JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

Safety and effectiveness of tofogliflozin in elderly Japanese patients with type 2 diabetes mellitus: A post-marketing study (J-STEP/EL Study)

Kazunori Utsunomiya[1], Naoki Shimmoto[2]*, Masayuki Senda[3], Yuji Kurihara[2], Ryoji Gunji[2], Shoko Fujii[2], Seigo Kakiuchi[2], Hisataka Fujiwara[2], Hiroyuki Kameda[3], Masahiro Tamura[4], Kohei Kaku[5]

[1]Division of Diabetes, Metabolism and Endocrinology, Department of Internal Medicine, Jikei University School of Medicine, [2]Post Marketing Surveillance Department, Kowa Company, Ltd., [3]Medical Affairs, [4]Diabetes & Cardiovascular Medical Operations, Sanofi K.K., Tokyo, and [5]Department of General Internal Medicine 1, Kawasaki Medical School, Kurashiki, Japan

Keywords
Elderly, Sodium-glucose transporter 2, Type 2 diabetes mellitus

***Correspondence**
Naoki Shimmoto
Tel.: +81-3-3279-7426
Fax: +81-3-5202-7245
E-mail address: n-simmot@kowa.co.jp

J Diabetes Investig 2017; 8: 766–775

doi: 10.1111/jdi.12626

ABSTRACT

Aims/Introduction: Although sodium-glucose cotransporter 2 inhibitors are a promising treatment for type 2 diabetes mellitus, they are associated with concerns about specific adverse drug reactions. We carried out a 1-year post-marketing study of tofogliflozin, a novel agent in this class, in Japanese elderly patients with type 2 diabetes mellitus.

Materials and Methods: This was a prospective, observational and multicenter post-marketing study carried out in the context of routine clinical practice. The study included all type 2 diabetes patients aged ≥65 years who started treatment with tofogliflozin during the first 3 months after its launch on 23 May 2014.

Results: Of 1,535 patients registered, 1,507 patients whose electronic case report forms were collected and who had at least one follow-up visit were included in the safety analysis. A total of 270 of 1,507 patients (17.92%) had at least one adverse drug reaction to tofogliflozin. The incidences of adverse drug reactions of special interest, namely, polyuria/pollakiuria, volume depletion-related events, urinary tract infection, genital infection, hypoglycemia and skin disorders were 2.92, 3.85, 2.06, 1.33, 1.06 and 2.39%, respectively. Among those patients evaluable for clinical effectiveness, the mean change in glycated hemoglobin and bodyweight from baseline to last visit was −0.46% ($P < 0.0001$) and −2.71 kg ($P < 0.0001$), respectively.

Conclusions: The present study showed that the incidence of adverse drug reactions to tofogliflozin in this study of elderly patients aged ≥65 years differed little from the incidence in the preapproval clinical trials. It was shown that tofogliflozin significantly decreased glycated hemoglobin levels.

INTRODUCTION

In the past two decades, there have been dramatic developments in the pharmaceutical options for treating type 2 diabetes mellitus[1,2]. Presently, approximately seven classes of oral antidiabetic drugs and two classes of injectables are available for treating type 2 diabetes mellitus[3,4]. Among these, sodium-glucose cotransporter (SGLT) 2 inhibitors are the newest class of agents[5,6]. SGLT2 inhibitors exert their antidiabetic effects by inhibiting SGLT2, which is localized in the proximal renal tubule, and is responsible for approximately 90% of glucose reabsorption in the kidney[7]. Suppression of renal glucose reabsorption and an increase in urinary glucose excretion results in decreased blood glucose levels in an insulin-independent manner[8]. Tofogliflozin is a potent and highly selective SGLT2 inhibitor with a 2,900-fold selectivity for SGLT2 over SGLT1[9–11]. Tofogliflozin was approved in Japan in 2014 for the treatment of type 2 diabetes mellitus as monotherapy or in combination with other antidiabetic agents[12,13]. Once-daily oral

Received 6 October 2016; revised 15 January 2017; accepted 16 January 2017

administration of tofogliflozin for 24–52 weeks showed clinically relevant improvements in glycemic control associated with weight loss in phase 3 and long-term clinical studies[14–16]. In these studies, tofogliflozin was well tolerated, and most adverse drug reactions (ADRs) were mild or moderate in severity. In a total of 1,060 patients, 397 (37.5%) had ADRs, with the main adverse events being hyperketonemia (11.0%), dry mouth (7.5%) and pollakiuria (7.5%). The risk of hypoglycemia was low (3.3%) when tofogliflozin was administered as monotherapy[17,18].

Six SGLT2 inhibitors were approved in Japan in 2014; ipragliflozin, dapagliflozin, luseogliflozin, tofogliflozin, canagliflozin and empagliflozin, and are currently widely used for the treatment of type 2 diabetes mellitus[19]. Shortly after the launch of SGLT2 inhibitors as a new class of antidiabetics, safety has become a major concern because of several serious ADRs recognized as class effects of SGLT2 inhibitors, including urinary tract and genital infections, ketoacidosis, dehydration, events resulting from dehydration, and skin disorders. These led to 'Recommendations on appropriate usage of SGLT2 inhibitors' being issued by a committee of Japanese experts in June 2014[20]. This statement recommended that special conditions must exist before treatment with any SGLT2 inhibitor in elderly patients is initiated, and all type 2 diabetes mellitus patients aged ≥65 years who started to receive these drugs within 3 months after its launch should be registered for inclusion in a post-marketing study.

A post-marketing study had been planned before approval according to the risk management plan and discussions with the regulatory agency before issuing of this recommendation statement. Accordingly, a post-marketing special drug use study of tofogliflozin in elderly patients with type 2 diabetes mellitus in routine clinical practice was initiated immediately after the launch[21,22]. The study registered all elderly patients (whenever possible) who started treatment with tofogliflozin during the early post-marketing period. Patients enrolled were followed up for 1 year from the date of treatment initiation. We reported the interim analysis when the first 12 weeks of data became available[23]. Here, the final results of the post-marketing study of tofogliflozin are reported.

MATERIALS AND METHODS

Study design

This Japanese Study of Tofogliflozin with Type 2 Diabetes Mellitus Patients in an Observational Study of the Elderly (J-STEP/EL) was a prospective, observational and multicenter post-marketing study co-sponsored by the manufacturers to investigate the safety and effectiveness of two tofogliflozin hydrate products, Deberza® 20-mg tablet (Kowa Company, Ltd., Nagoya, Japan) and Apleway® 20-mg tablet (Sanofi K.K., Tokyo, Japan). The study was carried out in accordance with the Japanese regulatory requirements stipulated in the Good Post-Marketing Study Practice[24]. All institutions that received a supply of a tofogliflozin hydrate product and started to use the product in elderly patients during the first 3 months after its launch were invited to participate in the study whenever possible. The present study was carried out from 23 May 2014 to 31 October 2015.

Participants and data assessment

All patients aged ≥65 years who started to receive tofogliflozin for treatment of type 2 diabetes mellitus within 3 months (12 weeks) of its launch in Japan were registered using a central registration system from 23 May 2014 to 22 August 2014. Each patient was followed up for 1 year (52 weeks) from the date of treatment initiation. Clinical data recorded in electronic case report forms included demographic and baseline characteristics, details of tofogliflozin treatment, concomitant antidiabetic treatment, clinical course (vital signs, glycated hemoglobin [HbA1c], fasting blood glucose, laboratory tests) and adverse events (AEs).

AEs that occurred during the observation period were collected regardless of causality to the drug. The physician reported the name of the AE, the date of onset, seriousness and actions carried out for the event, including treatment with tofogliflozin, the outcome, the date of outcome and relationship of the AE to the drug. The actual events reported were based on the physician's judgment. The effectiveness variable was the effect on glycemic control.

Statistical analysis

AEs and ADRs were categorized according to the Medical Dictionary for Regulatory Activities/Japanese edition (MedDRA/J) version 18.1. The safety analysis set was defined as all patients for whom electronic case report forms were collected, excluding those with no follow-up visits after baseline. The effectiveness analysis set included all patients in the safety analysis set excluding those who did not have any effectiveness data. The Fisher's exact test was used to investigate the association of the incidence of ADRs with patient characteristics and treatment at baseline. Measurements at baseline and after treatment were compared using one-sample *t*-test. Factors associated with ADRs of special interest were initially examined by univariate logistic regression analysis using variables from patient characteristics and treatment at baseline. After identifying potential influencing factors, multivariate logistic regression analysis was carried out in a stepwise fashion to further investigate factors that contribute to ADRs of special interest. All statistical tests were two-sided, and the significance level was set at 5%. Missing data at 52 weeks were imputed with the last observation carried forward (LOCF) method, and the change from baseline to 52 weeks was calculated using last observation carried forward data. Sas 9.3 (SAS Institute Japan Ltd., Tokyo, Japan) was used for the statistical analyses.

RESULTS

Patient disposition and characteristics

Of the 1,535 patients registered, 1,514 electronic case report forms were collected from 597 sites throughout Japan. The

safety analysis set consisted of 1,507 patients after exclusion of those who did not return to the site after treatment initiation (n = 4), those ineligible under the criteria (n = 2) and those registered, but for whom there was a contract deficiency (n = 1). Of the 1,507 patients, the effectiveness analysis set consisted of 1,424 patients after removal of 83 patients, because no effective data were available (Figure 1). The mean observation period ± standard deviation (SD) was 291.6 ± 141.1 days. In total, 549 patients (36.4%) discontinued tofogliflozin during the observation period. AEs were the most common reason for treatment discontinuation (n = 190; 12.6%), and other reasons included limited or no response (n = 116; 7.7%), failure to attend scheduled visits (n = 89; 5.9%), patient request (n = 84; 5.6%), improvement in diabetes (n = 21; 1.4%), physician request (n = 7; 0.5%) and others (n = 42; 2.8%). Table 1 summarizes the patient characteristics. Of the 1,507 patients included in the safety analysis set, 47.6% were men and 52.4% were women. The mean age ± SD was 72.4 ± 6.0 years, and 499 were aged ≥75 years (33.1%). The mean body mass index (BMI) ± SD was 26.8 ± 4.5 kg/m^2. The mean duration of diabetes, baseline HbA1c and estimated glomerular filtration rate (eGFR) were 10.8 ± 7.7 years, 7.7 ± 1.4% and 68.6 ± 20.2 mL/min/1.73 m^2, respectively. Overall, 82.9% of patients received concomitant antidiabetic drugs, with the mean number of two drugs per patient. The most commonly used oral antidiabetic drugs were dipeptidyl peptidase-4 inhibitors (64.7%), sulfonylureas (34.4%) and biguanides (28.8%). No combination of tofogliflozin with another SGLT2 agent was found. Diuretics were used in 195 patients (12.9%; Table 2). The number of patients who were treated with tofogliflozin monotherapy was 249 (16.5%), and among them, those who started taking tofogliflozin as their first treatment for type 2 diabetes mellitus numbered 158 (10.5%).

Safety results

The incidences of ADRs by system organ class for tofogliflozin in the present study and in clinical trials available at the time of drug approval are summarized in Table 3 (the ADRs by preferred term are shown in supporting Table S1). At approval, 397 patients (37.45%) had 685 ADRs, whereas in this study, 270 patients (17.92%) experienced 386 ADRs to tofogliflozin (the cumulative ADR incidence curve over time is shown in supporting Figure S1). The frequencies of the ADRs were 178 (17.66%) in patients aged ≥65 to <75 years, and 92 (18.44%) in those aged ≥75 years, respectively. The corresponding numbers of patients who developed serious ADRs were 20 (1.98%) and 13 (2.61%), respectively (supporting Table S2). In the present study, cerebral infarction or lacunar infarction occurred in five patients, and acute myocardial infarction occurred in two patients (Table S1). Six deaths were reported during the observation period. Of these, four were deemed to be unrelated to treatment, whereas the remaining two (acute myocardial infarction and brain stem infarction) were considered to be related to tofogliflozin.

Table 4 summarizes ADRs of special interest in the present study. ADRs associated with polyuria/pollakiuria were predominantly pollakiuria, which occurred in 33 patients (2.19%). These were observed in 16 patients within the first 4 weeks of treatment, 10 patients from 5–8 weeks and 18 patients after 9 weeks. Volume depletion-related events occurred in 58 patients (3.85%): 16 patients within the first 4 weeks, 11 patients from 5–8 weeks and 31 patients after 9 weeks. The most common ADRs associated with volume depletion were dehydration, constipation and thirst, which occurred in 24 (1.59%), 11 (0.73%) and nine (0.60%) patients, respectively. Incidences of thirst (0.60%) and constipation (0.73%) in the present study were lower than those in the preapproval clinical

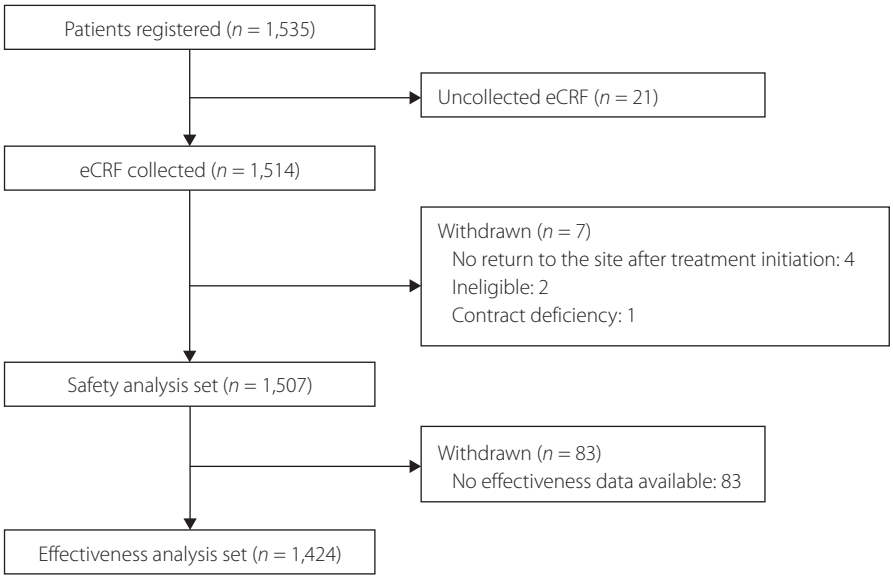

Figure 1 | Patient disposition. eCRF, electronic case report forms.

Table 1 | Patient characteristics

Variable	Safety analysis set	
	n	(%)
Total	1,507	(100)
Sex		
Male	718	(47.6)
Female	789	(52.4)
Age (years)		
Mean ± SD	72.4 ± 6.0	
≥65 to <75	1,008	(66.9)
≥75	499	(33.1)
Baseline BMI (kg/m^2)		
Mean ± SD	26.8 ± 4.5	
<22.0	132	(8.8)
≥22.0 to <25.0	260	(17.3)
≥25.0 to <30.0	492	(32.7)
≥30.0	219	(14.5)
Unknown	404	(26.8)
Diabetes duration (years)		
Mean ± SD	10.8 ± 7.7	
<1	44	(2.9)
≥1 to <10	407	(27.0)
≥10	454	(30.1)
Unknown	602	(40.0)
Liver function		
Normal	1,238	(82.2)
Dysfunction	224	(14.9)
Unknown	45	(3.0)
Kidney function		
Normal	647	(42.9)
Dysfunction	812	(53.9)
Unknown	48	(3.2)
Baseline eGFR (mL/min/1.73 m^2)		
Mean ± SD	68.6 ± 20.2	
<30	18	(1.2)
≥30 to <45	93	(6.2)
≥45 to <60	242	(16.1)
≥60 to <90	590	(39.2)
≥90	134	(8.9)
Unknown	430	(28.5)
Baseline HbA1c (%)		
Mean ± SD	7.7 ± 1.4	
<6.5	233	(15.5)
≥6.5 to <7.0	240	(15.9)
≥7.0 to <8.0	491	(32.6)
≥8.0	442	(29.3)
Unknown	101	(6.7)
Concomitant disease		
No	91	(6.0)
Yes	1,414	(93.8)
Unknown	2	(0.1)
Diabetic complications	460	(30.5)
Diabetic retinopathy	122	(8.1)
Diabetic nephropathy	319	(21.2)
Diabetic neuropathy	181	(12.0)
Liver disease	241	(16.0)
Kidney disease	162	(10.8)
Cardiovascular disease[†]	415	(27.5)
Cardiovascular disease	324	(21.5)
Cerebrovascular disease	129	(8.6)
Heart failure	108	(7.2)
Malignancy	21	(1.4)
Urinary tract infection	8	(0.5)
Hypertension	1,113	(73.9)
Dyslipidemia	1,063	(70.5)
Gout	40	(2.7)
Hyperuricemia	191	(12.7)
Osteoporosis	174	(11.6)

[†]Concomitant cardiovascular disease or medical history of cardiovascular disease. eGFR, estimated glomerular filtration rate; SD, standard deviation.

trials (7.55 and 2.17%, respectively), but the incidence of dehydration in the present study was higher than in the preapproval clinical trials (0.19%). A total of 15 serious ADRs were reported in this category, including dehydration (n = 4; 0.27%), cerebral infarction (n = 3; 0.20%), loss of consciousness (n = 2; 0.13%), lacunar infarction (n = 2; 0.13%) and others (n = 4; 0.27%).

Urinary tract infection-related ADRs included cystitis (n = 16; 1.06%) and urinary tract infection (n = 10; 0.66%). Among the urinary tract infections, pyelonephritis (n = 3), urinary tract infection (n = 1) and septic shock (n = 1) were serious, but improved after discontinuation of tofogliflozin. The most common type of genital infection-related ADRs was pruritus genital (n = 9; 0.60%). Genital infection-related ADRs occurred in nine patients within the first 4 weeks, but no consistent trend was seen in the time of onset of urinary tract infections. Women were significantly more likely to develop both urinary tract and genital infections than men, with the male-to-female ratio being 2:29 ($P < 0.0001$) and 3:17 ($P = 0.0029$), respectively. All cases of genital infection were non-serious.

Hypoglycemia was reported in 16 patients (1.06%), six of whom experienced the event within the first 4 weeks. Concomitant antidiabetic drugs, including insulin (n = 6), sulfonylurea (n = 8), biguanide (n = 9), DPP-4 inhibitors (n = 14) and Thiazolidinedione (n = 3), were used with tofogliflozin in 15 patients who developed hypoglycemia. More than two drugs were used with tofogliflozin in most cases, and concomitant insulin or sulfonylurea was used in 14 patients. One patient took tofogliflozin as monotherapy, and hypoglycemia occurred within the first 2 weeks. None of the cases of hypoglycemia was serious.

Table 2 | Concomitant antidiabetic treatment

Variable	Safety analysis set	
	n	(%)
Evaluable patients	1,507	(100)
Concomitant antidiabetic drugs		
No	249	(16.5)
Yes	1,249	(82.9)
Unknown	9	(0.6)
Oral antidiabetic drug		
No	282	(18.7)
Yes	1,216	(80.7)
Unknown	9	(0.6)
No. oral antidiabetic drugs		
Mean ± SD	2.0 ± 1.0	
1	452	(38.2)
2	415	(35.1)
3	229	(19.4)
4	78	(6.6)
5	9	(0.8)
Biguanide	434	(28.8)
Sulfonylurea	519	(34.4)
DPP-4 inhibitor	975	(64.7)
Fast-acting insulin secretagogue	64	(4.3)
α-Glucosidase inhibitor	224	(14.9)
Thiazolidinedione	279	(18.5)
Insulin	166	(11.0)
GLP-1 receptor agonist	31	(2.1)
Concomitant diuretics		
No	1,303	(86.5)
Yes	195	(12.9)
Unknown	9	(0.6)
Loop diuretics	69	(4.6)
Thiazides	86	(5.7)
Anti-aldosterone	44	(2.9)
Other diuretics	21	(1.4)
Mean daily dose of tofogliflozin		
<20 mg	125	(8.3)
20 mg	1,382	(91.7)

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SD, standard deviation.

Table 3 | Adverse drug reactions

	Present study	At approval
No. evaluable patients	1,507	1,060
No. patients with an ADR (%)	270 (17.92)	397 (37.45)
Type of ADR, no. patients (%)†		
Renal and urinary disorders	62 (4.11)	97 (9.15)
Metabolism and nutrition disorders	47 (3.12)	46 (4.34)
Infections and infestations	41 (2.72)	48 (4.53)
Skin and subcutaneous tissue disorders	36 (2.39)	16 (1.51)
Investigations	31 (2.06)	155 (14.62)
Gastrointestinal disorders	29 (1.92)	57 (5.38)
Nervous system disorders	25 (1.66)	23 (2.17)
General disorders and administration site conditions	21 (1.39)	95 (8.96)
Reproductive system and breast disorders	11 (0.73)	16 (1.51)
Cardiac disorders	8 (0.53)	12 (1.13)
Musculoskeletal and connective tissue disorders	8 (0.53)	9 (0.85)
Respiratory, thoracic and mediastinal disorders	7 (0.46)	3 (0.28)
Vascular disorders	7 (0.46)	7 (0.66)
Psychiatric disorders	5 (0.33)	2 (0.19)
Hepatobiliary disorders	3 (0.20)	3 (0.28)
Blood and lymphatic system disorders	2 (0.13)	5 (0.47)
Endocrine disorders	1 (0.07)	3 (0.28)
Injury, poisoning and procedural complications	1 (0.07)	1 (0.09)
Eye disorders	0 (0.00)	10 (0.94)
Ear and labyrinth disorders	0 (0.00)	7 (0.66)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0 (0.00)	3 (0.28)

†By system organ class (MedDRA version 18.1). ADR, adverse drug reaction.

Skin disorders were more common in the present study (2.39%) than in the preapproval clinical trials (1.51%). Onset was within the first 4 weeks among the 12 patients who experienced these disorders, the most common of which were rash and pruritus. One out of four cases of drug eruption was serious.

On multivariate logistic regression analysis of ADRs of special interest, female (odds ratio [OR] 1.45, 95% confidence interval [CI]: 1.06–1.98), kidney disorder (OR 1.74, 95% CI: 1.24–2.43) and concomitant use of glucagon-like peptide (GLP)-1 receptor agonist (OR 2.90, 95% CI: 1.32–6.33) were identified as factors influencing all ADRs of special interest, as shown in Table 5. Variables age ≥75 years (OR 2.06, 95% CI: 1.09–3.88), female (OR 23.18, 95% CI: 3.12–172.23) and concomitant use of GLP-1 receptor agonist (OR 7.11, 95% CI: 2.28–22.15) were factors influencing volume depletion, urinary tract infection and skin complications, respectively.

Effectiveness, changes in laboratory variables and vital signs

The mean HbA1c ± SD decreased from 7.64 ± 1.35% at baseline (n = 1,347) to 7.17 ± 1.17% (n = 1,404) at the last visit, a decrease of −0.46 ± 1.01% ($P < 0.0001$; Table 6). A significant reduction in HbA1c was observed in patients whose eGFR baseline was ≥45 mL/min/1.73 m^2, but no appreciable glucose-lowering effect of tofogliflozin was observed in patients whose eGFR were <45 mL/min/1.73 m^2 (supporting Table S3). BMI was not associated with the glucose-lowering effect of tofogliflozin (supporting Table S4).

The mean bodyweight ± SD decreased from 67.43 ± 12.52 kg at baseline (n = 1,037) to 64.67 ± 12.12 kg (n = 1,122) at the last of visit, a decrease of −2.71 ± 3.57 kg

Table 4 | Adverse drug reactions of special interest

	This study (n = 1,507)	
	All	Serious ADR
Polyuria/pollakiuria	44 patients (2.92%)	
Pollakiuria	33 (2.19)	0 (0.00)
Nocturia	12 (0.80)	0 (0.00)
Polyuria	8 (0.53)	0 (0.00)
Volume depletion-related events	58 patients (3.85%)	
Dehydration	24 (1.59)	4 (0.27)
Constipation	11 (0.73)	0 (0.00)
Thirst	9 (0.60)	0 (0.00)
Blood urea increased	6 (0.40)	0 (0.00)
Cerebral infarction	3 (0.20)	3 (0.20)
Hemoconcentration	2 (0.13)	0 (0.00)
Loss of consciousness	2 (0.13)	2 (0.13)
Lacunar infarction	2 (0.13)	2 (0.13)
Depressed level of consciousness	1 (0.07)	1 (0.07)
Diverticulum intestinal hemorrhagic	1 (0.07)	1 (0.07)
Ketoacidosis	1 (0.07)	1 (0.07)
Syncope	1 (0.07)	1 (0.07)
Heat illness	1 (0.07)	0 (0.00)
Urinary tract infection	31 patients (2.06%)	
Cystitis	16 (1.06)	0 (0.00)
Urinary tract infection	10 (0.66)	1 (0.07)
Pyelonephritis	3 (0.20)	3 (0.20)
Cystitis hemorrhagic	2 (0.13)	0 (0.00)
Pyelonephritis acute	2 (0.13)	0 (0.00)
Septic shock	1 (0.07)	1 (0.07)
Genital infection	20 patients (1.33%)	
Pruritus genital	9 (0.60)	0 (0.00)
Genital infection	4 (0.27)	0 (0.00)
Vulvovaginal candidiasis	3 (0.20)	0 (0.00)
Balanoposthitis	2 (0.13)	0 (0.00)
Vulvitis	2 (0.13)	0 (0.00)
Genital rash	1 (0.07)	0 (0.00)
Vaginal inflammation	1 (0.07)	0 (0.00)
Genital infection fungal	1 (0.07)	0 (0.00)
Genital infection female	1 (0.07)	0 (0.00)
Hypoglycemia	16 patients (1.06%)	
Hypoglycemia	16 (1.06)	0 (0.00)
Skin disorders	36 patients (2.39%)	
Rash	11 (0.73)	0 (0.00)
Pruritus	7 (0.46)	0 (0.00)
Drug eruption	4 (0.27)	1 (0.07)
Urticaria	4 (0.27)	0 (0.00)
Eczema	3 (0.20)	0 (0.00)
Dermatitis allergic	2 (0.13)	0 (0.00)
Erythema	2 (0.13)	0 (0.00)
Rash pruritic	2 (0.13)	0 (0.00)
Pruritus generalized	2 (0.13)	0 (0.00)
Miliaria	1 (0.07)	0 (0.00)
Papule	1 (0.07)	0 (0.00)
Rash scarlatiniform	1 (0.07)	0 (0.00)
Skin exfoliation	1 (0.07)	0 (0.00)
Tinea infection	1 (0.07)	0 (0.00)

MedDRA version 18.1. ADR, adverse drug reaction.

Table 5 | Variables associated with the incidence of adverse drug reaction of special interest in multivariate logistic regression analysis

Variables	OR (95% CI)	P-value
Overall		
Female	1.45 (1.06–1.98)	0.021
Kidney disorder	1.74 (1.24–2.43)	0.001
Concomitant use of GLP-1 receptor agonist	2.90 (1.32–6.33)	0.008
Polyuria/pollakiuria		
None	–	–
Volume depletion-related events		
≥75 years-of-age	2.06 (1.09–3.88)	0.026
Urinary tract infection		
Female	23.18 (3.12–172.23)	0.002
Skin complications		
Concomitant use of GLP-1 receptor agonist	7.11 (2.28–22.15)	<0.001

Total n = 1,032. Stepwise analysis used the following independent variables: sex (male/female), age (<75/≥75 years), baseline glycated hemoglobin (continuous value), baseline body mass index (continuous value), kidney function (normal/disorder), liver function (normal/disorder), diabetic complication (yes/no), cardio-cerebrovascular disease (yes/no), concomitant use of biguanide/sulfonylureas/dipeptidyl peptidase-4 inhibitors/fast-acting insulin secretagogues/α-glucosidase inhibitors/thiazolidinediones/insulins/glucagon-like peptide-1 (GLP-1) receptor agonist/diuretics (yes/no). CI, confidence interval; OR, odds ratio.

($P < 0.0001$; Table 6). There was no correlation between bodyweight loss and baseline eGFR (Table S3), but dependent on BMI (Table S4).

The effect of tofogliflozin on changes in other laboratory variables and vital signs is summarized in Table 6. Fasting blood glucose, BMI, systolic blood pressure, diastolic blood pressure and uric acid decreased significantly ($P < 0.0001$), whereas significant increases in high-density lipoprotein cholesterol, hematocrit and blood urea nitrogen were observed ($P < 0.0001$). There was no significant change in eGFR during the observation period.

DISCUSSION

We designed the present prospective, observational and multicenter post-marketing study to evaluate the safety and effectiveness of tofogliflozin in routine clinical practice. Elderly male and female patients aged ≥65 years with type 2 diabetes mellitus without exclusions for concomitant diseases and concomitant medications were enrolled. In contrast in the preapproval clinical trials, a number of elderly patients were excluded because of the number and/or severity of their comorbidities, which were defined in the exclusion criteria, resulting in limited safety information for elderly patients[25]. Furthermore, elderly patients aged ≥65 years comprise 63.4% of all type 2 diabetes

Table 6 | Surrogate marker of effectiveness, vital signs and laboratory variables

Variable	Baseline	4 weeks	12 weeks	24 weeks	36 weeks	52 weeks	LOCF	Change at last visit from baseline	*P*-value†
HbA1c (%)	7.64 ± 1.35 (1,347)	7.44 ± 1.24 (1,103)	7.21 ± 1.07 (1,152)	7.16 ± 1.01 (903)	7.19 ± 1.12 (832)	7.04 ± 1.01 (817)	7.17 ± 1.17 (1,404)	−0.46 ± 1.01 (1,329)	<0.0001
FBG (mg/dL)	156.19 ± 58.16 (821)	142.96 ± 50.11 (659)	141.66 ± 49.39 (679)	140.52 ± 47.66 (561)	138.17 ± 44.82 (489)	135.34 ± 46.70 (479)	139.77 ± 50.86 (1,015)	−16.34 ± 58.12 (779)	<0.0001
Body weight (kg)	67.43 ± 12.52 (1,037)	66.25 ± 12.44 (926)	65.62 ± 12.37 (908)	65.42 ± 11.88 (680)	65.71 ± 11.78 (580)	64.88 ± 11.97 (598)	64.67 ± 12.12 (1,122)	−2.71 ± 3.57 (995)	<0.0001
BMI (kg/m^2)	27.08 ± 4.55 (889)	26.51 ± 4.30 (802)	26.41 ± 4.32 (774)	26.46 ± 4.12 (587)	26.53 ± 4.06 (510)	26.30 ± 4.14 (517)	25.95 ± 4.26 (941)	−1.12 ±1.54 (857)	<0.0001
SBP (mmHg)	131.5 ± 14.7 (1,252)	128.5 ± 14.7 (1,118)	128.9 ± 13.9 (1,092)	130.8 ± 14.7 (864)	130.6 ± 14.6 (779)	128.1 ± 13.2 (760)	128.4 ± 14.1 (1,311)	−3.1 ± 15.1 (1,237)	<0.0001
DBP (mmHg)	72.6 ± 10.3 (1,251)	71.2 ± 10.1 (1,114)	71.8 ± 9.8 (1,088)	72.5 ± 9.8 (864)	72.0 ± 9.6 (778)	70.7 ± 9.1 (759)	71.1 ± 9.7 (1,308)	−1.6 ± 10.3 (1,235)	<0.0001
Pulse	74.2 ± 11.4 (749)	74.0 ± 11.0 (676)	73.6 ± 11.1 (644)	74.1 ± 11.1 (501)	73.6 ± 11.4 (449)	73.0 ± 10.8 (438)	73.7 ± 11.3 (856)	−0.6 ± 10.2 (719)	0.1209
TC (mg/dL)	184.64 ± 38.68 (640)	181.64 ± 38.04 (435)	180.98 ± 38.74 (528)	182.92 ± 39.30 (432)	185.37 ± 36.92 (406)	184.15 ± 38.26 (367)	184.04 ± 39.27 (776)	0.82 ± 34.15 (583)	0.5613
HDL-C (mg/dL)	52.86 ± 14.97 (942)	53.14 ± 15.61 (671)	53.84 ± 15.54 (706)	55.42 ± 14.93 (576)	57.15 ± 15.61 (538)	55.79 ± 15.56 (512)	55.55 ± 15.97 (1,095)	2.25 ± 9.24 (866)	<0.0001
LDL-C (mg/dL)	106.38 ± 30.77 (984)	103.91 ± 30.84 (692)	104.35 ± 30.14 (749)	105.26 ± 30.33 (596)	105.45 ± 28.65 (553)	106.62 ± 27.98 (530)	105.23 ± 29.94 (1,138)	−1.21 ± 27.08 (913)	0.1756
Non HDL-C (mg/dL)	132.56 ± 36.85 (536)	129.27 ± 36.79 (362)	126.68 ± 37.83 (431)	129.18 ± 36.88 (356)	128.96 ± 31.67 (337)	130.79 ± 35.75 (300)	129.57 ± 37.95 (641)	−1.01 ± 32.32 (470)	0.4963
TG (mg/dL)	139.61 ± 100.32 (505)	131.28 ± 85.57 (333)	140.46 ± 103.12 (373)	134.77 ± 150.04 (324)	139.60 ± 126.69 (315)	128.78 ± 62.05 (304)	133.44 ± 95.65 (696)	−2.80 ± 57.74 (435)	0.3124
Uric acid (mg/dL)	5.21 ± 2.86 (934)	4.73 ± 1.27 (664)	4.74 ± 1.28 (708)	4.71 ± 1.26 (574)	4.76 ± 1.29 (534)	4.76 ± 1.31 (499)	4.77 ± 1.34 (1,106)	−0.35 ± 1.15 (865)	<0.0001
Hematocrit (%)	40.33 ± 5.54 (855)	41.53 ± 5.23 (596)	42.34 ± 5.68 (675)	42.58 ± 5.54 (568)	43.11 ± 5.79 (523)	42.51 ± 5.45 (496)	42.26 ± 5.94 (1,019)	1.87 ± 5.23 (777)	<0.0001
Serum Cr (mg/dL)	0.80 ± 0.27 (1,030)	0.85 ± 0.35 (772)	0.81 ± 0.28 (825)	0.79 ± 0.30 (652)	0.79 ± 0.31 (605)	0.80 ± 0.30 (567)	0.82 ± 0.37 (1,203)	0.03 ± 0.26 (968)	0.0025
BUN (mg/dL)	17.34 ± 5.58 (876)	17.91 ± 6.22 (656)	17.98 ± 6.28 (701)	18.46 ± 6.88 (573)	18.34 ± 5.92 (526)	18.44 ± 5.91 (495)	18.35 ± 6.58 (1,068)	1.06 ± 5.84 (813)	<0.0001
eGFR (mL/min/1.73 m^2)	68.76 ± 20.16 (1,030)	65.05 ± 19.19 (772)	67.52 ± 20.42 (825)	69.59 ± 25.76 (652)	69.70 ± 21.24 (605)	68.76 ± 21.42 (567)	68.04 ± 24.04 (1,203)	−0.66 ± 10.88 (968)	0.0611

Values are presented as the mean ± standard deviation (number of patients). Effectiveness analysis set: 1,424 patients. †One-sample *t*-test. BMI, body mass index; BUN, blood urea nitrogen; Cr, creatinine; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LOCF, last observation carried forward analysis; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

mellitus patients treated in Japan[26]. The clinical and functional heterogeneity of elderly patients with type 2 diabetes mellitus requires special management by clinicians when making treatment decisions, and necessitates an individualized approach[27,28]. Therefore, it is extremely important to know how safe and effective tofogliflozin is in the real-world setting of type 2 diabetes mellitus, as it is encountered in routine clinical practice.

In the present study, the mean age ± SD was 72.4 ± 6.0 years, and 33.1% of the elderly patients were aged ≥75 years. Notably, the overall incidence of ADRs in this study (17.92%) was lower than it was at the time of approval (37.45%), but the types of ADRs were similar. SGLT2 inhibitors reduce sodium reabsorption and block glucose reabsorption from the proximal tubules of the kidney, resulting in a mild diuretic effect[7]. This osmotic diuresis could lead to pollakiuria and volume depletion-related events[29]. The incidence of dehydration (1.59%) in the present study was higher than that at approval (0.19%), but thirst (0.60%) was less frequent than at approval (7.55%). It is well known that the level of thirst experienced by elderly patients is often insufficient to ensure that they drink enough fluids to compensate for the amount of water lost, and consequently they tend to suffer from dehydration[30]. It should be considered that among the 40 serious ADRs in 33 patients in the present study, 15 were volume depletion-related events, and a multivariate logistic regression analysis identified age ≥75 years as a significant factor associated with these events. Although concomitant diuretics might increase the risk of volume depletion-related events, multivariate logistic regression analysis did not identify as an influencing factor.

The constant presence of glucose in the urine caused by SGLT2 inhibition theoretically could increase the risk of urinary tract infections and genital infections. Urinary tract and genital infections are widely recognized as class-related adverse events, and in the present study the incidence in women was higher than in men[31]. Although hypoglycemia is the most important safety concern associated with the use of antidiabetic agents, the risk of hypoglycemia in treatment with SGLT2 inhibitors is reported to be low because of its insulin-independent mechanism of action[32].

Most cases of hypoglycemia associated with administration of tofogliflozin in the present study occurred in combination with other classes of antidiabetics, such as insulin and sulfonylureas, which are known to cause hypoglycemia. Only one patient receiving tofogliflozin as monotherapy experienced hypoglycemia. Skin disorders are recognized as the most common ADRs associated with SGLT2 inhibitors[20], and these were reported in 36 patients (2.39%) in the present study.

Although it is unknown whether skin disorders are class adverse effects, there seems to be cross-reactivity among SGLT2 inhibitors, and the statement by a committee of Japanese experts recommends that patients who develop a skin rash should immediately consult a dermatologist[20]. Multivariate logistic regression analysis identified the variables of female, kidney disorder and concomitant use of GLP-1 receptor agonist as factors influencing all ADRs of special interest. Being female could be a major contributing factor to the incidence of urinary tract infection, but further study is required to elucidate why kidney disorder and concomitant use of a GLP-1 receptor agonist were factors associated with all ADRs of special interest.

Ketoacidosis is considered to be a serious acute complication of this class of compounds, particularly in the USA and European countries[32,33]. As of July 2015, three cases of diabetic ketoacidosis were reported in patients taking tofogliflozin[34]. One of them was documented in this study.

Intensive glycemic control with tofogliflozin in elderly patients with type 2 diabetes mellitus was shown in the present study, supporting the robust effectiveness demonstrated in previous randomized placebo-controlled double-blind preapproval trials[14]. Reduced renal function (eGFR of <45 mL/min/1.73 m^2) attenuated the glucose-lowering effects of tofogliflozin, similar to the clinical findings reported for other SGLT2 inhibitors[35]. In contrast, bodyweight loss was independent of baseline eGFR. This is the first time such an observation has been made, and requires further investigation.

There were limitations to the present study. Onset of most ADRs was observed to occur early in the treatment period. It is unclear whether this was due to drug properties or was a seasonal factor, as patients started to take tofogliflozin during the height of summer, when temperatures were high. Second, the present study focused solely on elderly patients, and therefore the outcomes do not necessarily apply to younger patients. Finally, an individual physician judged the appropriateness of treatment with tofogliflozin, but the recommendation statement issued by the committee of Japanese experts after this study commenced might influence patient selection in the future.

Randomized controlled trials can provide the highest levels of clinical evidence with the least bias, but cannot collect all data relevant to use in routine clinical practice. Therefore, the present post-marketing study is of paramount importance in that it provides feedback on the use of tofogliflozin in routine clinical practice. Based on the results of the interim analysis of all 6 SGLT2 inhibitors including tofogliflozin in Japan, the committee of Japanese experts updated the recommendation on 12 May 2016. The population in whom the use of SGLT2 inhibitors is not recommended consists of those aged ≥75 years or those aged between 65 and 74 years with geriatric syndromes, such as sarcopenia, cognitive decline and decline in the performance of activities of daily living.

In conclusion, the present post-marketing study of tofogliflozin showed that the incidence of ADRs in elderly patients aged ≥65 years was similar to that observed in preapproval trials with no additional special concerns. It was shown that treatment with tofogliflozin was associated with significant improvements in clinically relevant surrogate markers, such as HbA1c and bodyweight, in elderly Japanese patients with type 2 diabetes mellitus.

ACKNOWLEDGMENTS

The study was funded by Kowa Company, Ltd. and Sanofi K. K. The authors thank all physicians from 597 institutions who

participated in this study. The authors thank Dr Tetsuji Asao (SunFlare Co., Ltd.) for writing support. This assistance was funded by Kowa Company, Ltd. and Sanofi K. K.

DISCLOSURE

KU is a medical advisor of Kowa and Sanofi, and received honoraria lectures from Sanofi, MSD, Taisho Toyama Pharmaceutical, Eli Lilly, Terumo, Arkray, Astellas Pharma, Boehringer Ingelheim, Mitsubishi Tanabe Pharma, Ono Pharmaceutical, Novo Nordisk Pharma and Kissei Pharmaceutical. KK is an advisor to, received honoraria for lectures from, and received scholarship grants from Astellas Pharma, AstraZeneca, Boehringer Ingelheim, Sumitomo Dainippon Pharma, Fujifilm Pharma, Kissei Pharmaceutical, Kowa, MSD, Novartis Pharma, Ono Pharmaceutical, Sanofi, Takeda Pharmaceutical, Mitsubishi Tanabe Pharma, Taisho Toyama Pharmaceutical and Daiichi Sankyo. NS, YK, RG, SF, SK and HF are employees of Kowa Company, Ltd. MS, HK and MT are employees of Sanofi K. K.

REFERENCES

1. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. *Lancet* 2005; 365: 1333–1346.
2. Tahrani AA, Bailey CJ, Del Prato S, *et al.* Management of type 2 diabetes: new and future developments in treatment. *Lancet* 2011; 378: 182–197.
3. Esposito K, Chiodini P, Bellastella G, *et al.* Proportion of patients at HbA1c target <7% with eight classes of antidiabetic drugs in type 2 diabetes: systematic review of 218 randomized controlled trials with 78 945 patients. *Diabetes Obes Metab* 2012; 14: 228–233.
4. Bolen S, Tseng E, Hutfless S, *et al.* Diabetes Medications for Adults With Type 2 Diabetes: An Update. Comparative Effectiveness Reviews, No. 173. Agency for Healthcare Research and Quality 2016.
5. Fujita Y, Inagaki N. Renal sodium glucose cotransporter 2 inhibitors as a novel therapeutic approach to treatment of type 2 diabetes: clinical data and mechanism of action. *J Diabetes Investig* 2014; 5: 265–275.
6. Basile JN. The potential of sodium glucose cotransporter 2 (SGLT2) inhibitors to reduce cardiovascular risk in patients with type 2 diabetes (T2DM). *J Diabetes Complications* 2013; 27: 280–286.
7. DeFronzo RA, Davidson JA, Del Prato S. The role of the kidneys in glucose homeostasis: a new path towards normalizing glycaemia. *Diabetes Obes Metab* 2012; 14: 5–14.
8. List JF, Whaley JM. Glucose dynamics and mechanistic implications of SGLT2 inhibitors in animals and humans. *Kidney Int Suppl* 2011; 120: S20–S27.
9. Ohtake Y, Sato T, Kobayashi T, *et al.* Discovery of tofogliflozin, a novel C-arylglucoside with an O-spiroketal ring system, as a highly selective sodium glucose cotransporter 2 (SGLT2) inhibitor for the treatment of type 2 diabetes. *J Med Chem* 2012; 55: 7828–7840.
10. Suzuki M, Honda K, Fukazawa M, *et al.* Tofogliflozin, a potent and highly specific sodium/glucose cotransporter 2 inhibitor, improves glycemic control in diabetic rats and mice. *J Pharmacol Exp Ther* 2012; 341: 692–701.
11. Rosenwasser RF, Rosenwasser JN, Sutton D, *et al.* Tofogliflozin: a highly selective SGLT2 inhibitor for the treatment of type 2 diabetes. *Drugs Today (Barc)* 2014; 50: 739–745.
12. Pafili K, Papanas N. Tofogliflozin: the road goes ever on. *Expert Opin Pharmacother* 2014; 15: 1197–1201.
13. Poole RM, Prossler JE. Tofogliflozin: first global approval. *Drugs* 2014; 74: 939–944.
14. Kaku K, Watada H, Iwamoto Y, *et al.* Efficacy and safety of monotherapy with the novel sodium/glucose cotransporter-2 inhibitor tofogliflozin in Japanese patients with type 2 diabetes mellitus: a combined Phase 2 and 3 randomized, placebo-controlled, double-blind, parallel-group comparative study. *Cardiovasc Diabetol* 2014; 13: 65.
15. Ikeda S, Takano Y, Cynshi O, *et al.* A novel and selective sodium-glucose cotransporter-2 inhibitor, tofogliflozin, improves glycaemic control and lowers body weight in patients with type 2 diabetes mellitus. *Diabetes Obes Metab* 2015; 17: 984–993.
16. Tanizawa Y, Kaku K, Araki E, *et al.* Long-term safety and efficacy of tofogliflozin, a selective inhibitor of sodium-glucose cotransporter 2, as monotherapy or in combination with other oral antidiabetic agents in Japanese patients with type 2 diabetes mellitus: multicenter, open-label, randomized controlled trials. *Expert Opin Pharmacother* 2014; 15: 749–766.
17. Kowa Company, Ltd. Package insert for Deberza 20 mg Tablet (in Japanese). Available from: http://www.pmda.go.jp/PmdaSearch/iyakuDetail/270072_3969021F1032_1_06#CONTRAINDICATIONS. Accessed October 3, 2016.
18. Sanofi KK Package insert for Apleway 20 mg Tablet (in Japanese). Available from: http://www.pmda.go.jp/PmdaSearch/iyakuDetail/780069_3969021F1024_1_06#CONTRAINDICATIONS. Accessed October 3, 2016.
19. Tahara A, Takasu T, Yokono M, *et al.* Characterization and comparison of sodium-glucose cotransporter 2 inhibitors in pharmacokinetics, pharmacodynamics, and pharmacologic effects. *J Pharmacol Sci* 2016; 130: 159–169.
20. Yabe D, Nishikino R, Kaneko M, *et al.* Short-term impacts of sodium/glucose co-transporter 2 inhibitors in Japanese clinical practice: considerations for their appropriate use to avoid serious adverse events. *Expert Opin Drug Saf* 2015; 14: 795–800.
21. Kowa Company, Ltd. Risk management plan for Deberza 20 mg Tablet. December 2015 (in Japanese). Available from: http://www.pmda.go.jp/files/000209090.pdf. Accessed October 3, 2016.
22. Sanofi KK. Risk management plan for Apleway 20 mg Tablet. December 2015 (in Japanese). Available from: http://

www.pmda.go.jp/files/000209091.pdf. Accessed October 3, 2016.
23. Utsunomiya K, Shimmoto N, Senda M, *et al.* Japanese study of tofogliflozin with type 2 diabetes mellitus patients in an observational study of the elderly (J-STEP/EL): a 12-week interim analysis. *J Diabetes Investig* 2016; 7: 755–763.
24. Maeda K, Katashima R, Ishizawa K, *et al.* Japanese Physicians' views on drug post-marketing Surveillance. *J Clin Med Res* 2015; 7: 956–960.
25. Asahina Y, Sugano H, Sugiyama E, *et al.* Representation of older patients in clinical trials for drug approval in Japan. *J Nutr Health Aging* 2014; 18: 520–523.
26. Ministry of Health, Labour and Welfare Japan. Summary of Patient Survey 2011. Available from: http://www.mhlw.go.jp/english/database/db-hss/sps_2011.html. Accessed October 3, 2016.
27. Inzucchi SE, Bergenstal RM, Buse JB, *et al.* Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2012; 35: 1364–1379.
28. Moghissi E. Management of type 2 diabetes mellitus in older patients: current and emerging treatment options. *Diabetes Ther* 2013; 4: 239–256.
29. Leiter LA, Langslet G, Vijapurkar U, *et al.* Simultaneous reduction in both HbA1c and body weight with canagliflozin versus glimepiride in patients with type 2 diabetes on metformin. *Diabetes Ther* 2016; 7: 269–278.
30. Haas B, Eckstein N, Pfeifer V, *et al.* Efficacy, safety and regulatory status of SGLT2 inhibitors: focus on canagliflozin. *Nutr Diabetes* 2014; 4: e143.
31. Geerlings S, Fonseca V, Castro-Diaz D, *et al.* Genital and urinary tract infections in diabetes: impact of pharmacologically-induced glucosuria. *Diabetes Res Clin Pract* 2014; 103: 373–381.
32. Rosenstock J, Ferrannini E. Euglycemic diabetic ketoacidosis: a predictable, detectable, and preventable safety concern with SGLT2 inhibitors. *Diabetes Care* 2015; 38: 1638–1642.
33. Garber AJ, Abrahamson MJ, Barzilay JI, *et al.* Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm- 2016 executive summary. *Endocr Pract* 2016; 22: 84–113.
34. Ogawa W, Sakaguchi K. Euglycemic diabetic ketoacidosis induced by SGLT2 inhibitors: possible mechanism and contributing factors. *J Diabetes Investig* 2016; 7: 135–138.
35. Scheen AJ. Pharmacokinetics, Pharmacodynamics and Clinical Use of SGLT2 Inhibitors in Patients with Type 2 Diabetes Mellitus and Chronic Kidney Disease. *Clin Pharmacokinet* 2015; 54: 691–708.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 | Adverse drug reactions.
Table S2 | Adverse drug reactions of special interest by age.
Table S3 | Effectiveness by estimated glomerular filtration rate.
Table S4 | Effectiveness by body mass index.
Figure S1 | Cumulative incidence (%) of any adverse drug reactions (ADR).