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Risk of hypoglycemia in Japanese people with type 2 diabetes mellitus who initiated or switched to insulin glargine 300 U/mL: A subgroup analysis of 12-month post-marketing surveillance study (X-STAR study)

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ABSTRACT

Aims: This study investigated the hypoglycemia risk in people with type 2 diabetes (T2D) who initiated or switched to insulin glargine 300 U/mL (Gla-300) by stratifying them by age and renal function.

Methods: We examined data from 4621 people with T2D (1227 insulin-naïve and 3394 insulin-experienced) of the X-STAR study, a prospective, observational, 12-month study conducted from December 2015 to August 2018 in Japan. Participants were stratified by age (<65, 65 to <75, and ≥75 years) and estimated glomerular filtration rate (eGFR) (≥90, 60 to <90, 30 to <60, and <30 mL/min/1.73 m^2). Hypoglycemia was defined according to the Ministry of Health, Labour and Welfare manual of Japan.

Results: No apparent increase in the proportion of people who experienced hypoglycemia was found in all subgroups. The proportions were 2.9–3.5% and 2.7–5.2% of insulin-naïve and insulin-experienced people, respectively, for age subgroups, and 2.4–4.7% and 4.6–

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4.8%, respectively, for eGFR subgroups. The result was similar for HbA1c levels below and at or above 7.0% in all age subgroups.

Conclusions: Our study found no apparent increase in the hypoglycemia risk in people with older age and renal impairment who were administered Gla-300. These results would provide reassuring information on Gla-300 use.

1. Introduction

Insulin therapy is an established option to improve glycemic control in people with type 2 diabetes (T2D) and, in reality, tends to be reserved for those with advanced stage of diabetes. Insulin is highly efficacious in terms of lowering glucose; however, it imposes potential hypoglycemic risk [1]. Furthermore, hypoglycemia has a variety of negative impacts on people with diabetes (e.g., decline in cognitive function [2], arrhythmia [3,4], or cardiovascular events [5]) and eventually could lead to death [6].

Age is a well-known risk factor of hypoglycemia [7–9]. Specifically, age-related factors, such as difficulty in appropriate self-management (blood glucose monitoring, subcutaneous injection, and glucose intake for hypoglycemia) and diminished drug metabolism, are likely to increase the risk of hypoglycemia upon insulin treatment. Furthermore, blunted counterregulatory activation in response to hypoglycemia is often present in the elderly, which could also increase the risk of asymptomatic hypoglycemia and subsequent severe hypoglycemia [9,10]. Chronic kidney disease (CKD) is another risk factor of hypoglycemia, probably due to the decreased renal clearance of glucose-lowering drugs [11]. CKD is frequently associated with T2D. In Japan, 25.2% (775/3071) of people with T2D had CKD (eGFR < 60 mL/min/1.73 m^2) [12]. Thus, investigation on how age and renal function affect hypoglycemic events upon insulin treatment in the real-world clinical setting would provide essential information.

Insulin glargine 300 U/mL (Gla-300 [Toujeo® in the United States and Europe; Lantus® XR in Japan]), available since 2015, is a second-generation basal insulin that is characterized by more stable and prolonged pharmacokinetic and pharmacodynamic profiles compared to glargine 100 U/mL (Gla-100), thereby contributing to sustained glycemic control with a minimized risk of hypoglycemia [13–18]. Such beneficial effects of Gla-300 were also demonstrated in people aged ≥65 years with T2D [19–21]. The X-STAR study, a post-marketing study of Gla-300 in people with diabetes, was conducted in Japan with a maximum of 1-year follow-up [22]. Overall, the results suggest that Gla-300 is an effective treatment option with no new safety concerns. However, to date, whether Gla-300 can be safely used by people with a high-risk of hypoglycemia such as those with older age or renal impairment is yet to be explored in clinical settings in Japan.

The objective of this subgroup analysis was to investigate how the proportion of people with hypoglycemia who initiated or switched to Gla-300 varies with its known risk factors (i.e., age, renal impairment, and hypoglycemic history prior to Gla-300 initiation) using the data collected in the X-STAR study.

2. Methods

2.1. Study design

Details of the X-STAR study are available elsewhere [22]. In brief, the X-STAR study was a prospective, observational, 12-month study conducted from December 2015 to August 2018 in accordance with the pharmaceutical affairs law and the ministerial ordinance of Good Post-Marketing Study Practice in Japan. Ethical committee approval and written informed consent were waived for this study. People with diabetes to whom Gla-300 was newly prescribed were enrolled at the participating medical institutions under a contract with Sanofi K. K. (Tokyo, Japan) and were followed up for 12 months. The participants were centrally enrolled within 14 days from the day that Gla-300 was first administered, and their anonymized data were entered into an electronic data capturing system. The treating physicians managed doses of Gla-300 as they would in their routine practice in accordance with the Japanese package insert of Gla-300 [23]. Hypoglycemia was diagnosed by treating physicians according to reports from the participants when they had symptoms (dizziness, weakness, etc.), signs of sympathetic response (tachycardia, sweating, etc.) or by central nervous system dysfunction (coma, seizure, etc.), and glucose levels (<70 mg/dL) [24].

2.2. Study population

This study examined data from 4621 people with T2D (1227 insulin-naïve and 3394 insulin-experienced) enrolled in the X-STAR study. Among the enrolled, people who had never received insulin prior to the Gla-300 initiation at baseline were categorized as "insulin-naïve," and those who had been treated with other insulin products prior to Gla-300 administration at baseline were categorized as "insulin-experienced," for which Gla-300 either replaced previously used insulin products or was administered in combination. Details of the study enrollment (e.g., participating institutions, inclusion and exclusion criteria) are described in Odawara et al. [22].

To explore the hypoglycemia risk in subgroups during the Gla-300 administration for 12 months, both insulin-naïve and insulin-experienced people were stratified according to age (<65, 65–<75, and ≥75 years), estimated glomerular filtration rate (eGFR: <30, 30–<60, 60–<90, and ≥90 mL/min/1.73 m^2), and history of hypoglycemia within 3 months before Gla-300 administration.

2.3. Assessments

Baseline demographics and clinical characteristics examined in this study included age, sex, duration of diabetes, body weight, height, body mass index (BMI), comorbidities, hospitalization, types of insulins, and oral antidiabetic drugs. We assessed the Gla-300 daily dose monitored at baseline, month 6 (days 169–196), and month 12 (days 337–364). We also assessed HbA1c levels (National Glycohemoglobin Standardization Program), fasting plasma glucose (FPG, including laboratory measurement or self-monitored plasma glucose), and body weight measured at baseline (the latest data within 8 weeks prior to Gla-300 initiation), month 6 (±6 weeks) and month 12 (±6 weeks).

2.4. Statistical analysis

All data were expressed as mean ± standard deviation (SD) for continuous variables, or as number and proportion of people in each category for categorical data. Baseline characteristics of insulin-naïve and insulin-experienced people were stratified by subgroups of age and eGFR. The mean Gla-300 administration, HbA1c level, body weight, and FPG level were calculated at baseline and 12 months after separately for the age and eGFR subgroups, and changes between these time points were also calculated. For comparison of Gla-300 dose, HbA1c level, body weight, and FPG level data at month 12 (last observation carried forward [LOCF]) with those at baseline, the paired *t*-test was used. Analogous descriptive analysis as above was also performed for people who did or did not experience hypoglycemia during the study period.

Proportions of insulin-naïve and insulin-experienced people who experienced ≥1 hypoglycemia during the 12-month follow-up was calculated separately for the age and eGFR subgroups. The proportions by age were further stratified according to HbA1c level at month 12 (<6.5%, 6.5%–<7.0%, 7.0%–<7.5%, 7.5%–<8.0%, and ≥8.0%). The LOCF approach was used for imputing the missing value and described as month 12 (LOCF). All analyses were performed using the SAS software release 9.4 (SAS Institute, Inc., Cary, NC, USA). The significance level was defined as a two-sided p-value < 0.05.

3. Results

3.1. Study population

The baseline characteristics of 4621 people with T2D (1227 insulin-naïve and 3394 insulin-experienced) are summarized by age in Table 1 and by eGFR in Table 2. Of those aged <65, 65–<75, and ≥75 years, males represented 71.5%, 62.4%, and 55.9% in the insulin-naïve group and 63.0%, 59.8%, and 52.1% in insulin-experienced group, respectively. Mean ± SD BMI was 26.0 ± 5.0 kg/m^2, 23.8 ± 3.8 kg/m^2, and 23.0 ± 3.8 kg/m^2 in insulin-naïve and 26.9 ± 5.3, 24.7 ± 3.9, and 24.0 ± 3.8 in insulin-experienced people, respectively. There was no apparent trend in terms of sex and BMI among eGFR subgroups in both insulin-naïve and insulin-experienced groups, but the proportion of males were 69.3%, 67.5%, 69.4%, and 48.8% in eGFR < 30, 30 to <60, 60 to <90, and ≥90 mL/min/1.73 m^2, respectively in the insulin-naïve group (Table 2). In insulin-naïve people, baseline HbA1c levels were the highest in the subgroup aged <65 years (mean ± SD, 10.4 ± 2.3%) and with eGFR > 90 mL/min/1.73 m^2 (10.7 ± 2.3%). Also, in insulin-experienced group, these two subgroups showed slightly higher baseline HbA1c levels than other subgroups.

In both insulin-naïve and insulin-experienced people, dipeptidyl peptidase-4 (DPP-4) inhibitors were the commonly used oral antidiabetic drugs (OADs) with 60.2% and 44.6% among overall people, respectively. Particularly, DPP-4 inhibitors were more commonly prescribed to people with older age and lower eGFR. Biguanides and sulfonylureas were used by 40.8% and 42.5% in overall insulin-naïve people and by 31.3% and 13.8% in overall insulin-experienced people. Sodium-glucose transport protein 2 (SGLT2) inhibitors were used less commonly, with 16.4% and 15.6% of overall insulin-naïve and insulin-experienced people, respectively. Unlike DPP-4 inhibitors, the proportion of people taking SGLT2 inhibitors were lower in older and lower eGFR subgroups in both insulin-naïve and insulin-experienced groups (Tables 1 and 2). The baseline characteristics in subgroups of people with respect to hypoglycemia history before Gla-300 administration are provided in Supplementary Table 1.

3.2. Gla-300 dose, HbA1c level, body weight, and FPG level

The mean Gla-300 dose, HbA1c level, body weight, and FPG level are summarized in Table 3 by age and in Table 4 by eGFR. Changes ± SD in HbA1c levels from baseline to month 12 (LOCF) were −2.4 ± 2.5%, −1.6 ± 1.9%, and −1.4 ± 1.9% in insulin-naïve people aged <65, 65–<75, and ≥75 years, respectively, and those in insulin-experienced people were −0.3 ± 1.4%, −0.1 ± 1.0%, and −0.1 ± 1.0%, respectively (Table 3). With respect to the eGFR category, changes in HbA1c level from baseline to month 12 (LOCF) were −2.9 ± 2.6%, −2.0 ± 2.2%, −1.6 ± 2.1%, and −1.1 ± 1.7% in insulin-naïve people of eGFR ≥90, 60–<90, 30–<60, and <30 mL/min/1.73 m^2, respectively, and −0.3 ± 1.4%, −0.2 ± 1.2%, −0.2 ± 1.2%, and −0.2 ± 1.1%, respectively, in insulin-experienced people (Table 4). Results stratified by history of hypoglycemia before Gla-300 administration are provided in Supplementary Table 2.

Regarding HbA1c distribution at month 12 (LOCF) by age, 28.5%, 32.6%, and 22.3% of people aged <65, 65–<75, and ≥75 years old, respectively in the insulin-naïve group were below the HbA1c level of 7.0% (Fig. 1A), which is a target for the prevention of micro- and macrovascular complications [25]. In the insulin-experienced group, 23.1%, 24.2%, and 27.8% of people, respectively were below the HbA1c level of <7.0%.

3.3. Hypoglycemia by age or eGFR

The proportion of people who experienced ≥1 hypoglycemia during 12 months of Gla-300 administration had no general patterns across the age and eGFR subgroups (Fig. 1B). Hypoglycemia was found in 2.9%, 2.6%, and 3.5% of insulin-naïve people aged <65, 65–<75, and ≥75 years old, respectively, and 3.4%, 5.2%, and 2.7% of insulin-experienced people, respectively. With respect to eGFR, 2.4%, 3.4%, 4.1%, and

Table 1 – Baseline characteristics of insulin-naïve and insulin-experienced people with T2D in the age subgroups.

Characteristics	Insulin-naïve								Insulin-experienced							
	Total (n = 1227)		Age (years)						Total (n = 3394)		Age (years)					
			<65 (n = 620)		65-<75 (n = 351)		≥75 (n = 256)				<65 (n = 1450)		65-<75 (n = 1163)		≥75 (n = 781)	
Age, years, mean ± SD	62.1	± 14.1	50.7	± 9.4	69.2	± 3.0	80.1	± 4.5	64.9	± 12.5	53.3	± 8.9	69.1	± 2.9	80.0	± 4.1
Male, n (%)	805	(65.6)	443	(71.5)	219	(62.4)	143	(55.9)	2015	(59.4)	913	(63.0)	695	(59.8)	407	(52.1)
Duration of diabetes, n	827	–	440	–	230	–	157	–	2550	–	1107	–	894	–	549	–
Mean ± SD, years	11.3	± 8.8	7.9	± 6.8	14.7	± 9.1	15.6	± 9.6	16.3	± 9.4	13.2	± 7.8	17.7	± 9.2	20.4	± 10.7
Hospitalization, n (%)	174	(14.2)	61	(9.8)	55	(15.7)	58	(22.7)	121	(3.6)	43	(3.0)	33	(2.8)	45	(5.8)
Body weight, n	1022	–	527	–	287	–	208	–	2914	–	1267	–	1001	–	646	–
Mean ± SD, kg	66.0	± 15.6	72.0	± 16.3	62.0	± 12.1	56.6	± 11.0	66.9	± 15.2	73.4	± 16.7	63.8	± 11.8	58.8	± 10.7
BMI[†], n	1022	–	527	–	287	–	208	–	2910	–	1266	–	999	–	645	–
Mean ± SD, kg/m^2	24.8	± 4.7	26.0	± 5.0	23.8	± 3.8	23.0	± 3.8	25.5	± 4.7	26.9	± 5.3	24.7	± 3.9	24.0	± 3.8
Comorbidity																
Retinopathy	274	(22.3)	125	(20.2)	90	(25.6)	59	(23.0)	1242	(36.6)	509	(35.1)	457	(39.3)	276	(35.3)
Nephropathy	387	(31.5)	171	(27.6)	123	(35.0)	93	(36.3)	1445	(42.6)	544	(37.5)	532	(45.7)	369	(47.2)
Neuropathy	342	(27.9)	149	(24.0)	111	(31.6)	82	(32.0)	1208	(35.6)	467	(32.2)	444	(38.2)	297	(38.0)
Cardiovascular/ cerebrovascular diseases	203	(16.5)	50	(8.1)	79	(22.5)	74	(28.9)	713	(21.0)	192	(13.2)	283	(24.3)	238	(30.5)
HbA1c, n	1124	–	571	–	318	–	235	–	3217	–	1380	–	1103	–	734	–
Mean ± SD, %	9.8	± 2.2	10.4	± 2.3	9.2	± 1.9	9.3	± 2.0	8.0	± 1.5	8.3	± 1.7	7.8	± 1.2	7.8	± 1.3
FPG, n (%)	441	–	223	–	132	–	86	–	1037	–	448	–	361	–	228	–
Mean ± SD, mg/dl	232.0	± 95.4	237.8	± 95.3	210.4	± 84.5	250.1	± 105.9	156.3	± 68.2	161.0	± 75.7	149.9	± 56.3	157.2	± 69.4
eGFR, n (%)	905	–	455	–	255	–	195	–	2437	–	1002	–	854	–	581	–
Mean ± SD, mL/min/1.73 m^2	77.4	± 29.5	88.8	± 29.8	69.1	± 23.8	61.9	± 24.6	67.6	± 26.8	77.4	± 29.7	64.3	± 22.1	55.8	± 21.6
<60 mL/min/1.73 m^2, n (%)	236	(26.1)	60	(13.2)	80	(31.4)	96	(49.2)	934	(38.3)	243	(24.3)	347	(40.6)	344	(59.2)
GLP-1 receptor agonist[††]	120	(14.4)	60	(16.5)	41	(15.4)	19	(9.4)	341	(10.0)	184	(12.7)	91	(7.8)	66	(8.5)
Insulin[††], n (%)																
Long-acting	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3110	(91.6)	1334	(92.0)	1074	(92.3)	702	(89.9)
Intermediate	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	20	(0.6)	8	(0.6)	7	(0.6)	5	(0.6)
Premix	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	150	(4.4)	51	(3.5)	44	(3.8)	55	(7.0)
Regular	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	24	(0.7)	10	(0.7)	9	(0.8)	5	(0.6)
Rapid	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1422	(41.9)	630	(43.4)	499	(42.9)	293	(37.5)
Oral antidiabetic drugs[††], n (%)																
Sulfonylurea	353	(42.5)	135	(37.2)	129	(48.5)	89	(44.1)	470	(13.8)	190	(13.1)	175	(15.0)	105	(13.4)
Biguanide	339	(40.8)	170	(46.8)	114	(42.9)	55	(27.2)	1061	(31.3)	580	(40.0)	362	(31.1)	119	(15.2)
DPP-4 inhibitor	500	(60.2)	195	(53.7)	160	(60.2)	145	(71.8)	1514	(44.6)	576	(39.7)	552	(47.5)	386	(49.4)
SGLT2 inhibitor	136	(16.4)	83	(22.9)	40	(15.0)	13	(6.4)	530	(15.6)	337	(23.2)	142	(12.2)	51	(6.5)

T2D, type 2 diabetes mellitus; SD, standard deviation; BMI, body mass index; FPG, fasting plasma glucose; eGFR, estimated glomerular filtration rate; GLP, glucagon-like peptide; DPP-4, dipeptidyl peptidase-4; SGLT2, Sodium-glucose transport protein 2

[†] BMI is calculated as weight in kilograms divided by the square of the height in meters

[††] The medication used within 3 months before Gla-300 administration

Table 2 – Baseline characteristics of insulin-naïve and insulin-experienced people with T2D in the eGFR subgroups.

Characteristics	Insulin-naïve								Insulin-experienced							
	eGFR (mL/min/1.73 m^2)								eGFR (mL/min/1.73 m^2)							
	≥90, normal (n = 287)		60–<90, mild (n = 382)		30–<60, moderate (n = 193)		<30, severe (n = 43)		≥90, normal (n = 428)		60–<90, mild (n = 1075)		30–<60, moderate (n = 747)		<30, severe (n = 187)	
Age, years, mean ± SD	53.3	± 13.7	64	± 12.2	70.3	± 11.6	68.4	± 11.9	55.8	± 13.8	64.9	± 10.8	70.3	± 10.7	67.8	± 13.1
Male, n (%)	199	(69.3)	258	(67.5)	134	(69.4)	21	(48.8)	229	(53.5)	663	(61.7)	425	(56.9)	117	(62.6)
Duration of diabetes, n	206	–	265	–	138	–	25	–	339	–	827	–	596	–	139	–
Mean ± SD, years	7.4	± 7.5	11.5	± 9.1	15	± 9.7	14.1	± 8.2	12.6	± 7.6	16.5	± 9.7	17.8	± 9.8	19.9	± 9.5
Hospitalization, n (%)	35	(12.2)	56	(14.7)	44	(22.8)	11	(25.6)	19	(4.4)	32	(3.0)	49	(6.6)	11	(5.9)
Body weight, n	257	–	342	–	172	–	36	–	378	–	964	–	651	–	155	–
Mean ± SD, kg	68.9	± 18.0	65.6	± 15.2	64.2	± 12.5	63.1	± 18.9	69.2	± 19.1	66.4	± 14.4	65.8	± 13.9	68.1	± 15.6
BMI[†], n	257	–	342	–	172	–	36	–	377	–	964	–	649	–	155	–
Mean ± SD, kg/m^2	25.3	± 5.4	24.7	± 4.8	24.6	± 3.6	24.5	± 5.2	26.1	± 6.4	25.2	± 4.4	25.6	± 4.3	26.0	± 5.0
Comorbidity																
Retinopathy	52	(18.1)	89	(23.3)	59	(30.6)	22	(51.2)	119	(27.8)	365	(34.0)	350	(46.9)	114	(61.0)
Nephropathy	69	(24.0)	115	(30.1)	95	(49.2)	35	(81.4)	130	(30.4)	438	(40.7)	434	(58.1)	169	(90.4)
Neuropathy	66	(23.0)	114	(29.8)	70	(36.3)	25	(58.1)	133	(31.1)	371	(34.5)	351	(47.0)	102	(54.5)
Cardiovascular/ cerebrovascular diseases	252	(87.8)	320	(83.8)	150	(77.7)	29	(67.4)	378	(88.3)	880	(81.9)	524	(70.1)	118	(63.1)
HbA1c, n	284	–	377	–	191	–	34	–	425	–	1069	–	736	–	165	–
Mean ± SD, %	10.7	± 2.3	9.7	± 2.1	9.4	± 2.2	8.6	± 2.2	8.3	± 1.7	7.9	± 1.4	8.0	± 1.4	7.6	± 1.4
FPG, n (%)	119	–	164	–	74	–	14	–	153	–	381	–	244	–	57	–
Mean ± SD, mg/dl	244.6	± 103.7	221.0	± 81.8	235.3	± 114.9	236.1	± 79.3	167.6	± 78.2	147.7	± 60.5	155.1	± 69.5	158.4	± 84.0
eGFR, n (%)	287	–	382	–	193	–	43	–	428	–	1075	–	747	–	187	–
Mean ± SD, mL/min/1.73 m^2	110.8	± 18.5	74.2	± 8.0	47.5	± 8.3	18.0	± 7.5	107.2	± 19.5	73.9	± 8.2	48.3	± 8.2	17.9	± 8.7
GLP-1 receptor agonist[††]	23	(14.5)	41	(15.6)	23	(14.0)	5	(14.7)	54	(12.6)	123	(11.4)	78	(10.4)	18	(9.6)
Insulin[††], n (%)																
Long-acting	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	383	(89.5)	1001	(93.1)	670	(89.7)	168	(89.8)
Intermediate	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	5	(1.2)	6	(0.6)	5	(0.7)	2	(1.1)
Premix	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	16	(3.7)	44	(4.1)	37	(5.0)	7	(3.7)
Regular	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.7)	6	(0.6)	11	(1.5)	2	(1.1)
Rapid	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	181	(42.3)	446	(41.5)	362	(48.5)	96	(51.3)
Oral antidiabetic drugs[††], n (%)																
Sulfonylurea	61	(38.4)	106	(40.5)	70	(42.7)	6	(17.6)	60	(14.0)	177	(16.5)	79	(10.6)	11	(5.9)
Biguanide	80	(50.3)	120	(45.8)	54	(32.9)	6	(17.6)	196	(45.8)	384	(35.7)	174	(23.3)	5	(2.7)
DPP-4 inhibitor	86	(54.1)	152	(58.0)	111	(67.7)	30	(88.2)	170	(39.7)	480	(44.7)	361	(48.3)	96	(51.3)
SGLT2 inhibitor	31	(19.5)	42	(16.0)	22	(13.4)	1	(2.9)	95	(22.2)	194	(18.0)	84	(11.2)	6	(3.2)

T2D, type 2 diabetes mellitus; SD, standard deviation; BMI, body mass index; FPG, fasting plasma glucose; eGFR, estimated glomerular filtration rate; GLP, glucagon-like peptide; DPP-4, dipeptidyl peptidase-4; SGLT2, Sodium-glucose transport protein 2

[†] BMI is calculated as weight in kilograms divided by the square of the height in meters

[††] The medication used within 3 months before Gla-300 administration

Table 3 – The mean Gla-300 administration, HbA1c level, body weight, and FPG level at baseline and at months 6 and 12 (LOCF) and the changes between baseline and at month 12 (LOCF) among insulin-naïve and insulin-experienced people with T2D in the age subgroups.

Characteristics	Insulin-naïve Total (n = 1194)		Age (years) <65 (n = 605)		65–<75 (n = 339)		≥75 (n = 250)		Insulin-experienced Total (n = 3297)		Age (years) <65 (n = 1413)		65–<75 (n = 1120)		≥75 (n = 764)	
Gla-300 administration																
Mean ± SD, U/day																
Baseline	7.5	± 4.8	7.8	± 4.8	7.2	± 4.6	7.1	± 4.7	14.9	± 9.6	17.3	± 11.1	13.6	± 8.0	12.2	± 7.5
Month 6[†]	10.9	± 6.4	11.8	± 6.8	9.5	± 5.3	10.3	± 6.8	15.7	± 9.9	18.1	± 11.3	14.4	± 8.3	12.9	± 8.0
Month 12 (LOCF)	10.3	± 6.8	11.4	± 7.4	9.2	± 5.4	9.2	± 6.4	15.6	± 10.0	18.0	± 11.3	14.6	± 8.8	12.7	± 8.0
Change	2.8	± 5.8	3.6	± 6.7	2.0	± 4.2	2.1	± 5.1	0.7	± 3.8	0.7	± 4.1	0.9	± 3.6	0.5	± 3.4
Paired *t*-test[††], p-value	p < 0.001		p < 0.001		p < 0.001		p < 0.001		p < 0.001		p < 0.001		p < 0.001		p < 0.001	
HbA1c, n	1006	–	527	–	282	–	197	–	3079	–	1331	–	1050	–	698	–
Mean ± SD, %																
Baseline	9.8	± 2.2	10.4	± 2.3	9.1	± 1.8	9.4	± 2.0	8.0	± 1.5	8.3	± 1.7	7.8	± 1.2	7.8	± 1.3
Month 6[†††]	7.7	± 1.4	7.8	± 1.6	7.5	± 1.2	7.7	± 1.4	7.8	± 1.3	8.0	± 1.5	7.7	± 1.1	7.6	± 1.0
Month 12 (LOCF)	7.8	± 1.5	7.9	± 1.6	7.5	± 1.3	8.0	± 1.5	7.8	± 1.3	8.0	± 1.5	7.7	± 1.2	7.7	± 1.2
Change	−2.0	± 2.3	−2.4	± 2.5	−1.6	± 1.9	−1.4	± 1.9	−0.2	± 1.2	−0.3	± 1.4	−0.1	± 1.0	−0.1	± 1.0
Paired *t*-test[††], p-value	p < 0.001		p < 0.001		p < 0.001		p < 0.001		p < 0.001		p < 0.001		p = 0.006		p = 0.009	
Body weight, n	888	–	480	–	246	–	162	–	2706	–	1193	–	927	–	586	–
Mean ± SD, kg																
Baseline	66.7	± 15.6	72.1	± 16.3	62.4	± 11.9	57.3	± 11.2	67.2	± 15.2	73.7	± 16.7	63.8	± 11.8	59.3	± 10.6
Month 6[††††]	67.8	± 15.5	73.6	± 15.9	61.9	± 11.6	58.9	± 11.3	67.2	± 15.1	73.7	± 16.3	63.6	± 12.0	59.2	± 10.4
Month 12 (LOCF)	67.4	± 15.4	73.1	± 16.0	62.6	± 11.8	57.8	± 11.0	67.0	± 15.1	73.7	± 16.4	63.6	± 12.0	58.9	± 10.4
Change	0.7	± 4.1	0.9	± 4.6	0.2	± 3.4	0.5	± 3.5	−0.2	± 3.1	−0.1	± 3.4	−0.2	± 3.0	−0.4	± 2.6
Paired *t*-test[††], p-value	p < 0.001		p < 0.001		p = 0.352		p = 0.053		p = 0.003		p = 0.560		p = 0.051		p < 0.001	
FPG, n	332	–	164	–	104	–	64	–	905	–	400	–	308	–	197	–
Mean ± SD, mg/dl																
Baseline	229.2	± 91.6	230.9	± 88.0	209.0	± 81.6	257.5	± 108.1	156.8	± 69.4	162.8	± 77.4	147.1	± 54.1	159.7	± 71.9
Month 6[†††††]	149.4	± 44.7	147.9	± 42.1	152.9	± 53.9	147.5	± 34.0	143.9	± 52.0	145.8	± 53.2	143.0	± 50.4	141.3	± 52.2
Month 12 (LOCF)	147.2	± 55.0	145.0	± 50.5	143.2	± 57.8	159.4	± 60.2	147.5	± 59.7	151.2	± 62.3	144.5	± 58.1	144.6	± 56.2
Change	−82.0	± 97.0	−85.9	± 96.1	−65.9	± 90.9	−98.1	± 106.5	−9.3	± 69.5	−11.6	± 75.1	−2.6	± 65.2	−15.1	± 63.7
Paired *t*-test[††], p-value	p < 0.001		p < 0.001		p < 0.001		p < 0.001		p < 0.001		p = 0.002		p = 0.486		p = 0.001	

FPG, fasting plasma glucose; LOCF, last observation carried forward; T2D, type 2 diabetes mellitus; SD, standard deviation.

[†] n = 848, 447, 250, and 151 for insulin-naïve and n = 2940, 1267, 1024, and 649 for insulin-experienced and for total, <65, 65–<75, and ≥75 years, respectively

[††] Paired-*t* test was used to compare changes between baseline and at month 12 (LOCF).

[†††] n = 767, 413, 217, and 137 for insulin-naïve and n = 2739, 1185, 953, and 601 for insulin-experienced for total, age <65, 65–<75, and ≥75 years, respectively

[††††] n = 651, 358, 186, and 107 for insulin-naïve and n = 2312, 1039, 794, and 479 for insulin-experienced and for total, <65, 65–<75, and ≥75 years, respectively

[†††††] n = 181, 94, 56, and 31 for insulin-naïve and n = 610, 272, 207, and 131 for insulin-experienced and for total, <65, 65–<75, and ≥75 years, respectively

Table 4 – The mean Gla-300 administration, HbA1c level, body weight, and FPG level at baseline and at months 6 and 12 (LOCF) and the changes between baseline and at month 12 (LOCF) among insulin-naïve and insulin-experienced people with T2D in the eGFR subgroups.

Characteristics	Insulin-naïve								Insulin-experienced							
	eGFR (mL/min/1.73 m^2)								eGFR (mL/min/1.73 m^2)							
	≥90, normal (n = 280)		60–<90, mild (n = 373)		30–<60, moderate (n = 186)		<30, severe (n = 41)		≥90, normal (n = 420)		60–<90, mild (n = 1046)		30–<60, moderate (n = 719)		<30, severe (n = 178)	
Gla-300 administration, Mean ± SD, U/day																
Baseline	7.4	± 4.2	6.8	± 3.6	7.4	± 5.6	6.0	± 3.5	17.1	± 11.9	14.1	± 8.8	14.5	± 9.6	12.3	± 8.4
Month 6[†]	11.7	± 6.6	10.1	± 5.6	10.5	± 7.3	9.0	± 5.4	18.2	± 11.9	14.9	± 9.2	15.0	± 9.8	13.2	± 9.2
Month 12 (LOCF)	10.8	± 7.1	9.7	± 6.1	10.1	± 7.1	7.2	± 4.8	18.0	± 11.9	14.8	± 9.3	15.2	± 10.2	12.9	± 8.8
Change	3.5	± 6.7	2.9	± 5.7	2.6	± 5.3	1.2	± 4.1	0.9	± 5.0	0.7	± 3.0	0.7	± 3.9	0.6	± 3.6
Paired *t*-test[††], p-value	p < 0.001		p < 0.001		p < 0.001		p = 0.061		p < 0.001		p < 0.001		p < 0.001		p = 0.028	
HbA1c, n	253	–	343	–	163	–	26	–	410	–	1031	–	690	–	154	–
Mean ± SD, %																
Baseline	10.8	± 2.3	9.7	± 2.1	9.5	± 2.2	8.0	± 1.6	8.3	± 1.7	7.9	± 1.4	7.9	± 1.4	7.6	± 1.5
Month 6[†††]	7.8	± 1.6	7.6	± 1.3	7.7	± 1.5	6.6	± 1.1	8.0	± 1.4	7.8	± 1.2	7.7	± 1.2	7.4	± 1.3
Month 12 (LOCF)	7.9	± 1.6	7.8	± 1.5	7.8	± 1.6	6.9	± 1.4	8.0	± 1.3	7.8	± 1.3	7.8	± 1.3	7.4	± 1.2
Change	−2.9	± 2.6	−2.0	± 2.2	−1.6	± 2.1	−1.1	± 1.7	−0.3	± 1.4	−0.2	± 1.2	−0.2	± 1.2	−0.2	± 1.1
Paired *t*-test[††], p-value	p < 0.001		p < 0.001		p < 0.001		p = 0.003		p < 0.001		p < 0.001		p < 0.001		p = 0.021	
Body weight, n	235	–	295	–	146	–	27	–	355	–	897	–	591	–	142	–
Mean ± SD, kg																
Baseline	69.8	± 18.1	65.7	± 14.9	65.0	± 12.8	65.7	± 18.6	70.0	± 19.0	66.6	± 14.4	66.1	± 14.0	68.6	± 15.4
Month 6[††††]	71.2	± 18.2	67.0	± 14.7	65.2	± 13.1	67.5	± 17.8	70.2	± 18.6	66.7	± 14.4	66.0	± 14.1	67.7	± 14.0
Month 12 (LOCF)	71.1	± 18.2	66.0	± 14.4	65.3	± 12.8	66.7	± 18.1	70.0	± 18.6	66.4	± 14.3	65.8	± 14.1	68.5	± 16.0
Change	1.3	± 5.0	0.3	± 3.7	0.2	± 3.7	1.0	± 4.4	0.0	± 3.6	−0.2	± 3.0	−0.3	± 2.9	−0.1	± 3.8
Paired *t*-test[††], p-value	p < 0.001		p = 0.235		p = 0.461		p = 0.265		p = 0.830		p = 0.079		p = 0.016		p = 0.804	
FPG, n	94	–	115	–	55	–	10	–	136	–	334	–	208	–	47	–
Mean ± SD, mg/dl																
Baseline	239.6	± 98.6	218.5	± 83.3	231.8	± 111.0	233.5	± 69.8	168.4	± 80.5	149.0	± 61.4	152.1	± 68.5	162.1	± 90.4
Month 6[†††††]	154.5	± 48.6	136.3	± 38.2	149.3	± 50.0	128.0	± 26.2	144.7	± 50.9	141.1	± 54.3	138.2	± 46.8	144.8	± 60.7
Month 12 (LOCF)	149.7	± 54.5	142.7	± 53.4	145.6	± 65.9	155.0	± 65.2	147.7	± 54.5	144.4	± 54.8	142.4	± 49.5	138.7	± 49.7
Change	−89.9	± 103.9	−75.8	± 81.3	−86.2	± 121.9	−78.5	± 111.0	−20.7	± 72.4	−4.6	± 55.2	−9.7	± 65.2	−23.5	± 91.3
Paired *t*-test[††], p-value	p < 0.001		p < 0.001		p < 0.001		p = 0.052		p = 0.001		p = 0.125		p = 0.033		p = 0.084	

FPG, fasting plasma glucose; LOCF, last observation carried forward; T2D, type 2 diabetes mellitus; eGFR, estimated glomerular filtration rate; SD, standard deviation

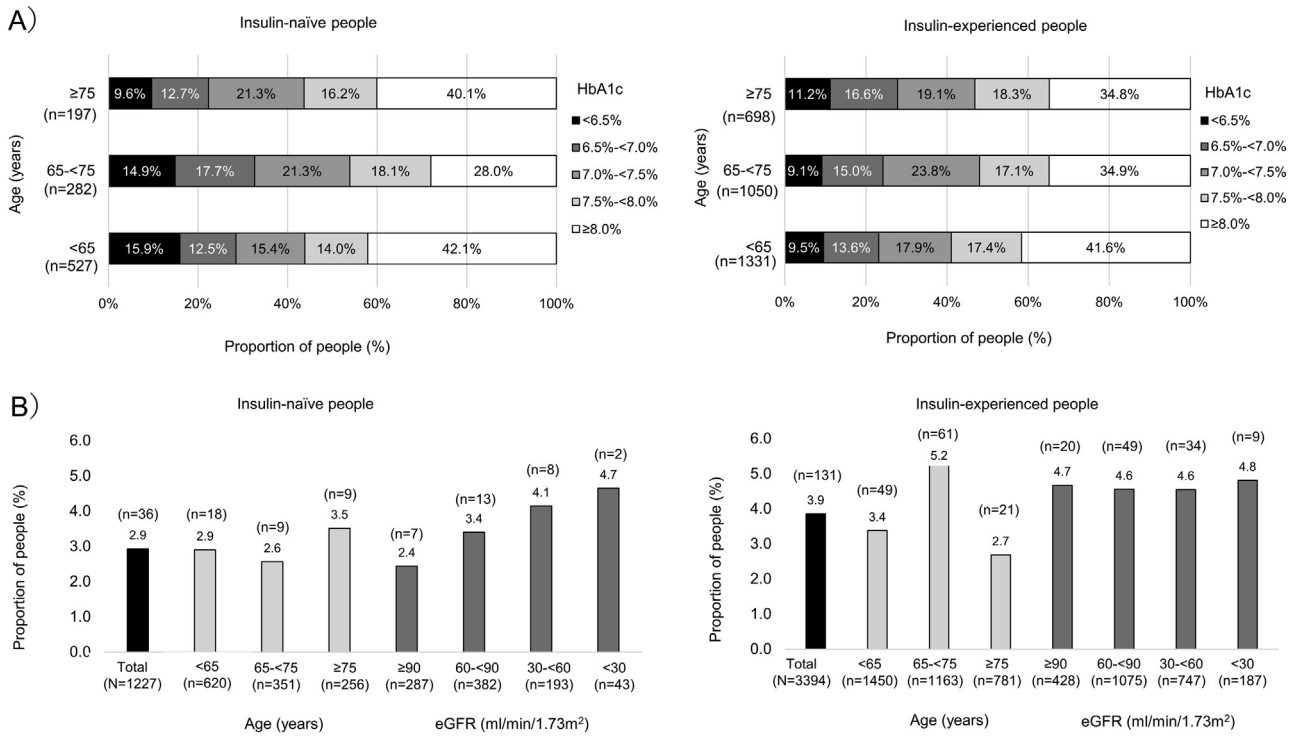
[†] n = 188, 267, 127, and 24 for insulin-naïve and n = 374, 952, 624, and 149 for insulin-experienced and for eGFR ≥90, 60–<90, 30–<60, and <30 mL/min/1.73 m^2, respectively

[††] Paired-*t* test was used to compare changes between baseline and at month 12 (LOCF).

[†††] n = 190, 252, 125, and 17 for insulin-naïve and n = 370, 923, 608, and 128 for insulin-experienced for eGFR ≥90, 60–<90, 30–<60, and <30 mL/min/1.73 m^2, respectively

[††††] n = 163, 216, 107, and 14 for insulin-naïve and n = 312, 753, 496, and 107 for insulin-experienced and for eGFR ≥90, 60–<90, 30–<60, and <30 mL/min/1.73 m^2, respectively

[†††††] n = 58, 52, 34, and 3 for insulin-naïve and n = 97, 227, 144, and 26 for insulin-experienced and for eGFR ≥90, 60–<90, 30–<60, and <30 mL/min/1.73 m^2, respectively



C)

HbA1c at month 12 (LOCF)	Insulin-naïve people						Insulin-experienced people					
	Age (years)						Age (years)					
	<65 (n=537)		65-<75 (n=293)		≥75 (n=201)		<65 (n=1,361)		65-<75 (n=1,083)		≥75 (n=713)	
	Total	hypoglycemia	Total	hypoglycemia	Total	hypoglycemia	Total	hypoglycemia	Total	hypoglycemia	Total	hypoglycemia
	n	n (%)	n	n (%)	n	n (%)	n	n (%)	n	n (%)	n	n (%)
<6.5%	86	1 (1.2)	42	0 (0.0)	19	1 (5.3)	134	9 (6.7)	101	6 (5.9)	80	1 (1.3)
6.5%-<7.0%	68	3 (4.4)	51	2 (3.9)	26	1 (3.8)	185	7 (3.8)	162	9 (5.6)	118	5 (4.2)
7.0%-<7.5%	81	3 (3.7)	62	2 (3.2)	42	0 (0.0)	243	11 (4.5)	259	15 (5.8)	135	3 (2.2)
7.5%-<8.0%	75	0 (0.0)	52	2 (3.8)	33	1 (3.0)	236	12 (5.1)	184	6 (3.3)	130	5 (3.8)
≥8.0%	227	9 (4.0)	86	3 (3.5)	81	3 (3.7)	563	10 (1.8)	377	22 (5.8)	250	6 (2.4)

Fig. 1 – (A) Percentage of insulin-naïve and insulin-experienced people with T2D categorized according to HbA1c level at month 12 (LOCF) and age, (B) proportion of people with ≥1 hypoglycemia at 12 months of Gla-300 administration among insulin-naïve and insulin-experienced people of the age and eGFR subgroups, (C) proportion of people with ≥1 hypoglycemia during Gla-300 administration among insulin-naïve and insulin-experienced people in subgroups of age and HbA1c level at 12 months (LOCF). T2D, type 2 diabetes mellitus; LOCF, last observation carried forward; eGFR, estimated glomerular filtration rate. Notes: People with missing HbA1c values or data on hypoglycemia were excluded when calculating the proportions. Data from the effective analysis population (A) and the safety analysis population (B, C) [22] were used for analysis.

4.7% of insulin-naïve and 4.7%, 4.6%, 4.6%, and 4.8% of insulin-experienced people in subgroups of ≥90, 60–<90, 30–<60, and <30 mL/min/1.73 m^2, respectively, experienced hypoglycemia (Fig. 1B).

The proportion of people who experienced hypoglycemia by both age and HbA1c value at month 12 (LOCF) is shown in Fig. 1C. In insulin-naïve people, the proportions of people who experienced hypoglycemia with HbA1c level below and at or above 7.0% were 0.0% to 5.3% and 0.0% to 4.0%, respectively, across the three age groups, whereas 1.3% to 6.7% and 1.8% to 5.8%, respectively, in insulin-experienced people. In all three age groups, people with lower HbA1c levels did not show apparent increase in hypoglycemia.

3.4. *People who did and did not experience hypoglycemia*

The baseline characteristics of people who did or did not experience hypoglycemia during this study period are summarized in Supplementary Table 3. Mean ± SD age (64.1 ± 15.7 years vs 62.1 ± 14.0 years in insulin-naïve, 64.7 ± 12.3 years vs 64.9 ± 12.5 years in insulin-experienced), eGFR (77.0 ± 37.8 mL/min/1.73 m^2 vs 77.5 ± 29.2 mL/min/1.73 m^2 in insulin-naïve, 66.8 ± 27.2 mL/min/1.73 m^2 vs 67.7 ± 26.8 mL/min/1.73 m^2 in insulin-experienced) and HbA1c at month 12 (LOCF) (7.9 ± 1.3% vs 7.8 ± 1.5% in insulin-naïve, 7.6 ± 1.1% vs 7.8 ± 1.3% in insulin-experienced) were comparable between the two groups. The proportions of people who experienced

hypoglycemia within 3 months before Gla-300 administration (5.6% vs 0.9% in insulin-naïve, 46.4% vs 8.7% in insulin-experienced) and who concomitantly used rapid insulin (33.3% vs 14.9% in insulin-naïve, 68.5% vs 43.6% in insulin-experienced) are higher and mean BMI (23.0 ± 3.9 kg/m^2 vs 24.9 ± 4.7 kg/m^2 in insulin-naïve, 24.7 ± 4.9 kg/m^2 vs 25.5 ± 4.7 kg/m^2 in insulin-experienced) was slightly lower in the group with hypoglycemia.

4. Discussion

This study investigated the risk of hypoglycemia in people with T2D who initiated or switched to Gla-300 in a real-world clinical setting in Japan, using the subgroup analysis with respect to age and eGFR.

Among the age-stratified subgroups, people aged <65 years in insulin naïve group showed the highest baseline HbA1c (10.4%) and the greatest reduction in HbA1c (−2.4%). At month 12 month (LOCF), there were no apparent trends in terms of HbA1c (Fig. 1A, Table 3) and the proportion of people with hypoglycemia (Fig. 1B). Regarding the relationship between the final HbA1c value at month 12 (LOCF) and the proportion of hypoglycemia, people with HbA1c level <7.0% did not show an apparent increase in hypoglycemia among any subgroups, compared to those with HbA1c level at or above 7.0% in both insulin-naïve and insulin-experienced people. Our results that people aged >65 years with HbA1c below 7.0% did not show an apparent increased risk of hypoglycemia may provide reassuring information on the use of Gla-300 for older people.

The Japan Diabetes Society (JDS) guideline recommends lower limits of HbA1c target values for older people according to their cognitive function, activities of daily living, and use of insulin-related agents (insulin or sulfonylurea) since 2016 to avoid (severe) hypoglycemia and minimize hypoglycemia-related consequences [26]. A survey of severe hypoglycemia conducted by JDS revealed that more cases of severe hypoglycemia were found in people with T2D having lower HbA1c levels (mean of 6.8%) and those with older age (mean of 77.0 years) [27]. It should be noted that older people may be unaware of their hypoglycemia status due to loss of forewarning symptoms [9]. As only 8 T2D individuals presented with severe hypoglycemia (1 [0.08%] insulin-naïve and 7 [0.21%] insulin-experienced) in the X-STAR study [22], there was difficulty in clarifying the association between age-HbA1c level and severe hypoglycemia. Further studies are required to evaluate the optimal range of HbA1c target values for older people with T2D using Gla-300.

Among eGFR subgroups, people with eGFR > 90 in insulin-naive group showed the highest baseline HbA1c (10.8%) and the greatest reduction in HbA1c (−2.9%), which is likely associated with younger age (53.3 years). At month 12, HbA1c levels at month 12 with eGFR < 60 were equal to or less than those with normal renal function in both groups. The proportion of people with hypoglycemia was generally similar in any of the eGFR subgroups, only with slight variation. Although hypoglycemia slightly increased from 2.4% to 4.7% as renal function declined in insulin-naïve people, there were only few people with eGFR < 60 mL/min/1.73 m^2 (eight and two individuals) (Fig. 1B). There was virtually no difference in insulin-experienced people among the eGFR subgroups, with 4.7% and 4.8% of people with hypoglycemia in the eGFR subgroups of ≥90 and <30 mL/min/1.73 m^2, respectively. In BRIGHT and EDITION trials, RCTs of Gla-300, hypoglycemia was observed more frequently in people with renal impairment [18,28]. It should be noted that these studies set the target FPG level for titration of basal insulin. Although we cannot yet reach conclusion, the findings from our subgroup analysis suggest that renal impairment may not increase the risk of hypoglycemia in people with T2D using Gla-300 in the real-world clinical practice in Japan.

The mean BMI of was 24.8 and 25.5 kg/m^2 in insulin-naïve and insulin-experienced peoples, respectively. This result was similar to another real-world data of population with T2D initiating basal insulin in Japan [29] and obviously lower than those who need insulin therapy in western countries (e.g., 32 kg/m^2, [30]). Along with lower BMI, decreased insulin secretion in the early stage of T2D is a well-recognized feature in Japanese population [31,32]. Thus, DPP-4 inhibitors are preferably prescribed from an early stage of diabetes [32–34]. In this study, we found that the proportion of people prescribed with DPP-4 inhibitors was particularly high in older (>65 years) and reduced renal function subgroups (eGFR < 30 mL/min/1.73 m^2) in contrast to SGLT2 inhibitors, sulfonylurea, and biguanides (Tables 1 and 2), which tend to be avoided in these subgroups. These results are probably explained by little safety concern of DPP-4 inhibitors in these subgroups [35,36]. Such prescription patterns of DPP-4 inhibitors in high-risk people may reflect that Japanese physicians have a strong sense of trust in this class of drugs.

This study has several limitations. Firstly, relatively small numbers of people with hypoglycemia found in this study could be due to hypoglycemia not strictly defined and measured in the X-STAR study unlike in clinical trials. A total of 36 (2.93%) insulin-naïve and 131 (3.86%) insulin-experienced people experienced hypoglycemia during the X-STAR study, and severe hypoglycemia were found in 1 (0.08%) and 7 (0.21%) in insulin-naïve and insulin experienced people) in the X-STAR study [22], but there might have been asymptomatic people not included in these numbers. Thus, hypoglycemia may have been underreported, and the results should be interpreted with care. However, our results provide important insights into the current situation of people with T2D in Japan where the population is rapidly aging, and the number of aged and people with diabetes is expected to rise [37]. Secondly, this observational study lacks a control group and prevents any comparative analysis against other types of insulins. This study also revealed the background characteristics and the preference of concomitant OADs when initiating and switching insulin therapy in clinical settings, and such information may inform clinical practice for glycemic control. Finally, because this is a post-marketing surveillance conducted in Japan, our study results may not be generalizable.

5. Conclusion

In this subgroup analysis among people with T2D who initiated or switched to Gla-300 extracted from the real-world X-STAR study in Japan, we found that the number of people who experienced hypoglycemia was generally similar across the age and eGFR subgroups, and people below the HbA1c level target of 7.0% did not show an apparent increase in hypoglycemic events in all age groups including people aged ≥75 years. Given that people with T2D who are older and/or with CKD are expected to rise in aging societies such as those in Japan, our result would provide reassuring information on Gla-300.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: T Hirose received honoraria from Sanofi K.K., Eli Lilly Japan K.K., Novo Nordisk Pharma Ltd., Takeda Pharmaceutical Company, Ltd., MSD K.K., Sumitomo Dainippon Pharma Co., Ltd., Novartis Pharma K.K., Nippon Boehringer Ingelheim Co., Ltd., Ono Pharmaceutical Co., Ltd., AstraZeneca K.K., Mitsubishi Tanabe Pharma Corp., and Kowa Company, Ltd.; research funding from Mitsubishi Tanabe Pharma Corp. and AstraZeneca K.K.; and subsidies or donations from Astellas Pharma Inc., Novartis Pharma K.K., Eli Lilly Japan K.K., MSD K.K., Sanofi K.K., Mitsubishi Tanabe Pharma Corp., Daiichi Sankyo Co., Ltd., Takeda Pharmaceutical Company, Ltd., Taisho Pharmaceutical Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Ono Pharmaceutical Co., Ltd., Novo Nordisk Pharma Ltd., Soiken, Inc., and Bayer Yakuhin, Ltd.

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R Koshida and M Senda are employees of Sanofi K.K.

Y Tanaka serves in an advisory role to Top Corp.; and received honoraria from MSD K.K., Kissei Pharmaceutical Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Astellas Pharma Inc., Takeda Pharmaceutical Company, Ltd., Arkray, Inc., and Sanofi K.K.: collaborative research funding from Nichirei Foods Inc.; and subsidies or donations from Sanofi K.K., Takeda Pharmaceutical Company, Ltd., MSD K.K., Daiichi Sankyo Co., Ltd., Novo Nordisk Pharma Ltd., Kissei Pharmaceutical Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Sanwa Kagaku Kenkyusho Co., Ltd., Arkray, Inc., AstraZeneca K.K., Mitsubishi Tanabe Pharma Corp., Ono Pharmaceutical Co., Ltd., and Astellas Pharma Inc.

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Appendix A. Supplementary material

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