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ORIGINAL ARTICLE

Absolute risk of acute coronary syndrome after severe hypoglycemia: A population-based 2-year cohort study using the National Database in Japan

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ABSTRACT

Aims/Introduction: Although the epidemiological relationship between hypoglycemia and increased risk of acute coronary syndrome (ACS) has been well established, the time period for increased risk of ACS after a severe hypoglycemic episode remains unknown. The present study aimed to determine the ACS risk after a severe hypoglycemic episode.

Materials and Methods: We carried out a retrospective population-based cohort study based on national claims data in Japan. We retrieved data of diabetes patients aged ≥35 years collected from April 2014 to March 2016. The absolute risk of ACS was defined as the occurrence of an emergency percutaneous coronary intervention after a severe hypoglycemic episode.

Results: In total, data of 7,909,626 patients were included in the analysis. The absolute risk of ACS was 2.9 out of 1,000 person-years in all patients. ACS risk in patients with severe hypoglycemic episodes was 3.0 out of 1,000 person-years. Severe hypoglycemic episodes increased the absolute risk of ACS in patients aged ≥70 years, but not in patients aged <70 years. The absolute risk of ACS was 10.6 out of 1,000 person-years within 10 days of a severe hypoglycemic episode. There was a significant trend between shorter duration after an episode and higher ACS risk.

Conclusions: Severe hypoglycemia was associated with an increased risk of ACS in elderly diabetes patients. ACS risk increased with a shorter period after a severe hypoglycemic episode, suggesting that severe hypoglycemia leads to an increased risk of ACS in diabetes patients. These findings show that it is important to avoid severe hypoglycemia while treating diabetes, particularly in elderly patients.

INTRODUCTION

Studies have shown that severe hypoglycemia is associated with a higher risk of cardiovascular disease[1–6]. Previous randomized controlled trials reported that intensive glucose-lowering therapy increased all-cause mortality and cardiovascular risk in type 2 diabetes patients[3,7,8]. Because severe hypoglycemia caused by intensive diabetes therapy might result in increased risk of mortality and cardiovascular episodes, many guidelines for diabetes management have been revised to avoid hypoglycemia, particularly in high-risk patients[9–11]. However, it remains uncertain whether severe hypoglycemia is a major causal factor for cardiovascular episodes. Although experiencing severe hypoglycemia at any time has been shown to be a significant predictor of all-cause mortality[3], the time-course (the duration of a severe hypoglycemic episode required for an acute

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coronary syndrome [ACS] event to occur) for the absolute risk of ACS after a severe hypoglycemic episode remains unknown.

Hypoglycemia has been reported to be the most common adverse event related to the use of diabetes medication[12]. However, because of the low incidence of ACS events after severe hypoglycemic episodes recorded in previous studies, it has been difficult to examine the relationship between the two variables. The National Database of Health Insurance Claims and Specific Health Check-ups of Japan (NDB) is a comprehensive database of health insurance claims covered by the Japanese National Health Insurance system. The NDB is one of the world's largest health-related databases, and contains complete datasets of medical care received by insured inpatients and outpatients. By using the NDB datasets, we retrospectively selected a sample cohort of >100 million individuals with very small selection bias[13]. Using the NDB, we were able to include all patients with ACS who underwent emergency percutaneous coronary intervention (PCI). Absolute risk has important implications in both clinical and public health policy. However, it would be impossible to carry out a randomized controlled trial or prospective cohort study for an in-depth investigation of the role of a specific risk factor in the etiology of a disease, because such a study would be too large and expensive. The NDB has an extremely large study population that enabled us to observe a sufficient number of individuals with relatively rare conditions, such as ACS after a severe hypoglycemic episode. The present study aimed to calculate the risk of ACS with respect to time of occurrence after a severe hypoglycemic episode.

METHODS

Design

The present study was a population-based, retrospective cohort study carried out using the NDB dataset. This study was approved by the ethics committee of Nara Medical University (1123-2).

The study cohort comprised individuals enrolled in the NDB; all patient data were anonymized. Japan has a universal health coverage system, and the NDB includes all patients with any type of insurance program. The health data of approximately 2 million citizens on welfare are not recorded in the NDB, because they are not covered by any insurance program. In addition, foreigners who stay for <3 months in Japan are not included, because they are a heterogenic group that might confound the results of the present longitudinal study, and because they are not covered by medical insurance. The NDB data provided information on personal identifier (ID0 variable[13]), date, age group, sex, description of the procedures carried out, World Health Organization International Classification of Diseases (ICD-10) diagnosis codes, medical care received, medical examinations carried out that did not contain results and prescribed drugs, which were independent of the doctor's or patient's reports. Drug information included prescription amount, brand name, generic name, dosage and number of days prescribed.

We designed this cohort study such that data of diabetes patients aged ≥35 years collected between April 2014 and March 2016 were included in the analysis.

Diabetes patient definition

We defined diabetes patients as those who had any of the diagnosis codes associated with diabetes and as those who were prescribed diabetes medication at least once. The diagnosis and medicine codes are shown in Tables S1 and S2. We included all patients with any type of diabetes who fulfilled the aforementioned criteria. Some diagnosis codes from the NDB do not provide information about the types of diabetes. Accordingly, we could not recognize the type of diabetes in each case according to the diagnosis codes alone. In Japan, patients with type 1 diabetes can be distinguished from those without type 1 diabetes by using medical practice codes regarding self-monitoring of blood glucose, which is based on a diagnosis determined by physicians. In the present study, type 1 diabetes patients were defined as those diagnosed with diabetes who also had medical practice codes about self-monitoring of blood glucose of 114009910, 114010010, 114010110, 114010210, 114015510 and 114015610.

Definition of severe hypoglycemic episodes

Severe hypoglycemia is an episode in which a patient requires the assistance of another person to actively administer carbohydrates or glucagon or take other corrective actions[10]. According to the Japanese guidelines, patients brought to the hospital should be quickly treated by intravenous administration of 50% glucose[9]. It has been reported that most patients with severe hypoglycemic episodes are administered 50% glucose in the hospital[14]. Determining the date of hypoglycemia based only on the diagnosis codes might be inaccurate, because the onset time of hypoglycemia could differ by several days from the time patients are diagnosed accurately, as the diagnosis codes can be inputted immediately or after several days or weeks. Thus, to accurately elucidate the effect of treatment after a severe hypoglycemic episode, the day patients experienced hypoglycemia should be identified accurately. Therefore, in the present study, we defined patients with severe hypoglycemic episodes as those who had diagnosis codes of hypoglycemia (i.e., diagnosis codes were 2510003, 2512004, 8845065, 8845094, 8838076, 8830649, 8837872 and 8837871; ICD-10 codes were E15, E100, E110, E140, E160, E161 and E162) and were prescribed intravenous injections of 50% glucose (medicine codes were 620006649, 620002599, 640460006 and 643230048) on the same day.

Primary outcome

The primary outcome was the first occurrence of ACS requiring emergency PCI, including acute myocardial infarction and unstable angina pectoris. We defined emergency PCI for ACS as use of the following five medical procedure codes: 150375210, 150375310, 150374910, 150375010 and 160107550

(K546, K549 and K550, which are Japanese original codes). Because the end-point occurred only once, assumptions of statistical independence were not violated.

Prior use of drugs and prior diagnosis definition

We considered patients at risk of ACS who had been prescribed drugs as patients with prior use of drugs. The disease codes of the NDB have a major drawback in that they cannot distinguish between the codes given before the diagnosis and the codes given after the diagnosis. There are two possibilities for patients with disease name codes. One was actually diagnosed and the other was not actually diagnosed. To exclude the latter, we defined patients with prior diagnosis as the patients who already had the diagnosis code at the risk period and those who had the codes for more than 1 month.

Statistical analysis

We regarded diabetes patients as a population at risk of ACS from the first insurance use to the first occurrence of ACS or until the last insurance use during the study period. For patients who did not experience a severe hypoglycemic episode, person-time was calculated from the date of the first visit in the follow-up period until the first occurrence of ACS or until the last visit in the follow-up period. For patients with a severe hypoglycemic episode who were at risk for ACS, person-time was calculated from the date of the first hypoglycemic event until the first occurrence of ACS, the second hypoglycemic event or the last follow-up visit. We calculated the absolute risk of ACS in all diabetes patients and those who did or did not experience a severe hypoglycemic episode. The absolute risks of ACS were calculated according to sex and median age (<70 or ≥70 years). We also calculated the absolute risk of ACS within each day category (1–10 days, 11–90 days, 91–365 days) after a severe hypoglycemic episode. In patients who had multiple hypoglycemic episodes, the person-time was calculated between the first and second episodes. Patients who experienced ACS and a severe hypoglycemic episode on the same day were excluded from the analysis. We used the standardized difference to measure covariate balance, whereby an absolute standardized difference >10% represented meaningful imbalance[15,16]. To further elucidate the increased risk of ACS among patients with a history of hypoglycemic episodes, a multiple regression analysis (Cox proportional hazards model) was carried out, as in previous studies. The variables for adjustment included the age group; sex; type 1 diabetes status; prior use of sulfonylureas, meglitinides, α-glucosidase inhibitors, biguanides, thiazolidines, dipeptidyl peptidase-4 inhibitors, sodium–glucose cotransporter 2 inhibitors, insulin, glucagon-like peptide-1 receptor agonists, antihypertensive drugs, lipid-lowering drugs, antiplatelet drugs and anticoagulants; and a prior diagnosis of ACS. A *P*-value <0.05 was considered statistically significant. All statistical analyses were carried out with Microsoft SQL Server 2016 Standard® (Microsoft Corp., Redmond, WA, USA) and IBM SPSS for Windows, version 25.0 (IBM, Armonk, NY, USA).

Role of the funding source

The Agency for Medical Research and Development and the Japan Society for the Promotion of Science had no role in the study design, data collection, data analysis, data interpretation, in the writing of the report or in the decision to submit the article for publication. The views and opinions expressed herein are those of the authors, and do not necessarily reflect those of Agency for Medical Research and Development or Japan Society for the Promotion of Science. The corresponding author had full access to all the data in the study and had the final responsibility for submitting the manuscript for publication.

RESULTS

Patient characteristics in the current analysis

Of the 125,779,650 patients (62,407,909,454 person-days) enrolled in the NDB, we identified 8,039,335 patients with diabetes and included 7,909,626 aged ≥35 years in the present study (Figure 1). Within the 2-year period, 48,118 at-risk patients experienced a severe hypoglycemic episode. Table 1 shows the characteristics of patients with and without a severe hypoglycemic episode. The former group tended to be older than the latter group. Furthermore, patients who experienced severe hypoglycemic episodes were more likely to receive insulin therapy than those who did not experience severe hypoglycemic episodes (79 vs 28%). Antiplatelet drugs and anticoagulants were prescribed at high rates to patients who experienced severe hypoglycemic episodes.

Absolute risk of ACS among diabetes patients in Japan

The absolute risk of ACS was 2.9 out of 1,000 person-years (37,486 cases/5,087,611,521 person-days) for all diabetes patients aged ≥35 years in Japan. Patients with and without type 1 diabetes had ACS risks of 2.1 out of 1,000 and 3.0 out of 1,000 person-years, respectively. The absolute ACS risk values in patients who did and did not experience severe hypoglycemic episodes were 3.0 out of 1,000 (104 cases/12,812,308 person-days) and 2.7 out of 1,000 person-years (37,382 cases/5,074,799,213 person-days), respectively (Table 2). The adjusted regression analysis showed that patients with severe hypoglycemia had a higher absolute risk of ACS than those without hypoglycemia, consistent with previous studies (Table 3). Figure 2 presents the absolute risk of ACS in patients with diabetes according to sex and age. Although women had a lower risk of ACS than men, a severe hypoglycemic episode increased the absolute risk among women. In terms of age, a severe hypoglycemic episode increased the absolute risk of ACS in patients aged ≥70 years. However, patients aged <70 years with and without severe hypoglycemic episodes had a similar risk of developing ACS (2.4 and 2.3/1,000 person-years, respectively).

ACS risk after severe hypoglycemic episodes

The absolute risk of ACS over time varied by the elapsed time after a severe hypoglycemic episode (Figure 3). The absolute

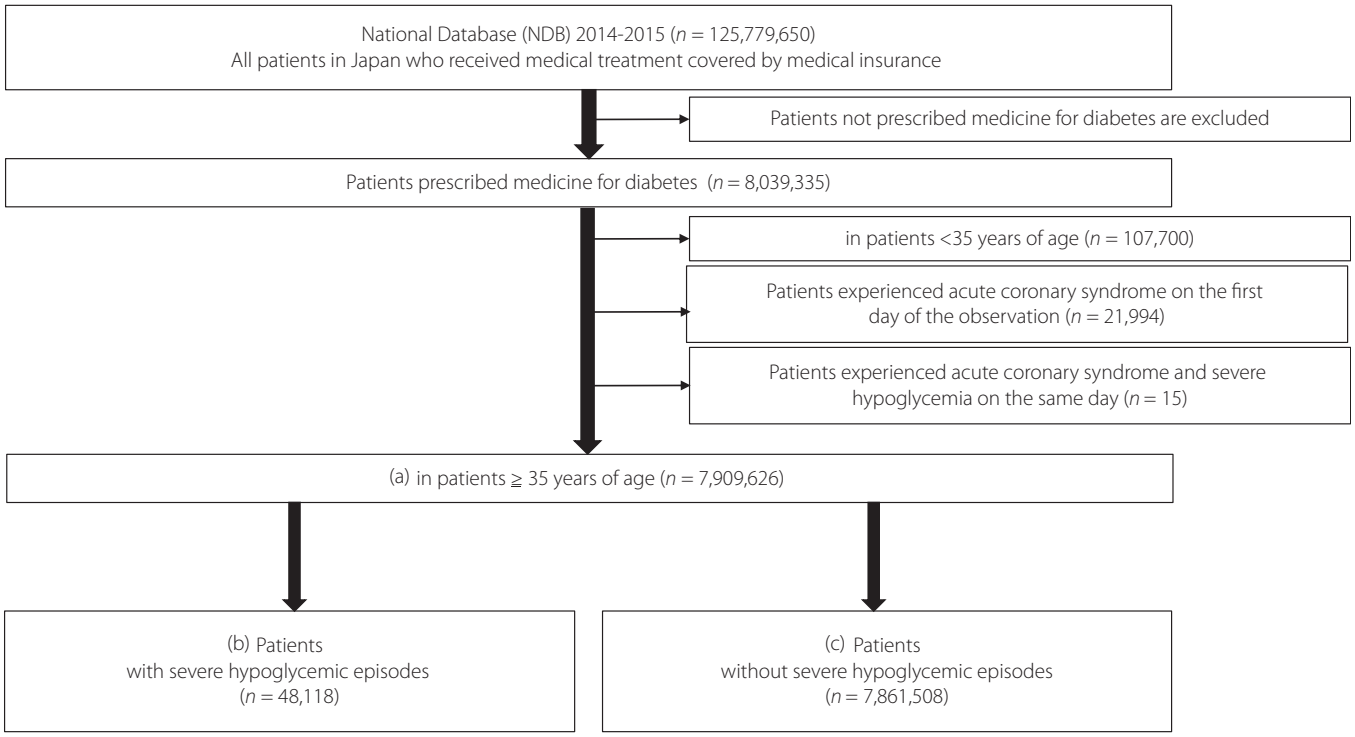

Figure 1 | Patient inclusion flow chart. (a) We defined diabetes patients as patients who were given the diagnosis codes denoting "diabetes mellitus" at least once and who were prescribed medicine for diabetes. (b) We defined patients with severe hypoglycemic episodes as patients who were given the diagnosis code of hypoglycemia and who were prescribed 50% glucose injections. (c) We defined patients without severe hypoglycemic episodes as patients who were not given the diagnosis codes of hypoglycemia and who were not prescribed 50% glucose injections.

risk of ACS was 10.6 out of 1,000 person-years within 10 days of a severe hypoglycemic episode, and a shorter period after a severe hypoglycemic episode correlated with a higher absolute risk of ACS. The absolute risk of ACS within 10 days of a severe hypoglycemic episode was higher than the absolute risk >11 days after a severe episode (Figure 3).

DISCUSSION

The universal health insurance coverage system in Japan ensures that all residents can receive lower-cost medical treatment. Using the Japanese NDB dataset, we carried out cohort studies involving most Japanese citizens who faced fewer economic restrictions on medical care. This is the first report on the absolute risks of ACS in all patients with diabetes in Japan from April 2014 to March 2016.

Previous reports have shown a lower risk of coronary artery diseases in the Japanese population than in Western populations[17–19]. A cohort study of the Japanese general population (5,498 participants; mean age 55.8 years in men and 54.2 years in women) showed that the incidence of acute myocardial infarction was 2.7 out of 1,000 person-years in men and 1.1 out of 1,000 person-years in women[17]. In this cohort study, just 6.4% of patients had diabetes at baseline. Diabetes is well known to increase the risk of ACS[18]. A study of Japanese patients with diabetes and no history of coronary artery disease (2,539 participants; mean age 65 years) reported an ACS incidence of 4.5 out of 1,000 person-years[20]. In contrast, the present findings appear to underestimate the risk of ACS. Patients with ACS who did not receive emergency PCI were not included in the present study, and therefore the outcome was determined using several medical procedure codes (emergency PCI for ACS). However, a Japanese registry recently reported that 85.1% of patients with ACS received emergency PCI, although just 2.0% underwent emergency coronary artery bypass grafting[21]. Thus, we could evaluate most cases of ACS in Japan by evaluating the medical procedure codes corresponding to emergency PCI for ACS in the NDB. Many Japanese medical institutions can carry out emergency PCI. However, regional disparities mean that the risk of ACS among residents in regions with poor medical resources might be underestimated.

The incidence of severe hypoglycemic episodes has increased[22], and recent reports have highlighted the potential importance of related adverse effects[2,23,24]. Particularly, several studies have shown a relationship between hypoglycemic episodes and an increased risk of cardiovascular adverse events in patients with both type 1 and type 2 diabetes[8,25,26]. The causal relationship between severe hypoglycemia and cardiovascular events can be

Table 1 | Characteristics of diabetes patients with or without severe hypoglycemic episodes

Characteristics	Total	Severe hypoglycemia		Standardized difference between with/without hypoglycemia
		With	Without	
	n (%)	*n* (%)	*n* (%)	
No. patients	7,909,626 (100)	48,118 (100)	7,861,508 (100)	
Age (years)				
Age group, *n* (%)				
35–39 years	97,709 (1)	504 (1)	97,205 (1)	−0.02
40–44 years	196,082 (2)	876 (2)	195,206 (2)	−0.05
45–49 years	295,040 (4)	1,148 (2)	293,892 (4)	−0.08
50–54 years	414,130 (5)	1,463 (3)	412,667 (5)	−0.11
55–59 years	570,056 (7)	1,986 (4)	568,070 (7)	−0.13
60–64 years	875,052 (11)	2,958 (6)	872,094 (11)	−0.18
65–69 years	1,373,850 (17)	5,304 (11)	1,368,546 (17)	−0.18
70–74 years	1,196,222 (15)	6,209 (13)	1,190,013 (15)	−0.06
75–79 years	1,152,151 (15)	7,850 (16)	1,144,301 (15)	0.05
80–84 years	930,510 (12)	8,846 (18)	921,664 (12)	0.19
85–89 years	545,982 (7)	6,838 (14)	539,144 (7)	0.24
≥90 years	262,842 (3)	4,136 (9)	258,706 (3)	0.23
Sex, *n* (%)				
Male	3,272,514 (41)	21,528 (45)	3,250,986 (41)	0.07
Diabetes type, *n* (%)				
Type 1 diabetes	207,660 (3)	7,673 (16)	199,987 (3)	0.48
Drug use, *n* (%)				
Sulfonylureas	2,844,479 (36)	18,341 (38)	2,826,138 (36)	0.04
Meglitinides	610,799 (8)	5,200 (11)	605,599 (8)	0.11
α-Glucosidase inhibitors	1,940,735 (25)	14,591 (30)	1,926,144 (25)	0.13
Biguanides	2,700,890 (34)	9,704 (20)	2,691,186 (34)	−0.32
Thiazolidinediones	1,152,031 (15)	5,456 (11)	1,146,575 (15)	−0.10
DPP4 inhibitors	5,449,606 (69)	27,715 (58)	5,421,891 (69)	−0.24
SGLT2 inhibitors	463,963 (6)	1,100 (2)	462,863 (6)	−0.18
Insulin	2,195,725 (28)	38,069 (79)	2,157,656 (27)	1.21
GLP1-RA	124,061 (2)	1,018 (2)	123,043 (2)	0.04
Antihypertensive drugs	4,684,424 (59)	32,657 (68)	4,651,767 (59)	0.18
Lipid-lowering drugs	4,009,087 (51)	23,222 (48)	3,985,865 (51)	−0.05
Antiplatelet drugs	2,281,376 (29)	21,469 (45)	2,259,907 (29)	0.33
Anticoagulants	1,669,658 (21)	23,222 (48)	1,646,436 (21)	0.60
Prior diagnosis, *n* (%)				
ACS	1,455,665 (18)	17,704 (37)	1,437,961 (18)	0.42

ACS, acute coronary syndrome; DPP4, dipeptidyl peptidase-4; GLP1-RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium–glucose cotransporter 2.

Table 2 | Absolute risk of acute coronary syndrome in patients with diabetes aged ≥35 years in Japan

Targets	Absolute risk of ACS (/1,000 person-years)
All patients	2.9
Patients with type 1 diabetes	2.1
Patients without type 1 diabetes	3.0
Patients with hypoglycemic episodes	3.0
Patients without hypoglycemic episodes	2.7

ACS, acute coronary syndrome.

explained by an increase in thrombotic tendency associated with abnormal cardiac repolarization, inflammation and atherosclerosis development[27–31]. The present study showed a high risk of ACS among patients who experienced severe hypoglycemic episodes (Tables 2, 3). Notably, the risk of ACS was higher immediately after a severe hypoglycemic episode (Figure 3), and this was confirmed by an adjusted regression analysis. These findings suggest that a severe hypoglycemic episode affects the onset of ACS during the subsequent 10-day period.

The risk of ACS increases with aging[17,32]. In our cohort, the absolute risk of ACS was higher in patients aged ≥70 years

Table 3 | Results of a multiple Cox proportional hazard model analysis comparing patients with and without severe hypoglycemia

Model	Hazard ratio	95% confidence interval	
Model 1	1.147	1.143	1.152
Model 2	1.077	1.073	1.082
Model 3	1.058	1.053	1.063
Model 4	1.031	1.026	1.035
Model 5	1.016	1.012	1.021

Model 1: univariate; model 2: adjusted for sex and age class; model 3: model 2 plus prior diagnosis of acute coronary syndrome; model 4: model 3 plus use of drug therapy for diabetes; model 5: adjusted for all variables in Table 1.

than in those aged <70 years, and a severe hypoglycemic episode was associated with a higher risk of ACS in the older patient group (Figure 2). The results highlight the importance of avoiding a hypoglycemic episode in elderly patients. Accordingly, many guidelines recommend a less stringent goal for glycemic control in elderly patients with diabetes, who face a higher risk of hypoglycemia[9,33,34]. For example, the Japanese guideline stipulates the individual determination of the hemoglobin A1c target based on age, activities of daily living and cognitive function. Furthermore, the use of common drug treatments for diabetes, including insulin and sulfonylureas, is not recommended[9], as these drugs are the most common cause of hypoglycemia[12]. Accordingly, most cardiovascular risks related to severe hypoglycemia might be preventable by changing the diabetes treatment. Furthermore, diabetes should be managed adequately in elderly patients to avoid severe hypoglycemia and thus prevent adverse cardiovascular events.

The present study had several limitations. First, we defined diabetes patients in the NDB as those with any diagnosis code corresponding to diabetes and who had been prescribed medication for diabetes. The National Health and Nutrition Survey in Japan reported that 7.7 million patients aged ≥20 years are receiving treatment for diabetes[35]. The number of diabetes patients in the present study (7,909,626) was very similar to the number in a previous survey. We did not include patients with diabetes who were treated using dietary and exercise therapy alone. Our patient selection procedure was appropriate, because severe hypoglycemic episodes are thought to occur in relation to medication use. Second, the NDB did not include any laboratory data, such as plasma glucose levels, and therefore we could not confirm these levels at the time of a severe hypoglycemic episode. Alternatively, we defined a severe hypoglycemic episode as the presence of diagnosis codes for hypoglycemia and intravenous administration of 50% glucose. Still, this alternative definition might underestimate the occurrence of severe hypoglycemic episodes. A retrospective cohort study in the USA reported annual severe hypoglycemia incidence proportions of 0.33 and 0.31% in 2014 and 2015, respectively[22]. A previous study also estimated that approximately 20,000 patients were transported annually to the emergency room for severe hypoglycemia in Japan[36]. According to our data, 24,509 patients experienced severe hypoglycemic episodes annually (annual incidence proportion 0.30%), which was consistent with the results of previous studies[22,36]. Third, we could not review the detailed medical records of each patient, including bodyweight, smoking history and family history. Although patients with and without severe hypoglycemic episodes were thought to show different characteristics, we could not evaluate these differences. Antiplatelet drugs and anticoagulants were

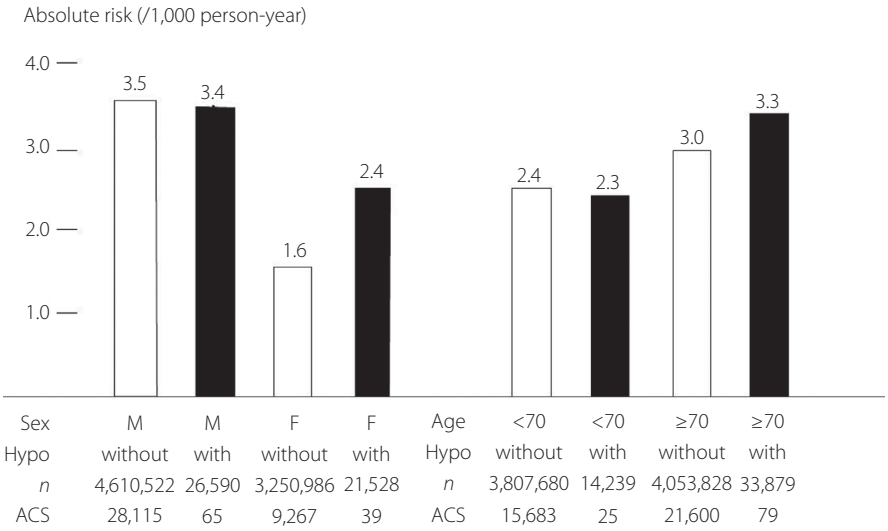

Figure 2 | Absolute risk of acute coronary syndrome (ACS) in diabetes patients according to age, sex and occurrence of hypoglycemic episodes (Hypo). <70, patients aged <70 years; ≥70, patients aged ≥70 years; F, female; M, male; With, patients with hypoglycemic episodes; Without, patients without hypoglycemic episodes.

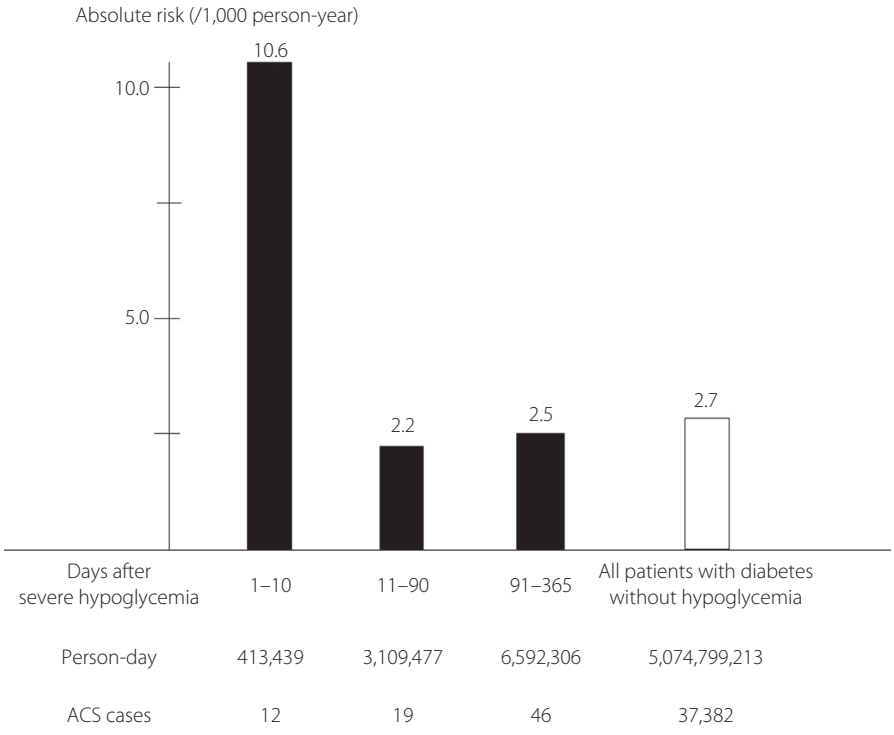

Figure 3 | Absolute risk of acute coronary syndrome (ACS) after a severe hypoglycemic episode.

commonly prescribed to patients with severe hypoglycemic episodes, suggesting that these patients might face a high risk of atherosclerotic diseases. The present findings imply that severe hypoglycemia should be avoided, particularly in patients with comorbid atherosclerotic cardiovascular disease. Finally, we defined ACS according to the medical procedure codes for emergency PCI for ACS in the NDB. Therefore, we could not evaluate patients with ACS who did not receive emergency PCI, including those for whom a significant amount of time had passed since the onset of ACS, those with a poor general health condition or decrease in activities of daily living, or those who experienced a silent, asymptomatic myocardial infarction. We also could not evaluate patients who underwent coronary artery bypass grafting. Although most ACS patients in Japan underwent emergency PCI[21], the incidence of ACS was underestimated in the present study.

In conclusion, the present study results suggest that severe hypoglycemia increases the risk of ACS in patients with diabetes, particularly within the first 10 days after a severe hypoglycemic episode. Further studies are required to set this time interval. The ACS risk was increased in elderly diabetes patients with severe hypoglycemic episodes. These findings highlight that it is important to avoid severe hypoglycemia while treating diabetes, particularly in elderly patients.

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DISCLOSURE

Dr Nishioka reports receiving consultant fees from Novo Nordisk. Dr Okada reports receiving lecturer's fees from Novo Nordisk, Mitsubishi Tanabe, Sumitomo Dainippon, MSD, Bayer, Eli Lilly, Boehringer Ingelheim, Ono, AstraZeneca, Sanofi, Takeda and ARKRAY. Dr Ishii reports receiving lecture fees and consultant fees from Takeda, Eli Lilly Japan, Sanofi, Merck & Co., Astellas, Mitsubishi Tanabe, Daiichi Sankyo, Ono, AstraZeneca, Taisho Toyama, Shionogi, Kowa, Boehringer Ingelheim, Novo Nordisk, Sumitomo Dainippon, and Kyowa Hakko Kirin. The other authors declare no conflict of interest.

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SUPPORTING INFORMATION

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

Table S1 | Diagnosis codes of diabetes.
Table S2 | Medicine codes for diabetes.