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ORIGINAL ARTICLE

Incidence rate and patient characteristics of severe hypoglycemia in treated type 2 diabetes mellitus patients in Japan: Retrospective Diagnosis Procedure Combination database analysis

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ABSTRACT

Aims/Introduction: To evaluate the incidence rate of and identify factors associated with severe hypoglycemic episodes in patients with treated type 2 diabetes mellitus.

Materials and Methods: Using Diagnosis Procedure Combination hospital-based medical database, we carried out a retrospective cohort study to assess the incidence rate of severe hypoglycemia in treated type 2 diabetes mellitus patients. We evaluated the associations between severe hypoglycemia and age, sex, complications, and current use of insulin or sulfonylurea (SU) in a nested case–control study.

Results: Of 166,806 eligible patients, 1,242 had episodes of severe hypoglycemia during the observational period. The incidence rate of the first hypoglycemic events was 3.70/1,000 patient years. Based on the nested case–control analysis, age was associated with hypoglycemic events with adjusted odds ratios (ORs) of 1.64 or 65–74-year-old patients and 3.79 for ≥75-year-old patients in comparison with 20–64-year-old patients. Comorbidities, such as cognitive impairment, cancer, macrovascular disease and diabetic complications (retinopathy, nephropathy and neuropathy), were associated with severe hypoglycemia, with adjusted ORs ranging from 1.25 to 3.80. Severe hypoglycemic events also increased in patients with current use of both SU and insulin, either SU or insulin, with adjusted ORs of 18.36, 6.31 or 14.07, respectively, compared with patients with other antihyperglycemic agents. In patients with an SU glimepiride, adjusted ORs increased dose-dependently from 3.65 (≤1 mg) to 13.34 (>2 mg).

Conclusions: The incidence rate of severe hypoglycemia in this cohort was 3.70/1,000 patient years. Age, cognitive impairment, cancer, diabetic complications, current use of insulin + SU and SU dosage were identified as risk factors for severe hypoglycemia.

INTRODUCTION

The number of patients with type 2 diabetes is increasing worldwide along with an increase in obesity rates, changes in lifestyle and an aging population[1]. In Japan, 15.5% of men and 9.8% of women are strongly suspected to have type 2 diabetes[2]. More importantly, the aging of patients with type 2 diabetes in Japan is remarkable compared with other countries. Among people aged >70 years, one-quarter of men and one-sixth of women are expected to have type 2 diabetes[2]. It is estimated that approximately two-thirds of type 2 diabetes patients are aged >65 years[2].

Although several clinical trials have shown that strict glycemic control reduces the risk of microvascular complications, such as diabetic nephropathy and retinopathy[3–5], hypoglycemia

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has been one of the clinical hurdles that limit medication options for patients with diabetes[3,5–8]. Treatment of type 2 diabetes patients has substantially advanced recently with the introduction of new medications. However, hypoglycemia has remained the most devastating side-effect.

Considering the heterogeneity of patients with diabetes and their diverse vulnerability to hypoglycemia, personalization of glycemic targets is necessary to optimize treatment in individual patients. The American Diabetes Association and the European Association for the Study of Diabetes published position statements that mention the patient-centered approach[9,10]. Japanese treatment guidelines for diabetes also recommend personalized diabetes management with individualized glycemic control targets to avoid hypoglycemia. Identification of risk factors for hypoglycemia could help physicians and patients select appropriate antidiabetic therapies and optimize glycemic control[11].

In particular, the vulnerability to hypoglycemia is substantially increased in elderly patients[12,13]; hence, avoiding hypoglycemia is an important consideration in choosing therapeutic agents and setting glycemic goals in this population. Given the risk, the American Diabetes Association, the American Geriatrics Society, the European Diabetes Working Party and the International Diabetes Federation have presented guidelines for elderly patients[14–17]. Subsequently, the joint committee of the Japan Diabetes Society and the Japan Geriatrics Society issued treatment guidance for elderly patients at the 59th Annual Meeting of the Japan Diabetes Society[18]. Given that hypoglycemia is a significant risk factor for dementia, treatment goals and medications are to be determined based on patient demographics, such as age, comorbidities, cognitive function and activities of daily living.

So far, there are limited large-scale epidemiological studies that have addressed severe hypoglycemic event rates in Japanese type 2 diabetes patients in real-world clinical settings. It has been shown that 0.36% of all emergency transportation resulted from severe hypoglycemic events in a cross-sectional study of 149 medical institutions[19]. The Nagano Study, a prospective cohort study of 390 patients with type 2 diabetes who were aged >65 years and receiving intensive antidiabetic treatments showed the incidence rate of severe hypoglycemia was 0.9 per 100 person-years[20]. An observational study[21] using a national inpatient database reviewed the 22.7 million discharge records in Japan, and estimated that approximately 20,000 diabetes patients were hospitalized for hypoglycemia annually in Japan. A claims database study[22] using the Japan Medical Data Center database of a larger population showed that incidence rates of overall hypoglycemia and hypoglycemia requiring hospitalization were 0.4 and 0.1 per 100 patient-years, respectively. However, patients included in the Japan Medical Data Center database were mostly aged <65 years, warranting further studies that include more elderly patients, who account for two-thirds of all patients with type 2 diabetes in Japan, and who are potentially at higher risk for hypoglycemia.

Preceding studies in Western populations led to the identification of several factors that are associated with increased risks of severe hypoglycemia, such as use of insulin and insulin secretagogues, age, cognitive impairment, diabetes complications, and prior hypoglycemic events[23–27]. However, it remains unclear whether these factors would apply to the Japanese population given differences in the underlying demographics, epidemiology and pathophysiology, as well as medications (e.g., treatment patterns, doses of drugs etc.).

In the present study, we evaluated the incidence rate and associated factors of severe hypoglycemia in type 2 diabetes patients receiving drug treatment using the Diagnosis Procedure Combination (DPC) hospital-based medical database in Japan provided by Medical Data Vision Co., Ltd (Tokyo, Japan; MDV).

METHODS

Data source

A hospital-based composite database constructed by Medical Data Vision Co., Ltd. was used in the present study. Detailed information about this database is described in previous literature[27]. In short, this commercially available database contains anonymous information from health insurance claims, administrative data and laboratory values stored in hospital electronic records since April 2008, covering approximately 10.5 million patients and 11% of DPC hospitals throughout Japan, as of May 2015. Age and sex distributions of the patients in the database are similar to that of national patient statistics in Japan[28].

This database has been used for several epidemiological studies in Japan including the study showing that the risk of acute pancreatitis is increased in Japanese patients with type 2 diabetes[29].

Study design and Population

We carried out two types of studies: (i) a retrospective cohort study to evaluate the incidence rate of severe hypoglycemia during outpatient treatment; and (ii) a nested case–control study to identify associations between severe hypoglycemia and age, sex, disease-specific complications, and medication use.

The study population encompassed all patients in the database who were prescribed any antihyperglycemic agents (AHAs; Table S1) between 1 April 2008 and 30 September 2014. Eligible patients had a diagnosis of diabetes mellitus (International Classification of Diseases-10: E11 or E14) during the study period and were aged >20 years at the first prescription of any AHAs. Patients who visited the hospitals on a regular basis for >6 months (<90-day mean outpatient visit intervals) were included. We excluded patients who had records of type 1 diabetes (E10 or E100–E109), gestational diabetes (O24.4 or O24.9), secondary diabetes diagnosis (E12 or E13) or were pregnant (O00-O99) during the study period. Patients with a diagnosis of seizure (epilepsy G400–G409) or unspecified convulsions (R56.9) without a diagnosis of hypoglycemia (E16.0,

E16.1 and E16.2, E11.0, E14.0, E15) on the same day were also excluded. The observation period was defined as the period between the index date and the last outpatient visit. Dates of hospital admission and discharge were included, but any inpatient periods were excluded from the observation period. If there was a period without an AHA prescription >30 days, the observation period terminated on the 30th day after the last prescription day.

Disease definition

Disease criteria were defined according to the International Classification of Diseases-10. We defined severe hypoglycemia as hypoglycemic coma (E11.0, E14.0, E15); hypoglycemic seizure (patients who have a seizure [epilepsy G400-G409] and unspecified convulsions [R56.9]) and hypoglycemia [E16.0, E16.1, E16.2, E11.0, E14.0, E15] on the same day); hospital admission for hypoglycemia; or emergency room visit for hypoglycemia (Table S2).

Medical history of complications was defined as shown in Table S3. Baseline complications were defined as complications diagnosed between the beginning of the study period and 6 months after the index date.

Statistical analysis

Cohort study

The incidence rate of the first recorded episode of severe hypoglycemia per 10,000 patient-years was calculated and assessed with 95% confidence intervals (CI). All eligible patients were followed from the index date until they developed severe hypoglycemia, died, left the medical practice or reached the end of the study period, whichever came earliest. Incidence rates in person-years were estimated as the number of events of severe hypoglycemia divided by the total follow-up period.

Patients were stratified by age (20–64, 65–74, ≥75 years), sex, complications (with or without cancer, cognitive impairment, macrovascular disease, retinopathy, nephropathy or neuropathy) and medication (with or without insulin or sulfonylurea [SU]), and incidence rates of severe hypoglycemia in each group were calculated. With regard to stratification by medication use, incidence rates in person-years were estimated as the number of events of severe hypoglycemia during treatment with each drug divided by the cumulative treatment period with that drug.

Nested case–Control study

Cases were defined as episodes of severe hypoglycemia recorded for the first time during the study periods. For each case of severe hypoglycemia, 10 controls without severe hypoglycemia were identified from the study population. The number of controls was determined on the basis of a previous study[27]. Controls were randomly selected from patients whose index date was within the same month as the case patients' index date, considering the change in the treatment pattern during the study period. Odds ratios for severe hypoglycemia were assessed in association with predefined factors: age, sex, complications (cancer, cognitive impairment, macrovascular disease, retinopathy, nephropathy and neuropathy) and current medications (insulin + SU, insulin alone, SU alone or other AHAs). Current medication was defined as the last prescription of any AHA before the event. We assessed odds ratios for severe hypoglycemia in association with these potential risk factors in a stratified analysis.

In the nested case–control analysis, conditional logistic regression analyses were carried out to calculate ORs with 95% CIs and *P*-values. A two-sided *P*-value of <0.05 was considered to be statistically significant. ORs were adjusted for potential risk factors: age, sex, complications (macrovascular disease, cognitive impairment, retinopathy, nephropathy and neuropathy) and medication (insulin + SU, insulin alone, SU alone and other AHAs). For the multivariate conditional logistic regression analysis, a variable selection procedure (i.e., backward elimination) was used to find the best subset of potential risk factors for severe hypoglycemia. Analyses were carried out using SAS statistical software, version 9.2 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Baseline patient characteristics

During the study period 9,401,144 patients were identified in the database. Among 292,929 patients who had at least one prescription for any AHA, 166,806 patients were eligible for this study (Figure 1). The average age was 66.2 ± 11.8 years, 62.1% were men and the average observation period was 737.4 ± 482.1 days. Of the total eligible patients, insulin users, SU users and patients who did not use SU or insulin accounted for 22.2, 37.9 and 42.3%, respectively, according to analysis of their initial prescriptions (Table 1). Medication patterns and changes during the observation period are shown in Table 2. Most of the patients seemed to stay on the same category of medication; however, prescriptions with both an SU and insulin tended to be shifted to other medication categories more frequently compared with the other categories.

Cohort study

The numbers of first and total episodes of severe hypoglycemia during the observation period were 1,242 and 1,397, respectively. The incidence rate of first hypoglycemic events was 3.70 per 1,000 patient-years (95% CI: 3.50–3.91). The incidence rates in patients stratified by age (20–64, 65–74 and ≥75 years) were 1.77, 3.37 and 7.59 per 1,000 patient-years, respectively. Hypoglycemic events were increased in patients with diabetic comorbidities, as well as in those with non-diabetic comorbidities, such as cognitive impairment (Table 3). The Kaplan–Meier curve of hypoglycemic episodes showed that the incidence rate of severe hypoglycemia increased in a linear fashion during the observation period, with the highest rate in patients aged ≥75 years (Figure 2).

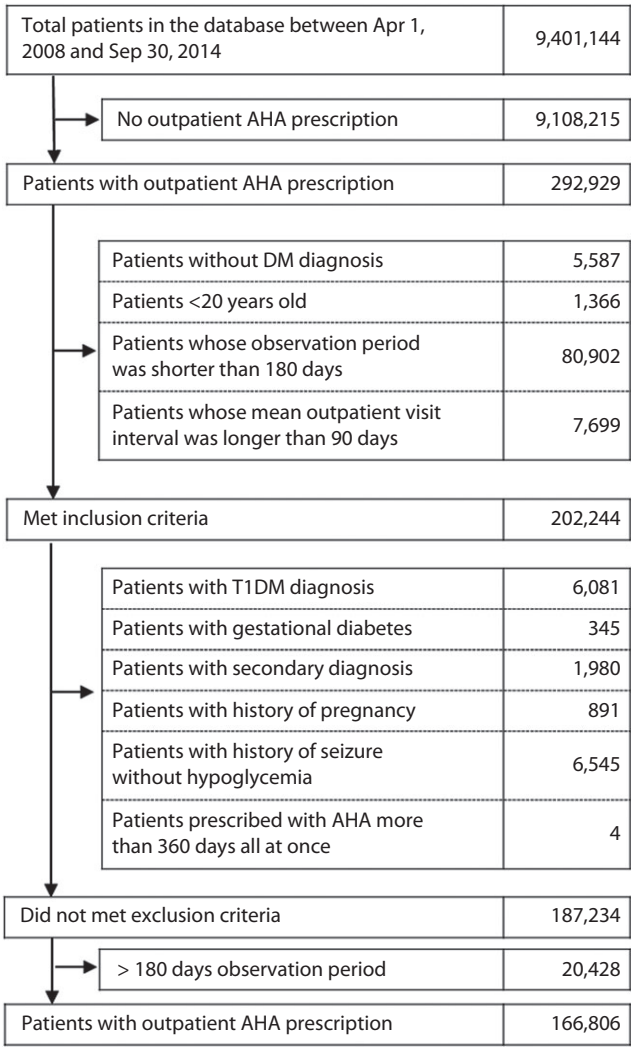

Figure 1 | Flow diagram summarizing patient selection criteria for cohort study. AHA, antihyperglycemic agents; DM, diabetes mellitus; T1DM, type 1 diabetes mellitus.

Table 1 | Baseline characteristics of the study population

No. patients	166,806
Age (years)	
Mean	66.2
SD	11.8
20–64	69,368 (41.6%)
65–74	54,967 (33.0%)
≥75	42,471 (25.5%)
Sex	
Male	103,553 (62.1%)
Female	63,253 (37.9%)
History	
Cancer	22,723 (13.6%)
Cognitive impairment	1,770 (1.1%)
Macrovascular disease	64,813 (38.9%)
Diabetic complications	66,240 (39.7%)
Diabetic retinopathy	35,050 (21.0%)
Diabetic nephropathy	30,775 (18.4%)
Diabetic neuropathy	21,396 (12.8%)
First prescribed medication	
SU only	15,925 (9.5%)
Insulin only	19,510 (11.7%)
Other AHAs only	70,629 (42.3%)
SU + insulin	978 (0.6%)
SU + other AHAs	43,265 (25.9%)
Insulin + other AHAs	13,500 (8.1%)
SU + insulin + other AHAs	2,999 (1.8%)
Observation period, days (mean ± SD)	737.4 ±482.1
Mean outpatient interval, days (mean ± SD)	33.65 ±17.53

First prescribed medication: first prescription found in the observation period; age: age at first prescription of antihyperglycemic agents (AHAs; including metformin, α-glycosidase inhibitors, dipeptidyl peptidase-4 inhibitors, sodium–glucose cotransporter-2 inhibitors, thiazolidinediones, glinides or glucagon-like peptide-1 receptor agonists). SD, standard deviation; SU, sulfonylurea.

Nested-case Control study

During the study period, 12,420 controls for the 1,242 case patients; that is, 10 controls for each case were identified (Figure 3). The average ages of patients and controls were 74.3 ± 10.5 and 66.5 ± 11.7, respectively (Table 4). Multivariate model analysis showed that patient age, history of cancer, cognitive impairment, macrovascular disease, retinopathy, nephropathy, neuropathy, current use of SU + insulin, SU alone, insulin alone and no AHAs were associated with severe hypoglycemic events (Table 4). Calculated by multivariate model analysis with backward elimination, relative risk estimates of severe hypoglycemia increased in patients who were aged 65–74 or ≥75 years in comparison with patients aged 20–64 years, with adjusted ORs of 1.64 (95% CI: 1.36–1.98) and 3.79 (95% CI: 3.17–4.53), respectively. Regarding sex, there was no significant difference in episodes of severe hypoglycemia between men and women. Medical history of cognitive impairment showed a higher adjusted OR (OR 3.80, 95% CI: 2.76–5.23) compared with a history of cancer (OR 1.77, 95% CI: 1.51–2.07), macrovascular disease (OR 1.45, 95% CI: 1.27–1.65), diabetic retinopathy (OR 1.37, 95% CI: 1.19–1.58), diabetic nephropathy (OR 2.00, 95% CI: 1.74–2.30) and neuropathy (OR 1.25, 95% CI: 1.07–1.46). Severe hypoglycemic events increased in patients with current use of both SU and insulin, as well as in those treated with SU or insulin alone in comparison with patients treated with other AHAs, with adjusted ORs of 18.36 (95% CI: 13.07–25.78), 6.31 (95% CI: 4.83–8.24) and 14.07 (95% CI: 10.79–18.36), respectively. Among 1,242 episodes of severe hypoglycemia, 45 were observed beyond the period covered by the last prescription or without any records of drug prescription. These were categorized into the 'No AHAs' group, because the association between the prescribed medication and the events in these patients was unclear. The adjusted OR for severe

Table 2 | Change in antihyperglycemic agent medications during the observation period

	No. patients	First prescribed medication			
		SU +Insulin +Other AHAs +/–	SU +Insulin –Other AHAs +/–	SU –Insulin +Other AHAs +/–	SU –Insulin –Other AHAs +/–
All	166,806	3,973	59,173	33,014	70,646
First prescribed medication (No. patients)					
SU only	15,925 (9.5%)	–	15,925 (26.9%)	–	–
Insulin only	19,510 (11.7%)	–	–	19,510 (59.1%)	–
Other AHAs only	70,629 (42.3%)	–	–	–	70,629 (100.0%)
SU + insulin	978 (0.6%)	978 (24.6%)	–	–	–
SU + other AHAs	43,265 (25.9%)	–	43,265 (73.1%)	–	–
Insulin + other AHAs	13,500 (8.1%)	–	–	13,500 (40.9%)	–
SU + insulin + other AHAs	2,999 (1.8%)	2,999 (75.4%)	–	–	–
Medication throughout the observation period (patient-years)					
SU only	24,300.1 (7.2%)	40.1 (0.5%)	23,233.8 (17.7%)	111.4 (0.2%)	914.8 (0.7%)
Insulin only	36,923.0 (11.0%)	723.9 (8.4%)	1,339.7 (1.0%)	34,009.9 (49.6%)	849.6 (0.7%)
Other AHAs only	124,882.2 (37.1%)	162.7 (1.9%)	11,296.2 (8.6%)	2,874.4 (4.2%)	110,548.9 (85.9%)
SU + insulin	1,845.7 (0.5%)	1,223.6 (14.1%)	356.2 (0.3%)	230.3 (0.3%)	35.6 (0.0%)
SU + other AHAs	97,830.7 (29.0%)	434.0 (5.0%)	86,959.9 (66.4%)	1,000.6 (1.5%)	9,436.1 (7.3%)
Insulin + other AHAs	34,555.1 (10.3%)	1,148.2 (13.3%)	2,041.9 (1.6%)	28,873.4 (42.1%)	2,491.5 (1.9%)
SU + insulin + other AHAs	8,237.9 (2.4%)	4,861.1 (56.1%)	2,280.2 (1.7%)	807.1 (1.2%)	289.5 (0.2%)
No AHAs	8,408.4 (2.5%)	65.4 (0.8%)	3,486.4 (2.7%)	677.4 (1.0%)	4,179.2 (3.2%)
Period in which patients stayed in the same medication /observation period		70.2%	84.1%	91.7%	85.9%

AHAs, antihyperglycemic agents (including metformin, α-glycosidase inhibitors, dipeptidyl peptidase-4 inhibitors, sodium–glucose cotransporter-2 inhibitors, thiazolidinediones, glinides or glucagon-like peptide-1 receptor agonists); SU, sulfonylurea.

Table 3 | Incidence rates of severe hypoglycemia

Variables	No. patients	Total person years	No. episodes	Incidence rate (per 1,000 person-years)	
				Point estimate	95% CI
All	166,806	335,753	1,242 (0.74%)	3.70	(3.50–3.91)
Age (years)					
20–64	69,368	141,793	251 (0.36%)	1.77	(1.56–2.00)
65–74	54,967	114,126	385 (0.70%)	3.37	(3.05–3.73)
≥75	42,471	79,834	606 (1.43%)	7.59	(7.01–8.22)
Sex					
Male	103,553	206,430	726 (0.70%)	3.52	(3.27–3.78)
Female	63,253	129,323	516 (0.82%)	3.99	(3.66–4.35)
Comorbidities					
Without cancer	144,083	295,052	997 (0.69%)	3.38	(3.18–3.60)
With cancer	22,723	40,702	245 (1.08%)	6.02	(5.31–6.82)
Without cognitive impairment	165,036	332,862	1,203 (0.73%)	3.61	(3.42–3.82)
With cognitive impairment	1,770	2,892	39 (2.20%)	13.49	(9.85–18.46)
Without macrovascular disease	101,993	205,023	615 (0.60%)	3.00	(2.77–3.25)
With macrovascular disease	64,813	130,730	627 (0.97%)	4.80	(4.44–5.19)
Without diabetic comorbidity	100,566	200,974	522 (0.52%)	2.60	(2.38–2.83)
With diabetic comorbidity	66,240	134,779	720 (1.09%)	5.34	(4.97–5.75)
Without diabetic retinopathy	131,756	263,877	870 (0.66%)	3.30	(3.09–3.52)
With diabetic retinopathy	35,050	71,876	372 (1.06%)	5.18	(4.68–5.73)
Without diabetic nephropathy	136,031	275,171	844 (0.62%)	3.07	(2.87–3.28)
With diabetic nephropathy	30,775	60,582	398 (1.29%)	6.57	(5.95–7.25)
Without diabetic neuropathy	145,410	290,863	962 (0.66%)	3.31	(3.10–3.52)
With diabetic neuropathy	21,396	44,890	280 (1.31%)	6.24	(5.55–7.01)
AHAs[†]					
SU+, insulin+, other AHAs+/–	14,756	10,050	110 (0.75%)	10.95	(9.08–13.19)
SU+, insulin–, other AHAs+/–	69,810	121,873	395 (0.57%)	3.24	(2.94–3.58)
SU–, insulin +, other AHAs+/–	49,394	70,856	624 (1.26%)	8.81	(8.14–9.53)
SU–, insulin–, other AHAs+	92,874	124,600	68 (0.07%)	0.55	(0.43–0.69)
No AHAs	101,588	8,375	45 (0.04%)	5.37	(4.01–7.20)

[†]Antihyperglycemic agents (AHAs; including metformin, α-glycosidase inhibitors, dipeptidyl peptidase-4 inhibitors, sodium–glucose cotransporter-2 inhibitors, thiazolidinediones, glinides, or glucagon-like peptide-1 receptor agonists) during the observation period: if patients changed AHAs during the observation period, they were counted in both initial medication and new medication in terms of numbers of patients. CI, confidence interval; SU, sulfonylurea.

hypoglycemia in this category was 17.59 (95% CI: 11.38–27.20).

Subsequently, we evaluated the association between the SU dosage and severe hypoglycemia. We evaluated SU dose dependency among patients without insulin, because dose self-adjustment of insulin is generally carried out along with self-monitoring of blood glucose in these patients, and consequently, insulin might have masked the impact of an SU dose. Among patients without insulin, the majority of the patients treated with SUs (75%) were given glimepiride; hence, we focused on the dosage of glimepiride. As shown in Table 5, adjusted ORs were higher in patients with 1 mg < glimepiride ≤ 2 mg and >2 mg glimepiride compared with those treated with ≤1 mg glimepiride, with adjusted ORs of 13.34 (95% CI: 9.62–18.50), 14.15 (95% CI: 10.84–18.47) and 6.69 (95% CI: 4.72–9.48), respectively.

DISCUSSION

In the present study 1,242 severe hypoglycemic episodes were detected using the DPC hospital-based MDV database. To our knowledge, this study evaluated the largest number of hypoglycemic events in Japan[20,22,30,31]. We focused on the evaluation of: (i) the incidence rate of severe hypoglycemia; and (ii) patient- and drug-related factors associated with severe hypoglycemia in a nested case–control cohort. In the previous single-hospital study, 135 severe hypoglycemic events were detected, and the association between severe hypoglycemia and SU and insulin use was shown; however, the association between severe hypoglycemia and patient characteristics was not analyzed[8].

The incidence rate of severe hypoglycemia calculated in the present study was 3.70 per 1,000 patient-years (95% CI: 3.50–3.91) in patients with type 2 diabetes treated with AHAs in the

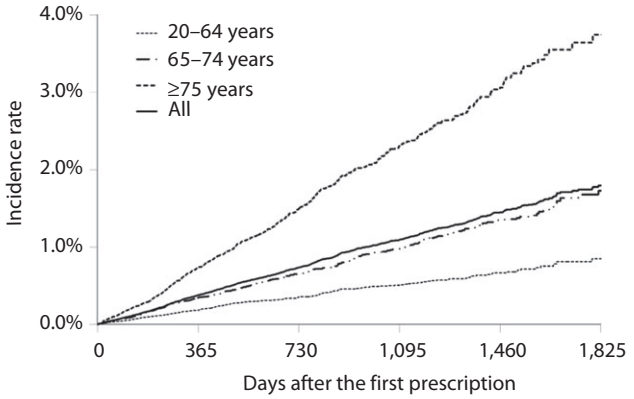

Figure 2 | Kaplan–Meier estimates of hypoglycemia episodes in the antihyperglycemic agents (AHA)-treated type 2 diabetes population. Patients are stratified into three groups by age at the first prescription.

database. The previous cohort studies reported incidence rates of (severe) hypoglycemia in type 2 diabetes patients ranging from 0.75 to 33.8 per 1,000 patient-years[20,22,24,27,32–36]. Those studies imply that incidence rates are affected by various factors including the definition of severe hypoglycemia and enrolled patient characteristics. Because the current study included patients visiting DPC hospitals, it is speculated that patients with more severe comorbidities were accumulated in this study compared with the general type 2 diabetes population. This might explain relatively higher incidence rates detected in the present study than those in other studies that included newly diagnosed or younger patients[3,22]. Even with the higher incidence rate, there is a possibility that the incidence rate was underestimated in the present study, as hypoglycemic events could not be captured in situations where the patients utilized other hospitals for care. In addition, available data regarding emergency room visits were limited, and patients were captured only if their treatment required additional fees at the emergency room; therefore, some patients who visited emergency rooms were not captured.

The major predictors of severe hypoglycemic events identified in the present study were age and current use of insulin and/or SU, which have also been reported as risk factors for hypoglycemia in previous studies[24–28,32–36]. In Japan, an investigational study[13] carried out by the Japan Diabetes Society

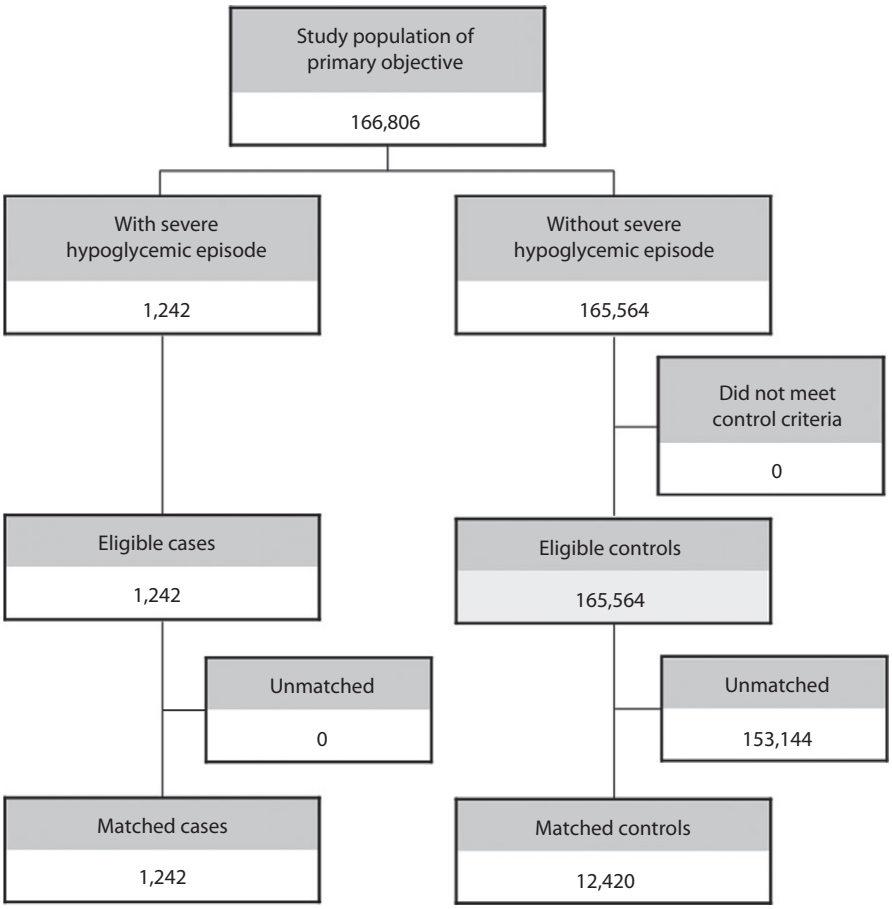

Figure 3 | Flow diagram of patient selection for the nested case–control study.

Table 4 | Crude and adjusted odds ratios of severe hypoglycemia associated with the potential risk factors

Variables	Category	Case *n* = 1,242	Controls *n* = 12,420	Crude odds ratio			Adjusted odds ratio†		
				Point estimate	95% CI	*P*-value	Point estimate	95% CI	*P*-value
Age (years)	Mean ± SD	74.3 ± 10.5	66.5 ± 11.7						
	20–64	213 (17.1%)	4,935 (39.7%)	Reference	–	[<0.001]‡	Reference	–	[<0.001]‡
	65–74	351 (28.3%)	4,248 (34.2%)	1.917	(1.608–2.284)	<0.001	1.644	(1.363–1.982)	<0.001
	≥75	678 (54.6%)	3,237 (26.1%)	4.909	(4.178–5.768)	<0.001	3.787	(3.169–4.526)	<0.001
Sex	Male	726 (58.5%)	7,658 (61.7%)	Reference	–	–			
	Female	516 (41.5%)	4,762 (38.3%)	1.145	(1.016–1.289)	0.026			
History									
Without cancer		928 (74.7%)	10,627 (85.6%)	Reference	–	–	Reference	–	–
With cancer		314 (25.3%)	1,793 (14.4%)	2.015	(1.755–2.313)	<0.001	1.767	(1.508–2.071)	<0.001
Without cognitive impairment		1,147 (92.4%)	12,280 (98.9%)	Reference	–	–	Reference	–	–
With cognitive impairment		95 (7.6%)	140 (1.1%)	7.392	(5.634–9.699)	<0.001	3.800	(2.761–5.228)	<0.001
Without macrovascular disease		526 (42.4%)	7,498 (60.4%)	Reference	–	–	Reference	–	–
With macrovascular disease		716 (57.6%)	4,922 (39.6%)	2.071	(1.840–2.331)	<0.001	1.447	(1.267–1.653)	<0.001
Without retinopathy		770 (62.0%)	9,539 (76.8%)	Reference	–	–	Reference	–	–
With retinopathy		472 (38.0%)	2,881 (23.2%)	2.041	(1.805–2.307)	<0.001	1.367	(1.186–1.575)	<0.001
Without nephropathy		727 (58.5%)	10,016 (80.6%)	Reference	–	–	Reference	–	–
With nephropathy		515 (41.5%)	2,404 (19.4%)	3.000	(2.653–3.392)	<0.001	1.997	(1.735–2.298)	<0.001
Without neuropathy		906 (72.9%)	10,701 (86.2%)	Reference	–	–	Reference	–	–
With neuropathy		336 (27.1%)	1,719 (13.8%)	2.304	(2.013–2.638)	<0.001	1.253	(1.073–1.463)	0.004
Current AHAs									
SU+, insulin+, Other AHAs+/–		110 (8.9%)	352 (2.8%)	23.607	(17.094–32.600)	<0.001	18.355	(13.067–25.784)	<0.001
SU+, insulin-, Other AHAs+/–		395 (31.8%)	4,162 (33.5%)	7.296	(5.615–9.481)	<0.001	6.312	(4.833–8.243)	<0.001
SU–, insulin +, Other AHAs+/–		624 (50.2%)	2,618 (21.1%)	18.205	(14.089–23.524)	<0.001	14.070	(10.783–18.359)	<0.001
SU–, insulin–, Other AHAs+		68 (5.5%)	5,111 (41.2%)	Reference	–	[<0.001]‡	Reference	–	[<0.001]‡
No AHAs		45 (3.6%)	177 (1.4%)	19.737	(13.112–29.710)	<0.001	17.594	(11.382–27.195)	<0.001

†Adjusted odds ratio adjusted for age, comorbidities, and current AHAs by multivariate conditional logistic regression model after backward elimination. ‡*P*-values with [ ] are for variables. *P*-values without [ ] are for categories compared with the reference category. Age, age at the first prescription of antihyperglycemic agents; CI, confidence interval; current AHAs, the last prescription of antihyperglycemic agents before the hypoglycemic episodes (if the hypoglycemic events occurred after the prescription period of the last prescription, patients were categorized into the 'No AHAs' group); other AHAs, antihyperglycemic agents including metformin, α-glycosidase inhibitors, dipeptidyl peptidase-4 inhibitors, sodium–glucose cotransporter-2 inhibitors, thiazolidinediones, glinides or glucagon-like peptide-1 receptor agonists; SD, standard deviation; SU, sulfonylurea.

Table 5 | Crude and adjusted odds ratios of severe hypoglycemia associated with potential risk factors: detailed analysis with glimepiride dosage

Variables	Category	Case n = 1,242	Controls n = 12,420	Crude odds ratio			Adjusted odds ratio†		
				Point estimate	95% CI	*P*-value	Point estimate	95% CI	*P*-value
Current AHAs									
SU+, insulin+; SU except glimepiride		27 (2.2%)	62 (0.5%)	35.129	(20.858–59.166)	<0.001	25.093	(14.390–43.756)	<0.001
SU+, insulin+; Glimepiride		83 (6.7%)	290 (2.3%)	21.627	(15.341–30.489)	<0.001	17.089	(11.885–24.572)	<0.001
SU+, insulin−; SU except glimepiride		98 (7.9%)	825 (6.6%)	9.429	(6.834–13.008)	<0.001	7.305	(5.244–10.176)	<0.001
SU+, insulin−; ≤1 mg glimepiride		107 (8.6%)	1,944 (15.7%)	4.204	(3.084–5.729)	<0.001	3.646	(2.655–5.006)	<0.001
SU+, insulin−; 1 mg < glimepiride ≤2 mg		77 (6.2%)	770 (6.2%)	7.671	(5.476–10.746)	<0.001	6.693	(4.723–9.483)	<0.001
SU+, insulin−; >2 mg glimepiride		113 (9.1%)	623 (5.0%)	14.342	(10.461–19.663)	<0.001	13.342	(9.624–18.497)	<0.001
SU−, insulin+		624 (50.2%)	2,618 (21.1%)	18.351	(14.194–23.726)	<0.001	14.149	(10.838–18.472)	<0.001
SU−, insulin−, other AHAs+		68 (5.5%)	5,111 (41.2%)	Reference	–	[<0.001]‡	Reference	–	[<0.001]‡
No AHAs		45 (3.6%)	177 (1.4%)	19.920	(13.223–30.010)	<0.001	18.097	(11.696–28.002)	<0.001

†Adjusted odds ratio adjusted for age, comorbidities and current antihyperglycemic agents (AHAs) by multivariate conditional logistic regression model after backward elimination. ‡*P*-values with [ ] are for variables. *P*-values without [ ] are for categories compared to the reference category. Age, age at the first prescription of antihyperglycemic agents; CI, confidence interval; Current AHAs, the last prescription of antihyperglycemic agents before the hypoglycemic episodes (if the hypoglycemic events occurred after the prescription period of the last prescription, patients are categorized into No AHAs. Except for the categories 'SU−, insulin−, other AHAs+' and 'No AHAs', patients with or without other AHAs are included); other AHAs, antihyperglycemic agents including metformin, α-glycosidase inhibitors, dipeptidyl peptidase-4 inhibitors, sodium–glucose cotransporter-2 inhibitors, thiazolidinediones, glinides or glucagon-like preptide-1 receptor agonists; SD, standard deviation; SU, sulfonylurea.

showed the most frequently administered AHAs in patients with severe hypoglycemic episodes were insulin (60.8%) and SUs (33.1%). Single-hospital studies also showed that hypoglycemia occurs more frequently in elderly patients and patients using insulin and SUs[30,31]; however, it remains uncertain whether SU dosage is associated with the frequency of hypoglycemic events. Recently, Ahren *et al.*[37] reported that patients treated with low-dose glimepiride (2 mg) developed more hypoglycemia than patients treated with high-dose glimepiride (6 mg) regardless of their glycemic control in a pooled analysis of randomized clinical trials in Europe. In the current study, ORs of severe hypoglycemia dose-dependently increased in glimepiride-treated patients without insulin. Possible explanations for the discrepancy between the two studies are: (i) the difference between the real-world clinical setting and well-controlled clinical trials; and (ii) the current study did not include the duration of type 2 diabetes as a potential risk factor, which might be correlated with the dosage of SUs. Over time, the glucose-lowering efficacy of AHAs might diminish as a result of the progressive nature of type 2 diabetes. Therefore, the SU dose might be higher in patients with a longer duration of type 2 diabetes. Because of the nature of the MDV database, the duration of type 2 diabetes was not included as a risk factor in the present study. In this study, the OR of hypoglycemia was higher in patients with SU, except glimepiride was 7.31 (95% CI: 5.24–10.18). Among those 98 patients with hypoglycemic events, 84 and 14 patients were prescribed glibenclamide and gliclazide, respectively, whereas 400 and 417 patients were prescribed glibenclamide and gliclazide, respectively, in the control group. As previous studies showed[38,39], this implies that glibenclamide could cause severe hypoglycemia more frequently than gliclazide.

Another prominent factor associated with severe hypoglycemia was a history of dementia. The complexity of type 2 diabetes treatment, such as the need for patients to comply with the medication regimen, and to be able to perceive hypoglycemia and express its occurrence, requires normal cognitive function. Therefore, it is assumed that decline of cognitive function might be a risk factor for adverse events, such as severe hypoglycemia. Post-hoc epidemiological analysis of the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and Action to Control Cardiovascular Risk in Diabetes (ACCORD) trials showed that poor cognitive function increases the risk for severe hypoglycemia[40,41]. One population-based prospective study[42] also showed that patients with dementia at baseline had a significantly higher risk for severe hypoglycemia than those who did not have dementia.

Cancer was also identified as a risk factor of severe hypoglycemia in the present study. Malnutrition and cachexia occur in cancer patients as a result of loss of appetite due to the cancer itself and to medications, including chemotherapy[43]. In patients with advanced cancer, hypoglycemia is also occasionally found[44]. Some specific organ cancers, including pancreas

and liver cancer, can also cause hypoglycemia[45]. In addition, it is speculated that changes in diabetes medications and more intensive treatment while undergoing cancer treatments, including chemotherapy and surgery, might increase rates of hypoglycemia.

We found that microvascular and macrovascular complications of diabetes were associated with severe hypoglycemia. We cannot exclude the possibility that diabetic complications might have reflected the severity and duration of diabetes in the present study, because the duration was not captured. Previous studies including randomized controlled trials evaluated those complications as risk factors for (severe) hypoglycemia, and some studies showed that they are moderate but significant risk factors, independent of duration of diabetes[8].

Patients who were not prescribed any AHAs in the database also had a high incidence rate of severe hypoglycemia in the present study. This might be due to the inclusion of patients who visited hospitals that prescribed the AHAs and were not tracked by the MDV database. Also, the administration period was defined as the period starting from the first day of the prescription and lasted for the number of days prescribed. It is speculated that patients who took previously prescribed AHAs beyond the prescription period and showed severe hypoglycemic symptoms were included in this segment.

The present study had some limitations. First, the MDV database is a hospital-based composite database; therefore, this study shares the essential limitations of hospital-based research. Patients might have been diagnosed with type 2 diabetes and prescribed AHAs at other hospitals before the index date, hence patients in the study were not limited to new users of AHAs. Second, patients might have visited other hospitals during the follow-up period when hypoglycemic events might have occurred. Third, the database likely reflects a more ill type 2 diabetes population with more comorbidities. In addition, the proportion of cancer patients might have been higher because >40% of the hospitals in the database were designated as cancer care hospitals. Fourth, possible confounders including duration of diabetes, glycated hemoglobin at the event, duration of insulin treatment, regional differences and so on remained unadjusted in the present study. Fifth, severe hypoglycemia, type 2 diabetes and its other complications were identified using International Classification of Diseases-10 codes in the database, and were not confirmed with either laboratory data or chart review.

The present study shows that age, insulin and/or SU use, and complications, including cognitive impairment, are major factors associated with severe hypoglycemia in Japan. These findings support treatment guidance for elderly patients in whom glycemic targets are determined by types of medications and health status, including cognitive function, to avoid severe hypoglycemic events.

The present study remains an exploratory analysis. Further studies are required to confirm these findings and evaluate the incidence rate of severe hypoglycemia generalizable to the type 2 diabetes patient population.

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YI, TK, MA and ST have disclosed that they are employed by MSD K.K., Tokyo, Japan, and own stock or stock options in Merck & Co., Inc., Kenilworth, NJ, USA. EO is an employee of AC Medical Inc., which was contracted by MSD K.K., Tokyo, Japan, to carry out the statistical analysis.

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SUPPORTING INFORMATION

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

Table S1 | Definitions of Anatomical Therapeutic Chemical (ATC) codes and antihyperglycemic agents.
Table S2 | Definition of emergency room visit.
Table S3 | Definition of comorbidities.