Adv Ther (2025) 42:413–426
https://doi.org/10.1007/s12325-024-03050-1

ORIGINAL RESEARCH

Investigation of Severe Hypoglycemia Risk Among Patients with Diabetes Treated with Ultra-Rapid Lispro in Japan

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Received: September 2, 2024 / Accepted: October 21, 2024 / Published online: November 21, 2024

ABSTRACT

Introduction: There is no information on the incidence of severe hypoglycemia in real-world patients with diabetes receiving ultra-rapid lispro (URLi). This post-marketing, observational, safety study assessed the incidence proportion and incidence rate of the first severe hypoglycemia event requiring a hospital visit in URLi-treated patients. It also compared the risk of severe hypoglycemia between patients treated with URLi or other rapid-acting insulin analogs (RAIAs).

Methods: Claims data were obtained from a nationwide hospital-based administrative database in Japan (Medical Data Vision). Adults with diabetes who initiated URLi or other RAIA on/after June 01, 2020, were followed up through May 31, 2023. Severe hypoglycemia was identified using a validated algorithm. Incidence proportion and incidence rate of the first severe hypoglycemia event requiring a hospital visit was described in URLi-treated patients (descriptive analysis). These outcomes were also compared against propensity score (PS)-matched other RAIA-treated patients (comparator; comparative analysis). Hazard ratio (HR) and 95% confidence interval (CI) was estimated with a Cox proportional hazards model.

Results: The descriptive analysis' URLi-treated cohort included 17,838 patients [mean (standard deviation, SD) age 65.9 (15.7) years; 58.3% male]. The majority had type 2 diabetes (75.7%). The incidence proportion of the first severe hypoglycemia event requiring a hospital visit was 0.6% (95% CI 0.5, 0.8) and the incidence rate was 1.7 per 100 person-years (95% CI 0.7, 4.3). The comparative analysis included 10,592 URLi-treated and 52,917 comparator-treated patients. The incidence rate of severe hypoglycemia did not significantly differ between these cohorts (HR 0.8; 95% CI 0.5, 1.1; $p = 0.132$;.

Conclusion: This study did not show a statistically significant increase in the incidence and risk of the first severe hypoglycemia event requiring a hospital visit in real-world URLi-treated patients in Japan, compared with a PS-matched cohort of other RAIA-treated patients.

Seiko Mizuno and Machiko Minatoya equally contributed to this manuscript and are first co-authors.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12325-024-03050-1.

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Keywords: Japan; Ultra-rapid lispro; Severe hypoglycemia; Post-marketing safety study; Diabetes; Claims data; Real-world; Observational study; Propensity score matching

Key Summary Points

Why carry out this study?

The incidence of severe hypoglycemia in real-world patients with diabetes receiving ultra-rapid lispro (URLi) is unknown.

This post-marketing safety study was conducted using data from a Japanese claims database to assess the incidence proportion and incidence rate of the first severe hypoglycemia event requiring a hospital visit in URLi-treated patients, and also compare the risk of severe hypoglycemia between patients treated with URLi or other rapid-acting insulin analogs (RAIAs).

What was learned from the study?

In the URLi-treated cohort, the incidence proportion of the first severe hypoglycemia event requiring a hospital visit was 0.6% [95% confidence interval (CI): 0.5, 0.8] and the incidence rate was 1.7 per 100 person-years (95% CI 0.7, 4.3).

The incidence rate of the first severe hypoglycemia event requiring a hospital visit did not significantly differ between the URLi-treated and other RAIA-treated cohorts [hazard ratio (HR) 0.8; 95% CI 0.5, 1.1; $p = 0.132$].

INTRODUCTION

The Japanese Clinical Practice Guidelines for Diabetes 2019 recommend treating type 1 diabetes (T1D) with insulin therapy, and type 2 diabetes (T2D) with oral hypoglycemic agents, insulin therapy, or glucagon-like peptide 1 receptor agonists [1]. Ultra-rapid lispro (URLi), a novel ultra-rapid insulin lispro formulation launched on June 17, 2020, in Japan [2], improves post-prandial glucose control by closely matching physiological insulin secretion [3].

Hypoglycemia, i.e., a blood glucose level of < 70 mg/dL, is a major side effect of insulin therapy (including URLi); it is classified into non-severe and severe hypoglycemia based on the level of assistance required [1, 4]. Non-severe hypoglycemia can be resolved by self-administering oral carbohydrates; however, severe hypoglycemia requires assistance from others to administer glucagon, glucose, or other medical treatments [1, 4]. Since severe hypoglycemia can lead to loss of consciousness, seizures, coma, or death [5, 6], it is listed as an important identified risk in URLi's Japan risk management plan (data on file).

In clinical trials, the incidence rate of severe hypoglycemia in URLi-treated patients ranged from 2.4 to 17.6 per 100 person-years, and the incidence proportion ranged from 0.9 to 7.3% [7–13], due to differences in diabetes type, study period, and drug administration. Among insulin-treated patients with diabetes, the incidence rate of severe hypoglycemia differs in the real world (0.0–1.6 episodes/patient/year) and in controlled clinical trials (0.0–0.5 episodes/patient/year) [14]. Hence, it is necessary to evaluate the real-world risk of hypoglycemia by analyzing health records or medical claims, as conducted in the past [15, 16].

To our knowledge, there is no information on the incidence of severe hypoglycemia in patients receiving URLi in the real-world setting. Furthermore, no study to date has compared the risk of severe hypoglycemia after treatment with URLi versus other rapid-acting insulin analogs (RAIAs). Hence, this post-marketing safety study assessed the incidence proportion and incidence rate of the first severe hypoglycemia event requiring a hospital visit for URLi-treated patients (i.e., a descriptive analysis). This study also compared the risk of severe hypoglycemia among patients treated with URLi or other RAIAs (i.e., a comparative analysis). Considering the diverse treatment regimens in the real world, this study also evaluated the aforementioned objectives in multiple subgroups as described later.

METHODS

Study Design

This cohort study utilized secondary data from the Medical Data Vision (MDV) database, a nationwide hospital-based administrative database in Japan. This database contains de-identified Diagnosis Procedure Combination (DPC) data from acute care Japanese hospitals (including inpatient and outpatient administrative claims) [17]. DPC is a case-mix classification system linked to a flat-fee payment system. As of June 2024, the MDV database included 48.0 million patients from over 480 hospitals (i.e., approximately 28% of acute care or advanced treatment hospitals in Japan) [17, 18].

The study period was December 01, 2019, through May 31, 2023, and the period between 183 days before the index date through the index date was defined as the baseline period (Fig. 1). The patient selection period started from June 01, 2020, to coincide with URLi's launch in Japan in June 2020, and continued through May 31, 2023. Patients were followed up until occurrence of either the first severe hypoglycemia visit requiring a hospital visit, or until a censoring event, i.e., any inpatient hospitalization due to reasons other than the severe hypoglycemia event (considering the glycemic control situation between the inpatient and outpatient setting), in-hospital death, prescription of other RAIAs (insulin lispro, insulin glulisine, insulin aspart, and Fiasp®, Novo Nordisk), prescription of sulfonylurea or glinide, or date of last claim of any kind in the database (no later than May 31, 2023). The date of the first URLi or comparator prescription during the patient selection period was the index date for the URLi-treated cohort or comparator-treated cohort, respectively.

This study was conducted in accordance with ethical principles originating from the Declaration of Helsinki of 1964 and its later amendments, and that were consistent with Good Pharmacoepidemiology Practices. Due to the nature of the study and use of de-identified data, ethical review by an Institutional Review Board and informed consent from patients were not required. This is in accordance with the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects. Data were purchased from MDV after obtaining the necessary permissions.

Patient Population

The initial descriptive and comparative analyses are hereafter collectively referred to as the 'main analysis' when required. For the main analysis, this study included patients who were newly prescribed URLi (URLi-treated cohort) or other RAIAs (comparator-treated cohort) during the patient selection period, were ≥ 18 years old at the index date, were diagnosed with diabetes within 30 days prior to or on the index date, and had ≥ 1 claim in the MDV database during the baseline period except the index date. Diabetes diagnoses were identified using the International Classification of Diseases, 10th revision (ICD-10) codes E10, E11, E14, O24.0, O24.1, and O24.9 in the MDV database. This study excluded patients with a disease code for gestational diabetes in

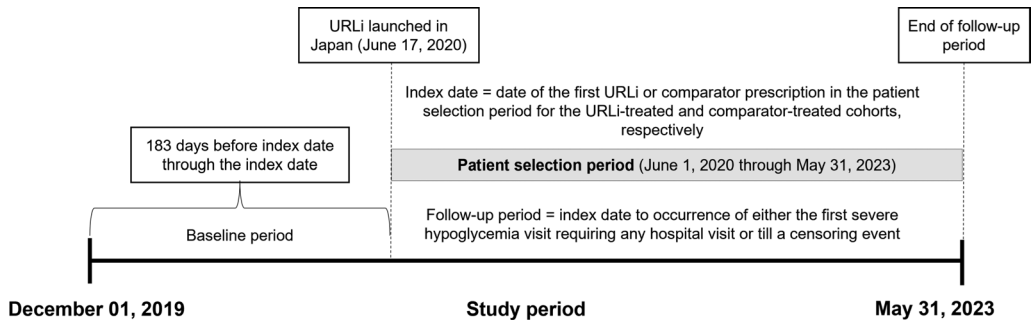

Fig. 1 Study design. *URLi* ultra-rapid lispro

the baseline period and those with a prescription claim of sulfonylureas or glinides on the index date. However, it included pregnant women previously diagnosed with diabetes.

The study also included these subgroups: patients using continuous subcutaneous insulin infusion (CSII), patients treated using combination therapy with long-acting insulin analogs (LAIA), and patients diagnosed with T1D or T2D. Additional inclusion criteria for the respective subgroups were presence of a procedural code for CSII on the index date, ≥ 1 prescription of an LAIA during the baseline period, and presence of a diagnosis code for T1D or T2D during the baseline period.

Except prescriptions of other RAIAs, all the other aforementioned criteria were applicable for the URLi-treated cohort of the descriptive analysis. In the comparative analysis, patients with a prescription of RAIAs during the baseline period were excluded from both the URLi-treated and comparator-treated cohorts, i.e., only new URLi or RAIA users were included.

Variables and Outcomes

Baseline characteristics including patient demographics, duration of diabetes, history of complications related to diabetes, comorbidities, and medication history were described separately for the descriptive and comparative analyses. Severe hypoglycemia requiring a hospital visit during the follow-up period was the outcome of interest. Severe hypoglycemia was identified using a validated algorithm [19] wherein possible hypoglycemia was defined as the presence (including suspected diagnoses) of ICD-10 diagnostic codes (E10.0, E11.0, E14.0, E15.0, E16.0, E16.1, and E16.2) and prescription of high-concentration (≥ 20% mass/volume) injectable glucose. The positive predictive value (PPV) of this algorithm was 78% and sensitivity was 39%.

Statistical Analysis

Baseline variables were described with descriptive statistics. For the calculation of incidence rate, the at-risk period was defined as days from the index date to the first severe hypoglycemia event requiring a hospital visit, or a censoring event. Incidence rate and 95% confidence interval (CI) of the first severe hypoglycemia event requiring a hospital visit among the URLi-treated cohort were calculated as the number of events per 100 person-years.

In the comparative analysis, propensity scores (PSs) were estimated using a logistic regression model predicting the probability of being included in the URLi-treated cohort rather than the comparator-treated cohort. The model included potential covariates, such as age categories (18–49, 50–64, 65–69, 70–74, 75–79, 80–84, and ≥ 85 years), sex, hospital size, history of severe hypoglycemia (event occurred and treated during the baseline period before the index date), Charlson Comorbidity Index (CCI) [20], history of complications related to diabetes (diabetic nephropathy, diabetic retinopathy, diabetic neuropathy); antidiabetic drugs other than insulin, and insulin use. These covariates were selected based on a priori clinical knowledge, previous research on association of covariates and severe hypoglycemia [21, 22], and availability in the MDV database. PS matching was performed with 1:5 (URLi-treated cohort:comparator-treated cohort) nearest-neighbor matching without replacement and with a maximum caliper width of 0.2 of the standard deviation (SD) of the logit of the PS. The balance of covariates between the two groups before and after matching was evaluated by the absolute standardized difference, with a value of < 0.1 considered as good balance.

Hazard ratios (HRs) and 95% CIs for the first severe hypoglycemia event requiring a hospital visit were calculated using Cox proportional hazards model for the data after PS matching.

Subgroup and Sensitivity Analyses

Descriptive analysis was performed in these subgroups: patients using CSII, patients treated using combination therapy with LAIAs, and patients diagnosed with T1D or T2D. On the other hand, subgroup comparative analysis was only performed among patients treated using combination therapy with LAIAs. Patients in this subgroup were matched using the PSs estimated

for the overall population by Wang et al. [23]. All other statistical methods for the subgroup comparative analyses were the same as the main analysis.

Supplementary material Table S1 describes the sensitivity analyses in detail. Both descriptive and comparative analysis were performed for the exposure time sensitivity analysis, LAIA sensitivity analysis, and outcome sensitivity analysis. Only descriptive analysis was performed for the URLi-treated cohort sensitivity analysis and only comparative analysis was performed for the comparator-treated cohort sensitivity analysis.

RESULTS

Descriptive Analyses

Patient Characteristics at Baseline

The final URLi-treated cohort for descriptive analysis included 17,838 patients (Fig. 2i) [mean (SD) age 65.9 (15.7) years and 58.3% male] (Table 1). Approximately 9.0% of the patients were ≥ 85 years old. The patients had diabetes for an average of 3.0 years, and the majority (75.7%) had T2D (Table 2). During the baseline period, 0.9% of the patients had a history of severe hypoglycemia requiring a hospital visit. Dipeptidyl peptidase-4 inhibitors (DPP4i; 24.9%) and sodium glucose cotransporter-2 inhibitors (SGLT2i; 19.2%) were the most common concomitant antidiabetic drugs. Many patients (63.8%) were prescribed an LAIA along with URLi. Very few patients (0.6%) received RAIAs via CSII. More than half the patients (57.9%) had a CCI ≥ 5 (Table 2).

Incidence Proportion and Incidence Rate of the First Severe Hypoglycemia Event

A total of 115 events of severe hypoglycemia were observed over a follow-up period of 6792 person-years in the URLi-treated cohort (n = 17,838). The incidence proportion of the

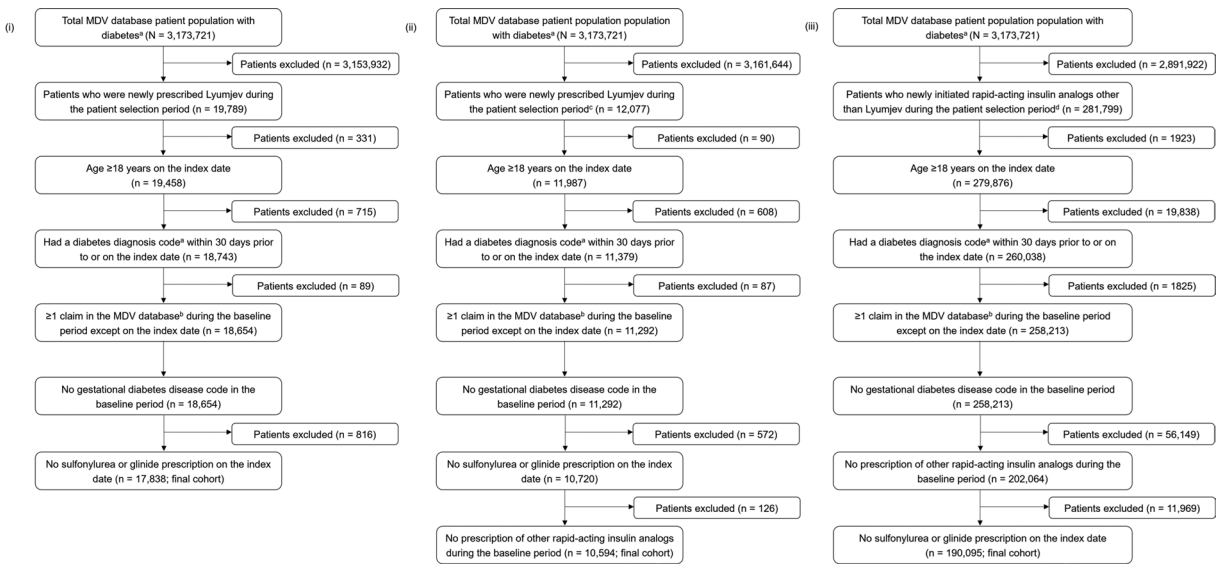

Fig. 2 Patient selection for the descriptive and comparative analyses: *i* Patient selection for the URLi-treated cohort (descriptive analysis), and *ii* and *iii* patient selection for the URLi-treated and comparator-treated cohorts, respectively (comparative analysis). *MDV* medical data vision.[a] International Classification of Diseases, 10th revision codes E10, E11, E14, O24.0, O24.1, and O24.9[b] Includes disease codes, prescription codes, procedure codes, or Diagnosis Procedure Combination data[c] Excluding patients who were prescribed rapid-acting insulin analogs other than URLi prior to the first prescription of URLi during the patient selection period[d] Excluding patients who were prescribed URLi prior to the first prescription of rapid-acting insulin analogs other than URLi during the patient selection period

Table 1 Demographic characteristics of the URLi-treated cohort at baseline (descriptive analysis)

	URLi-treated cohort (*n* = 17,838)
Age in years, mean (SD)	65.9 (15.7)
Age category, *n* (%)	
18–49	2928 (16.4)
50–64	4071 (22.8)
65–69	2010 (11.3)
70–74	2985 (16.7)
75–79	2427 (13.6)
80–84	1836 (10.3)
≥ 85	1581 (8.9)
Sex, *n* (%)	
Male	10,395 (58.3)
Female	7443 (41.7)
Height in cm, mean (SD)[a]	160.6 (9.9)
Weight in kg, mean (SD)[b]	61.7 (15.4)
BMI in kg/m^2, mean (SD)[c]	23.8 (4.8)
Hospital size (number of beds), *n* (%)	
< 200	1090 (6.1)
≥ 200, < 500	9293 (52.1)
≥ 500	7455 (41.8)

SD standard deviation, *URLi* ultra-rapid lispro

[a] *n* = 11,797

[b] *n* = 11,884

[c] *n* = 11,761

first severe hypoglycemia event requiring a hospital visit was 0.6% (95% CI 0.5, 0.8) and the incidence rate was 1.7 per 100 person-years (95% CI 0.7, 4.3).

Subgroup Analyses

In the CSII subgroup (*n* = 110), no patient experienced severe hypoglycemia requiring a hospital visit. Hence, the incidence proportion and rate were 0.0 and their 95% CI were not calculated (Table 3). In all other subgroups, the incidence proportion ranged from 0.4 to 1.5% and the incidence rate ranged from 1.2 to 2.5 per 100 person-years.

Sensitivity Analyses

In the exposure time sensitivity analysis, the incidence proportion was 0.6% (95% CI 0.5, 0.7) and the incidence rate was 2.1 per 100 person-years (95% CI 0.9, 5.0) (Supplementary material Table S2). In the LAIA sensitivity analysis, the incidence proportion was 0.9% (95% CI 0.7, 1.0) and the incidence rate was 1.9 per 100 person-years (95% CI 0.7, 5.2) (Supplementary material Table S3). Two hypoglycemia-identifying algorithms were assessed in the outcome sensitivity analysis. For algorithm 1, the incidence proportion was 7.6% (95% CI 7.2, 8.0) and the incidence rate was 21.5 per 100 person-years (95% CI 15.9, 29.1) (Supplementary material table S4). For algorithm 2, the incidence proportion was 3.4% (95% CI 3.1, 3.7) and the incidence rate was 9.4 per 100 person-years (95% CI 6.6, 13.3). In the URLi-treated cohort sensitivity analysis, the incidence proportion was 1.2% (95% CI 0.9, 1.5) and the incidence rate was 2.0 per 100 person-years (95% CI 0.6, 6.3) (Supplementary material Table S5).

Comparative Analyses

Patient Characteristics at Baseline

The unmatched URLi-treated cohort and comparator-treated cohort for comparative analysis included 10,594 and 190,095 patients, respectively (Fig. 2ii, iii). After PS matching, all the patient characteristics at baseline were well balanced between the cohorts, i.e., the absolute standardized difference was < 0.1 (Supplementary material Table S6).

Table 2 Clinical characteristics of the URLi-treated cohort at baseline (descriptive analysis)

	URLi-treated cohort (*n* = 17,838)
Diagnosis of diabetes, *n* (%)	
T1D	4339 (24.3)
T2D	13,499 (75.7)
Duration of diabetes in years, mean (SD)	3.0 (3.4)
History of severe hypoglycemia requiring a hospital visit, *n* (%)	152 (0.9)
History of complications related to diabetes, *n* (%)	
Diabetic nephropathy	3285 (18.4)
Diabetic retinopathy	2892 (16.2)
Diabetic neuropathy	1263 (7.1)
Duration of antidiabetic drugs in years, mean (SD)	2.6 (3.3)
Antidiabetic drugs other than insulin, *n* (%)	
DPP4i	4444 (24.9)
SGLT2i	3426 (19.2)
Biguanide	2982 (16.7)
Alpha glucosidase inhibitor	1482 (8.3)
GLP-1 RA	1474 (8.3)
Sulfonylurea	675 (3.8)
Glinide	669 (3.8)
Thiazolidine	372 (2.1)
Imeglimin	80 (0.4)
Duration of insulin use in years, mean (SD)	2.1 (3.0)
Insulin use, *n* (%)	
Rapid-acting insulin	17,838 (100)
Basal insulin	11,597 (65.0)
Regular insulin	4314 (24.2)
Biphasic insulin	669 (3.8)
Intermediate-acting insulin	105 (0.6)
Use of LAIAs, *n* (%)	11,387 (63.8)
Number of types of RAIAs used prior to index date, *n* (%)	
0	11,329 (63.5)
1	6200 (34.8)

Table 2 continued

	URLi-treated cohort (*n* = 17,838)
≥ 2	309 (1.7)
Administration route of rapid-acting insulin including URLi at index date, *n* (%)	
Injection	17,728 (99.4)
CSII	110 (0.6)
CGM use, *n* (%)	2674 (15.0)
Charlson Comorbidity Index, *n* (%)	
0	630 (3.5)
1–2	2684 (15.0)
3–4	4194 (23.5)
≥ 5	10,330 (57.9)
Comorbidities, *n* (%)	
Diabetes without chronic complication	8554 (48.0)
Diabetes with chronic complication	6980 (39.1)
Any malignancies	3874 (21.7)
Cerebrovascular disease	3598 (20.2)
Congestive heart failure	3052 (17.1)
Mild liver disease	2584 (14.5)
Peptic ulcer disease	2522 (14.1)
Chronic pulmonary disease	2035 (11.4)
Renal disease	1896 (10.6)
Peripheral vascular disease	1596 (8.9)
Myocardial infarction	904 (5.1)
Dementia	918 (5.1)
Metastatic solid tumor	830 (4.7)
Rheumatic disease	702 (3.9)
Liver dysfunction	273 (1.5)
Hemiplegia or paraplegia	179 (1.0)
AIDS/HIV	10 (0.1)

AIDS acquired immunodeficiency syndrome, *BMI* body mass index, *CGM* continuous glucose monitoring, *CSII* continuous subcutaneous insulin infusion, *DPP4i* dipeptidyl peptidase-4 inhibitor, *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *HIV* human immunodeficiency virus, *LAIA* long-acting insulin analog, *RAIA* rapid-acting insulin analog, *SD* standard deviation, *SGLT2i* sodium glucose cotransporter-2 inhibitor, *T1D* type 1 diabetes, *T2D* type 2 diabetes, *URLi* ultra-rapid lispro

Table 3 Incidence proportion and incidence rate of the first severe hypoglycemia event in the subgroups (descriptive analysis)

	CSII (*n* = 110)	Combination therapy with LAIAs (*n* = 11,387)	T1D (*n* = 4339)	T2D (*n* = 13,499)
Number of events	0	99	63	52
Follow-up period duration (person-years)	66	5080	2484	4308
Incidence proportion (95% CI) (%)	0.0 (–, –)	0.9 (0.7, 1.1)	1.5 (1.1, 1.9)	0.4 (0.3, 0.5)
Incidence rate (95% CI) (per 100 person-years)	0.0 (–, –)	1.9 (0.7, 5.2)	2.5 (0.5, 12.3)	1.2 (0.4, 4.0)

CI confidence interval, *CSII* continuous subcutaneous insulin infusion, *LAIA* long-acting insulin analog, *T1D* type 1 diabetes, *T2D* type 2 diabetes

Incidence proportion and Incidence Rate of the First Severe Hypoglycemia Event

Incidence proportion and incidence rate were numerically similar in the unmatched populations (Table 4). After PS matching, the incidence proportion of the first severe hypoglycemia event requiring a hospital visit was 0.3% (95% CI 0.2, 0.5) in the URLi-treated cohort and 0.5% (95% CI 0.4, 0.5) in the comparator-treated cohort. Incidence rate did not differ significantly between the URLi-treated and comparator-treated cohort (HR 0.8; 95% CI 0.5, 1.1; $p = 0.132$).

Subgroup Analysis

After PS matching, the incidence proportion among patients using combination therapy with LAIA was 0.4% (95% CI 0.3, 0.7) in the URLi-treated cohort (n = 5030) and 0.6% (95% CI 0.6, 0.8) in the comparator-treated cohort (*n* = 25,126) (Table 5). Incidence rate did not differ significantly between the URLi-treated and comparator-treated cohort (HR 0.8; 95% CI 0.5, 1.2; $p = 0.208$).

Table 4 Incidence proportion and incidence rate of the first severe hypoglycemia event (comparative analysis)

	Unmatched cohorts		Matched cohorts	
	URLi-treated (*n* = 10,594)	Comparator-treated (*n* = 190,095)	URLi-treated (*n* = 10,592)	Comparator-treated (*n* = 52,917)
Number of events	34	855	34	239
Follow-up period duration (person-years)	2614	58,174	2614	15,566
Incidence proportion (95% CI) (%)	0.3 (0.2, 0.5)	0.5 (0.4, 0.5)	0.3 (0.2, 0.5)	0.5 (0.4, 0.5)
Incidence rate (95% CI) (per 100 person-years)	1.3 (0.2, 7.9)	1.5 (1.0, 2.1)	1.3 (0.2, 7.9)	1.5 (0.8, 2.9)
HR (95% CI)	–	–	0.8 (0.5, 1.1)	
p value	–	–	0.132	

HR calculated using Cox proportional hazards model

CI confidence interval, *HR* hazard ratio

Table 5 Incidence proportion and incidence rate of the first severe hypoglycemia event among patients treated using combination therapy with long-acting insulin analogs (comparative analysis)

	Matched cohorts	
	URLi-treated (*n* = 5030)	Comparator-treated (n = 25,126)
Number of events	22	162
Follow-up period duration (person-years)	1268	7932
Incidence proportion (95% CI) (%)	0.4 (0.3, 0.7)	0.6 (0.6, 0.8)
Incidence rate (95% CI) (per 100 person-years)	1.7 (0.2, 13.4)	2.0 (1.1, 3.8)
HR (95% CI)	0.8 (0.5, 1.2)	–
p value	0.208	–

HR calculated using Cox proportional hazards model

CI confidence interval, *HR* hazard ratio

Sensitivity Analyses

After PS matching, the incidence proportion of the first severe hypoglycemia event in the URLi-treated cohort requiring a hospital visit ranged from 0.3% (95% CI 0.2, 0.4) in the exposure time sensitivity analysis to 6.4% (95% CI 6.0, 6.9) in the outcome sensitivity analysis (Supplementary material Tables S7–S9). The incidence proportion in the comparator-treated cohort ranged from 0.4% (95% CI 0.3, 0.4) in the exposure time sensitivity analysis to 6.7% (95% CI 6.5, 6.9) in the outcome sensitivity analysis. Incidence rate did not differ significantly between the URLi-treated and comparator-treated cohort in any sensitivity analysis.

In the comparator-treated cohort sensitivity analysis, the incidence proportion and incidence rate ranged from 0.4% (95% CI 0.4, 0.5) and 1.4 per 100 person-years (95% CI 0.9, 2.3) (both for insulin lispro), to 0.6% (95% CI 0.4, 1.0) and 2.1 per 100 person-years (95% CI 0.2, 18.3) (both for Fiasp®) (Supplementary material table S10).

DISCUSSION

URLi is beneficial for patients because of its faster onset and shorter duration of action compared with insulin lispro [3]. However, ultra-RAIAs such as URLi are more likely to cause severe hypoglycemia within 4 h of a meal [7, 9, 12, 24, 25]. Per the literature, other risk factors for severe hypoglycemia include old age, low glycated hemoglobin, medication of insulin and/or sulfonylureas, a prior history of severe hypoglycemia in patients with T2D, and comorbidities such as renal dysfunction, cardiovascular disorders, liver cirrhosis, and cancer [26–29]. Nevertheless, the current study's results did not show a statistically significant increase in the incidence and risk of the first severe hypoglycemia event requiring a hospital visit in URLi-treated patients, compared with a PS-matched cohort of other RAIA-treated patients (HR 0.8; 95% CI 0.5, 1.1; $p = 0.132$). The pattern of risk estimates in the subgroup and sensitivity analyses were generally consistent with the main analysis. In the descriptive analysis, the incidence rate of the main analysis (1.7 per 100 person-years) and the incidence rates of the outcome sensitivity analyses (algorithm 1: 21.5 per 100 person-years, and algorithm 2: 9.4 per 100 person-years) were quite different due to the varying algorithms used to identify severe hypoglycemia, as explained in the Methods and Supplementary material Table S1. The claims system in Japan has a 'suspected' flag to reimburse

insurance for diagnosis-related tests. Notably, both the main analysis' algorithm and outcome sensitivity analysis algorithm 1 included 'suspected diagnoses', while algorithm 2 excluded 'suspected diagnoses', i.e., it only included confirmed diagnoses. Moreover, the main analysis' algorithm assessed claims for both ICD-10 codes and prescription of ≥ 20% high-concentration glucose, while algorithm 1 assessed claims for either the ICD-10 code or prescription of ≥ 20% high-concentration glucose. Thus, algorithm 1 had high sensitivity but low PPV, resulting in the high incidence rate.

So far, only clinical trials have reported the incidence proportion and incidence rate of severe hypoglycemia among URLi-treated patients [7–13]. In these studies, the incidence proportion and incidence rate of severe hypoglycemia ranged from 4.6% to 7.3% and from 12.3 to 16.5 per 100 person-years in patients with T1D [7–10]. On the other hand, the incidence proportion (0.9%) and incidence rate (2.4 per 100 person-years) were numerically lower in patients with T2D [11, 12]. Consistent with the trials' results, incidence proportion and incidence rate in the T1D subgroup of the current study (1.5% and 2.5 per 100 person-years, respectively) were numerically higher than in the T2D subgroup (0.4% and 1.2 per 100 person-years, respectively). Incidence proportions and incidence rates were lower in the current study compared with the trials since this study only evaluated the first severe hypoglycemia event requiring a hospital visit. Therefore, patients with the first severe hypoglycemia event not requiring a hospital visit and patients with ≥ 2 severe hypoglycemia events were excluded.

Two real-world studies have reported the incidence of severe hypoglycemia in Swedish patients with T1D or T2D treated with insulin lispro, aspart, or glulisine [30, 31]. Lak et al. [30] reported the incidence rate of severe hypoglycemia in patients with T1D to be 0.4–0.9 per 100 person-years, which is numerically lower than that of URLi-treated patients with T1D in the current study (2.5 per 100 person-years). However, in Svensson et al.'s study [31], the incidence rate of severe hypoglycemia in patients with T2D (3.8–5.8 per 100 person-years) is numerically higher than that of URLi-treated patients with T2D in the current study (1.2 per 100 person-years). The difference in results between the studies in Sweden and our study could be attributed to the difference in patients' background, such as duration of diabetes and use of concomitant oral antidiabetic medications and insulins other than RAIA.

URLi has a faster onset and shorter duration of action compared with insulin lispro [3], leading to better management of post-prandial glucose excursions [7, 12]. Due to its fast onset of action, URLi can be administered at the start of a meal or within 20 min after starting a meal instead of several minutes before the meal [2, 32]. Patients using continuous glucose monitoring (CGM) can view the real-time glycemic changes, fine-tune the dose, and administer correction boluses when required [3, 33]. In fact, in the phase 3b PRONTO-Time in Range study, Bailey et al. [34] used CGM to monitor post-URLi glycemic changes and titrate insulin dosage to improve glycemic control. These advantages of URLi are carried over to the real world, as Japanese patients with diabetes reported greater treatment satisfaction with new RAIAs such as URLi over conventional RAIAs [35].

Strengths and Limitations

A major strength of this study is its novelty, as it is the first study to generate evidence on the incidence of severe hypoglycemia in patients with diabetes who were treated with URLi in the real-world/routine care setting. Furthermore, this study evaluated outcomes in various subgroups which represent the real-world treatment of diabetes. However, this study has several limitations. The MDV database includes data for patients treated in acute care hospitals and not for those treated in primary care or non-participating hospitals. This may cause underestimation of the incidence of severe hypoglycemia in Japan, and impact generalizability of the study findings to the overall population with diabetes. The length of the patient's clinical and treatment history in claims databases are usually shorter than that of clinical trials because the databases measure these variables only after the patient joins the database [36]. Additionally, since the MDV database sources information

from hospital-based claims data, clinical information from medical facilities, other than the acute care hospitals where patients were treated with URLi or other RAIAs, was unavailable. Thus, information about patients' baseline characteristics may have been missed. Due to the limitation of accuracy regarding patient baseline characteristics, PS might have been misestimated, which may lead to bias in the analysis results. Body mass index (BMI) data were only available for patients with a history of hospital admission. Hence, BMI was not considered as a covariate for PS matching in the comparative analysis to avoid selection bias. However, there was no confounding caused by BMI since it was balanced between the cohorts after PS matching. The MDV database does not record data on insulin prescription supply, alcohol use, and physical activity level. To address unavailability of insulin prescription supply, this study used two approaches to determine exposure time. In the main analysis, exposure was assumed until the severe hypoglycemia event or censoring event occurred, and in the sensitivity analysis a 90-day treatment supply, i.e., exposure, was considered. The patient selection period coincided with the study period end to maximize patient enrolment, resulting in limited follow-up time for patients who entered the study just before its end. Although the study used a Japan-specific validated algorithm to identify severe hypoglycemia with a sensitivity of 39% and PPV of 78% [19], it is possible to miss some claims that are beyond the algorithm's sensitivity and PPV limit. Considering these limitations, this study's findings should be interpreted with caution.

CONCLUSION

No evidence in this study indicated a higher incidence and risk of the first severe hypoglycemia event requiring a hospital visit in real-world URLi-treated Japanese patients with diabetes, compared with PS-matched patients treated with other RAIAs.

ACKNOWLEDGEMENTS

Medical Writing, Editorial, and Other Assistance. Leo J. Philip Tharappel of Eli Lilly Services India Private Limited, Bengaluru, India provided medical writing and editorial support, which was funded by Eli Lilly Japan K.K.

Author Contributions. All authors (Seiko Mizuno, Machiko Minatoya, Satoshi Osaga, Rina Chin, Makoto Imori) contributed to the study conception, design, analysis, and interpretation. Seiko Mizuno drafted the manuscript, and all authors reviewed the drafts. All authors read and approved the final manuscript.

Funding. Eli Lilly Japan K.K funded this study and provided the rapid access and open access fees.

Data Availability. The datasets generated and/or analyzed during the current study are available at Eli Lilly Japan K.K on reasonable request.

Declarations

Conflict of Interest. All authors (Seiko Mizuno, Machiko Minatoya, Satoshi Osaga, Rina Chin, Makoto Imori) are employees of Eli Lilly Japan K.K. and are minor stockholders of Eli Lilly and Company.

Ethical Approval. This study was conducted in accordance with ethical principles originating from the Declaration of Helsinki of 1964 and its later amendments and that were consistent with Good Pharmacoepidemiology Practices. This study used retrospective de-identified data so ethical review and informed consent were not required, consistent with the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects. Data were purchased from MDV after obtaining the necessary permissions.

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