ORIGINAL RESEARCH

Association Between Severe Hypoglycemia and Cardiovascular Disease Risk in Japanese Patients With Type 2 Diabetes

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***Background*—**It remains unclear whether severe hypoglycemia is associated with cardiovascular disease (CVD) in Asian populations with type 2 diabetes (T2D). Furthermore, no study in Japan, where the prescription patterns differ from those in other countries, has examined this association.

***Methods and Results*—**We retrospectively included 58 223 patients (18–74 years old) with T2D. First, we examined the potential predictors of severe hypoglycemia. Then, we investigated the association between severe hypoglycemia and CVD risk. Finally, we performed an updated systematic review and meta-analysis to incorporate our findings and recently published studies into the previous systematic review and meta-analysis. During 134 597 person-years from cumulative observation periods, 128 persons experienced severe hypoglycemia and 550 developed CVD events. In a multivariate Cox proportional hazard model, severe hypoglycemia was strongly and positively associated with the risk of CVD (multivariate-adjusted adjusted hazard ratio, 3.39; 95% CI, 1.25–9.18). In a propensity score–matched cohort that had similar baseline characteristics for patients with severe hypoglycemia and those without, severe hypoglycemia was more strongly associated with the risk of CVD. An updated systematic review and meta-analysis that included 10 studies found that severe hypoglycemia was associated with an ≈2-fold increased risk of CVD (pooled relative risk, 1.91; 95% CI, 1.69–2.15).

***Conclusions*—**Our results suggest that severe hypoglycemia is strongly associated with an increased risk of CVD in Japanese patients with T2D, further supporting the notion that avoiding severe hypoglycemia may be important in preventing CVD in this patient population. **(*J Am Heart Assoc*. 2016;5:e002875 doi: 10.1161/JAHA.115.002875)**

Key Words: cardiovascular disease • cohort study • epidemiology • meta-analysis • type 2 diabetes mellitus

Accumulating epidemiologic evidence, primarily from European populations, suggests that severe hypoglycemia—a critical condition induced by diabetes treatment—may be associated with an increased risk of cardiovascular disease (CVD) among persons with type 2 diabetes (T2D).[1–3] In a recent systematic review and meta-analysis of cohort studies that included 903 510 patients with T2D, severe hypoglycemia was associated with a 2-fold increased risk of CVD.[1] Subsequently, several cohort studies have reported similar results.[4,5] This association is biologically plausible, given that severe hypoglycemia induces sympathoadrenal activation,[6] inflammation,[7] endothelial dysfunction,[8] and cardiac ischemia or fatal arrhythmia,[9–11] all of which have potential adverse cardiovascular effects. These findings have brought widespread attention to the importance of avoiding severe hypoglycemia in order to prevent CVD among patients with T2D.

Asian populations have a relatively higher risk of stroke and a lower risk of ischemic heart disease than Western populations[12]; however, there has been only one study from Taiwan[13] that examined the association between severe hypoglycemia and risk of CVD in patients with T2D. Furthermore, no study in Japan has examined this association. Of note, there are marked differences in the initial prescription patterns for diabetes between Japan and other countries, with a low rate of metformin prescriptions (≈25%) and relatively high prescription rates for dipeptidyl peptidase 4 (DPP-4) inhibitors (≈40%) and sulfonylureas (≈25%).[14] This is in contrast with the high rate of metformin prescriptions in other countries (55–65% in the United States,[15,16] ≈75% in the United Kingdom,[17] and ≈70% in Taiwan[18]). This difference may be partially because the Japanese guidelines on

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diabetes management do not specify the first-line agent to be used, but rather recommend that the selection of glucose-lowering agents should be made on the basis of individual patient characteristics.[19] This advice is in contrast with most clinical practice guidelines that suggest metformin as a first-line glucose-lowering agent for patients with T2D.[20–22] Investigating the association between severe hypoglycemia and risk of CVD in Japan, where the prescription patterns differ from those of other countries, may provide further insight into the role of severe hypoglycemia in the development of CVD in patients with T2D. Therefore, we performed a retrospective cohort study based on a claims database in Japan to clarify the putative association between severe hypoglycemia and the risk of CVD in a Japanese population.

Methods

Study Design

In this retrospective cohort study, we obtained deidentified, individual-level data from the JMDC database, a medical database maintained by the Japan Medical Data Center Co, Ltd (JMDC; Tokyo, Japan).[23,24] All Japanese citizens are covered by health insurance programs, such as Employees' Health Insurance programs, the National Health Insurance program, and the Insurance System for Latter-Stage Elderly People for citizens age ≥75 years old. The JMDC medical database contains medical claims data and health screening data provided by multiple Employees' Health Insurance programs. The medical claims data include patient demographics, diagnosis codes recorded as the standardized local (Japanese) codes of diseases defined by the Medical Information System Development Center and the International Classification of Diseases (ICD)-10 codes, prescriptions, medical procedures, and medical tests. The diagnosis codes were originally recorded as the standardized local (Japanese) codes and were mapped to the ICD-10 codes. The health screening data include questionnaires concerning lifestyle factors (eg, smoking and alcohol consumption), anthropometric data (eg, height, weight, and blood pressure), and laboratory data (eg, blood glucose, hemoglobin A1c, and cholesterol levels). From January 2005 to July 2014, the database collected the medical claims of 3 102 074 persons using the Employees' Health Insurance programs, either the insured persons (ie, company employees) or their dependents (mainly family members). Approximately 30% to 50% of these persons had data from at least one health screening. This study was approved by the institutional review board of the National Center for Global Health and Medicine. Because data were anonymized, the requirement for informed consent was waived for this analysis.

Study Participants

Study inclusion criteria were as follows: (1) diagnosis of T2D or unspecified diabetes mellitus (ICD-10 code: E11 or E14); (2) a prescription for a glucose-lowering agent; and (3) observation for a continuous period of at least 6 months from January 2005 to July 2014. Exclusion criteria included the following: (1) diagnosis of T2D (ICD-10 code: E10); (2) age <18 years old or ≥75 years old; (3) history of severe hypoglycemia; and (4) history of CVD. Persons age ≥75 years old were excluded because they are covered by the Insurance System for Latter-Stage Elderly People, but not by Employees' Health Insurance programs. Among the 3 102 074 persons in the JMDC database, 170 224 had a diagnosis of T2D or unspecified diabetes mellitus. Among them, we excluded 107 200 persons who did not have a prescription for a glucose-lowering agent and 1446 who had a diagnosis of type 1 diabetes. In addition, we excluded 219 patients age <18 years old or ≥75 years old, 449 with a history of CVD, and 26 with a history of severe hypoglycemia. Finally, we excluded 2661 patients who did not have an observation at 6 months before the first claim for a glucose-lowering agent prescription. Patients with <6 months of claim data were assigned an index date of 6 months after the first claim date. For patients with ≤6 months of claim data, the index date was the first claim date of using a glucose-lowering agent. Thus, both groups had a minimum of 6 months of baseline observation data before the index date. Thus, 58 223 patients were included in the present study and observed from their index date until July 2014. During their observation periods, 429 (0.7%) patients died, 26 115 (44.9%) left their insurance plan, and 3477 (6.0%) had no claim spanning a continuous period of 6 months.

Definitions of Severe Hypoglycemia and CVD

Occurrences of severe hypoglycemia and CVD were assessed from the index date until the end of observation. We defined severe hypoglycemia as conditions with both (1) a diagnosis of hypoglycemia (ICD-10 code: E162 and/or "hypoglycemia" in the standardized local codes) and (2) a prescription for either 50% dextrose solution or glucagon infusion. CVDs were defined as conditions during hospitalization with both (1) a diagnosis of CVD (ischemic heart disease, stroke, or peripheral artery disease) and (2) either a medical procedure performed or a prescription to treat CVD (described below). Ischemic heart disease was defined as having the following conditions during hospitalization: (1) "angina pectoris," "acute myocardial infarction," or "acute coronary syndrome" in the standardized local codes (corresponding ICD-10 codes: I20–24); and (2) treatment with urokinase infusion, alteplase infusion, monteplase infusion, percutaneous transluminal

coronary angioplasty, percutaneous transluminal coronary recanalization, coronary artery bypass grafting, coronary arterial revascularization, thromboendarterectomy, or coronary atherectomy, and/or rehabilitation for a CVD. Stroke was defined as having the following conditions during hospitalization: (1) "cerebral infarction," "intracranial hemorrhage," or "subarachnoid hemorrhage" in the standardized local codes (corresponding ICD-10 codes: I60–69); and (2) treatment with alteplase infusion, argatroban infusion, ozagrel infusion, edaravone infusion, endovascular surgery, craniotomy, surgical anastomosis, percutaneous transluminal angioplasty, and/or rehabilitation for cerebrovascular diseases. Peripheral artery disease was defined as having the following conditions during hospitalization: (1) "peripheral artery disease" or "arteriosclerosis obliterans" in the standardized local codes (corresponding ICD-10 codes: I702, I709, I739), and (2) treatment with urokinase infusion, argatroban infusion, percutaneous transluminal angioplasty and stenting, amputation, bypass grafting, or thromboendarterectomy.

Baseline Demographics and Clinical Characteristics

Patients' characteristics were identified during the 6–12 months before their index date. Patient demographics (age and sex) and clinical characteristics that might affect severe hypoglycemia or CVDs were determined and considered as potential confounding factors. These factors included the duration of diabetes, history of microvascular disease, Charlson Comorbidity Index (CCI),[25] use of glucose-lowering agents (insulin, sulfonylureas, metformin, pioglitazone, alpha–glucosidase inhibitors, glinides, DPP-4 inhibitors, and glucagon-like peptide 1 [GLP-1] receptor agonists), use of antihypertensive agents, use of statins, and use of antiplatelet agents. Clinical characteristics were defined as having certain disease codes (eg, for a history of microvascular disease, ICD-10 code: E142-144, or E112-114 and/or "diabetic nephropathy," "diabetic retinopathy," or "diabetic neuropathy" in the standardized local codes) or prescriptions for specific diseases (eg, use of antihypertensive agents).

Statistical Analysis

A total of 58 223 participants contributed person-years from their index date to the censoring events: first CVD event, death, insurance withdrawal, no claims for a continuous period of 6 months, or July 2014.

First, we investigated possible predictors of severe hypoglycemia in this population by using time-dependent Cox proportional models and estimated the hazard ratio (HRs) with 95% CIs. We estimated both crude HRs and multivariate-adjusted HRs by mutually adjusting for all covariates. Covariates included age, sex, duration of diabetes, history of microvascular disease, CCI, and time-dependent covariates updated every year during the observation periods (use of insulin, sulfonylureas, metformin, pioglitazone, alpha-glucosidase inhibitors, glinides, DPP-4 inhibitors, and GLP-1 receptor agonists).

Second, to evaluate the association of severe hypoglycemia with CVD risk, we used time-dependent Cox proportional hazards models and HRs with 95% CIs. In the crude model, the presence of severe hypoglycemia as a time-dependent exposure was included in the model to avoid an immortal time bias. For those who experienced severe hypoglycemia, the person-years from their index date to the severe hypoglycemic events were considered as "unexposed," whereas the person-years from their severe hypoglycemic events to the censoring events were considered as "exposed." In the multivariate-adjusted model, we adjusted for age, sex, duration of diabetes, history of microvascular disease, CCI, and time-dependent covariates updated every year during the observation periods (use of insulin, sulfonylureas, metformin, pioglitazone, alpha-glucosidase inhibitors, glinides, DPP-4 inhibitors, GLP-1 receptor agonists, antihypertensive agents, statins, and antiplatelet agents).

Next, we performed 5:1 propensity score matching to minimize the possibility of residual confounding attributed to the measured covariates.[26,27] We used 5:1 instead of 1:1 matching to increase the power of detecting an association. Matching each exposed patient to fewer unexposed subjects (eg, 4:1 matching) resulted in similar point estimates but wider CIs. We first estimated the propensity score by regressing severe hypoglycemia on age, sex, duration of diabetes, history of microvascular disease, CCI, baseline use of insulin, sulfonylureas, metformin, pioglitazone, alpha-glucosidase inhibitors, glinides, DPP-4 inhibitors, GLP-1 receptor agonists, antihypertensive agents, statins, and antiplatelet agents. We then performed 5:1 nearest-neighbor matching within caliper widths equal to 0.2 of the SD of the logit of the propensity score.[27] In the propensity score–matched population, we used a time-dependent Cox proportional hazards model with robust SEs to account for clustering in matched sets with severe hypoglycemia as a time-dependent exposure.

Finally, we conducted an updated systematic review and meta-analysis of severe hypoglycemia and CVD risk that incorporated our findings and recently published studies included in our previous systematic review and meta-analysis.[1] Because the previous review involved a search of the literature through February 27, 2013,[1] we updated the search by using Medline, Embase, the Cochrane library, and the Web of Science from February 28, 2013 through September 2015; the search strategy is available upon request from the corresponding author. The inclusion criteria

were as follows: (1) cohort study of patients with T2D; (2) CVD reported as a study outcome; and (3) provision of an association between hypoglycemia and CVD. By using adjusted relative risk estimates and their 95% CIs, we estimated the pooled relative risks with a random-effects model.[28]

The threshold for significance was set at $P<0.05$. Analyses were performed with SAS (version 9.3; SAS Institute Inc, Cary, NC) or Stata software (version 13.1; StataCorp LP, College Station, TX).

Results

During 134 597 person-years (mean, 2.3 years) from the collective observation periods, 128 (0.2%) patients experienced severe hypoglycemia and 550 (0.9%) experienced CVD events (ischemic heart disease, 191 [0.3%] cases; stroke, 333 [0.6%] cases; peripheral artery disease, 26 [0.04%] cases). Compared with patients who did not experience hypoglycemia, those who experienced severe hypoglycemia were significantly older ($P=0.03$); have a longer duration of diabetes ($P<0.001$); have higher CCI ($P<0.001$); have a higher frequency of microvascular complications ($P<0.001$); be users of insulin ($P<0.001$); and be nonusers of metformin ($P=0.01$), pioglitazone ($P<0.001$), and DPP-4 inhibitors ($P<0.001$; Table 1).

When mutually adjusted for covariates, older age, longer duration of diabetes, higher CCI, and use of insulin were positively associated with the risk of developing severe hypoglycemia. Use of metformin and pioglitazone was inversely associated with risk of developing severe hypoglycemia (Table 2).

In the full cohort, patients who experienced severe hypoglycemia developed CVD more frequently than those who did not have severe hypoglycemia (Table 3; 16.7 vs 4.1 events per 1000 person-years). In the crude Cox proportional hazard model, severe hypoglycemia was strongly and positively associated with the risk of CVD (crude HR, 6.72; 95% CI, 2.51–18.0). Estimates were attenuated after further adjustments for potential confounding factors, including time-dependent covariates, but still remained strong (multivariate-adjusted HR, 3.39; 95% CI, 1.25–9.18).

In the propensity score–matched cohort, those with severe hypoglycemia had similar baseline characteristics to the propen-

Table 1. Baseline Characteristics by Episodes of Severe Hypoglycemic Attack

	Full Cohort			Propensity Score–Matched Cohort		
	Severe Hypoglycemia			Severe Hypoglycemia		
	(+)	(−)		(+)	(−)	
	n=128	n=58 095	*P* Value*	n=128	n=640	Diff.†
Age, y	55.7±11.7	53.8±10.1	0.03	55.7±11.7	55.7±10.6	0.001
Male, %	63.3	69.6	0.12	63.3	64.5	0.03
Diabetes duration, y	5.3±6.0	3.2±4.0	<0.001	5.3±6.0	4.9±5.3	0.07
History of microvascular disease, %	45.3	26.7	<0.001	45.3	42.3	0.06
Charlson Comorbidity Index	2.2±2.1	1.3±1.5	<0.001	2.2±2.1	2.4±2.6	0.08
Diabetic medications, %						
Insulin	57.8	13.6	<0.001	57.8	59.4	0.03
Sulfonylureas	35.9	39.4	0.47	35.9	34.2	0.04
Metformin	19.5	29.9	0.01	19.5	17.5	0.05
Pioglitazone	8.6	20.6	<0.001	8.6	9.4	0.03
Alpha-glucosidase inhibitors	32.8	27.8	0.24	32.8	29.4	0.07
Glinides	3.9	6.7	0.28	3.9	4.2	0.02
DPP-4 inhibitors	13.3	28.4	<0.001	13.3	13.8	0.01
GLP-1 analogues	0	0.5	>0.99	0	0	—
Antihypertensive agents, %	55.5	48.1	0.11	55.5	55.8	0.006
Statins, %	31.3	34.5	0.46	31.3	32.5	0.03
Antiplatelet agents, %	15.6	11.2	0.12	15.6	18.4	0.08

Data are means±SD.

*Fisher's exact test was used to analyze discrete variables, and Student *t* test for equal group means was used to analyze continuous variables.

†Standardized differences between patients with severe hypoglycemia and those without severe hypoglycemia.

Table 2. Predictors of Severe Hypoglycemia

Predictors	Crude HR (95% CI)	Multivariate-Adjusted HR (95% CI)*
Age (per 10 years)	1.51 (1.24–1.83)	1.24 (1.02–1.52)
Male	0.73 (0.51–1.05)	0.94 (0.65–1.35)
Diabetes duration (per 10 years)	2.74 (2.03–3.72)	1.58 (1.14–2.20)
History of microvascular disease	2.13 (1.50–3.03)	1.06 (0.73–1.55)
Charlson Comorbidity Index	1.33 (1.24–1.42)	1.14 (1.05–1.23)
Insulin	8.55 (5.83–12.6)	7.05 (4.68–10.6)
Sulfonylureas	0.64 (0.45–0.91)	0.92 (0.63–1.34)
Metformin	0.45 (0.31–0.66)	0.53 (0.35–0.80)
Pioglitazone	0.47 (0.31–0.73)	0.62 (0.39–0.96)
DPP-4 inhibitors	0.64 (0.45–0.91)	1.05 (0.73–1.53)
Alpha-glucosidase inhibitors	0.97 (0.68–1.39)	1.04 (0.72–1.50)
Glinides	0.98 (0.59–1.62)	1.03 (0.62–1.71)
GLP-1 analogues	0.37 (0.05–2.62)	0.26 (0.04–1.85)

HR indicates hazard ratio.
*All factors listed in the table were mutually adjusted by using multivariate Cox proportional hazard models with age, sex, duration of diabetes, history of microvascular disease, Charlson Comorbidity Index, and time-dependent covariates during observation periods (use of insulin, sulfonylureas, metformin, pioglitazone, alpha-glucosidase inhibitors, glinides, DPP-4 inhibitors, and GLP-1 receptor agonists).

sity score–matched patients without severe hypoglycemia. For all characteristics, the standardized differences between groups were less than 0.1, suggesting that the 2 groups were balanced with regard to their characteristics (Table 1).[27] For CVD events, patients with severe hypoglycemia had a higher rate than the propensity score–matched patients without severe hypoglycemia (Table 3; 16.7 vs 9.4 events per 1000 person years). The Cox proportional hazard model with robust SE for the propensity score–matched cohort indicated that severe hypoglycemia was more strongly associated with the risk of CVD (HR, 7.31; 95% CI, 1.87–28.6) than the multivariate-adjusted estimates for the full cohort.

Table 3. Association Between Severe Hypoglycemia and Cardiovascular Disease Risk

Full Cohort (N=58 223)			
Severe Hypoglycemia	Crude Incidence Rates (95% CI)*	Crude HR (95% CI)	Multivariate-Adjusted HR (95% CI)†
(−)	4.1 (3.8–4.4)	1.00	1.00
(+)	16.7 (5.4–51.6)	6.72 (2.51–18.0)	3.39 (1.25–9.18)
Propensity Score–Matched Cohort (n=768)			
Severe Hypoglycemia	Crude Incidence Rates (95% CI)*	Robust HR (95% CI)	
(−)	9.4 (5.7–15.6)	1.00	
(+)	16.7 (5.4–51.6)	7.31 (1.87–28.6)	

HR indicates hazard ratio.
*Crude incidence rates per 1000 person-years.
†Multivariate model adjusted for age, sex, duration of diabetes, history of microvascular disease, Charlson Comorbidity Index, and time-dependent covariates during observation periods (use of insulin, sulfonylureas, metformin, pioglitazone, alpha-glucosidase inhibitors, glinides, DPP-4 inhibitors, GLP-1 receptor agonists, antihypertensive agents, statins, and antiplatelet agents).

In addition, we performed an updated systematic review and meta-analysis to incorporate our new findings and data from recently published studies. Among 354 potential citations identified by an updated literature search, 3 studies[4,5,29] met our inclusion criteria (Table 4). One study reported estimates separately for those with and without a history of CVD,[29] and 2 estimates were included in the model separately. In total, we included 10 studies (including our study)[2–5,13,29–32] in this updated systematic review and meta-analysis. Frequencies of hypoglycemia substantially varied across studies, ranging from 0.2% (our study) to 14% (Table 4).[29] Four studies[2–5] were prospective cohort studies and six[13,29–32] (including our study) were retrospective cohort studies. All studies involved adequate adjustment for measured potential confounding factors (Table 5). In the random-effects meta-analysis, we found severe hypoglycemia to be associated with an ≈2-fold increased risk of CVD (pooled relative risk, 1.91; 95% CI, 1.69–2.15) with a moderate degree of heterogeneity (I^2 statistics, 60.1%; Figure).

Discussion

In this large-scale, retrospective cohort study in a Japanese population, without CVD at baseline, severe hypoglycemia was strongly associated with an increased risk of CVD. In a propensity score–matched cohort that had similar baseline characteristics for patients with severe hypoglycemia and those without, severe hypoglycemia was more strongly associated with risk of CVD. Finally, our updated systematic review and meta-analysis including data from 10 studies demonstrated that severe hypoglycemia is associated with an ≈2-fold increased risk of CVD.

To the best of our knowledge, this is the first study in Japan to show a positive association between severe hypoglycemia and the risk of CVD. It is noteworthy to observe this association in a relatively young Japanese population with a low cardiovascular risk. As shown in Figure, all studies included in our updated systematic review and meta-analysis showed an increased risk of CVD associated with severe hypoglycemia. Although the prescription patterns in Japan are different from those in other countries, the impact of severe hypoglycemia on CVD may not substantially differ. The magnitude of association in our study was larger than that in other studies with the exception of the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified

Table 4. Characteristics of the Studies Included in the Updated Systematic Review and Meta-Analysis

Study (Year of Publication)	Male (%)	Mean Age (yr)	Follow-up (yr)	No. of Participants	Duration of Diabetes (yr)	Frequency of Severe Hypoglycemic Episode (%)
ADVANCE (2010), Asia, Australia/ New Zealand, Canada, Europe[3]	58	66	5.0 (median)	11 140	8 (mean)	2.1
VADT (2011), USA[2]	97	60	5.6 (median)	1791	11.5 (mean)	5.8
Johnston et al. (2011), USA[30]	51	61	1.0 (mean)	860 845	NA	3.1
Zhao et al. (2012), USA[31]	96	63	3.9 (median)	1522	NA	1.7
Rathmann et al. (2013), Germany[32]	53	67	2.0 (mean)	25 712	3.2 (mean)	0.7
Hsu et al. (2013), Taiwan[13]	47	65	2.8 (mean)	2500	3.8 (mean)	0.6
ORIGIN (2013)*†, North America, South America, Europe, Russia, Asia, Australia[4]	65	64	6.2 (median)	12 537	5.4 (mean)†	3.8
Bedenis et al. (2014)*, Scotland[5]	51	68	4 (mean)	1.066	8.1 (mean)	8.2
Khunti et al. (2015)*, UK[29]	56	63	4.8 (median)	10 422	NA	14.0
Goto et al. (2016)*, Japan	70	54	2.3 (mean)	58 223	3.2 (mean)	0.2

NA indicates not available.
*Newly added in this updated systematic review and meta-analysis.
†Twelve percent of the participants had impaired glucose tolerance or impaired fasting glucose level.

Release Controlled Evaluation (ADVANCE) trial.[3] This seems to indicate that the impact of severe hypoglycemia is relatively strong in our study population, although the CI was wide. Taken together, our findings add to the growing body of evidence that severe hypoglycemia is associated with an increased risk of CVD.

It is unclear why the estimates from the propensity score–matched cohort showed larger HRs than the adjusted HRs from the full cohort. Further adjustment for the time-dependent covariates had little impact on the estimates (HR, 7.43; 95% CI, 2.06–26.8; not shown in Table 3). In addition, we further adjusted for fixed covariates (age, sex, duration of diabetes, history of microvascular disease, and CCI); however, the results did not materially change (HR, 7.09; 95% CI, 1.80–27.9; not shown in Table 3). Importantly, in the propensity score–matched cohort, the standardized differences between groups were less than 0.1 and the 2 groups were suggested to be balanced with regard to their characteristics. These seem to suggest that the results from the propensity score–matched cohort might be closer to the true

Table 5. Quality Assessments on the Studies Included in the Updated Systematic Review and Meta-Analysis

Study	1. Is This a Prospective Study?*,†	2. Is the Source Population Clearly Defined?	3. Was the Follow-up Time Longer Than 1 Year?	4. Was the Exposure Clearly Defined?	5. Was the Outcome Reviewed by an Endpoints Committee?	6. Were Measured Potential Confounding Factors Adequately Adjusted for?‡
ADVANCE[3]	Yes	Yes	Yes	Yes	Yes	Yes
VADT[2]	Yes	Yes	Yes	Yes	Yes	Yes
Johnston et al.[30]	No	No	No	No	No	Yes
Zhao et al.[31]	No	No	Yes	No	No	Yes
Rathmann et al.[32]	No	No	Yes	No	No	Yes
Hsu et al.[13]	No	No	Yes	No	No	Yes
ORIGIN[4]	Yes	Yes	Yes	Yes	Yes	Yes
Bedenis et al.[5]	Yes	Yes	Yes	No	No	Yes
Khunti et al.[29]	No	No	Yes	No	No	Yes
Goto et al.	No	No	Yes	No	No	Yes

*Prospective studies: studies that prospectively identify a group of persons, assess exposures of interest, and follow them for incidence of outcome events.
†Retrospective studies: studies that use existing data records to retrospectively identify a group of persons and assess exposures of interest and incidence of outcome events.
‡Adjustment of following measured potential confounding factors: age, sex, history of cardiovascular disease, history of microvascular complications or its surrogate, baseline health status, and use of diabetic medications.

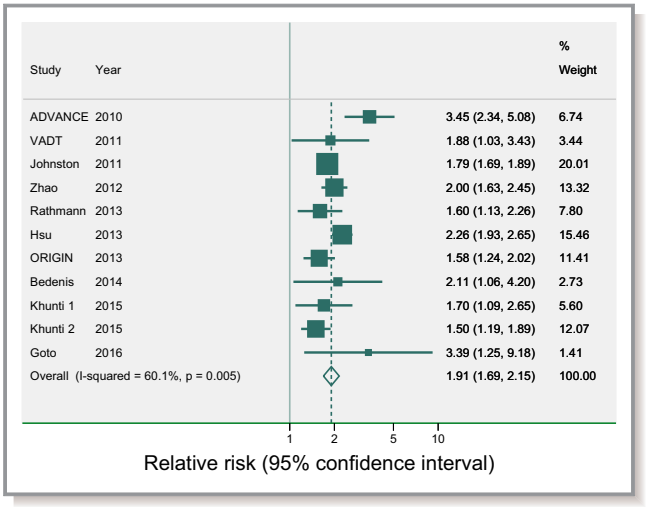

Figure. Random-effects meta-analysis. ADVANCE indicates Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; ORIGIN, Outcomes Reduction with an Initial Glargine Intervention; VADT, Veterans Affairs Diabetes Trial. Khunti 1 denotes the estimates for patients with a history of cardiovascular disease; Khunti 2 denotes the estimates for patients without a history of cardiovascular disease. Dots indicate the relative risks for severe hypoglycemia and cardiovascular risk in patients with type 2 diabetes. Horizontal lines indicate 95% CIs for relative risks. Diamond markers represent the pooled relative risk estimates with 95% CIs.

results. Alternatively, because the matching greatly reduced the number of subjects being analyzed, the differences in the HRs between the full sample and matched sample may be resulting from a heterogeneity in the study sample.

Although it is difficult to directly compare the frequencies of severe hypoglycemia among different databases, health care systems, and patient characteristics (eg, age, severity of diabetes), frequency of severe hypoglycemia was relatively low (0.2%) in our study population compared with that in other studies (Table 4). However, our estimate of the frequency of severe hypoglycemia is in agreement with the report from a nation-wide study in Japan that used a national inpatient database of acute care hospitals in the country; the annual admission for hypoglycemia in 2012 was 2.1 per 1000 patients with diabetes and 4.1 per 1000 patients receiving glucose-lowering agents.[33] The study also found that the admission rate for hypoglycemia has declined after 2010. These findings seem to suggest that the frequency of severe hypoglycemia is relatively low and decreasing; however, it remains to be investigated whether the recent trends of pharmaceutical approach in Japan (eg, the high prescription rate for DPP-4 inhibitors) have contributed to the decreased rate of severe hypoglycemia.

Although the association between severe hypoglycemia and the risk of CVD is biologically plausible,[6–11] the association may be confounded. For example, it has been suggested that severe hypoglycemia may be a marker of vulnerability to CVD events[3] because the risk of hypoglycemia is increased in patients with comorbid illnesses that are risk factors for serious adverse health outcomes. However, in our previous report, we have shown that comorbid illnesses alone are unlikely to fully explain the increased risk of CVD in patients who experienced severe hypoglycemia.[1]

Given the possibility of severe hypoglycemia being a risk factor for CVD, health care providers should minimize the risk of severe hypoglycemia in patients with T2D. The appropriate choice of glucose-lowering agents and treatment goal[20] should be further promoted to avoid further disease burden secondary to severe hypoglycemia. In line with previous studies,[34] we found that insulin use was associated with a higher risk of severe hypoglycemia and that metformin use was associated with a lower risk of severe hypoglycemia. Thus, prioritizing metformin use and avoiding unnecessary insulin use may potentially prevent severe hypoglycemia. Also, pioglitazone was associated with a lower risk of severe hypoglycemia in our study, which corroborates its pharmacological properties. Sulfonylureas have a propensity to induce hypoglycemia[20]; however, use of sulfonylureas was not statistically significantly associated with risk of severe hypoglycemia in our study. This seems to suggest that the characteristics of our study population, such as the relatively young age and low frequency of comorbid illness, may have been protective against severe hypoglycemic events induced by sulfonylureas. DPP-4 inhibitors generally have a low risk for hypoglycemia because of their glucose-dependent mechanism of action; however, their use in combination with sulfonylureas or insulin may increase the risk.[35] In our multivariate-adjusted analysis, DPP-4 inhibitors were not significantly associated with the risk of severe hypoglycemia. The relatively high proportion of sulfonylurea or insulin use may have masked a possible protective effect of DPP-4 inhibitors against hypoglycemia. Alternatively, the time since the approval of DPP-4 inhibitors in Japan (first approved in 2010) may have been too short to examine their association with severe hypoglycemia. Importantly, it was recently reported that severe hypoglycemic episodes were preceded by a variation in food intake (a missed or delayed meal or reduced carbohydrate intake), exercise, and inappropriate insulin use.[34] Thus, severe hypoglycemic episodes are potentially preventable through appropriate patient education.[34]

The strengths of the present study include the evaluation of a large sample, the use of the time-dependent Cox proportional models, the use of propensity score matching, and a comprehensive assessment through an updated systematic review and meta-analysis. However, several limitations of this study merit consideration. First, the retrospective nature of this study raises the possibility of selection bias

and information bias. Nearly half of our study patients have left their insurance plan during the follow-up periods, which may have led to a selection bias. Furthermore, the disease coding may be inaccurate, possibly leading to misclassification of exposure and confounding factors. To increase the specificity of exposure classification and outcome classification, we defined severe hypoglycemia and CVD on the basis of a combination of (1) disease codes and (2) a medical procedure and/or a prescription to treat the condition. Second, information on anthropometric factors (eg, body mass index) or lifestyle factors, including smoking, physical activity, and alcohol consumption, was only available for 33% of our study population. Thus, these factors were not used as potential confounding factors. Third, because of the low rate of CVD incidence in our study, we were unable to examine the associations between severe hypoglycemia and CVD subtypes. Finally, our findings may not be applicable to other populations with different genetic and environmental backgrounds. However, because our findings are consistent with those of previous studies, including well-designed, prospective studies such as the ADVANCE study[3] and the Outcomes Reduction with an Initial Glargine Intervention (ORIGIN) study,[4] we believe that the findings can be generalized to broader populations.

In conclusion, our retrospective cohort study in a Japanese population suggests that severe hypoglycemia is strongly associated with a higher risk of CVD in Japanese patients with T2D. Furthermore, our updated systematic review and meta-analysis of 10 studies suggested that severe hypoglycemia is associated with a 2-fold increased risk of CVD. These findings support the notion that avoiding severe hypoglycemia is important in preventing CVD in patients with T2D.

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