ORIGINAL ARTICLE

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

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ABSTRACT

Aims/Introduction: This subanalysis aimed to assess the safety and effectiveness of tofogliflozin by using data from the Japanese Study of Tofogliflozin with Type 2 Diabetes Mellitus Patients in an Observational Study of the Elderly to categorize elderly Japanese patients with type 2 diabetes mellitus by the number of concomitant oral antidiabetic drugs (OADs) and insulin use at baseline.

Materials and Methods: Japanese Study of Tofogliflozin with Type 2 Diabetes Mellitus Patients in an Observational Study of the Elderly is a 1-year prospective, observational and multicenter post-marketing study that enrolled all patients with type 2 diabetes mellitus aged ≥65 years who started tofogliflozin during the first 3 months after its launch in May 2014 in Japan.

Results: The safety and effectiveness analysis sets included 1,497 and 1,422 patients, respectively. Overall, 18.10 and 2.20% of the patients experienced adverse drug reactions (ADRs) and serious ADRs, respectively. ADRs of special interest in the total, 0 OAD, one OAD, two OADs, three or more OADs and insulin groups occurred in 12.22, 10.04, 12.35, 13.32, 11.27 and 14.91% of patients, respectively. Volume depletion-related events were the most frequently observed ADRs of special interest. Hypoglycemia occurred in 1.07% of patients. Overall, glycated hemoglobin and bodyweight were significantly decreased, but the estimated glomerular filtration rate was not significantly changed.

Conclusions: Our finding suggests that tofogliflozin could be safely and effectively used in elderly Japanese patients with type 2 diabetes mellitus, irrespective of the number of OADs and the use of insulin.

INTRODUCTION

The appropriate management of elderly Japanese patients with type 2 diabetes mellitus is of great importance and a topical issue. In 2016, the Ministry of Health, Labour and Welfare in Japan announced that approximately 10 million people were suspected to have type 2 diabetes mellitus[1]. The proportion of these people who are aged ≥60 years is increasing for both men and women[1].

The treatment of elderly patients with type 2 diabetes mellitus is complex. The difficulties lie in the clinical, mental and functional heterogeneity of elderly patients with type 2 diabetes mellitus[2–6]. For example, elderly patients with type 2 diabetes mellitus have numerous comorbidities and difficulties, such as diabetic complications, including micro- and macrovascular diseases, cognitive impairment, urinary incontinence, sarcopenia, and increased fall risk[5–7]; consequently, the management of these might necessitate polypharmacy. Polypharmacy can be problematic, as it increases the risk of adverse drug events[8,9], drug–drug interactions[10,11] and falls[6,12], and raises treatment costs[13].

Among the various pharmacological treatments for type 2 diabetes mellitus, such as oral antidiabetic drugs (OADs),

insulins and glucagon-like peptide 1 receptor agonists, sodium–glucose cotransporter 2 (SGLT2) inhibitors have emerged as a comparatively new class of OADs. Tofogliflozin hydrate (Apleway®; Sanofi K.K., Tokyo, Japan; and Deberza®; Kowa Company, Ltd., Nagoya, Japan) is an SGLT2 inhibitor that was approved in Japan in 2014 for the treatment of type 2 diabetes mellitus[14,15]. The safety and effectiveness of tofogliflozin have been shown in previous clinical trials and studies[16–19].

The insulin-independent mechanism of SGLT2 inhibitors carries a low risk of hypoglycemia, and leads to the reduction of glycated hemoglobin (HbA1c) and bodyweight. However, the unique mechanism of SGLT2 inhibitors also contributes to urinary tract and genital infections, and events resulting from dehydration, all of which are now well-known adverse drug reactions (ADRs) of SGLT2 inhibitors. Owing to these ADRs, a post-marketing study was planned before approval, as part of the risk management plan[20,21]. Strong concerns about the safety of SGLT2 inhibitors have been indicated by the recommendation for SGLT2 inhibitor use, which was first issued by experts in 2014, shortly after the launch of SGLT2 inhibitors[22,23]. This recommendation warned that SGLT2 inhibitors should be used with caution in elderly patients, and further stated that all patients aged ≥65 years with type 2 diabetes mellitus who started to receive these drugs within 3 months after their launch should be registered for inclusion in a post-marketing study[22]. Studies of elderly patients were required not only because of the recommendation, but also because of the scarcity of available information on the safety and effectiveness of SGLT2 inhibitors, including tofogliflozin, in elderly patients, because pre-approval clinical trials mainly included non-elderly patients with type 2 diabetes mellitus for the evaluation of safety concerns.

Thus, we carried out a 1-year post-marketing study of tofogliflozin in elderly Japanese patients (aged ≥65 years) in real-world settings (Japanese Study of Tofogliflozin with Type 2 Diabetes Mellitus Patients in an Observational Study of the Elderly [J-STEP/EL]). We have previously reported the overall results of safety and effectiveness[24,25]. As information on the safety and effectiveness in relation to the number of OADs and the use of insulin are clinically important for type 2 diabetes mellitus management and future therapeutic strategy, we carried out a subanalysis of the J-STEP/EL study data[25] to further assess the safety and effectiveness of tofogliflozin by categorizing patients by the number of OADs and the use of insulin at baseline. Herein, we report the results of this subanalysis.

METHODS
Study design
The details of the study are available elsewhere[25]. In brief, this was a prospective, observational and multicenter post-marketing study carried out in Japan. Patients were enrolled between 23 May 2014 and 22 August 2014, and followed for 1 year (52 weeks) from the date of tofogliflozin initiation. Sanofi K.K. and Kowa Company, Ltd. co-sponsored this study.

We carried out the present study in compliance with the ethical principles of the Declaration of Helsinki, and the Japanese authorized standards for post-marketing surveillance, Good Post-marketing Study Practice, without intervening in the dosage and administration of tofogliflozin. Because Good Post-marketing Study Practice does not require the patients' consent and approval of study protocol by the institutional review board of each participating center, we did not obtain patients' consent.

Patients
All patients aged ≥65 years with type 2 diabetes mellitus who started to receive tofogliflozin within 3 months of its launch in Japan were enrolled in this study; there were no restrictions on concomitant diseases and concomitant medications.

Data collection and definition
The patients were registered through a central registration system, and patients' data were recorded in electronic case report forms. The investigated items included demographic and baseline characteristics, details of tofogliflozin treatment, concomitant antidiabetic treatment, clinical course (vital signs, HbA1c, fasting blood glucose, laboratory tests), adverse events (AE), and ADRs.

ADRs were defined as AEs whose causal relationship with tofogliflozin administration could not be excluded, based on the physician's judgment. The ADRs of special interest were defined as polyuria/pollakiuria, volume depletion-related events, urinary tract infection, genital infection, hypoglycemia, and skin disorders. ADRs were categorized according to the Medical Dictionary for Regulatory Activities/Japanese edition version 18.1.

Statistical analysis
Based on the information at baseline on the number of concomitant OADs and the use of insulin, we categorized the patients into groups of 0 OAD, one OAD, two OADs, three or more OADs and insulin. The patients who used insulin at baseline were categorized into the insulin group.

The patients' characteristics, concomitant antidiabetic and diuretic treatments at baseline, and safety evaluations (ADRs and ADRs of special interest) were analyzed descriptively using the safety analysis set, which was defined as all patients for whom electronic case report forms were collected, excluding those with no follow-up visits after baseline and those for whom concomitant pharmacological treatment information was unavailable. Using the χ^2-test, ADRs of special interest were analyzed to explore the differences between groups.

Effectiveness analyses were carried out on the effectiveness analysis set, which was defined as all patients in the safety analysis set, excluding those without effectiveness data. The mean values of HbA1c, bodyweight, estimated glomerular filtration rate [eGFR] and insulin dose (U/day, in the insulin group) were descriptively summarized. Missing data at 52 weeks were

imputed by using the last observation carried forward (LOCF) method. The change from baseline to LOCF data was calculated and tested by one-sample t-test.

Patients were also categorized by the types of concomitant drugs at baseline, as follows: naïve (patients with no OAD or insulin use), dipeptidyl peptidase-4 inhibitors (DPP4i), biguanides (BG), sulfonylureas (SU), DPP4i + BG, DPP4i + SU, BG + SU, DPP4i + BG + SU, insulin and other (including all patients that did not belong to the aforementioned groups) groups. ADRs of special interest and effectiveness (HbA1c, bodyweight and eGFR) were analyzed by using the same methods described above.

All statistical tests were two-sided, with the significance level set at 5%. All analyses were calculated by using SAS® version 9.4 (SAS Institute, Cary, NC, USA) software.

RESULTS

Patient disposition and characteristics

Of the 1,507 patients in the safety analysis set of the previous study[25], 10 patients with unavailable concomitant pharmacological treatment information were excluded; thus, the safety analysis set comprised 1,497 patients in the present study. The effectiveness analysis set comprised 1,422 patients. Details of patients' disposition and discontinuation are reported elsewhere[25].

The patients' characteristics are shown in Table 1. At baseline, 279 patients (18.6%), 405 patients (27.1%), 368 patients (24.6%), 284 patients (19.0%) and 161 patients (10.8%) used 0 OAD, one OAD, two OADs, three or more OADs and insulin, respectively. Overall, 47.6% of patients were men and 52.4% were women. The mean ± standard deviation (SD) age was 72.4 ± 6.0 years, with 33.2% of patients aged ≥75 years. Overall, the mean ± SD values for HbA1c, bodyweight and eGFR were 7.7 ± 1.4%, 66.8 ± 12.4 kg and 68.7 ± 20.2 mL/min/1.73 m², respectively. The baseline characteristics of diabetes duration, kidney function, HbA1c, diabetic complications and cardiovascular disease differed by the number of OADs and the use of insulin; the groups of patients with multiple OADs and insulin were in a worse condition than the groups of patients with no or fewer OADs.

Concomitant antidiabetic and diuretic treatments at baseline are summarized in Table 2. Overall, 81.6% of the patients received concomitant antidiabetic drugs at baseline. The most commonly used OADs were DPP4i (62.0%), SU (32.5%) and BG (26.7%). In the insulin group, 126 patients (78.3%) concomitantly used OADs at baseline: 37.3, 37.3, 22.2 and 3.2% of the patients used one, two, three and four OADs, respectively. Diuretics were concomitantly used by 12.6% of the patients at baseline.

The mean ± SD total insulin dose in the insulin group (n = 148) was 30.55 ± 30.77 U at baseline, and 29.33 ± 30.52 U at 52-week LOCF, with the mean ± SD change as −1.22 ± 7.11 U (P = 0.039) from baseline to 52-week LOCF (Table S1).

Safety

Overall, 271 patients (18.10%) and 33 patients (2.20%) experienced ADRs and serious ADRs, respectively (Table 3). ADRs of special interest in the total, 0 OAD, one OAD, two OADs, three or more OADs and insulin groups were observed in 183 patients (12.22%), 28 patients (10.04%), 50 patients (12.35%), 49 patients (13.32%), 32 patients (11.27%) and 24 patients (14.91%), respectively. Overall, volume depletion-related events were the most frequently observed ADRs of special interest (59 patients, 3.94%), followed by polyuria/pollakiuria (44 patients, 2.94%) and skin disorders (36 patients, 2.40%). Hypoglycemia occurred in 16 patients (1.07%).

Of the volume depletion-related events, dehydration was the most commonly observed, and the incidence did not largely differ between groups (total incidence: 1.67%; incidence range for all groups: 1.06–1.90%). Ketoacidosis occurred in one patient in the one OAD group who was concomitantly taking DPP4i.

Polyuria/pollakiuria incidence was the highest in the insulin group, and the incidences in the other groups were generally similar (the insulin group: 4.35% vs the 0 to ≥3 OADs groups: 2.47–2.99%). Among the polyuria/pollakiuria ADRs of special interest, pollakiuria was the most frequent; furthermore, patients in the insulin group experienced pollakiuria more often (the insulin group: 3.73% vs the 0 to ≥3 OADs groups: 1.90–2.15%).

Among the skin disorders that were defined as the ADRs of special interest, rash occurred most frequently; furthermore, the insulin group experienced rash most frequently (the insulin group: 1.86% vs the 0 to ≥3 OADs groups: 0.27–0.99%).

Overall, 2.07 and 1.34% of patients experienced urinary tract infection and genital infection, respectively. The 0 and two OADs groups experienced comparatively high incidences of urinary tract infection (0 and 2 OADs groups: 2.87 and 2.99% vs the 1 and ≥3 OADs and insulin groups: 1.06–1.86%), whereas no notable difference in genital infection incidence was observed between the groups (all groups: 1.23–1.43%).

Hypoglycemia occurred more often in the groups of three or more OADs and insulin than in the groups of 0 or fewer OADs (the ≥3 OADs and insulin groups: 1.76 and 3.73% vs the 0 to 2 OADs groups: 0.25–0.82%). Severe hypoglycemia was not reported.

Effectiveness

The results of HbA1c, bodyweight, and eGFR for each group are shown in Figure 1 and Table 4. HbA1c and bodyweight decreased from baseline to LOCF in all groups.

The mean ± SD HbA1c (%) at baseline and LOCF, and the mean ± SD change from baseline to LOCF were 7.64 ± 1.35, 7.17 ± 1.16 and −0.46 ± 1.02 (P < 0.001) in the total group. The mean ± SD baseline HbA1c (%) was 7.00 ± 1.12, 7.48 ± 1.28, 7.73 ± 1.32, 7.88 ± 1.34 and 8.43 ± 1.40 in the 0 OAD, one OAD, two OADs, three or more OADs and insulin groups, respectively. The mean ± SD (%) change was −

Table 1 | Patients' characteristics

Variable	Safety analysis set (*n* = 1,497)											
	Total		0 OAD		1 OAD		2 OADs		≥3 OADs		Insulin	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Total	1,497	100	279	18.6	405	27.1	368	24.6	284	19.0	161	10.8
Sex												
Male	713	47.6	112	40.1	190	46.9	186	50.5	149	52.5	76	47.2
Female	784	52.4	167	59.9	215	53.1	182	49.5	135	47.5	85	52.8
Age (years)												
Mean ± SD	72.4 ± 6.0		73.3 ± 6.3		73.3 ± 6.2		72.1 ± 6.0		71.3 ± 5.4		71.1 ± 5.2	
≥65 to <75	1,000	66.8	177	63.4	242	59.8	256	69.6	207	72.9	118	73.3
≥75	497	33.2	102	36.6	163	40.2	112	30.4	77	27.1	43	26.7
Bodyweight (mean ± SD, kg)												
Overall	66.8 ± 12.4		66.4 ± 12.0		65.2 ± 12.5		67.0 ± 11.7		68.4 ± 13.1		68.3 ± 12.3	
Male	71.0 ± 12.2		70.0 ± 11.0		69.1 ± 12.4		71.2 ± 11.6		73.1 ± 13.1		71.8 ± 12.1	
Female	62.9 ± 11.3		63.8 ± 12.1		61.7 ± 11.6		62.6 ± 10.2		62.8 ± 10.7		65.1 ± 11.7	
Diabetes duration (years)												
Mean ± SD	10.8 ± 7.7		6.0 ± 5.5		8.9 ± 5.9		10.9 ± 7.8		13.2 ± 7.9		16.5 ± 8.1	
<1	44	2.9	27	9.7	6	1.5	8	2.2	3	1.1	0	0.0
≥1 to <10	407	27.2	78	28.0	133	32.8	112	30.4	65	22.9	19	11.8
≥10	454	30.3	30	10.8	102	25.2	111	30.2	126	44.4	85	52.8
Unknown	592	39.5	144	51.6	164	40.5	137	37.2	90	31.7	57	35.4
Liver function												
Normal	1,230	82.2	224	80.3	343	84.7	290	78.8	242	85.2	131	81.4
Dysfunction	224	15.0	40	14.3	57	14.1	62	16.8	38	13.4	27	16.8
Unknown	43	2.9	15	5.4	5	1.2	16	4.3	4	1.4	3	1.9
Kidney function												
Normal	638	42.6	163	58.4	169	41.7	147	39.9	95	33.5	64	39.8
Dysfunction	811	54.2	103	36.9	227	56.0	204	55.4	184	64.8	93	57.8
Unknown	48	3.2	13	4.7	9	2.2	17	4.6	5	1.8	4	2.5
Baseline eGFR (mL/min/1.73 m^2)												
Mean ± SD	68.7 ± 20.2		67.7 ± 19.4		68.5 ± 20.9		70.1 ± 19.7		68.0 ± 18.8		68.1 ± 22.7	
<30	17	1.1	4	1.4	6	1.5	4	1.1	2	0.7	1	0.6
≥30 to <45	93	6.2	17	6.1	22	5.4	20	5.4	20	7.0	14	8.7
≥45 to <60	242	16.2	40	14.3	69	17.0	53	14.4	52	18.3	28	17.4
≥60 to <90	589	39.3	92	33.0	163	40.2	159	43.2	119	41.9	56	34.8
≥90	134	9.0	20	7.2	38	9.4	38	10.3	22	7.7	16	9.9
Unknown	422	28.2	106	38.0	107	26.4	94	25.5	69	24.3	46	28.6
Baseline HbA1c (%)												
Mean ± SD	7.7 ± 1.4		7.0 ± 1.1		7.5 ± 1.3		7.7 ± 1.3		7.9 ± 1.3		8.5 ± 1.4	
<6.5	232	15.5	86	30.8	68	16.8	46	12.5	26	9.2	6	3.7
≥6.5 to <7.0	240	16.0	54	19.4	78	19.3	57	15.5	42	14.8	9	5.6
≥7.0 to <8.0	491	32.8	59	21.1	144	35.6	135	36.7	100	35.2	53	32.9
≥8.0	441	29.5	39	14.0	89	22.0	114	31.0	110	38.7	89	55.3
Unknown	93	6.2	41	14.7	26	6.4	16	4.3	6	2.1	4	2.5
Concomitant disease												
No	83	5.5	32	11.5	24	5.9	17	4.6	7	2.5	3	1.9
Yes	1,413	94.4	246	88.2	381	94.1	351	95.4	277	97.5	158	98.1
Unknown	1	0.1	1	0.4	0	0.0	0	0.0	0	0.0	0	0.0
Diabetic complications	460	30.7	32	11.5	93	23.0	127	34.5	116	40.8	92	57.1
Diabetic retinopathy	122	8.1	4	1.4	18	4.4	24	6.5	36	12.7	40	24.8
Diabetic nephropathy	319	21.3	26	9.3	65	16.0	88	23.9	86	30.3	54	33.5
Diabetic neuropathy	181	12.1	9	3.2	25	6.2	47	12.8	54	19.0	46	28.6
Liver disease	241	16.1	39	14.0	66	16.3	62	16.8	44	15.5	30	18.6

Table 1 (Continued)

Variable	Safety analysis set (n = 1,497)											
	Total		0 OAD		1 OAD		2 OADs		≥3 OADs		Insulin	
	n	%	n	%	n	%	n	%	n	%	n	%
Kidney disease	161	10.8	31	11.1	48	11.9	38	10.3	23	8.1	21	13.0
Cardiovascular disease[†]	326	21.8	39	14.0	86	21.2	85	23.1	54	19.0	62	38.5
Cardiovascular disease	276	18.4	32	11.5	67	16.5	73	19.8	49	17.3	55	34.2
Cerebrovascular disease	74	4.9	8	2.9	26	6.4	20	5.4	9	3.2	11	6.8
Heart failure	108	7.2	17	6.1	26	6.4	29	7.9	16	5.6	20	12.4
Malignancy	21	1.4	3	1.1	6	1.5	7	1.9	2	0.7	3	1.9
Urinary tract infection	8	0.5	1	0.4	2	0.5	3	0.8	0	0.0	2	1.2
Hypertension	1,112	74.3	200	71.7	312	77.0	277	75.3	202	71.1	121	75.2
Dyslipidemia	1,062	70.9	174	62.4	279	68.9	262	71.2	227	79.9	120	74.5
Gout	40	2.7	10	3.6	11	2.7	9	2.4	10	3.5	0	0.0
Hyperuricemia	190	12.7	44	15.8	50	12.3	45	12.2	35	12.3	16	9.9
Osteoporosis	174	11.6	42	15.1	62	15.3	38	10.3	18	6.3	14	8.7

The groups are categorized by the numbers of concomitant oral antidiabetic drugs (OADs) and the use of insulin at baseline. [†]Concomitant cardiovascular disease or medical history of cardiovascular disease. eGFR, estimated glomerular filtration rate; SD, standard deviation.

0.34 ± 0.91, -0.42 ± 1.06, -0.56 ± 1.03, -0.50 ± 1.07 and -0.44 ± 0.89 in the 0 OAD, one OAD, two OADs, three or more OADs and insulin groups, respectively ($P < 0.001$ for all).

As for the bodyweight, the mean ± SD (kg) at baseline and LOCF, and the mean ± SD change from baseline to LOCF were 67.44 ± 12.52, 64.68 ± 12.12 and -2.72 ± 3.59 ($P < 0.001$) overall. The mean ± SD (kg) change from baseline to LOCF was -3.11 ± 3.75, -2.61 ± 3.18, -2.65 ± 3.10, -2.61 ± 3.35 and -2.77 ± 5.18 in the 0 OAD, one OAD, two OADs, three or more OADs and insulin groups, respectively ($P < 0.001$ for all).

The mean ± SD eGFR (mL/min/1.73 m^2) at baseline and LOCF, and the mean ± SD change from baseline to LOCF were 68.81 ± 20.14, 68.09 ± 24.02 and -0.64 ± 10.89 ($P = 0.070$), respectively. The mean ± SD (mL/min/1.73 m^2) change from baseline to LOCF was -0.17 ± 11.26 ($P = 0.858$), -0.21 ± 11.13 ($P = 0.757$), -0.41 ± 9.49 ($P = 0.498$), -1.41 ± 9.27 ($P = 0.034$) and -1.47 ± 14.99 ($P = 0.318$) in the 0 OAD, one OAD, two OADs, three or more OADs and insulin groups, respectively.

Safety and effectiveness by types of concomitant drugs at baseline

The ADRs of special interest and effectiveness by types of concomitant drugs at baseline are available as supplementary information. In all groups, the ADRs of special interest, HbA1c, bodyweight and eGFR results were generally similar (Table S2; Figure S1). Hypoglycemia did not occur in the patients with concomitant SU use at baseline (Table S2).

DISCUSSION

We carried out a 1-year post-marketing study of tofogliflozin among elderly Japanese patients with type 2 diabetes mellitus aged ≥65 years, and have previously reported the overall results[24,25]. The present subanalysis study aimed to further assess the safety and effectiveness of tofogliflozin, by categorizing the patients by the number of OADs and the use of insulin at baseline. ADRs of special interest in the total, 0 OAD, one OAD, two OADs, three or more OADs and insulin groups were observed in 12.22% of patients, with 10.04, 12.35, 13.32, 11.27 and 14.91% of patients in each group, respectively. Overall, HbA1c and bodyweight significantly decreased (−0.46% and −2.72 kg, respectively) whereas eGFR did not significantly change (−0.64 mL/min/1.73 m^2).

Overall, the safety profile of tofogliflozin in the present study was similar to that reported in other 1-year SGLT2 inhibitor post-marketing studies of elderly Japanese patients with type 2 diabetes mellitus (e.g., ADR incidence was 18.10% in this study vs 9.09–16.91% in other post-marketing studies)[26–30]. A 1-year dapagliflozin post-marketing study in elderly Japanese patients with type 2 diabetes mellitus reported that ADRs occurred in 9.5, 11.2, 16.7 and 12.8% in the groups of the patients using 0 AD, one AD, two ADs and three or more ADs, respectively[27]. Even though the direct comparison with this study is limited by the differences in group categorization (i.e., the previous study's "antidiabetic drug group" included insulin and glucagon-like peptide 1), the results were not considerably different. In line with other SGLT2 inhibitor post-marketing studies, we confirmed the safety of tofogliflozin in real-world settings among elderly patients.

Elderly patients might be unaware of the symptoms of ADRs of tofogliflozin, such as hypoglycemia and dehydration. In the present study, hypoglycemia occurred in a total of 1.07% of the patients, which was generally consistent with previous studies (0.22–0.68% in other post-marketing studies)[26–30]. The incidence of hypoglycemia was highest in the insulin group (3.73% in the insulin group vs 0.25–1.76% in the other groups), which

Table 2 | Concomitant antidiabetic and diuretic treatment at baseline

Variable	Safety analysis set (n = 1,497)										
	Total (n = 1,497)		0 OAD (n = 279)		1 OAD (n = 405)		2 OADs (n = 368)		≥3 OADs (n = 284)		Insulin (n = 161)	
	n	%	n	%	n	%	n	%	n	%	n	%
No. OADs												
Mean ± SD	2.0 ± 1.0		–		1.0 ± 0.0		2.0 ± 0.0		3.3 ± 0.5		1.9 ± 0.8	
1	452	38.2	0		405	100	0	0	0	0	47	37.3
2	415	35.1	0		0	0	368	100	0	0	47	37.3
3	229	19.4	0		0	0	0	0	201	70.8	28	22.2
4	78	6.6	0		0	0	0	0	74	26.1	4	3.2
5	9	0.8	0		0	0	0	0	9	3.2	0	0
Class of OADs, insulin and GLP-1 receptor agonist												
Biguanide	400	26.7	0	0	45	11.1	111	30.2	182	64.1	62	38.5
Sulfonylurea	486	32.5	0	0	69	17.0	171	46.5	221	77.8	25	15.5
DPP4 inhibitor	928	62.0	0	0	263	64.9	307	83.4	269	94.7	89	55.3
Fast-acting insulin secretagogue	45	3.0	0	0	3	0.7	17	4.6	20	7.0	5	3.1
α-Glucosidase inhibitor	206	13.8	0	0	18	4.4	51	13.9	98	34.5	39	24.2
Thiazolidinedione	261	17.4	0	0	7	1.7	79	21.5	154	54.2	21	13.0
Insulin	161	10.8	0	0	0	0	0	0	0	0	161	100.0
GLP-1 receptor agonist	22	1.5	4	1.4	8	2.0	4	1.1	2	0.7	4	2.5
Concomitant diuretics at baseline												
No	1,308	87.4	254	91.0	359	88.6	327	88.9	239	84.2	129	80.1
Yes	189	12.6	25	9.0	46	11.4	41	11.1	45	15.8	32	19.9
Class of diuretics												
Loop diuretics	64	4.3	10	3.6	16	4.0	17	4.6	12	4.2	9	5.6
Thiazides	84	5.6	12	4.3	21	5.2	17	4.6	15	5.3	19	11.8
Anti-aldosterone	41	2.7	6	2.2	12	3.0	4	1.1	11	3.9	8	5.0
Other diuretics	21	1.4	1	0.4	3	0.7	6	1.6	10	3.5	1	0.6

The groups are categorized by the numbers of concomitant oral antidiabetic drugs (OADs) and the use of insulin at baseline. DPP4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SD, standard deviation.

is obvious, because insulins are associated with the risk of hypoglycemia[31,32]. Compared with other classes of drugs and basal insulin, a meta-analysis found that SGLT2 inhibitors, for monotherapy in particular, were less associated with hypoglycemia in patients with type 2 diabetes mellitus[33]. Dehydration was experienced by 1.67% of the patients, and this value is generally comparable with other post-marketing studies (0.58–0.8%)[26–29]. With these points in mind, appropriate insulin reduction for preventing hypoglycemia, and proper instruction on sufficient liquid intake for preventing dehydration are essential for treating elderly patients with tofogliflozin. Continuous safety investigation of tofogliflozin is indeed required.

The combined use of DPP4i and SU has been reported to increase the risk of hypoglycemia[34]. In the present study, an increase in the incidence of hypoglycemia was not seen in patients with concomitant tofogliflozin and SU use at baseline (0 patients reporting hypoglycemia). This might be attributed to the recommendation for SGLT2 inhibitor use, which requires careful attention to hypoglycemia when using SGLT2 inhibitors concomitantly with SU. However, this result should be interpreted with care owing to the possible effects of other concomitant drugs and the relatively small number of patients in the SU group (n = 69).

The incidence of other ADRs of special interest in the present study was consistent with that reported in other post-marketing studies (3.94% vs 0.73–3.13% for volume depletion-related events, 2.94% vs 1.2–4.62% for polyuria/pollakiuria, 2.07% vs 0.67–1.74% for urinary tract infection, 1.34% vs 0.65–1.95% for genital infection and 2.40% vs 1.17–3.16% for skin disorders in this study vs other post-marketing studies)[26–30]. Considering the number of OADs and insulin use in the present study, the incidence of volume depletion-related events and genital infections was not substantially different, whereas incidences of polyuria/pollakiuria, urinary tract infection and skin disorders varied slightly.

For effectiveness, HbA1c and bodyweight were decreased by −0.46% and −2.72 kg from baseline to LOCF, with no notable differences between groups; the overall changes in HbA1c and bodyweight were consistent with those seen in other post-marketing studies (HbA1c change as −0.44 to −0.77%, bodyweight change as −2.41 to −2.91 kg, respectively, in other post-marketing studies)[26–30]. It is of note that bodyweight decreased after

Table 3 | Adverse drug reactions and adverse drug reactions of special interest

ADRs	Safety analysis set (n = 1,497)													P-value[†]
	Total (n = 1,497)		0 OAD (n = 279)		1 OAD (n = 405)		2 OADs (n = 368)		≥3 OADs (n = 284)		Insulin (n = 161)		
	n	%	n	%	n	%	n	%	n	%	n	%	
ADRs	271	18.10	37	13.26	72	17.78	74	20.11	55	19.37	33	20.50	
Serious ADRs	33	2.20	4	1.43	9	2.22	10	2.72	6	2.11	4	2.48	
ADRs of special interest	183	12.22	28	10.04	50	12.35	49	13.32	32	11.27	24	14.91	
Hypoglycemia	16	1.07	1	0.36	1	0.25	3	0.82	5	1.76	6	3.73	0.0028
Polyuria/pollakiuria	44	2.94	8	2.87	10	2.47	11	2.99	8	2.82	7	4.35	0.8343
Pollakiuria	33	2.20	6	2.15	8	1.98	7	1.90	6	2.11	6	3.73	
Nocturia	12	0.80	1	0.36	2	0.49	3	0.82	4	1.41	2	1.24	
Polyuria	8	0.53	3	1.08	0	0	3	0.82	1	0.35	1	0.62	
Volume depletion-related events	59	3.94	9	3.23	18	4.44	16	4.35	10	3.52	6	3.73	0.9157
Dehydration	25	1.67	5	1.79	7	1.73	7	1.90	3	1.06	3	1.86	
Constipation	11	0.73	1	0.36	3	0.74	4	1.09	3	1.06	0	0	
Thirst	9	0.60	1	0.36	3	0.74	2	0.54	2	0.70	1	0.62	
Blood urea increased	6	0.40	1	0.36	1	0.25	1	0.27	2	0.70	1	0.62	
Cerebral infarction	3	0.20	0	0	0	0	3	0.82	0	0	0	0	
Hemoconcentration	2	0.13	0	0	1	0.25	0	0	0	0	1	0.62	
Loss of consciousness	2	0.13	1	0.36	0	0	0	0	0	0	1	0.62	
Lacunar infarction	2	0.13	0	0	0	0	0	0	1	0.35	1	0.62	
Depressed level of consciousness	1	0.07	0	0	1	0.25	0	0	0	0	0	0	
Diverticulum intestinal hemorrhagic	1	0.07	1	0.36	0	0	0	0	0	0	0	0	
Ketoacidosis	1	0.07	0	0	1	0.25	0	0	0	0	0	0	
Syncope	1	0.07	0	0	1	0.25	0	0	0	0	0	0	
Heat illness	1	0.07	0	0	0	0	1	0.27	0	0	0	0	
Urinary tract infection	31	2.07	8	2.87	6	1.48	11	2.99	3	1.06	3	1.86	0.3341
Cystitis	16	1.07	2	0.72	3	0.74	6	1.63	3	1.06	2	1.24	
Urinary tract infection	10	0.67	6	2.15	1	0.25	2	0.54	1	0.35	0	0	
Pyelonephritis	3	0.20	0	0	1	0.25	1	0.27	0	0	1	0.62	
Cystitis hemorrhagic	2	0.13	0	0	1	0.25	1	0.27	0	0	0	0	
Pyelonephritis acute	2	0.13	0	0	0	0	1	0.27	0	0	1	0.62	
Septic shock	1	0.07	0	0	0	0	1	0.27	0	0	0	0	
Genital infection	20	1.34	4	1.43	5	1.23	5	1.36	4	1.41	2	1.24	0.9993
Pruritus genital	9	0.60	3	1.08	3	0.74	1	0.27	2	0.70	0	0	
Genital infection	4	0.27	0	0	1	0.25	1	0.27	2	0.70	0	0	
Vulvovaginal candidiasis	3	0.20	0	0	0	0	2	0.54	0	0	1	0.62	
Balanoposthitis	2	0.13	0	0	1	0.25	0	0	1	0.35	0	0	
Vulvitis	2	0.13	0	0	0	0	0	0	1	0.35	1	0.62	
Genital rash	1	0.07	0	0	0	0	0	0	1	0.35	0	0	
Vaginal inflammation	1	0.07	1	0.36	0	0	0	0	0	0	0	0	
Genital infection fungal	1	0.07	1	0.36	0	0	0	0	0	0	0	0	
Genital infection female	1	0.07	0	0	0	0	1	0.27	0	0	0	0	
Skin disorders	36	2.40	3	1.08	15	3.70	6	1.63	7	2.46	5	3.11	0.1782
Rash	11	0.73	2	0.72	4	0.99	1	0.27	1	0.35	3	1.86	
Pruritus	7	0.47	0	0	2	0.49	0	0	4	1.41	1	0.62	
Drug eruption	4	0.27	0	0	1	0.25	2	0.54	0	0	1	0.62	
Urticaria	4	0.27	1	0.36	3	0.74	0	0	0	0	0	0	
Eczema	3	0.20	0	0	1	0.25	0	0	1	0.35	1	0.62	
Dermatitis allergic	2	0.13	0	0	2	0.49	0	0	0	0	0	0	
Erythema	2	0.13	0	0	0	0	1	0.27	1	0.35	0	0	
Rash pruritic	2	0.13	0	0	0	0	0	0	2	0.70	0	0	
Pruritus generalized	2	0.13	0	0	0	0	2	0.54	0	0	0	0	

Table 3 (Continued)

ADRs	Safety analysis set (n = 1,497)												P-value[†]
	Total (n = 1,497)		0 OAD (n = 279)		1 OAD (n = 405)		2 OADs (n = 368)		≥3 OADs (n = 284)		Insulin (n = 161)		
	n	%	n	%	n	%	n	%	n	%	n	%	
Miliaria	1	0.07	0	0	1	0.25	0	0	0	0	0	0	
Papule	1	0.07	0	0	1	0.25	0	0	0	0	0	0	
Rash scarlatiniform	1	0.07	0	0	1	0.25	0	0	0	0	0	0	
Skin exfoliation	1	0.07	0	0	0	0	0	0	0	0	1	0.62	
Tinea infection	1	0.07	0	0	1	0.25	0	0	0	0	0	0	

The groups are categorized by the numbers of concomitant oral antidiabetic drugs (OADs) and the use of insulin at baseline. [†]The χ^2-test. Medical Dictionary for Regulatory Activities/Japanese edition version 18.1. ADR, adverse drug reaction.

tofogliflozin administration even in the insulin group, although insulin administration usually leads to weight gain[35].

In the present study, the mean baseline eGFR and its change from baseline to LOCF were 68.81 and −0.64 mL/min/1.73 m^2, respectively. These results are in agreement with other post-marketing studies, with the mean baseline eGFR as 67.86–69.7 mL/min/1.73 m^2 and its change from baseline to final observation as −0.85 to −1.0 mL/min/1.73 m^2[26,28]. Tofogliflozin administration should be avoided for patients with severe renal impairment, as instructed in the package insert, because tofogliflozin might not be effective for such patients. Previous SGLT2 inhibitor studies reported a compromised HbA1c-lowering effect in patients with moderate renal impairment (eGFR 30 to <60 mL/min/1.73 m^2)[36,37]. Levels of eGFR should be taken into consideration before tofogliflozin administration, with its careful monitoring particularly for patients with renal impairment.

In Japan, tofogliflozin is rarely used as a first-line type 2 diabetes mellitus treatment. Patients in the present study also concomitantly used other OADs, such as DPP4i, SU and insulin at baseline. As discussed above, we found no peculiar ADRs or substantial increase in ADRs of special interest, accompanied with HbA1c and bodyweight reduction effects across all groups of elderly patients with type 2 diabetes mellitus in Japan. Although it is essential to accumulate more safety data of tofogliflozin, considering that elderly patients might not recognize the symptoms, such as hypoglycemia and dehydration, the present findings suggest tofogliflozin as another safe and effective first-line and additional treatment for elderly patients in Japan.

Although tofogliflozin may be used safely and effectively, irrespective of the number of OADs, the avoidance of polypharmacy should be sought wherever possible when treating elderly patients with type 2 diabetes mellitus. As mentioned in the Introduction, polypharmacy increases the risk of adverse drug events[8,9] (e.g., dementia[38]), drug–drug interactions[10,11], falls[6,12] and treatment costs[13]. Furthermore, polypharmacy can result in low adherence to medication[6,39]. The present study results partially support the previous findings, as relatively high

incidences of ADRs were found in the groups with multiple OAD use (i.e., the 1 OAD, 2 OADs and ≥3 OADs groups) than in the 0 OAD group. For instance, hypoglycemia was slightly higher in the three or more OADs group than in the groups with no or fewer OADs. Polypharmacy might be inevitable for some elderly patients with type 2 diabetes mellitus for the management of their comorbidities and diabetic complications. However, considering the risks of polypharmacy, simple type 2 diabetes mellitus treatment might be the key for optimal, safe and beneficial management. Tofogliflozin could contribute to a simple therapeutic strategy for elderly patients with type 2 diabetes mellitus, as its safety and effectiveness were confirmed to be unrelated to the number of OADs and the use of insulin in the present study.

Some limitations of this study should be acknowledged. First, the study population might have been in better health than the general elderly Japanese population with type 2 diabetes mellitus, as this study was carried out before the revised recommendation for SGLT2 inhibitor use in 2016. Because a wider range of elderly patients had been advised of the careful use of SGLT2 inhibitors before the revision of recommendation in 2016, the investigators in the present study might have carefully chosen the elderly patients in better physical condition for the administration of tofogliflozin; for example, patients with a relatively high bodyweight. Second, the present subanalysis categorized the patients based on the number and type of drugs at baseline, and did not take into consideration the effects on patients who added or reduced their concomitant drugs during the study. Third, owing to the nature of this study, the effects of treatment on patients cannot be solely attributable to tofogliflozin. Fourth, hypoglycemia incidence might have been underestimated in this study, as elderly patients are more likely to be unaware of hypoglycemia events[5,40]. Finally, further studies over a longer duration are warranted to explore the safety and effectiveness of tofogliflozin in elderly Japanese patients.

In conclusion, the present findings suggest that tofogliflozin can be safely and effectively used by elderly Japanese patients
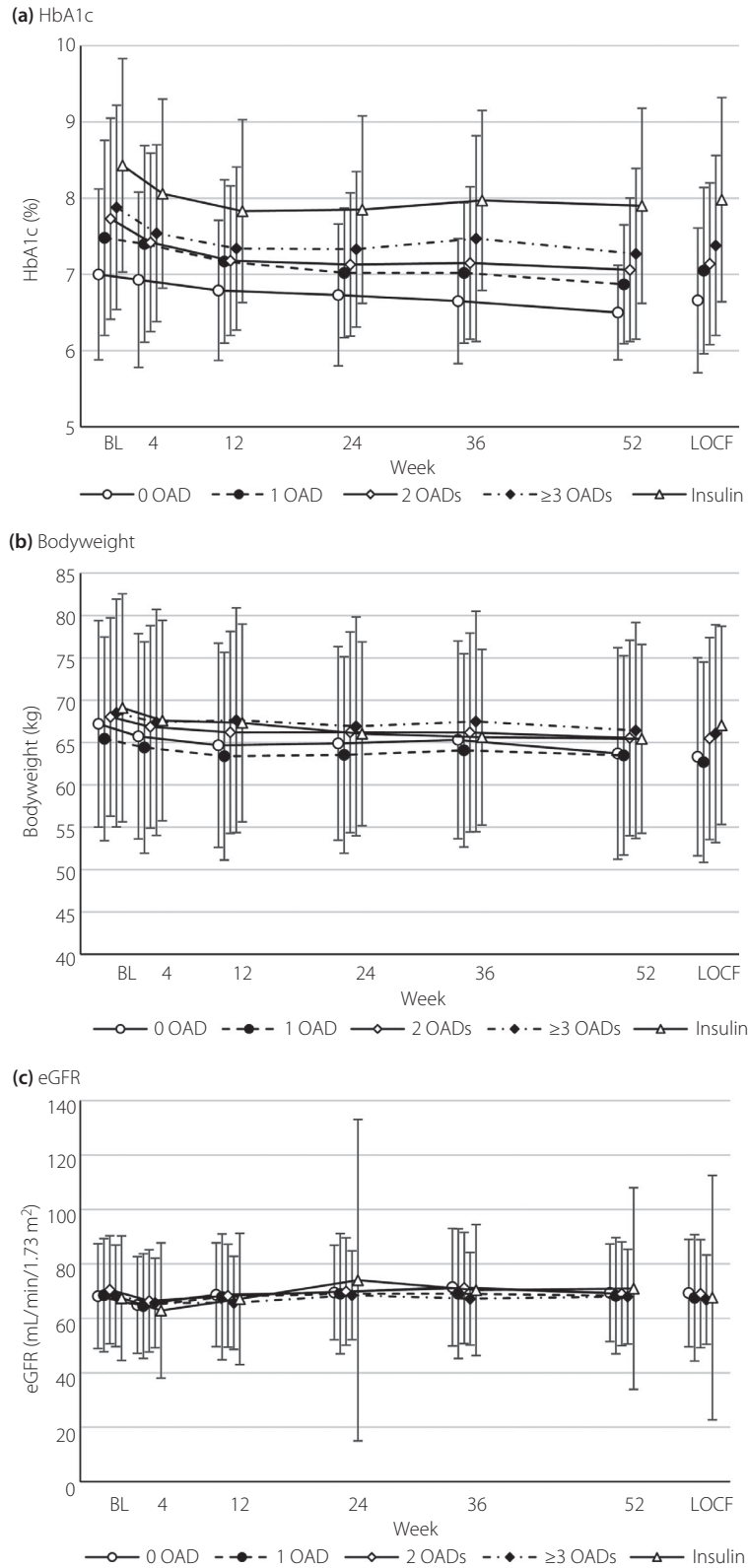
Figure 1 | Plot of mean values of (a) glycated hemoglobin (HbA1c), (b) bodyweight and (c) estimated glomerular filtration rate (eGFR) by visit. The groups are categorized by the number of concomitant oral antidiabetic drug (OADs) and the use of insulin at baseline (BL).

Table 4 | Mean values and changes in glycated hemoglobin, bodyweight and estimated glomerular filtration rate

Variable	Effectiveness analysis set ($n = 1,422$)											
	Total		0 OAD		1 OAD		2 OADs		≥3 OADs		Insulin	
	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n
HbA1c (%)												
Baseline	7.64 ± 1.35	1,345	7.00 ± 1.12	228	7.48 ± 1.28	368	7.73 ± 1.32	333	7.88 ± 1.34	266	8.43 ± 1.40	150
Week 4	7.44 ± 1.24	1,101	6.93 ± 1.15	161	7.40 ± 1.29	292	7.42 ± 1.17	286	7.54 ± 1.16	233	8.06 ± 1.24	129
Week 12	7.21 ± 1.07	1,150	6.79 ± 0.92	198	7.17 ± 1.07	311	7.18 ± 0.98	291	7.34 ± 1.07	228	7.83 ± 1.20	122
Week 24	7.16 ± 1.01	903	6.73 ± 0.93	143	7.02 ± 0.85	251	7.13 ± 0.94	230	7.33 ± 1.02	179	7.85 ± 1.23	100
Week 36	7.19 ± 1.12	832	6.65 ± 0.82	132	7.02 ± 0.92	225	7.15 ± 1.00	214	7.47 ± 1.35	171	7.97 ± 1.18	90
Week 52	7.04 ± 1.01	816	6.50 ± 0.62	131	6.87 ± 0.78	230	7.06 ± 0.94	208	7.27 ± 1.12	165	7.90 ± 1.28	82
LOCF	7.17 ± 1.16	1,402	6.66 ± 0.95	252	7.05 ± 1.09	383	7.14 ± 1.06	346	7.38 ± 1.18	271	7.98 ± 1.34	150
Change from baseline to LOCF, mean ± SD (P-value[†])	−0.46 ± 1.02 ($P < 0.001$)	1,327	−0.34 ± 0.91 ($P < 0.001$)	222	−0.42 ± 1.06 ($P < 0.001$)	362	−0.56 ± 1.03 ($P < 0.001$)	330	−0.50 ± 1.07 ($P < 0.001$)	265	−0.44 ± 0.89 ($P < 0.001$)	148
Bodyweight (kg)												
Baseline	67.44 ± 12.52	1,036	67.20 ± 12.19	160	65.44 ± 12.03	276	68.02 ± 11.71	251	68.49 ± 13.45	222	69.10 ± 13.45	127
Week 4	66.25 ± 12.44	925	65.73 ± 12.12	134	64.42 ± 12.48	245	66.85 ± 11.95	230	67.38 ± 13.34	197	67.59 ± 11.83	119
Week 12	65.63 ± 12.37	907	64.68 ± 12.05	141	63.39 ± 12.26	245	66.20 ± 11.92	229	67.64 ± 13.27	185	67.32 ± 11.68	107
Week 24	65.42 ± 11.88	680	64.90 ± 11.43	96	63.54 ± 11.60	186	66.21 ± 11.85	175	66.91 ± 12.92	142	66.03 ± 10.86	81
Week 36	65.71 ± 11.78	580	65.31 ± 11.67	77	64.08 ± 11.41	153	66.18 ± 11.75	150	67.48 ± 13.02	122	65.63 ± 10.37	78
Week 52	64.88 ± 11.97	598	63.71 ± 12.49	86	63.48 ± 11.76	163	65.54 ± 11.54	161	66.43 ± 12.75	121	65.44 ± 11.15	67
LOCF	64.68 ± 12.12	1,122	63.32 ± 11.69	172	62.68 ± 11.83	309	65.47 ± 11.93	274	66.05 ± 12.85	234	67.03 ± 11.70	133
Change from baseline to LOCF, mean ± SD (P-value[†])	−2.72 ± 3.59 ($P < 0.001$)	994	−3.11 ± 3.75 ($P < 0.001$)	151	−2.61 ± 3.18 ($P < 0.001$)	261	−2.65 ± 3.10 ($P < 0.001$)	243	−2.61 ± 3.35 ($P < 0.001$)	217	−2.77 ± 5.18 ($P < 0.001$)	122
eGFR (mL/min/1.73 m^2)												
Baseline	68.81 ± 20.14	1,028	68.17 ± 19.23	164	68.50 ± 20.83	289	70.54 ± 19.85	259	68.29 ± 18.65	206	67.43 ± 22.90	110
Week 4	65.11 ± 19.17	770	64.91 ± 17.79	98	64.52 ± 19.24	216	66.40 ± 18.79	205	65.65 ± 16.49	158	62.88 ± 24.83	93
Week 12	67.58 ± 20.39	823	68.68 ± 19.06	130	67.88 ± 23.10	227	68.32 ± 18.90	208	65.70 ± 17.12	172	67.13 ± 24.10	86
Week 24	69.66 ± 25.72	651	69.49 ± 17.38	96	69.04 ± 22.11	197	69.88 ± 19.70	162	68.48 ± 16.32	136	74.02 ± 59.03	60
Week 36	69.70 ± 21.24	605	71.46 ± 21.61	87	69.06 ± 23.82	162	71.16 ± 20.41	165	67.22 ± 17.01	133	70.40 ± 24.04	58
Week 52	68.83 ± 21.37	566	69.38 ± 17.90	86	68.30 ± 21.37	169	69.03 ± 19.07	149	68.00 ± 17.41	113	70.97 ± 37.05	49
LOCF	68.09 ± 24.02	1,202	69.30 ± 19.72	202	67.54 ± 23.22	335	69.05 ± 19.87	297	66.88 ± 16.39	242	67.62 ± 44.93	126
Change from baseline to LOCF, mean ± SD (P-value[†])	−0.64 ± 10.89 ($P = 0.070$)	967	−0.17 ± 11.26 ($P = 0.858$)	148	−0.21 ± 11.13 ($P = 0.757$)	271	−0.41 ± 9.49 ($P = 0.498$)	245	−1.41 ± 9.27 ($P = 0.034$)	198	−1.47 ± 14.99 ($P = 0.318$)	105

The groups are categorized by the numbers of concomitant oral antidiabetic drug (OADs) and use of insulin at baseline. [†]One-sample *t*-test. eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; LOCF, last observation carried forward analysis; SD, standard deviation.

with type 2 diabetes mellitus, irrespective of the number of OADs and the use of insulin, as no peculiar ADRs or substantial increase in ADRs of special interest were observed across groups, and HbA1c and bodyweight were decreased in all groups.

DISCLOSURE

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SUPPORTING INFORMATION

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

Figure S1 | Changes in glycated hemoglobin, bodyweight and estimated glomerular filtration rate by the type of concomitant drugs at baseline, from baseline to the 52-week last observation carried forward.

Table S1 | Insulin dose in the insulin group at each study point (effectiveness analysis set).

Table S2 | Adverse drug reactions of special interest presented by the concomitant drug type at baseline.