60.36%)
SGLT2 inhibitors		
Yes	0	(0.00%)
Rapid-acting insulin secretagogues		
Yes	435	(6.48%)
α-Glucosidase inhibitors		
Yes	867	(12.92%)
Thiazolidines		
Yes	979	(14.59%)
Others		
Yes	1	(0.01%)
Insulin preparations		
Yes	806	(12.01%)
Unknown	72	(1.07%)
Short-acting		
Yes	272	(4.05%)
Rapid-acting		
Yes	4	(0.06%)
Intermediate-acting		
Yes	7	(0.10%)
Pre-mixed		
Yes	165	(2.46%)

Table 1 (Continued)

Characteristic	n	% or mean ± SD
Soluble, long-acting		
Yes	649	(9.67%)
GLP-1 receptor agonists		
Yes	381	(5.68%)
Unknown	72	(1.07%)
Concomitant use of diuretics		
Yes	534	(7.96%)

Values are n (%) or mean ± standard deviation. BMI, body mass index; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; SGLT2, sodium–glucose cotransporter 2.

the patient’s request (371; 5.53%). Among 6,711 patients, 60.83% were men, the mean disease duration was 8.20 ± 6.40 years, mean HbA1c was 8.00 ± 1.48% and mean eGFR was 82.53 ± 22.46 mL/min/1.73 m² (Table 1). Other oral hypoglycemic drugs were used as concomitant therapy in 78.97% of patients, and insulin was used in 12.01%. The duration of treatment with tofogliflozin was ≥156 weeks for 3,958 patients.

Safety

Overall population

Adverse drug reactions occurred in 846 of 6,711 patients (12.61%) in the safety population (Table 2). Serious ADRs occurred in 101 patients (1.50%), including cardiac disorders in 18 patients (0.27%), nervous system disorders in 18 patients (0.27%), infections/infestations in 14 patients (0.21%), metabolism/nutrition disorders in 13 patients (0.19%) and neoplasms in 11 patients (0.16%). Serious ADRs (≥3 patients) were cerebral infarction (8 patients, 0.12%), acute myocardial infarction (8 patients, 0.12%), hypoglycemia (6 patients, 0.09%), renal impairment (5 patients, 0.07%), and pneumonia, pyelonephritis acute, dehydration, lacunar infarction and myocardial infarction (3 patients each, 0.04%; Table S1).

Regarding incidences of ADRs of special interest (Table 3), volume depletion-related disorders were reported in 2.01%, genital infections in 1.74%, urinary tract infections in 1.36%, polyuria/pollakiuria in 1.34%, hypoglycemia in 0.92% and cardiac or cerebrovascular diseases in 0.91% of patients. A total of 44 patients (0.66%) experienced lower limb-related disorders, but no cases of leg amputation occurred. Ketoacidosis-related ADRs occurred in 0.25% of patients, including urine ketone bodies present in eight patients, blood ketone bodies increased in seven patients, and diabetic ketoacidosis, acetonemia and urine ketone bodies in one patient each. Fracture/bone-related disorders occurred in two patients. Both of these ADRs were reported as osteoporosis. We also evaluated the incidence of MACE using four different sets of preferred terms (Table 4):

Table 2 | Adverse drug reactions in the safety population by system organ class

	All	Serious
Any ADR	846 (12.61%)	101 (1.50%)
ADR by system organ class		
Infections and infestations	173 (2.58%)	14 (0.21%)
Metabolism and nutrition disorders	133 (1.98%)	13 (0.19%)
Investigations	126 (1.88%)	5 (0.07%)
Renal and urinary disorders	118 (1.76%)	8 (0.12%)
Gastrointestinal disorders	76 (1.13%)	7 (0.10%)
Reproductive system and breast disorders	70 (1.04%)	0
Nervous system disorders	57 (0.85%)	18 (0.27%)
Skin and subcutaneous tissue disorders	50 (0.75%)	1 (0.01%)
Cardiac disorders	41 (0.61%)	18 (0.27%)
Hepatobiliary disorders	36 (0.54%)	7 (0.10%)
General disorders and administration site conditions	32 (0.48%)	1 (0.01%)
Vascular disorders	27 (0.40%)	1 (0.01%)
Musculoskeletal and connective tissue disorders	25 (0.37%)	3 (0.04%)
Blood and lymphatic system disorders	13 (0.19%)	0
Respiratory, thoracic and mediastinal disorders	13 (0.19%)	1 (0.01%)
Neoplasms benign, malignant and unspecified	11 (0.16%)	11 (0.16%)
Psychiatric disorders	9 (0.13%)	2 (0.03%)
Eye disorders	8 (0.12%)	4 (0.06%)
Immune system disorders	5 (0.07%)	1 (0.01%)
Injury, poisoning and procedural complications	4 (0.06%)	1 (0.01%)
Ear and labyrinth disorders	2 (0.03%)	0
Congenital, familial and genetic disorders	1 (0.01%)	1 (0.01%)

Total $n = 6,711$. Values are n (%). ADR, adverse drug reaction.

broad SMQ (56 patients, 0.83%), narrow SMQ (53 patients, 0.79%), FDA custom MACE (34 patients, 0.51%) and company custom MACE (58 patients, 0.86%).

ADRs in subgroups of patients

We also examined the frequency of ADRs in subgroups of patients by age, sex, BMI and eGFR (Figure 2a–d). The incidence of ADRs of special interest was generally similar between patients aged <65 or ≥ 65 years, except for volume depletion-related disorders and polyuria/pollakiuria, which were more frequent in patients aged ≥ 65 years (2.58 and 1.90%, respectively) than in younger patients (Figure 2a).

When compared between men and women, genital and urinary tract infections were both more common in women, whereas the incidences of other ADRs were comparable (Figure 2b).

As shown in Figure 2c, the incidence of hypoglycemia tended to be greater in patients with BMI <25.0 kg/m² at baseline, whereas genital infections were more frequent in patients with a baseline BMI of ≥ 25.0 kg/m².

When patients were divided by eGFR at baseline, we found that there were trends toward a higher incidence of ADRs among patients with lower baseline eGFR (Figure 2d), particularly volume depletion-related disorders, polyuria/pollakiuria, renal disorders and hypoglycemia.

Effectiveness

Effectiveness was assessed in terms of changes in HbA1c and bodyweight. HbA1c decreased from $8.00 \pm 1.48\%$ at baseline ($n = 6,227$) to $7.32 \pm 1.22\%$ ($n = 6,364$) at LOCF, with a mean change from baseline of $-0.68 \pm 1.34\%$ ($n = 6,158$) that was statistically significant ($P < 0.0001$; Figure 3a). Among 4,649 patients with HbA1c $\geq 7\%$ at baseline, HbA1c decreased to <7% in 1,598 at LOCF (34.37%). Bodyweight decreased from 77.84 ± 16.70 kg ($n = 5,373$) to 74.68 ± 16.45 kg ($n = 5,613$) at LOCF, with a statistically significant mean change from baseline of -3.13 ± 4.67 kg ($-3.95 \pm 5.81\%$; $n = 5,213$, $P < 0.0001$; Figure 3b). When analyzed by age, BMI and eGFR at baseline (Figure 4a–c), we found that the changes in HbA1c were numerically greater in younger patients and in patients with higher eGFR at baseline. However, the changes in bodyweight (absolute and percent) were generally consistent among the five eGFR subgroups.

Vital signs and clinical laboratory tests

Table S2 shows the changes in vital signs and clinical laboratory tests from baseline to LOCF. Overall, there were significant changes (improvements) in most of the variables, including blood pressure, liver enzymes and lipids. As expected from its mechanism of action, blood ketone bodies increased, although

Table 3 | Adverse drug reactions of special interest

	All	Serious
Volume depletion-related disorders	135 (2.01%)	18 (0.27%)
Dehydration	31 (0.46%)	3 (0.04%)
Constipation	29 (0.43%)	0
Blood urea increased	21 (0.31%)	0
Tachycardia	10 (0.15%)	0
Cerebral infarction	9 (0.13%)	8 (0.12%)
Thirst	9 (0.13%)	0
Hematocrit increased	7 (0.10%)	0
Myocardial infarction	4 (0.06%)	3 (0.04%)
Blood pressure decreased	4 (0.06%)	0
Lacunar infarction	3 (0.04%)	3 (0.04%)
Polycythemia	3 (0.04%)	0
Heat illness	2 (0.03%)	1 (0.01%)
Hemoglobin increased	2 (0.03%)	0
Hypotension	2 (0.03%)	0
Depressed level of consciousness	1 (0.01%)	1 (0.01%)
Acute kidney injury	1 (0.01%)	1 (0.01%)
Blood pressure ambulatory decreased	1 (0.01%)	0
Blood pressure diastolic decreased	1 (0.01%)	0
Blood sodium increased	1 (0.01%)	0
Dry mouth	1 (0.01%)	0
Hemoconcentration	1 (0.01%)	0
Heart rate increased	1 (0.01%)	0
Red blood cell count increased	1 (0.01%)	0
Sinus tachycardia	1 (0.01%)	0
Genital infections	117 (1.74%)	0
Pruritus genital	41 (0.61%)	0
Vulvovaginal candidiasis	22 (0.33%)	0
Genital infection	18 (0.27%)	0
Balanoposthitis	9 (0.13%)	0
Vulvovaginal pruritus	6 (0.09%)	0
Vulvitis	5 (0.07%)	0
Vulvar erosion	5 (0.07%)	0
Vaginal infection	4 (0.06%)	0
Candida infection	3 (0.04%)	0
Genital candidiasis	2 (0.03%)	0
Balanitis candida	1 (0.01%)	0
Genital herpes	1 (0.01%)	0
Penile ulceration	1 (0.01%)	0
Prostatitis	1 (0.01%)	0
Genital infection female	1 (0.01%)	0
Urinary tract infections	91 (1.36%)	6 (0.09%)
Cystitis	43 (0.64%)	1 (0.01%)
Urinary tract infection	32 (0.48%)	2 (0.03%)
Urethritis	6 (0.09%)	0
Pyelonephritis acute	3 (0.04%)	3 (0.04%)
Pyelonephritis	3 (0.04%)	1 (0.01%)
Septic shock	2 (0.03%)	2 (0.03%)
Bacteriuria	2 (0.03%)	0
Cystitis-like symptom	2 (0.03%)	0
Sepsis	1 (0.01%)	1 (0.01%)
White blood cells urine	1 (0.01%)	0
Red blood cells urine	1 (0.01%)	0
Cystitis bacterial	1 (0.01%)	0

Table 3 (Continued)

	All	Serious
Polyuria/pollakiuria	90 (1.34%)	0
Pollakiuria	66 (0.98%)	0
Nocturia	13 (0.19%)	0
Polyuria	8 (0.12%)	0
Urine output increased	3 (0.04%)	0
Hypoglycemia	62 (0.92%)	6 (0.09%)
Hypoglycemia	62 (0.92%)	6 (0.09%)
Cardiac and cerebrovascular diseases	61 (0.91%)	34 (0.51%)
Tachycardia	10 (0.15%)	0
Cerebral infarction	9 (0.13%)	8 (0.12%)
Acute myocardial infarction	8 (0.12%)	8 (0.12%)
Myocardial infarction	4 (0.06%)	3 (0.04%)
Lacunar infarction	3 (0.04%)	3 (0.04%)
Angina pectoris	3 (0.04%)	2 (0.03%)
Cardiac failure	3 (0.04%)	2 (0.03%)
Atrial fibrillation	3 (0.04%)	1 (0.01%)
Palpitations	3 (0.04%)	0
Cerebral hemorrhage	2 (0.03%)	2 (0.03%)
Arrhythmia	2 (0.03%)	0
Prinzmetal angina	2 (0.03%)	0
Transient ischemic attack	2 (0.03%)	0
Angina unstable	1 (0.01%)	1 (0.01%)
Brain stem infarction	1 (0.01%)	1 (0.01%)
Cardiac failure congestive	1 (0.01%)	1 (0.01%)
Hemiplegia	1 (0.01%)	1 (0.01%)
Subarachnoid hemorrhage	1 (0.01%)	1 (0.01%)
Heart rate increased	1 (0.01%)	0
Sinus tachycardia	1 (0.01%)	0
Ventricular extrasystoles	1 (0.01%)	0
Renal disorders	53 (0.79%)	7 (0.10%)
Blood urea increased	21 (0.31%)	0
Renal impairment	10 (0.15%)	5 (0.07%)
Blood creatinine increased	6 (0.09%)	0
Protein urine present	4 (0.06%)	0
Albumin urine present	2 (0.03%)	0
Proteinuria	2 (0.03%)	0
Renal disorder	2 (0.03%)	0
Diabetic nephropathy	2 (0.03%)	0
Glomerular filtration rate decreased	1 (0.01%)	1 (0.01%)
Acute kidney injury	1 (0.01%)	1 (0.01%)
Azotemia	1 (0.01%)	0
Hyperkalemia	1 (0.01%)	0
Hyponatremia	1 (0.01%)	0
Renal failure	1 (0.01%)	0
Urine albumin/creatinine ratio increased	1 (0.01%)	0
Nephrogenic anemia	1 (0.01%)	0
Urinary sediment abnormal	1 (0.01%)	0
Skin diseases	53 (0.79%)	3 (0.04%)
Pruritus	10 (0.15%)	0
Rash	10 (0.15%)	0
Eczema	8 (0.12%)	0
Urticaria	3 (0.04%)	0
Pruritus generalized	3 (0.04%)	0
Cellulitis	2 (0.03%)	1 (0.01%)

Table 3 (Continued)

	All	Serious
Rash erythematous	2 (0.03%)	0
Rash generalized	2 (0.03%)	0
Rash pruritic	2 (0.03%)	0
Gangrene	1 (0.01%)	1 (0.01%)
Skin ulcer	1 (0.01%)	1 (0.01%)
Dermatitis	1 (0.01%)	0
Drug eruption	1 (0.01%)	0
Erythema	1 (0.01%)	0
Folliculitis	1 (0.01%)	0
Herpes zoster	1 (0.01%)	0
Palmoplantar keratoderma	1 (0.01%)	0
Seborrheic dermatitis	1 (0.01%)	0
Skin disorder	1 (0.01%)	0
Skin erosion	1 (0.01%)	0
Skin infection	1 (0.01%)	0
Tinea pedis	1 (0.01%)	0
Liver disorders	46 (0.69%)	5 (0.07%)
Hepatic function abnormal	23 (0.34%)	2 (0.03%)
Alanine aminotransferase increased	5 (0.07%)	1 (0.01%)
Blood alkaline phosphatase increased	4 (0.06%)	0
Aspartate aminotransferase increased	3 (0.04%)	0
Gamma-glutamyl transferase increased	3 (0.04%)	0
Hepatic steatosis	3 (0.04%)	0
Jaundice	2 (0.03%)	0
Liver disorder	2 (0.03%)	0
Chronic hepatitis	1 (0.01%)	1 (0.01%)
Liver abscess	1 (0.01%)	1 (0.01%)
Blood bilirubin increased	1 (0.01%)	0
Hepatic enzyme increased	1 (0.01%)	0
Liver function test increased	1 (0.01%)	0
Lower limb-related disorders	44 (0.66%)	6 (0.09%)
Dehydration	31 (0.46%)	3 (0.04%)
Hypoesthesia	3 (0.04%)	0
Cellulitis	2 (0.03%)	1 (0.01%)
Diabetic neuropathy	2 (0.03%)	0
Gangrene	1 (0.01%)	1 (0.01%)
Osteomyelitis	1 (0.01%)	1 (0.01%)
Skin ulcer	1 (0.01%)	1 (0.01%)
Neuropathy peripheral	1 (0.01%)	0
Skin erosion	1 (0.01%)	0
Skin infection	1 (0.01%)	0
Peripheral arterial occlusive disease	1 (0.01%)	0
Weight loss-related events	20 (0.30%)	3 (0.04%)
Weight decreased	14 (0.21%)	1 (0.01%)
Decreased appetite	4 (0.06%)	2 (0.03%)
Feeding disorder	1 (0.01%)	0
Fat tissue decreased	1 (0.01%)	0
Ketoacidosis (including diabetic ketoacidosis)	17 (0.25%)	1 (0.01%)
Urine ketone bodies present	8 (0.12%)	0
Blood ketone bodies increased	7 (0.10%)	0
Diabetic ketoacidosis	1 (0.01%)	1 (0.01%)
Acetonemia	1 (0.01%)	0
Ketosis	1 (0.01%)	0
Urine ketone bodies	1 (0.01%)	0

Table 3 (Continued)

	All	Serious
Malignant tumors	11 (0.16%)	11 (0.16%)
Colon cancer	2 (0.03%)	2 (0.03%)
Pancreatic carcinoma	2 (0.03%)	2 (0.03%)
Bile duct cancer	1 (0.01%)	1 (0.01%)
Bladder cancer	1 (0.01%)	1 (0.01%)
Breast cancer	1 (0.01%)	1 (0.01%)
Lung neoplasm malignant	1 (0.01%)	1 (0.01%)
Metastases to liver	1 (0.01%)	1 (0.01%)
Ovarian neoplasm	1 (0.01%)	1 (0.01%)
Renal cell carcinoma	1 (0.01%)	1 (0.01%)
Soft tissue sarcoma	1 (0.01%)	1 (0.01%)
Fracture/bone-related disorders	2 (0.03%)	0
Osteoporosis	2 (0.03%)	0

Values are *n* (%).

this was not significant and was only recorded in a small proportion of patients.

DISCUSSION

This 36-month surveillance study was carried out to examine the safety and effectiveness of tofogliflozin prescribed to patients in real-world clinical practice in Japan. The present data extend those reported in the interim analyses at 3, 12 and 24 months^{26–28}, and the key findings of this new analysis, which included 3,958 patients who continued treatment with tofogliflozin for 3 years, the longest study of tofogliflozin treatment to date, are as follows. Of note, there were no unprecedented safety concerns identified in the relatively large group of patients included in the safety analysis (*n* = 6,711), with low rates of ADRs of special interest, especially ketoacidosis-related ADRs, lower limb-related ADRs (no cases of leg amputation) and fracture/bone-related disorders. Another novel finding is that MACE occurred in <1.0%, regardless of the definition of MACE. Collectively, these results should provide assurance to patients and physicians about the overall safety of tofogliflozin during long-term use. Based on indirect comparisons, the incidence of overall ADRs (12.61%) observed in this surveillance is equivalent to that of the other post-marketing studies of SGLT2 inhibitors (ipragliflozin, 10.71% over a period of 2 years³³; canagliflozin, 9.09% over a period of 1 year³⁴; empagliflozin, 8.5% over a period of 3 years³⁵).

From a safety perspective, it was reported that SGLT2 inhibitors might be associated with increased risks of diabetic ketoacidosis, leg amputation and fracture^{2,4,12–15}. In the present surveillance, diabetic ketoacidosis was reported as an ADR in one patient. This patient continued to receive tofogliflozin on a sick day (acute bronchitis). Whether it was euglycemic was unknown, because of the lack of blood glucose level data.

Table 4 | Major adverse cardiovascular events

	All		Serious			
Broad SMQ	56 (0.83%)		46 (0.69%)			
Narrow SMQ	53 (0.79%)		46 (0.69%)			
FDA custom	34 (0.51%)		32 (0.48%)			
Company custom	58 (0.86%)		54 (0.80%)			
Preferred term	All	Serious	Broad SMQ	Narrow SMQ	FDA custom	Company custom
Acute myocardial infarction	10 (0.15%)	10 (0.15%)	×	×	×	×
Angina unstable	3 (0.04%)	3 (0.04%)	×	×		×
Aphasia	1 (0.01%)	0	×			
Blood creatine phosphokinase increased	2 (0.03%)	0	×			
Brain stem infarction	1 (0.01%)	1 (0.01%)	×	×	×	×
Carotid artery stenosis	2 (0.03%)	2 (0.03%)	×	×		
Cerebral hemorrhage	3 (0.04%)	3 (0.04%)	×	×		×
Cerebral infarction	14 (0.21%)	13 (0.19%)	×	×	×	×
Hemiplegia	1 (0.01%)	1 (0.01%)	×	×		
Myocardial infarction	5 (0.07%)	4 (0.06%)	×	×	×	×
Subarachnoid hemorrhage	2 (0.03%)	2 (0.03%)	×	×		×
Subdural hematoma	2 (0.03%)	2 (0.03%)	×	×		
Transient ischemic attack	3 (0.04%)	1 (0.01%)	×	×		×
Lacunar infarction	3 (0.04%)	3 (0.04%)	×	×	×	×
Cerebral arteriosclerosis	1 (0.01%)	0	×	×		
Carotid arteriosclerosis	2 (0.03%)	0	×	×		
Thrombotic cerebral infarction	1 (0.01%)	1 (0.01%)	×	×	×	×
Angina pectoris [†]	6 (0.09%)	6 (0.09%)				×
Cardiac failure	4 (0.06%)	2 (0.03%)				×
Cardiac failure acute	1 (0.01%)	1 (0.01%)				×
Cardiac failure congestive	2 (0.03%)	2 (0.03%)				×
Coronary artery stenosis	2 (0.03%)	2 (0.03%)				×

Values are *n* (%). [†]Only patients who underwent coronary recanalization. FDA, US Food and Drug Administration; SMQ, standardized MedDRA queries.

However, the risk of diabetic ketoacidosis would be very low in type 2 diabetes mellitus patients receiving tofogliflozin. In contrast, no cases of leg amputation or fracture were reported. The present results are consistent with those of prior studies, which found no increased risk of leg amputation or fracture among patients treated with SGLT2 inhibitors^{17–19}.

SGLT2 inhibitors lower glucose levels through an insulin-independent mechanism of action, and are associated with a low risk of hypoglycemia, especially when used alone. In this surveillance, hypoglycemia was reported as an ADR in 62 patients (0.92%) overall, including 0.41% in patients receiving tofogliflozin monotherapy. In contrast, the incidence was higher in patients prescribed tofogliflozin in combination with a sulfonylurea (1.30%), and in combination with insulin (3.72%). Among them, six cases were serious; four cases occurred within the first year after starting tofogliflozin, as previously described²⁸, and two cases occurred on days 908 and 922. In these patients, tofogliflozin was administered together with dipeptidyl peptidase-4 inhibitors (three patients), sulfonylureas (two patients) and insulin products (three patients), of which

two were taking both dipeptidyl peptidase-4 inhibitors and sulfonylureas. In consideration of these findings, it might be necessary to lower the sulfonylurea or insulin dose when starting tofogliflozin in patients at increased risk of hypoglycemia.

We also found that the incidence of hypoglycemia was higher in patients with BMI <25.0 kg/m² (1.81% with BMI <22 kg/m² and 2.05% with BMI 22 to <25 kg/m²), which might be related to confounding factors (e.g., liver function, renal function, lifestyle habits, decline in cognitive functions³⁶), and was also higher in patients with impaired renal function (2.70% with eGFR 30–45 mL/min/1.73 m²) in which the glucose-lowering effect of SGLT2 inhibitors is diminished in theory³⁷. It has been suggested that renal impairment is associated with an increased risk of hypoglycemia, which is, at least partly, attributed to a decrease in clearance of antidiabetics, such as sulfonylurea and insulin^{38–41}. Therefore, there might be a need for greater vigilance for hypoglycemia when prescribing antidiabetic drugs, which is not limited to tofogliflozin, to patients with impaired renal function.

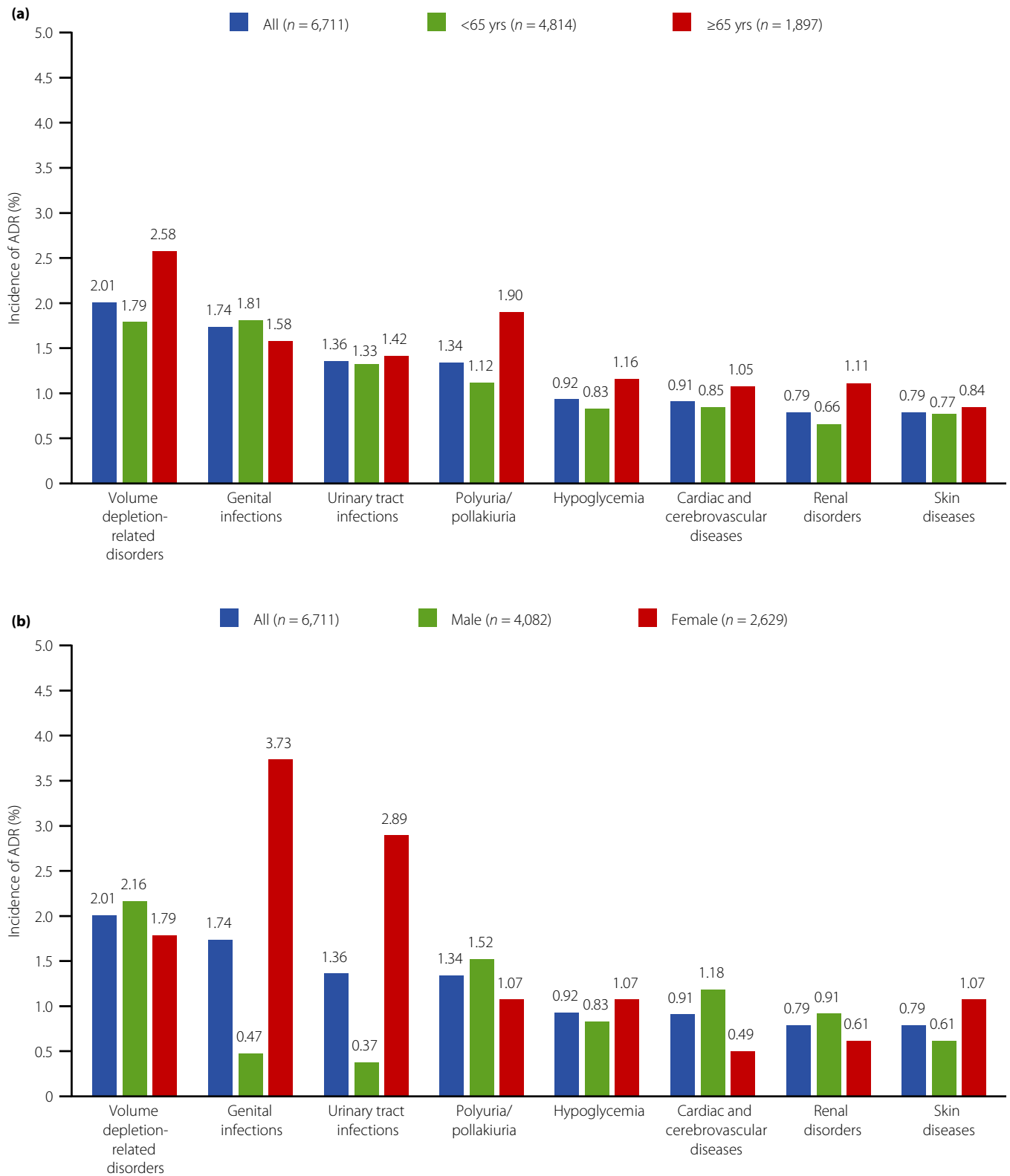


Figure 2 | Adverse drug reactions (ADRs) of special interest according to (a) age at baseline (in years), (b) sex, (c) body mass index at baseline (in kg/m²) and (d) eGFR at baseline (in mL/min/1.73 m²).

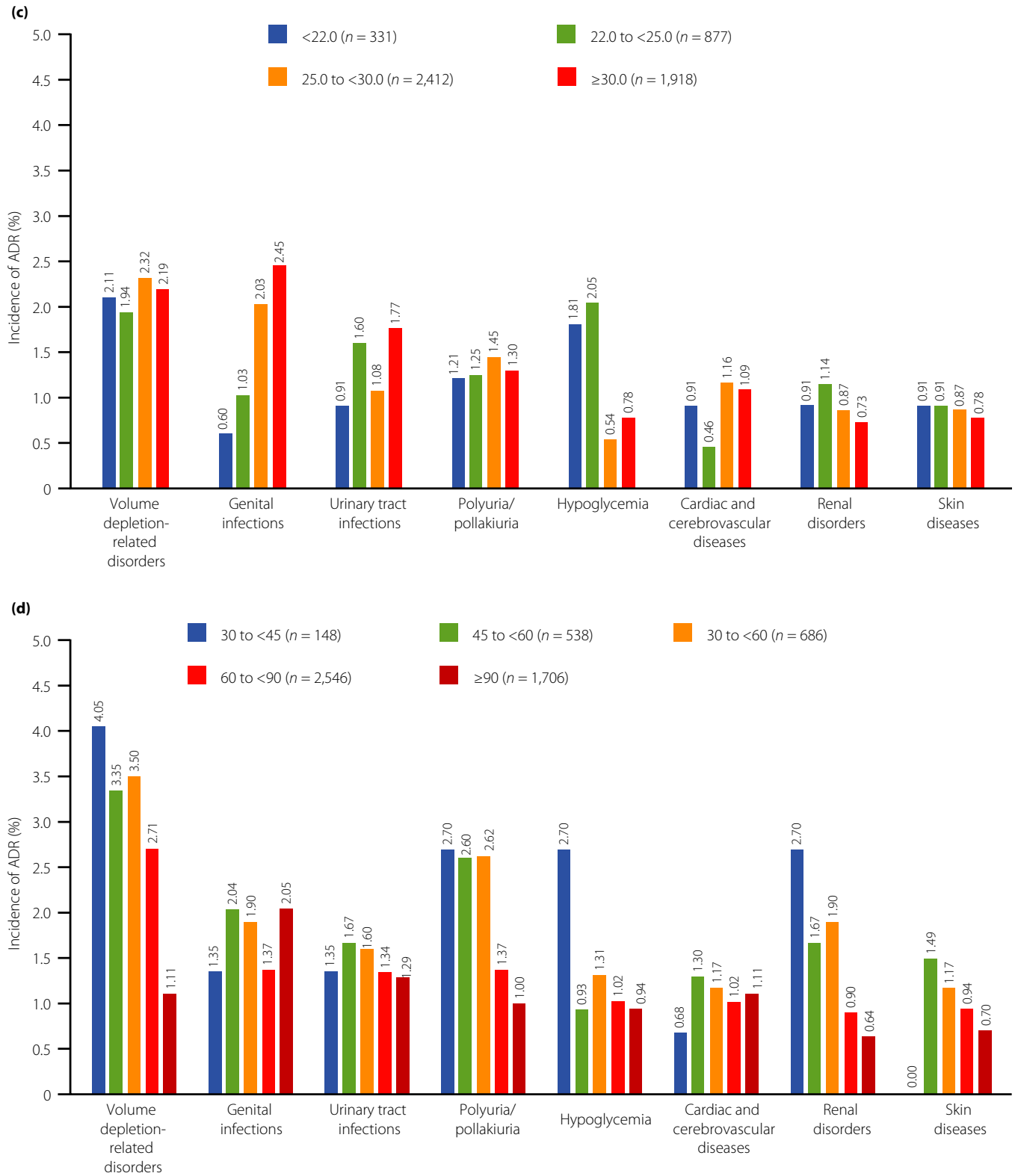


Figure 2 | (Continued).

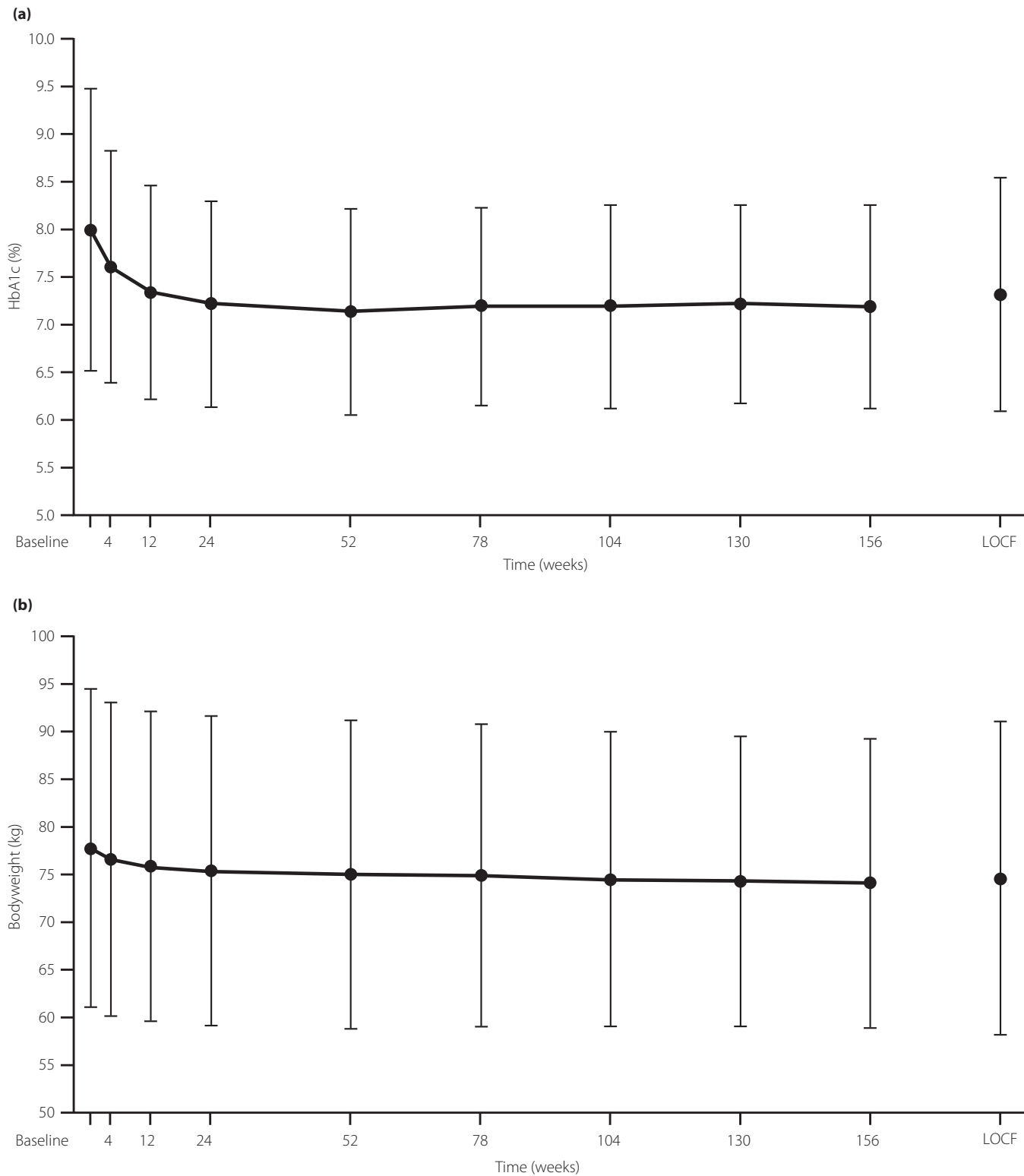


Figure 3 | Evolution of (a) glycated hemoglobin (HbA1c) and (b) bodyweight from baseline through to last observation carried forward (LOCF) in all patients combined.

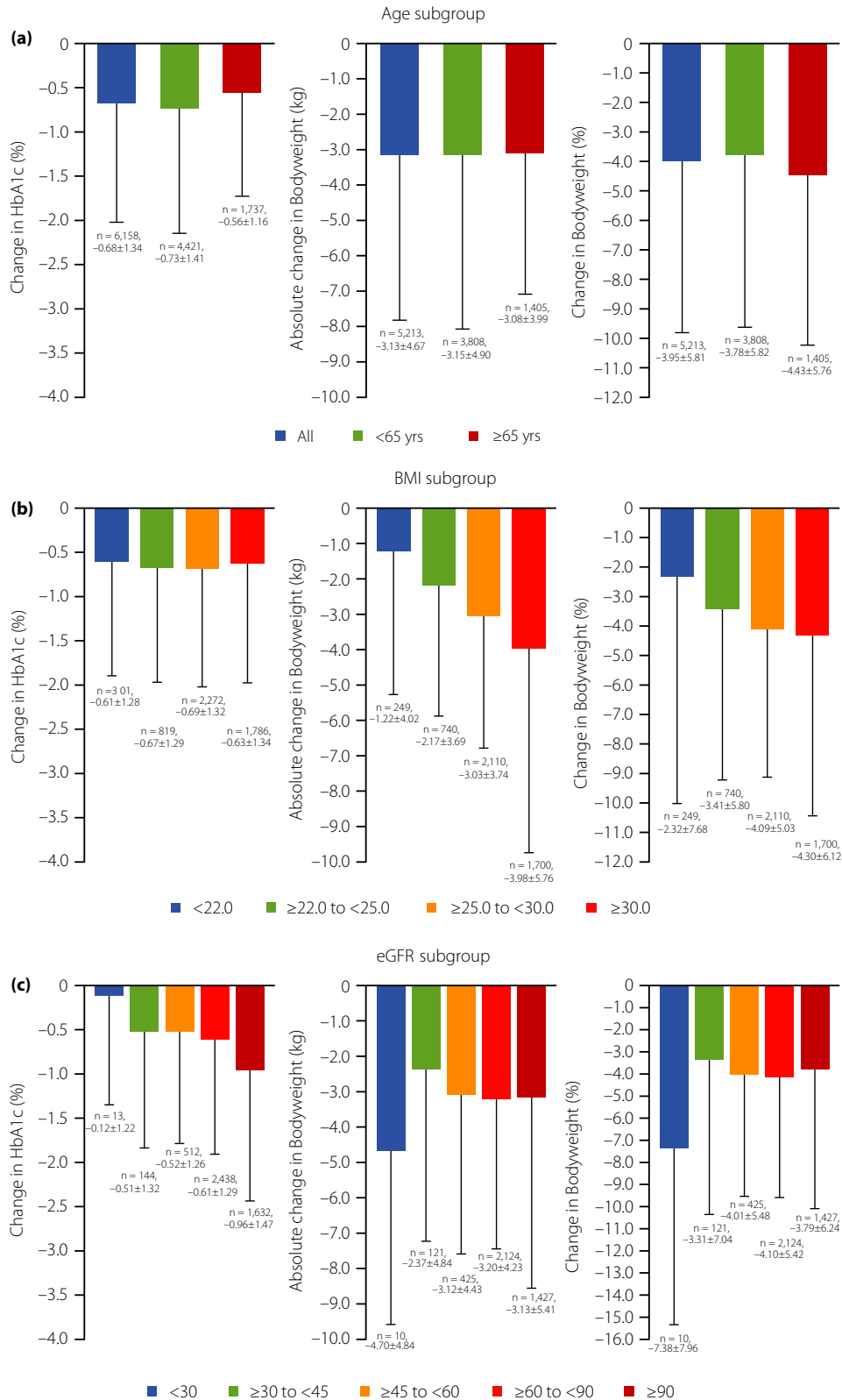


Figure 4 | Change in glycated hemoglobin (HbA1c; left), absolute change in bodyweight (middle) and percentage change in bodyweight (right) from baseline to last observation carried forward according to (a) age at baseline (in years), (b) body mass index (BMI; in kg/m²) and (c) estimated glomerular filtration rate (eGFR) at baseline (in mL/min/1.73 m²).

Polyuria/pollakiuria and fluid loss are anticipated due to the effects of SGLT2 inhibitors on renal glucose excretion, which increases osmotic diuresis and can result in fluid loss. Furthermore, fluid loss could worsen renal function, especially for patients with renal impairment. Patients aged >65 years showed slight increases in the prevalence of polyuria/pollakiuria (1.12% in <65 years vs 1.90% in ≥65 years) and volume depletion-related disorders (1.79 vs 2.58%). Although the incidence of renal disorders was also higher in patients aged ≥65 years (0.66 vs 1.11%), it was not elevated in patients aged ≥75 years (0.61%, data not shown). We speculate that aged people receiving tofogliflozin are not necessarily vulnerable to renal disorders. In contrast, lower baseline eGFR levels appear to be associated with a higher incidence of renal disorders. We found that the AE “blood urea increased”, which is closely related to dehydration, mostly accounted for this trend (0.73% in patients with eGFR 30 to <60 mL/min/1.73 m², 0.47% in 60 to <90 mL/min/1.73 m², 0.12% in >90 mL/min/1.73 m², data not shown). Regarding severe cases of renal disorders, we detected no apparent trend with baseline eGFR levels (0–3 cases per subgroup). Therefore, older patients and patients with renal impairment should be encouraged to drink enough water to help reduce the risk of volume depletion-related disorders and renal disorders.

Genital infection occurred in 117 patients (1.74%), and urinary tract infection occurred in 91 patients (1.36%). Prior studies have documented an increased risk of genital infection in patients treated with SGLT2 inhibitors^{42–46}. Regarding urinary tract infection, this was originally reported in middle-aged women, but there is no relationship between SGLT2 inhibitors and urinary tract infection^{43,44,46}. Notably, the incidence of genital infections seemed to increase with increasing BMI (0.60% to 2.45%), and similar findings have been reported for dapagliflozin⁴⁷ and canagliflozin^{47,48}. Although the causal relationship between obesity and genital infection is unknown, the patients' clinical condition might have been mild. Precautionary hygienic measures might be necessary when urinating to reduce the risk of genital infection.

Cardiovascular safety is a major concern in the management of diabetes. The US Food and Drug Administration requires evaluation of cardiovascular risk of new antidiabetic drugs²⁹. Although the incidence of cardiac and cerebrovascular diseases (0.91%) was analyzed as ADRs, this includes events such as arrhythmia and vasospastic angina. Therefore, we also evaluated the cardiovascular safety in terms of AEs using MACE. The incidence of MACE over a period of 3 years was <1% in the present study, which appears to be as low as those in other studies of Japanese patients with type 2 diabetes (Japanese Diabetes Clinical Data Management 20: 8.3 per 1,000 person-years; Japanese Diabetes Outcome Intervention Trial 3: 3.4% during the first 3 years)^{49,50}.

As for the effectiveness of tofogliflozin, the significant reductions from baseline in HbA1c (−0.68%, $P < 0.0001$) and bodyweight (−3.13 kg, $P < 0.0001$) over a period of 36 months in

the context of real-world clinical practice broadly reflect those observed in shorter clinical trials (≤52 weeks), in which reductions in HbA1c and bodyweight were −0.5 to −0.8% and −1 to −3 kg, respectively^{21–24}. We also observed improvements in patients divided by baseline age, BMI and eGFR, with slight differences among some subgroups. In particular, we might anticipate a greater capacity for weight loss among patients with higher BMI at baseline. Meanwhile, the differences in HbA1c reductions among eGFR groups are also reasonable considering the essential role of the kidney in the glucose-lowering effects of SGLT2 inhibitors¹. We consider that these differences might be partly attributed to other factors (e.g., concomitant medications). Nevertheless, the present results suggest that tofogliflozin might lower HbA1c and improve bodyweight in various subgroups of patients by age, BMI and eGFR.

We must also mention possible limitations of this surveillance. In particular, the surveillance did not include a control group, although this is an inherent feature of post-marketing surveillance studies, which are aimed at monitoring the safety of a newly approved drug once it enters clinical practice. It is possible that undocumented changes in concomitant antidiabetic medications during the observation period might contribute to the safety and/or effectiveness findings observed in this surveillance. It is possible that some ADRs, such as hypoglycemia, that are reliant on the patients reporting their symptoms, were underreported. In clinical trials, hypoglycemia might be detected as changes in self-monitored blood glucose or more frequent laboratory testing, as stipulated in trial protocols. Finally, HbA1c, bodyweight and other clinical laboratory tests/vital signs were not available for all patients. However, this reflects real-life practice, where laboratory tests are not routinely carried out, unlike clinical trials where blood tests and vital signs are measured at prespecified intervals.

In conclusion, J-STEP/LT, a 3-year, prospective, observational, post-marketing study in Japan, found no unprecedented ADRs in tofogliflozin-treated patients.

Although one episode of diabetic ketoacidosis occurred, there were no reported cases of leg amputation and fracture. Regarding MACE, there were no data that raised concerns about the cardiovascular safety of tofogliflozin. Although we cannot confirm causality, the reductions from baseline in HbA1c and bodyweight were maintained over the observation period. Therefore, the present results provide further evidence that tofogliflozin is safe and well-tolerated for Japanese patients with type 2 diabetes.

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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 | Adverse drug reactions by system organ class and preferred term.

Table S2 | Changes in vital signs and laboratory tests.