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Severe Hypoglycemia and Cardiovascular or All-Cause Mortality in Patients with Type 2 Diabetes

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Background: We investigated the association between severe hypoglycemia (SH) and the risk of cardiovascular (CV) or all-cause mortality in patients with type 2 diabetes.
Methods: The study included 1,260 patients aged 25 to 75 years with type 2 diabetes from the Vincent Type 2 Diabetes Resgistry (VDR), who consecutively enrolled (n=1,260) from January 2000 to December 2010 and were followed up until May 2015 with a median follow-up time of 10.4 years. Primary outcomes were death from any cause or CV death. We investigated the association between the CV or all-cause mortality and various covariates using Cox proportional hazards regression analysis.
Results: Among the 906 participants (71.9%) who completed follow-up, 85 patients (9.4%) had at least one episode of SH, and 86 patients (9.5%) died (9.1 per 1,000 patient-years). Patients who had died were older, had a longer duration of diabetes and hypertension, received more insulin, and had more diabetic microvascular complications at baseline, as compared with surviving patients. The experience of SH was significantly associated with an increased risk of all-cause mortality (hazard ratio [HR], 2.64; 95% confidence interval [CI], 1.39 to 5.02; P=0.003) and CV mortality (HR, 6.34; 95% CI, 2.02 to 19.87; P=0.002) after adjusting for sex, age, diabetic duration, hypertension, mean glycosylated hemoglobin levels, diabetic nephropathy, lipid profiles, and insulin use.
Conclusion: We found a strong association between SH and increased risk of all-cause and CV mortality in patients with type 2 diabetes.

Keywords: Cardiovascular diseases; Diabetes mellitus, type 2; Mortality; Severe hypoglycemia

INTRODUCTION

Hypoglycemia is a well-known acute complication of diabetes treatment and regarded as a major obstacle to reach glycemic targets in patients with type 2 diabetes [1]. Because intensive glycemic control has demonstrated beneficial effects of lowering glucose on microvascular or macrovascular complications, the incidence of severe hypoglycemia (SH) has increased significantly according to the implementation of stringent glycemic control and use of intensive insulin therapy [2-4]. In both the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and Action to Control Cardiovascular Risk in Diabetes (ACCORD) studies, incidence of SH was significantly higher in the intensive therapy group compared with the standard treatment group [5,6].

Because accumulated evidence from cardiovascular (CV) trials has suggested that not all patients benefit from intensive glycemic treatment, recent clinical practice guidelines recommend individualized glycemic target goals to avoid SH episodes or weight gain [7-9]. The UK Prospective Diabetes Study (UKPDS), comprising subjects with recently diagnosed diabe-

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tes, showed that an improvement in glycemic control reduced microvascular complication and myocardial infarction (MI) [2]. Meanwhile, in the ACCORD study, individuals with older age, glycosylated hemoglobin (HbA1c) of 7.5% or more, and cardiovascular disease (CVD) or additional CV risk factors were recruited and compared with those in UKPDS. These differences suggested that individuals in the ACCORD study receiving intensive therapy had greater risk factors for CV morbidity and mortality compared with those in the UKPDS [2,5].

Further, many studies related to SH and CV outcomes have been performed. A meta-analysis of six observational studies, including 903,510 people with type 2 diabetes, showed that SH was strongly associated with a higher risk of CVD [10]. In addition, the ADVANCE study also revealed that SH was strongly associated with increased risks of adverse clinical outcomes, including vascular events and death in patients with long-standing type 2 diabetes [6].

Although the pathogenic mechanisms implicated in CV outcome or CV mortality among patients with hypoglycemia or SH remain elusive, recent evidence suggests that hypoglycemia or SH may contribute to the increased risk of adverse CV events. These findings suggested that SH is of greater clinical significance as a predictable marker for future development of serious CV events. If so, patients with type 2 diabetes with SH episodes, beyond hypoglycemia management, should be recommended for the evaluation of CV risk or active screening for the presence of asymptomatic CVD.

Therefore, we investigated whether experience of SH was associated with an increased risk of CV mortality or death from any cause in Korean patients with type 2 diabetes using the Vincent Type 2 Diabetes Registry (VDR), a long-term prospective observational cohort study.

METHODS

Population

One thousand four hundred twenty-eight patients with type 2 diabetes, aged 25 to 75 years from the VDR, were consecutively recruited from January 2000 to December 2010, and underwent follow-up until May 2015 at the university-affiliated Diabetes Center of St. Vincent's Hospital in South Korea [11]. Patients were excluded if they were older than 75 years; were mentally ill; were unable to undertake self-care behaviors; had a previous episode of SH; or had cognitive dysfunction, alcoholism, or any severe illness, such as malignancy, end-stage renal disease, severe infection, or liver cirrhosis. All subjects underwent follow-up every 3 to 6 months on an outpatient basis. After participants were enrolled, their clinical outcomes were monitored until their time of death or May 2015.

This prospective cohort study was approved by the Institutional Review Board of St. Vincent's Hospital, College of Medicine, The Catholic University of Korea (IRB No. VC10OISE0152). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Evaluation of SH

SH was defined as hypoglycemic episodes requiring the assistance of medical care in an emergency department, or hospitalization [12,13]. Patients were asked if they had experienced SH episodes or visited an emergency department because of SH during the enrollment period. If patients did not visit our clinic for any reason, we attempted to contact the patient by telephone to evaluate the occurrence of SH. Even if the patients visited other hospitals, we reviewed all medical records describing their SH episodes and confirmed the events.

Evaluation of CV death or all-cause death

The primary outcome of this study was death from any cause or CV death. CV death included deaths resulting from an acute MI, sudden cardiac death, death because of heart failure, and other CV causes [14].

CVD was defined as a diagnosis of coronary artery disease (CAD) and stroke. CAD was defined as a diagnosis history of angina pectoris, MI, or coronary revascularization (coronary bypass surgery or coronary angioplasty) [15]. Stroke manifestation included previous transient ischemic attack or cerebral infarction [15,16]. Diagnosis of clinically established CVD was based on verified medical records, and the diagnosis was confirmed by a specialist (cardiologist, neurologist, or neurosurgeon). All patients were followed up for mortality or CV mortality preponderantly, from the time of enrollment to May 2015. Causes of death were determined from the death certificates, clinical records, and hospital records.

Assessment of clinical variables

Anthropometric measurements and participants' information, including medical history, current cigarette smoking status, and the use of medications, were obtained using a detailed questionnaire. Hypertension was defined as systolic blood pressure

≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or the use of antihypertensive medications [17]. Blood samples were collected after fasting for 8 hours overnight. Fasting and 2-hour postprandial plasma glucose, lipid profiles for total cholesterol, triglyceride, and high density lipoprotein cholesterol were measured by an enzymatic method using an automatic analyzer (model 736-40; Hitachi, Tokyo, Japan). The HbA1c level was measured every 6 months during the follow-up period. The estimated glomerular filtration rate was used to determine a classification of stages of chronic kidney disease using the 4-component Modification of Diet in Renal Disease equation [18].

Diabetic retinopathy was assessed from retinal photographs at baseline, and the findings were reviewed by an ophthalmologist. Diabetic nephropathy was considered if a patient showed microalbuminuria (30 to 300 mg/day) or macroalbuminuria (≥300 mg/day). The urinary albumin excretion rate was measured from a 24-hour urine collection using immunoturbidimetry (Eiken, Tokyo, Japan).

Statistical analysis

All results were expressed as the mean±standard deviation or as proportions or median (interquartile range). $P<0.05$ was considered significant. Chi-square tests were used to test differences in the proportion of categorical variables, and independent Student *t*-tests were used for continuous variables. If a patient had multiple SH events, the first recorded event was used in this analysis. After verifying the proportional hazards assumption by means of log-minus log-survival plots and testing with the methods described elsewhere [19], univariable and multivariable Cox proportional hazards regression analysis was applied to test associations between the CV or all-cause mortality and potential explanatory variables. The relationships were analyzed after adjustment for the following prognostic factors: sex, age, duration of diabetes, presence of hypertension, diabetic nephropathy, mean HbA1c throughout the study, and the use of insulin, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or CVD history. The results were presented as hazard ratios (HR) and 95% confidence intervals (CIs). All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

RESULTS

Clinical characteristics

In total, 1,428 patients were recruited, and 168 patients were excluded from the study. Among the 1,260 patients who were enrolled, 906 (71.9%) completed the follow-up. The median follow-up time was 10.4 years. Further, 354 patients did not receive follow-up care, and 86 patients (9.5%) died during the

Table 1. Baseline characteristics of the groups with and without severe hypoglycemia

Characteristic	SH (–)	SH (+)	*P* value
Number	821	85	
Female sex	481 (58.6)	56 (65.9)	0.193
Age, yr	55.3±9.8	60.2±10.4	<0.001
Diabetes duration, yr	7.9±6.5	10.8±8.4	0.003
Hypertension	398 (48.5)	49 (57.6)	0.107
BMI, kg/m^2	24.8±3.4	24.1±3.4	0.070
Smoking	203 (24.7)	16 (18.8)	0.226
CVD history	52 (6.3)	30 (35.3)	<0.001
Insulin	209 (25.5)	42 (49.4)	<0.001
Sulfonylurea	515 (62.7)	42 (49.4)	0.016
Metformin	314 (38.2)	28 (32.9)	0.337
ACE inhibitor/ARBs	256 (31.2)	31 (36.5)	0.318
Statin	98 (11.9)	11 (12.9)	0.786
Acetylsalicylic acid	63 (7.7)	7 (8.2)	0.854
Diabetic retinopathy[a]	168/810 (22.9)	29/810 (38.7)	0.002
Diabetic nephropathy	192 (23.4)	28 (32.9)	0.050
Laboratory finding at baseline			
FPG, mg/dL	176.8±66.1	182.9±85.1	0.432
eGFR, mL/min/1.73 m^2	92.9±17.1	82.4±21.9	<0.001
Baseline HbA1c, %	8.8±2.1	9.2±2.1	0.094
Total cholesterol, mg/dL	183.2±37.0	190.7±39.5	0.992
Triglyceride, mg/dL	159.7±103.4	150.4±68.6	0.414
HDL-C, mg/dL	43.0±10.3	43.5±12.1	0.659
LDL-C, mg/dL	108.3±32.6	117.1±33.2	0.018
UAE, mg/day	10.0 (5.7–30.0)	15.3 (8.0–65.5)	0.010

Values are presented as number (%), mean±standard deviation, or median (interquartile range).
SH, severe hypoglycemia; BMI, body mass index; CVD, cardiovascular disease; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; FPG, fasting plasma glucose; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; UAE, urinary albumin excretion.
[a]Diabetic retinopathy was assessed from retinal photographs and the findings were reviewed by one ophthalmologist.

follow-up period. There were no significant differences between the participants who completed the follow-up evaluation and those who did not with respect to sex ratio (P=0.303), age (55.7±10.0 years vs. 57.0±10.8 years, P=0.055), diabetes duration (8.2±6.7 years vs. 8.2±7.1 years, P=0.907), presence of hypertension (P=0.742), or history of prior CVD (P=0.100).

The mean age and diabetic duration in the patients who completed follow-up were 55.7±10.0 and 8.2±6.7 years, respectively. Among 906 patients who completed follow-up, 85 patients (9.5%) experienced at least one episode of SH. Eighty-two of the participants (9.1%) had a history of CVD before enrollment.

Table 1 shows baseline data of the patients with SH and those without SH. Patients with SH were older (P<0.001), had a longer duration of diabetes (P=0.003), had a history of CVD (P<0.001), and used more insulin (P<0.001) at baseline, compared with patients without SH. In addition, the patients with SH experienced higher incidences of diabetic retinopathy (P=0.002). However, there were no statistically significant differences in baseline HbA1c between the two groups (P=0.094) (Table 1).

CV or all-cause mortality

After excluding 82 patients with CVD history, 153 patients (15.6%) experienced CV events among 824 patients without prior CVD episodes during the follow-up period. During the same period, 86 patients (9.5%) were dead, and 21 patients

Table 2. Comparison of baseline parameters between the patients who survived and died

Characteristic	Total	Survived	Died	*P* value
Number	906	820	86	
Female sex	537 (59.3)	493 (60.1)	44 (51.2)	0.108
Age, yr	55.7±10.0	55.0±9.8	62.7±9.2	<0.001
Diabetes duration, yr	8.2±6.7	7.8±6.4	11.9±8.6	<0.001
Hypertension	447 (49.3)	385 (47.0)	62 (72.1)	<0.001
Body mass index, kg/m^2	24.7±3.4	24.7±3.3	24.6±4.1	0.829
Smoking	219 (24.2)	189 (23.0)	30 (34.9)	0.015
CVD history	82 (9.1)	65 (7.9)	17 (19.8)	<0.001
Severe hypoglycemia	85 (9.4)	68 (8.3)	17 (19.8)	0.001
Insulin	251 (27.7)	207 (25.2)	44 (51.2)	<0.001
ACE inhibitor/ARBs	287 (31.7)	255 (31.1)	32 (37.2)	0.246
Statin	109 (12.0)	102 (12.4)	7 (8.1)	0.244
Acetylsalicylic acid	70 (7.7)	58 (7.1)	12 (14.0)	0.023
Diabetic retinopathy	197/810 (21.7)	164/810 (22.0)	33/810 (50.8)	<0.001
Diabetic nephropathy	220 (24.3)	160 (22.0)	40 (46.5)	<0.001
Laboratory finding at baseline				
FPG, mg/dL	177.4±68.1	176.6±65.1	184.5±91.9	0.441
eGFR, mL/min/1.73 m^2	91.9±17.8	93.5±16.5	76.5±22.4	<0.001
Baseline HbA1c, %	8.9±2.1	8.8±2.1	9.3±2.2	0.058
Total cholesterol, mg/dL	183.9±37.3	184.0±37.1	183.2±39.1	0.841
Triglyceride, mg/dL	158.8±100.6	160.7±103.5	141.5±65.0	0.016
HDL-C, mg/dL	43.1±10.5	43.3±10.3	40.6±12.2	0.023
LDL-C, mg/dL	109.1±32.8	108.6±32.8	114.2±32.3	0.130
UAE, mg/day	10.0 (5.8–30.0)	10.0 (5.6–28.1)	21.6 (9.1–344.8)	<0.001

Values are presented as number (%), mean±standard deviation, or median (interquartile range).
CVD, cardiovascular disease; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; FPG, fasting plasma glucose; eGFR, estimated glomerular filtration rate; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; UAE, urinary albumin excretion.

died from CV events. The most common causes of death were sepsis (29.1%) and CV events (24.4%). In addition, patients died from malignancy (21.1%), hemorrhagic stroke (5.8%), acute exacerbation of chronic disease (9.3%), and unknown or other causes (9.3%) in this cohort. The median time from the onset of SH to the first CV death or death from any cause was 2.25 and 3 years, respectively.

Table 2 shows baseline clinical parameters of the patients who survived and those who died. Patients who died were older, had a longer duration of diabetes, hypertension, and more diabetic microvascular complications; and received more insulin at baseline, compared with surviving patients. Patients who died demonstrated a significantly higher incidence of SH (19.8% vs. 8.3%, $P=0.001$) or history of CVD (19.8% vs. 7.9%, $P<0.001$) compared with the surviving group (Table 2).

Association between SH and all-cause or CV mortality

In univariable Cox regression analysis, age, diabetes duration (≥10 years), presence of hypertension, smoking, history of CVD, treatment with insulin and acetylsalicylic acid, diabetic nephropathy, SH, and estimated GFR were significantly associated with all- cause mortality or CV mortality (Table 3). After adjustment for multiple confounding factors, we found a significantly higher risk for all-cause mortality in the patients with SH than in those without SH (HR, 2.64; 95% CI, 1.39 to 5.02; $P=0.003$) in multivariable Cox regression analysis (Table 4, Fig. 1A).

In addition, SH remained a significant prognostic factor for death from CV events (HR, 6.34; 95% CI, 2.02 to 19.87; $P=0.002$) after adjusting for various confounding factors (Table 4, Fig. 1B).

Table 3. Univariable Cox proportional hazards model of severe hypoglycemia for predicting cardiovascular mortality and all-cause mortality

Characteristic	CV mortality		All-cause mortality	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Female sex	0.74 (0.31–1.91)	0.453	0.70 (0.46–1.07)	0.099
Age (per 10 years)	3.75 (2.07–6.80)	<0.001	2.51 (1.93–3.26)	<0.001
Diabetes duration, yr		0.012		0.012
<5	1.00		1.00	
5 to <10	0.71 (0.13–3.90)	0.714	1.04 (0.54–2.03)	0.899
≥10	4.13 (1.37–12.46)	0.012	2.63 (1.58–4.38)	<0.001
Hypertension (yes vs. no)	2.83 (1.10–7.30)	0.032	2.88 (1.80–4.62)	<0.001
Body mass index, kg/m^2	1.11 (0.98–1.25)	0.099	0.99 (0.92–1.05)	0.656
Smoking (yes vs. no)	0.54 (0.16–1.83)	0.323	1.72 (1.10–2.68)	0.016
CVD history (yes vs. no)	3.85 (1.28–11.62)	0.017	3.97 (2.32–6.78)	<0.001
Insulin use (yes vs. no)	3.21 (1.36–7.55)	0.008	3.07 (2.01–4.69)	<0.001
ACEi/ARB (yes vs. no)	1.70 (0.72–4.03)	0.23	1.32 (0.86–2.05)	0.208
Statin (yes vs. no)	0.76 (0.18–3.27)	0.713	0.65 (0.30–1.40)	0.267
Acetylsalicylic acid (yes vs. no)	3.17 (1.07–9.45)	0.038	2.17 (1.18–3.99)	0.013
FPG (per 10 mg/dL)	1.03 (0.97–1.09)	0.367	1.02 (0.99–1.05)	0.277
LDL-C (per mg/dL)	1.01 (0.99–1.02)	0.475	1.01 (0.99–1.01)	0.114
eGFR, mL/min/1.73 m^2	0.94 (0.92–0.96)	<0.001	0.95 (0.94–0.96)	<0.001
Mean HbA1c (per 1% increment)	1.20 (0.88–1.65)	0.245	1.18 (1.01–1.38)	0.044
Diabetic nephropathy (yes vs. no)	3.32 (1.41–7.83)	0.006	3.13 (2.05–4.78)	<0.001
SH (yes vs. no)	16.4 (5.94–45.07)	<0.001	7.52 (4.29–13.20)	<0.001

CV, cardiovascular; CI, confidence interval; CVD, cardiovascular disease; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; FPG, fasting plasma glucose; LDL-C, low density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; SH, severe hypoglycemia.

Table 4. Multivariable Cox proportional hazards model of severe hypoglycemia for cardiovascular mortality and all-cause mortality

Variable	Hazard ratio (95% CI)			
	Model 1	Model 2	Model 3	Model 4
CV mortality				
SH history	9.16 (3.24–25.94)	8.86 (2.93–26.80)	6.56 (2.14–20.08)	6.34 (2.02–19.87)
P for trend	<0.001	<0.001	0.001	0.002
All-cause mortality				
SH history	4.92 (2.76–8.77)	4.18 (2.25–7.77)	3.09 (1.67–5.76)	2.64 (1.39–5.02)
P for trend	<0.001	<0.001	<0.001	0.003

Multivariable Cox proportional hazards models were adjusted for the following covariates: model 1, sex, age; model 2: model 1+diabetes duration, hypertension, cardiovascular disease history, smoking, body mass index, mean glycosylated hemoglobin, diabetic nephropathy; model 3: model 2+fasting plasma glucose, estimated glomerular filtration rate, low density lipoprotein cholesterol; model 4: model 3+insulin, angiotensin-converting enzyme inhibitor/angiotensin receptor blockers, statin, acetylsalicylic acid.
CI, confidence interval; CV, cardiovascular; SH, severe hypoglycemia.

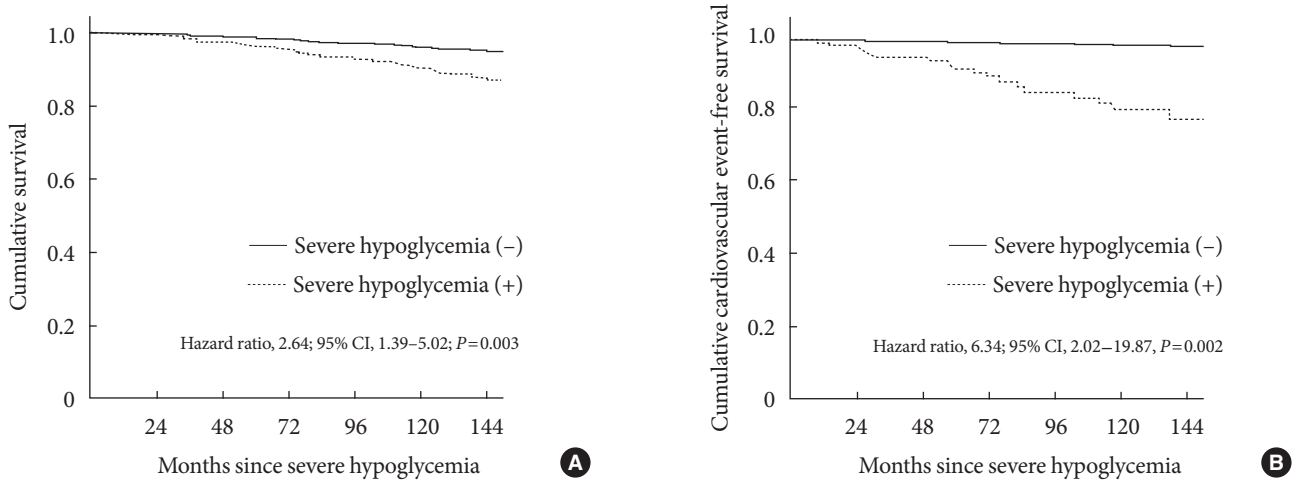

Fig. 1. Cumulative overall survival and cumulative cardiovascular event-free survival of patients with severe hypoglycemia (SH) estimated by Cox regression analysis. (A) Overall survival after SH. (B) Cardiovascular event-free survival after SH. CI, confidence interval.

DISCUSSION

In this long-term, prospective observational cohort study, we found that SH was significantly associated with increased risks of death from both CV events and any cause in Korean patients with type 2 diabetes. Especially, in this study, patients with experience of SH had 2.64 times higher risk of all-cause mortality during the follow-up period, as compared with those without an SH episode. The results were independent of glycemic control status, diabetic duration, age, diabetic nephropathy, use of insulin, or history of CVD.

Large epidemiologic studies have shown the relationship between SH events and CV or all-cause mortality. According to the Hong Kong Diabetes Registry, patients with SH had a higher incidence of mortality (32.8% vs. 11.2%, $P<0.0001$) than those without SH did. Moreover, SH was associated with advanced age, renal dysfunction, poor glycemic control, and cancer sub-phenotypes [20]. In the retrospective study using data from Taiwan National Health Research Institutes, including 77,611 people with type 2 diabetes, clinically mild or severe symptomatic hypoglycemia was associated with an increased risk of CV events (HR, 2.09; 95% CI, 1.63 to 2.67), all-cause hospitalization (HR, 2.51; 95% CI, 2.00 to 3.16), and all-cause mortality (HR, 2.48; 95% CI, 1.41 to 4.38) [21]. In the Edinburgh Type 2 Diabetes Study and ORIGIN trial, a significant association was observed between a history of preceding

SH and a higher frequency of subsequent macrovascular events [22,23]. Recent studies have suggested that SH reflects the effects of comorbidities and unmeasured confounding variables; therefore, it is a marker of an increased risk of adverse clinical outcomes rather than a direct cause [6,24].

Consistent with previous studies, we also found that subjects with SH events have a higher mortality rate than those without SH do in Korean patients with type 2 diabetes. In our study, CVD events accounted for 24.4% of all-cause death. Remarkably, death from sepsis or infection (29.1%) and malignancy (22.1%) were the major causes of death in our study population. Moreover, the median time from the onset of SH to the first CV death or death from any cause was within 3 years. Therefore, SH episodes seemed to reflect combined critical comorbidity or denote patients who are vulnerable to any cause of death [19]. In other words, the presence of SH should raise clinical suspicion of the patients' susceptibility to CV death or any cause of death, and patients with SH events need more clinical attention to prevent adverse outcomes.

There has been increasing debate about the causality between hypoglycemia and CV mortality, and its mechanism. Although the pathogenic mechanism between SH and CVD also remains inconclusive, there have been several hypotheses to explain their relationship. Hypoglycemia has been suggested to have acute effects on sympathoadrenal activation, inflammation, increased platelet and neutrophil activation, coagulation, endothelial function, and inflammatory mediators or cytokines [22,25], all of which have potential adverse effects on myocardium or vascular hemodynamics [10,23]. In addition, cardiac ischemia, corrected QT interval prolongation, or fatal arrhythmia during SH may be responsible for the increased risk of CVD or sudden CV death among patients with SH [26-28]. In addition, an interaction between hypoglycemia and CV autonomic neuropathy contributes to the risk of sudden death in patients with diabetes [29].

The main strength of our study is the long-term, well-characterized prospective approach, which was conducted in a large hospital-based cohort in Korea, to ascertain the risk factors of SH and CV mortality in patients with type 2 diabetes. There are few long-term observational, prospective high-quality cohort studies analyzing the relationship between SH and CV mortality [6]. Some of them were based on self-reporting of SH and had small number of participants or short observation period and; therefore, may be unreliable or prone to recall bias [20,30]. We also confirmed CV outcomes or SH episodes with strict criteria and verification procedures.

Despite these strengths, our study has some limitations. First, this cohort study was conducted in a relatively small area by single-center experience and in one ethnic group. We analyzed only SH episodes, but the effect of minor hypoglycemia episodes on mortality was not evaluated. Last, peripheral artery disease and carotid endarterectomy were not included in the definition of CVD.

In conclusion, we demonstrated that the SH was an independent risk factor for CV or all-cause mortality in Korean patients with type 2 diabetes. To reduce the risk of CV mortality or all-cause mortality, it is important to not only take measures to prevent SH but also carefully screen the type 2 diabetes population with a high risk of CVD and a history of SH. Moreover, additional studies are needed to clarify the underlying mechanisms linking CVD and SH.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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