Severe Hypoglycemia is a Risk Factor for Atrial Fibrillation in Type 2 Diabetes Mellitus: Nationwide Population-Based Cohort Study

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Abstract

Aims: This study investigated the association between severe hypoglycemia (SH) and new onset atrial fibrillation (AF) and all-cause mortality in adult patients with type 2 diabetes mellitus (T2DM).

Methods: Retrospective data on patients with T2DM aged between 30 and 75 years who received healthcare checkups from January 1, 2005 to December 31, 2008 were analyzed using the National Health Insurance Database in Korea. The primary outcome was newly diagnosed non-valvular AF occurring after SH episode using ICD-10 codes.

Results: Among 1,509,280 subjects, 10,864 (0.72%) patients had experienced SH events in the three years prior to health examination, and a total of 48,916 (3.24%) first-time AF episodes occurred during the follow-up period of 8.5 years. The incidence of AF was significantly higher in the group with SH than the group without SH. After multivariable adjustment, previous SH was a significant risk factor for the development of AF (HR 1.10, 95% CI 1.01–1.19). All-cause mortality was also significantly increased in patients with previous SH events and prior SH with subsequent AF occurrence, compared to patients without SH events.

Conclusions: Prior SH events were associated with a higher risk of new onset AF and all-cause mortality in patients with T2DM.

Keywords

Diabetes type 2; severe hypoglycemia; atrial fibrillation; all-cause mortality

1. Introduction

Many large epidemiological studies have shown that glycemic control within the target range is the only proven strategy for the prevention of diabetic vascular complications.[1] To achieve this goal active use of oral antidiabetic agents or insulin should be initiated, along with lifestyle modification after the diagnosis of diabetes, matching the individual's situation. [2] However, with intensive glycemic control with antidiabetic medication, patients with type 2 diabetes mellitus inevitably incur the risk of hypoglycemia.[3,4]

A hypoglycemic episode, regardless of its severity, is clinically important due to its association with increased cardiovascular (CV) events and mortality.[5] A meta-analysis including 903,510 subjects with type 2 diabetes demonstrated that severe hypoglycemia (SH) was significantly associated with a higher risk of cardiovascular disease (CVD).[6] Moreover, a strong association has been found between SH and an increased risk of all-cause and CV mortality in patients with type 2 diabetes mellitus.[7]

The pathophysiologic link between SH and CVD or CV death has not been fully elucidated. Hypoglycemia has the potential to trigger fatal arrhythmic events by more than one mechanism in patients with high CV risk.[8] Previous studies have demonstrated that hypoglycemia directly or indirectly influences myocardial ischemia or QT interval prolongation by abnormal repolarization, enhanced adrenergic tone, and cardiac autonomic dysfunction.[9,10] During an SH episode, the QTc interval has been known to be prolonged significantly, independent of diabetic duration, age, diabetic medications (insulin or sulfonylurea), and glycemic control status in type 2 diabetes.[11] According to an Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial, SH was associated with an increased risk for arrhythmic death (HR 1.77) in patients with high CV risk and dysglycemia.[12]

Atrial fibrillation (AF) is the most common arrhythmia in the general population, with an estimated lifetime risk of 25% worldwide.[13] Clinically, AF is important due to its association with increased risk of stroke, heart failure, myocardial infarction, and total mortality.[14] Diabetes itself has been identified as a risk factor for AF, increasing the risk of new onset AF by 34–40%.[15] With numerous metabolic defects, atrial structural, electrical, and electromechanical remodeling are suggested mechanisms in the relationship between diabetes and AF.[16] AF has been reported as a complication of hypoglycemia in case reports [17,18] and severe hypoglycemia was reported in a single-center retrospective cohort study in patients with diabetes.[19] However, there are few studies focusing on the relationship between SH and new onset AF in patients with type 2 diabetes mellitus.

In Korea, the national health care program, the National Health Insurance Service (NHIS), covers the entire Korean population as a social insurance benefits scheme.[20] Based on the NHI program, the computerized database contains all of the national health examination data, claim data, including drug prescriptions, diagnostic codes for the International Classification of Disease-10 (ICD-10) disease coding system, and claimed treatment details. [20,21] From this database, claim data regarding patients with type 2 diabetes mellitus with a prior history of SH within a certain period and subsequent development of CV events can be extracted.

The aim of this study was to investigate the association between previous SH episodes and the risk of AF and all-cause mortality in adult patients with type 2 diabetes mellitus using the NHIS claim database from January 1, 2002 to December 31, 2015 in Korea.

2. Subjects, Materials and Methods

2.1. Source of the database

In this retrospective cohort study, we used the NHI database maintained by the Korean NHIS, a government-affiliated agency under the Korean Ministry of Health and Welfare that supervises all medical services in Korea. All Korean people aged 30 years and older are encouraged to receive regular biennial or pre-employment healthcare checkups provided by the NHIS. This regular healthcare checkup includes anthropometric measurements, blood pressure, social habits, physical activity, and laboratory tests after overnight fasting, including serum glucose, total cholesterol, creatinine, liver function, and urinalysis. Quality control procedures for laboratory tests were performed in accordance with the Korean Association of Laboratory Quality Control.[21] Past history, alcohol, smoking, and exercise habits were collected by standardized self-reporting questionnaires. Additionally, the NHIS contains information on the patients' demographics, medical use, transaction information, healthcare checkups, and claim database.[20,21]

This study was approved by the institutional review board of the Catholic University of Korea (VIRB-0E237-001). The study was conducted in compliance with the Declaration of Helsinki.

2.2. Definition of type 2 diabetes, severe hypoglycemia, and atrial fibrillation

Among all of the NHI beneficiaries, the source population for this study consisted of patients who visited clinics or hospitals with an ICD-10 of type 2 diabetes mellitus (E11, E14) from January 1, 2002 to December 31, 2015. A diagnosis of type 2 diabetes mellitus based on ICD-10 codes included the principal diagnosis and up to four additional accompanying diagnoses to reflect clinical significance in the current condition. Patients were classified as having type 2 diabetes mellitus when they had at least one service claim with a diagnosis of type 2 diabetes, either in outpatient or inpatient care, and were prescribed at least one antidiabetic drug any time during a given year to exclude prediabetic or non-diabetic subjects.[20]

The inclusion criteria for patients with type 2 diabetes mellitus were as follows 1) between 30 and 75 years of age; 2) received healthcare checkups between January 1, 2005 and

December 31, 2008; 3) treated with hypoglycemic agents (including insulin) on claim database or fasting plasma glucose 126 mg/dL on healthcare checkup examination (newly diagnosed diabetes); and 4) subjects who had not been diagnosed with AF before January 1, 2005 to exclude participants with a prior history of AF (Fig. 1). Type 1 diabetes, gestational diabetes, subjects with missing data, and those diagnosed with mitral stenosis (I050, I52, I059), or mechanical heart valves (Z952-Z954) were excluded.[21]

Severe hypoglycemia (SH) was defined as any hypoglycemic events requiring the assistance of another person to actively administer carbohydrates, other corrective actions, hospitalization, or medical care.[22] Plasma glucose levels may not be available, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence.[22] Due to the limitation of claim data, in which glucose concentrations during SH events could not be confirmed, we used the ICD-10 codes of SH. To investigate the effect of previous SH events on the future development of AF, we collected all admission episodes reporting SH (ICD-10 codes of E16.x, E11.63, E13.63, E14.63) from the inpatients or emergency room claim dataset between January 1, 2002 and December 31, 2007 (Additional file, Figure 1) among the patients with type 2 diabetes mellitus. To obtain high enough number of SH events, we searched whether the participants had experienced at least one SH episode within the 3 years prior to the date of the current health examination using ICD-10 codes.

Hypertension was defined with the ICD-10 codes of I10-I13, and I15 and treatment with anti-hypertensive agents, or systolic or diastolic blood pressure 140 mmHg / 90 mmHg, hyperlipidemia as E78 with treatment with lipid-lowering agents or total cholesterol 240 mg/dL, congestive heart failure (CHF) as I50, and end-stage renal disease (ESRD) as N18–19, Z49, Z940, Z90, Z992.[20,21,23] Previous medical history of ischemic stroke or myocardial infarction was defined as ICD-10 codes of I63-I64 or I21-I22 before the date of the health examination.[23] Previous history of hyperthyroidism was defined as ICD-10 code of E05.

Demographic characteristics were abstracted, including age, sex, body mass index (BMI), and urbanization level of residence. We identified low socioeconomic status population as lowest quartile income status. Heavy drinking was defined as alcohol habits of 5 days/week, and physical activity was defined as 1 /week of moderate exercise.

The primary outcome was newly diagnosed non-valvular AF, either one diagnosis (ICD-10 code of I48.0-I48.4, I48.9) during hospitalization, more than twice at outpatient clinics, or until censoring by death.[21] Development of AF after an SH event was considered to be newly developed AF if the patient had no previous diagnosis of AF before the healthcare checkup. For all-cause mortality, those patients who died of any cause were selected. Individuals with SH episodes occurring after the beginning of follow-up for AF were excluded.

2.3. Statistical analysis

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). Descriptive characteristics were presented as mean ± SD or 95% confidence interval. Data were also expressed as numbers and as a frequency percentage (%). The χ^2 test was used to

determine differences in the proportion of categorical variables, and independent Student's *t* tests evaluated differences between the means of two continuous variables. Incidence rates were expressed as events per 1,000 patient-years and adjusted for age and sex using a direct method. Participants were followed until the first diagnosis of AF, death, or December 31, 2015. Cox proportional hazards regression analysis was used to estimate the hazard ratios (HRs) and 95% confidence interval (CIs) for the association between the prior SH events and development of AF after adjustment for sex, age, BMI, hypertension, heavy alcohol drinking, current smoking, exercise, presence of ESRD, history of ischemic stroke or myocardial infarction, insulin use, history of hyperthyroidism, and CHF. Potential confounders were identified *a priori* based on the literature review. The proportional hazards assumption was evaluated by Schoenfeld residuals, with the logarithm of the cumulative hazards function based on Kaplan-Meier curves estimated for the presence or absence of prior SH events. The potential effect modification by age, sex, and various accompanying clinical conditions was evaluated through the stratified analysis and interaction testing using the likelihood ratio test, and the *P* value for interaction was presented with a significance of < 0.25. All-cause mortality according to the absence of SH events, SH, and SH with AF was analyzed using the Kaplan-Meier curve. The multivariable-adjusted proportional hazards model was used to evaluate the association between prior SH events, incident AF, and all-cause mortality. A two-sided *P* value < 0.05 was considered statistically significant.

3. Results

3.1.1 Clinical characteristics of the study population according to SH events and the development of AF

From January 1, 2005 to December 31, 2008, 17,737,303 subjects had received a national health examination. After exclusion, 1,509,280 participants with type 2 diabetes mellitus who had not been diagnosed with AF were included in this study (Fig. 1). Among them, we identified 10,864 (0.72%) patients who had experienced SH episodes within the 3 years before the date of the current health examination.

Patients with a prior history of SH were older (61.3 ± 9.6 vs. 54.9 ± 10.9 years), had a lower BMI level (24.1 ± 3.5 vs. 25.0 ± 3.3 kg/m^2) and a lower proportion of males (51.6% vs. 63.9%), as compared to those without SH. They also had a higher rate of the presence of hypertension (66.7% vs. 53.3%), myocardial infarction (6.5% vs. 1.5%), congestive heart failure (7.1 % vs. 2.2%), and insulin treatment (29.7% vs. 6.3%), compared to the patients without SH (Table 1).

During the follow-up period of 8.5 years, 48,916 individuals (3.24% of the total patients with type 2 diabetes) were newly diagnosed with AF, with an incidence rate of 3.5 per 1,000 person-years. The mean time from SH events to AF development was 7.7 years (median 8.3 years). The proportion of subjects who developed AF was significantly different between the no SH and prior SH groups (3.2% vs. 5.5%, *P* < 0.001). The incidences of AF in patients with type 2 diabetes with previous SH and without SH were 7.09 and 3.79 per 1,000 person-years, respectively (*P* < 0.001) (Table 2). The incidence rate of AF was significantly increased with increasing age, both in the no SH and prior SH groups (*P* value for trend < 0.001 both, Supplement Fig. 2).

3.2. Risk factors for incident AF

The age and sex-adjusted HR for AF according to SH experience was 1.36 (95% CI 1.26–1.48) (Table 2). This significant association also persisted after adjusting for age, sex, BMI, smoking and drinking habits, socioeconomic status, the presence of hypertension or ESRD, history of heart failure, myocardial infarction, ischemic stroke, or hyperthyroidism, and insulin or sulfonylurea use (HR 1.10, 95% CI 1.01–1.19) (Table 3, Fig 2A). Additionally, in females (HR 1.56, 95% CI 1.53–1.59), the presence of hypertension (HR 1.39, 95% CI 1.36–1.42), congestive heart failure (HR 2.57, 95% CI 2.49–2.66), use of sulfonylurea (SU) (HR 1.07, 95% CI 1.05–1.09), and use of insulin (HR 1.51, 95% CI 1.46–1.55) were also significant predictive factors for the development of AF (Table 3).

In subgroup analysis, the association between prior SH and incident AF was stronger in patients aged < 55 years (HR 1.52, 95% CI 1.22–1.89) than in aged   55 years (1.14, 95% CI 1.05–1.25) (*P* for interaction = 0.0001). Patients without underlying CHF had a stronger association with incident AF (HR 1.15, 95% CI 1.06–1.26) than incident AF with underlying CHF (HR 0.92, 95% CI 0.74–1.15) (*P* for interaction = 0.032). Also, patients without underlying myocardial infarction (HR 1.11, 95% CI 1.02–1.21) or ischemic stroke (HR 1.12, 95% CI 1.02–1.23) had a stronger association with incident AF than incident AF with underlying myocardial infarction (HR 0.95, 95% CI 0.73–1.24) or ischemic stroke (HR 1.01, 95% CI 0.85–1.19) (*P* for interaction = 0.206 and 0.066, respectively) (Fig 3).

3.3. All-cause mortality after SH

During the observation period 128,335 subjects (8.5%) died. More patients from the SH group died than in the non-SH group (23.4% vs. 8.4%, *P* < 0.001). The all-cause mortality in people with type 2 diabetes who had experienced SH was 52.9 per 1,000 patient-years. When the subjects were divided into 3 groups according to the presence of prior SH events and SH following AF events, the mortality rate was significantly higher in patients with prior SH events and prior SH with following AF events compared to that in patients from the non-SH episode group (28.6 vs. 63.9 vs. 9.1 per 1,000 patient-years, *P* < 0.001). Compared to patients without SH events, the all-cause mortality was significantly higher in patients with previous SH events (HR 1.57, 95% CI 1.50–1.64) and prior SH with subsequent AF occurrence (HR 4.64, 95% CI 4.55–4.74) after adjustment for multiple variables (Fig. 2B).

4. Discussion

In this analysis using a national database of health insurance claims in Korea, we found substantial and significant development of AF after SH episodes in patients with type 2 diabetes mellitus during the past decade. To the best of our knowledge, the present study is the first evidence of SH as a risk factor for AF in a large number of patients with type 2 diabetes mellitus. Importantly, the development of AF after SH was independent of preexisting cardiovascular disease.

Data has suggested that type 2 diabetes mellitus is strongly associated with an increased risk of AF.[15] In a meta-analysis involving 108,703 cases of AF in 1,686,097 patients from cohort and case-control studies, diabetes was associated with an overall 34% increase in the risk of

AF.[15] Diabetic cardiomyopathy, cardiac autonomic dysfunction, sympathetic over-activity, electrical, electromechanical, and structural remodeling, oxidative stress, and glycemic fluctuations were considered pathophysiological mechanisms implicating AF in diabetes.[24] Paroxysmal AF episodes are preceded by autonomic fluctuations, with a primary increased sympathetic tone followed by a marked modulation toward vagal predominance.[25] Additionally, excess CV morbidity and mortality are attributable to AF in patients with diabetes. According to the ADVANCE (Action in Diabetes and Vascular Disease: PreterAx and Diamicron-MR Controlled Evaluation) study, AF was associated with an increased risk of all-cause mortality, CV death, stroke, and heart failure in patients with type 2 diabetes.[26]

Intensive glycemic control is inevitably accompanied by an increased frequency and severity of hypoglycemic episodes in patients with type 2 diabetes. According to the ADVANCE Collaborative group study, 231 of 11,140 patients with type 2 diabetes (2.1%) had at least one SH event.[4] Moreover, SH was significantly associated with an increased risk of macrovascular complications, adverse clinical outcomes, and all-cause mortality.[4–7] However, the effect of SH on new-onset AF in patients with type 2 diabetes is still unknown.

Hypoglycemia increased the risk of arrhythmia in patients with type 2 diabetes and high CV risk. Bradycardia, QTc prolongation, and atrial and ventricular ectopic beats were significantly higher during hypoglycemic or severe hypoglycemic events.[27] This hypoglycemia-associated arrhythmia has been proposed as a predisposing factor for SH-induced CV morbidity and mortality. Although hypoglycemia or SH-associated fatal cardiac arrhythmia is difficult to confirm because simultaneous monitoring of glucose level and cardiac rhythm is rarely undertaken, arrhythmic deaths were reported as a direct cause of mortality.[28] The arrhythmogenic effect of hypoglycemia is likely to be greatest in patients with pre-existent cardiac disease and diabetes.[10]

In this study, we demonstrated that previous SH episodes were significantly associated with an incident AF onset in patients with type 2 diabetes mellitus. After adjustment of multiple clinical covariates, a previous SH event was significantly associated with an incident AF. Additionally, old age, male sex, current smoking status, heavy alcohol use, presence of hypertension, ESRD, pre-existing myocardial infarction, ischemic stroke, hyperthyroidism or CHF, and the use of insulin or sulfonylurea were also associated with AF development after SH events. In subgroup analysis, the AF development after SH events was significantly increased in patients aged 55 years and younger and in patients without CHF or CVD experiences. Importantly, compared to patients without SH, patients with SH or SH with incident AF showed a significantly increased all-cause mortality during the observation period. With our study design, we can't definitively say that there is a direct causal relationship between SH and AF due to the long lag time (7.7 years) from SH experience to AF occurrence. We showed only a close association between SH episode and AF or all-cause mortality. We believed that AF development combined with SH history could be an important risk factor for increased mortality in patients with type 2 diabetes mellitus.

There were some limitations in this analysis. First, because health insurance coverage is confined to the allowable range based on the recommendations of antidiabetic drug combinations made by the Health Insurance Review and Assessment Service in Korea,

prescriptions not covered by health insurance were missed in this analysis. Second, subjects with disease codes E11–14 who were not on anti-diabetic medication were not included in this analysis. Third, this analysis relied only on claim data; therefore, we could not obtain clinical information on HbA1c levels, diabetic duration, glucose level during the SH event, or electrocardiographic findings. AF was diagnosed only by claim data. Also, SH episodes without claim, which were not presented to emergency departments or clinics, asymptomatic or mild to moderate hypoglycemia could not be detected. Therefore, some individuals with symptomatic or paroxysmal AF may have been missed. Finally, the cause of death could not be confirmed by claim data.

Despite these limitations, the major strength of this study was that the data, including anthropometric, clinical information, and baseline laboratory results, were based on a nationwide Korean population covering nearly 100% of Korean patients with type 2 diabetes, which provided evidence regarding real-world clinical practice.

In conclusion, previous SH events were important independent risk factors for incident onset of AF and all-cause mortality in patients with type 2 diabetes mellitus. Importantly, compared to patients with SH, subjects with SH with subsequent AF showed significantly higher mortality. Therefore, SH events should be avoided in patients with type 2 diabetes mellitus who are vulnerable to cardiac arrhythmia or preexisting cardiac disease. Future research should be conducted to define the mechanism between SH and cardiac arrhythmia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

List of Abbreviations:

AF	atrial fibrillation
BMI	body mass index
CHF	congestive heart failure
CVD	cardiovascular disease
ESRD	end-stage renal disease
ICD-10	International Classification of Diseases, 10th revision
NHIS	National Health Insurance Service
SH	severe hypoglycemia

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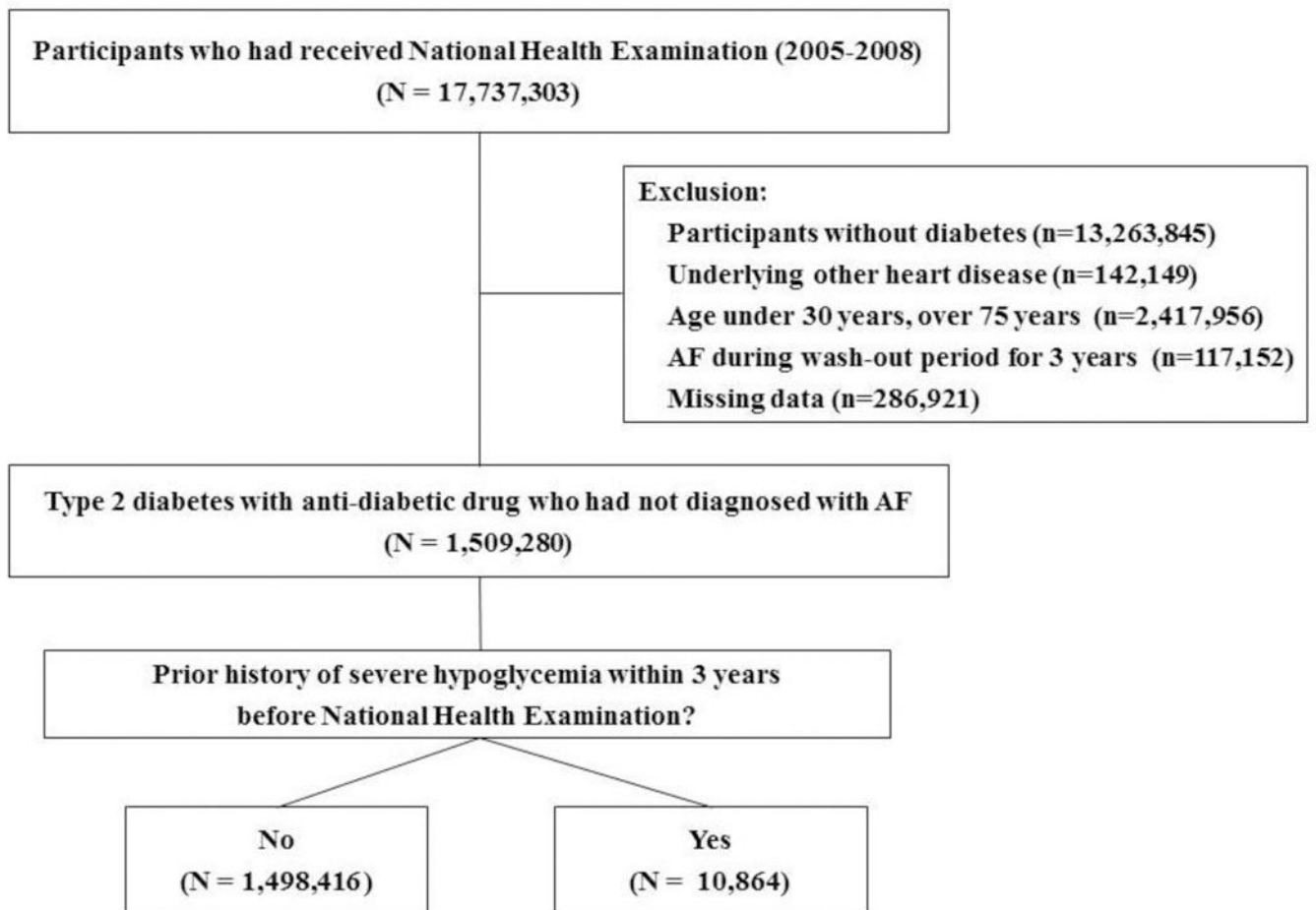
Fig. 1.
Sample recruitment from the database of National Health Insurance Service

		HR [95% CI]	P for interaction
Age	<55 years	1.52 [1.22 , 1.89]	0.0001
	≥ 55 years	1.14 [1.05 , 1.25]	
Sex	Male	1.09 [0.97 , 1.21]	0.6696
	Female	1.15 [1.01 , 1.29]	
Hypertension	No	1.10 [0.92 , 1.31]	0.8457
	Yes	1.12 [1.02 , 1.23]	
High TC	No	1.07 [0.97 , 1.19]	0.4074
	Yes	1.18 [1.03 , 1.36]	
BMI (kg/m^2)	< 25	1.15 [1.03 , 1.28]	0.0929
	≥ 25	1.05 [0.92 , 1.20]	
Heart failure	No	1.15 [1.06 , 1.26]	0.0321
	Yes	0.92 [0.74 , 1.15]	
Myocardial infarction	No	1.11 [1.02 , 1.21]	0.2062
	Yes	0.95 [0.73 , 1.24]	
Ischemic stroke	No	1.12 [1.02 , 1.23]	0.0655
	Yes	1.01 [0.85 , 1.19]	
ESRD	No	1.12 [1.03 , 1.22]	0.5467
	Yes	0.96 [0.65 , 1.42]	
Hyperthyroidism	No	1.13 [1.03 , 1.23]	0.2596
	Yes	0.99 [0.75 , 1.31]	

Hazard Ratio

0.50   1.00   1.50   2.00

Fig. 2.
(A) Prior severe hypoglycemia (SH) events and the risk of atrial fibrillation (AF). (B) All-cause mortality according to the presence of SH events.

Fig. 3.
Hazard ratios for the risk of AF following severe hypoglycemia (SH) in subgroups.
Data are HRs (95% CI). TC, total cholesterol; BMI, body mass index; ESRD, end-stage
renal disease.

Table 1.

Baseline characteristics of study participants according to prior hypoglycemic events

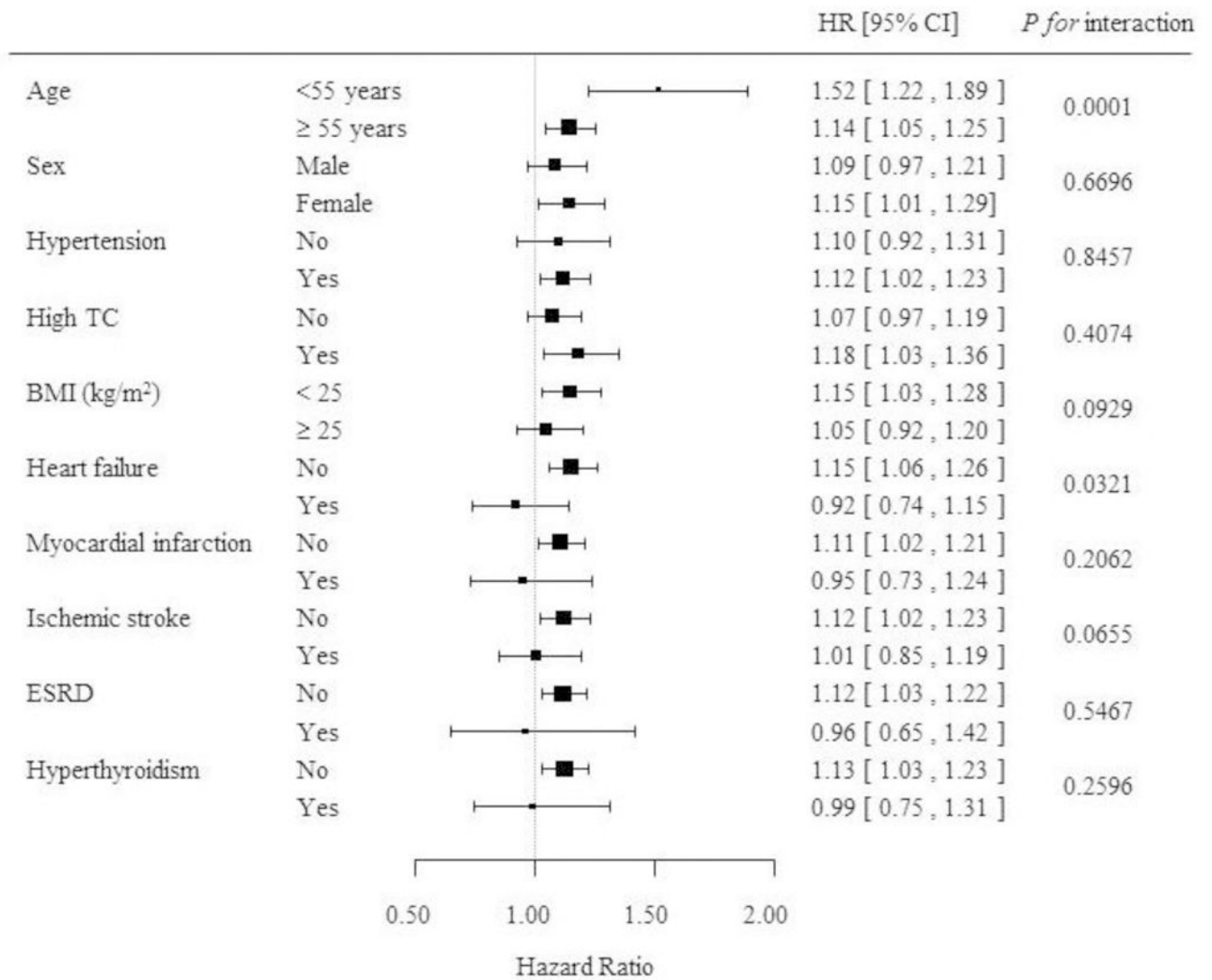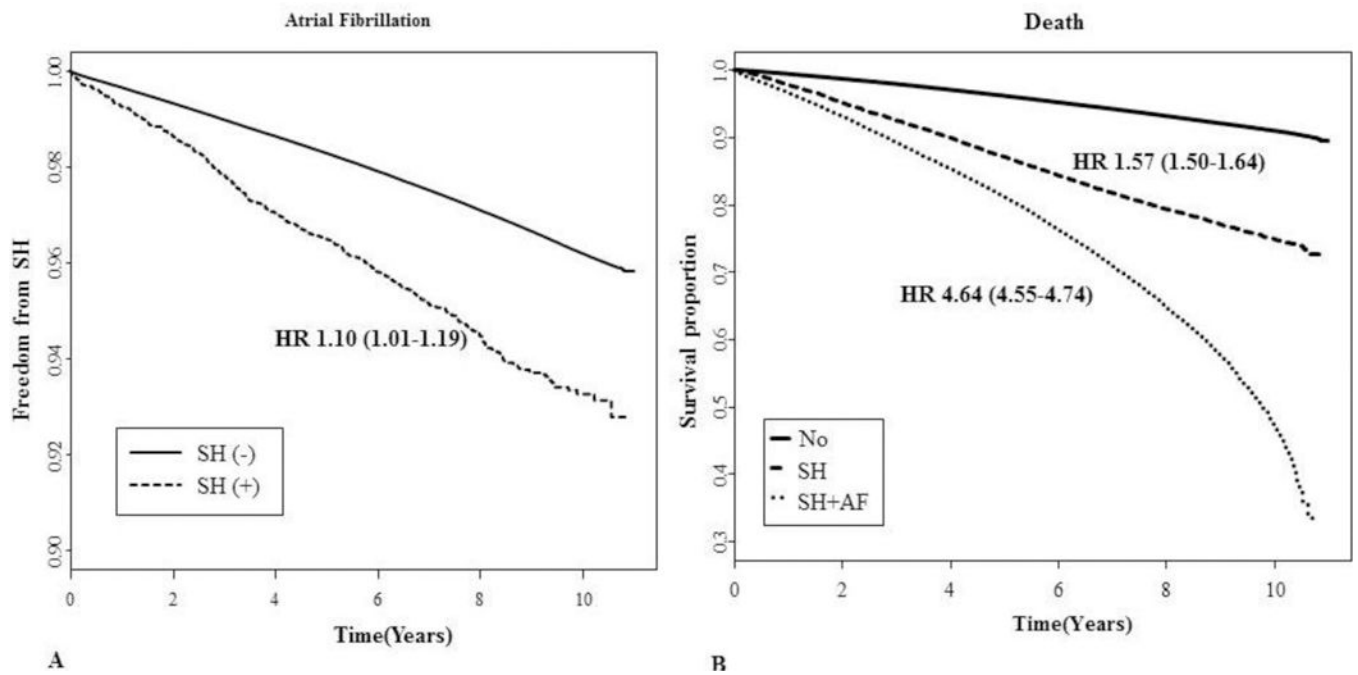| ☐	Severe Hypoglycemia		*P* value
	NO	YES	
N (%)	1,498,416 (99.3)	10,864 (0.7)	
Age (year-old)	54.9 ± 10.9	61.3 ± 9.6	<0.001
Age (55 year-old) (%)	775,460 (51.8)	8,213 (75.6)	<0.001
Sex (male)(%)	957,587 (63.9)	5,600 (51.6)	<0.001
Height (cm)	162.9 ± 9.0	159.6 ± 9.1	<0.001
Weight (kg)	66.5 ± 11.2	61.5 ± 10.9	<0.001
BMI (kg/m^2)	25.0 ± 3.3	24.1 ± 3.5	<0.001
BMI (25 kg/m^2) (%)	719,520 (48.0)	4,171 (38.4)	<0.001
Systolic blood pressure (mmHg)	130.7 ± 17.0	130.7 ± 17.9	0.9919
Diastolic blood pressure (mmHg)	80.5 ± 10.8	78.8 ± 10.7	<0.001
Current smoking (%)	412,025 (27.5)	2,051 (18.9)	<0.001
Drinker (heavy) (%)	74,598 (5.0)	486 (4.47)	0.0159
Exercise (yes) (%)	759,217 (50.7)	4,802 (44.2)	<0.001
Hypertension (yes) (%)	798,214 (53.3)	7,251 (66.7)	<0.001
Low economic status (%)	397,663 (26.5)	2,838 (26.1)	0.328
Rural area (%)	872,444 (55.6)	6,716 (62.5)	<0.001
Hyperlipidemia (%)	471,195 (31.5)	3,853 (35.5)	<0.001
Heart failure (%)	33,280 (2.2)	769 (7.1)	<0.001
Myocardial infarction (%)	23,035 (1.5)	706 (6.5)	<0.001
Ischemic stroke (%)	83,825 (5.6)	1,971 (18.1)	<0.001
End stage renal disease (%)	1,746 (0.1)	250 (2.3)	<0.001
Hyperthyroidism (%)	54,969 (3.7)	805 (7.4)	<0.001
Total cholesterol (mg/dL)	201.4 ± 43.0	191.2 ± 45.6	<0.001
Fasting glucose (mg/dL)	149.6 ± 51.6	145.4 ± 67.7	<0.001
Antidiabetic therapy			
Insulin (%)	94,582 (6.3)	3,224 (29.7)	<0.001
Sulfonylurea (%)	661,037 (44.1)	7,037 (64.8)	<0.001
Metformin (%)	504,599 (33.7)	5,785 (53.3)	<0.001

Data are mean ± SD or number (%). BMI, body mass index

Table 2.

Incidence rate and hazard ratios for the risk of atrial fibrillation in subgroups analysis

	SH	Event	Duration (year)	IR of AF*	Age, sex-adjusted HR (95% CI)	P value	P for interaction
SH	No	48,323	12,760,497	3.79	1		
	Yes	593	83,668	7.09	1.36 (1.26–1.48)	<.0001	
Age (years)							<.0001
< 55	No	10,734	6,312,940	1.70	1		
	Yes	84	21,761	3.86	2.09 (1.69–2.59)	<.0001	
55	No	37,589	6,447,558	5.83	1		
	Yes	509	61,907	8.22	1.30 (1.19–1.42)	<.0001	
Sex							0.753
Male	No	31,568	8,101,323	3.90	1		
	Yes	321	41,445	7.75	1.35 (1.21–1.51)	<.0001	
Female	No	16,755	4,659,174	3.60	1		
	Yes	272	42,223	6.44	1.37 (1.22–1.55)	<.0001	
Hypertension							0.041
No	No	14,735	6,037,202	2.44	1		
	Yes	130	28,924	4.50	1.29 (1.08–1.53)	0.004	
Yes	No	33,588	6,723,295	4.50	1		
	Yes	463	54,744	8.46	1.36 (1.24–1.49)	<.0001	
BMI (kg/m^2)							0.041
< 25	No	24,011	6,591,888	3.64	1		
	Yes	369	50,103	7.37	1.48 (1.34–1.64)	<.0001	
25	No	24,312	6,168,609	3.94	1		
	Yes	224	33,564	6.67	1.24 (1.09–1.41)	0.0014	
Heart failure							0.649
No	No	44,575	12,502,302	3.57	1		
	Yes	507	78,626	6.45	1.33 (1.22–1.45)	<.0001	
Yes	No	3,748	258,195	14.5	1		
	Yes	86	5,041	17.1	1.07 (0.86–1.32)	0.563	
MI							0.045
No	No	46,527	12,578,387	3.70	1		
	Yes	531	78,694	6.75	1.33 (1.22–1.45)	<.0001	
Yes	No	1,796	182,110	9.86	1		
	Yes	62	4,974	12.5	1.14 (0.88–1.47)	0.322	
Stroke							0.181
No	No	42,950	12,092,206	3.55	1		
	Yes	452	69,701	6.49	1.35 (1.23–1.49)	<.0001	
Yes	No	5,373	668,291	8.04	1		

	SH	Event	Duration (year)	IR of AF[*]	Age, sex-adjusted HR (95% CI)	*P* value	*P* for interaction
	Yes	141	13,967	10.10	1.17 (0.99–1.38)	0.0716	
Insulin use							0.733
No	No	42,977	12,025,972	3.57	1		
	Yes	360	61,106	5.89	1.19 (1.07–1.32)	0.0011	
Yes	No	5,346	734,525	7.28	1		
	Yes	233	22,561	10.3	1.25 (1.10–1.43)	0.0007	
SU use							0.008
No	No	22,021	7,124,365	3.09	1		
	Yes	203	29,331	6.92	1.55 (1.35–1.78)	<.0001	
Yes	No	26,302	5,636,132	4.67	1		
	Yes	390	54,337	7.18	1.27 (1.15–1.40)	<.0001	
ESRD							0.356
No	No	48,098	12,750,093	3.77	1		
	Yes	561	82,323	6.82	1.31 (1.21–1.42)	<.0001	
Yes	No	225	10,404	21.6	1		
	Yes	32	1,345	23.8	1.09 (0.75–1.57)	0.663	
Hyperthyroidism							0.222
No	No	45,682	12,300,520	3.71	1		
	Yes	542	77,520	6.99	1.36 (1.25–1.48)	<.0001	
Yes	No	2,641	459,977	5.74	1		
	Yes	51	6,148	8.30	1.16 (0.88–1.53)	0.2486	

[*], incidence rate of AF (events/1,000 patient-years)

SH, severe hypoglycemia; BMI, body mass index; MI, myocardial infarction; SU, sulfonylurea; ESRD, end-stage renal disease

Table 3.

Multivariate cox proportional hazard regression analysis of incident occurrence of atrial fibrillation in patients with type 2 diabetes

	Hazard ratio (95% CI)	P value
Severe hypoglycemia (yes)	1.10 (1.01–1.19)	0.0300
Age (years)		< 0.0001
30–39	1	
40–49	2.17 (2.02–2.33)	
50–59	4.16 (3.88–4.45)	
60–74	8.61 (8.04–9.22)	
Sex (male)	1.56 (1.53–1.59)	< 0.0001
BMI 25 kg/m^2	1.11 (1.09–1.13)	< 0.0001
Smoking (current)	1.06 (1.03–1.08)	< 0.0001
Alcohol (heavy)	1.19 (1.15–1.24)	< 0.0001
Exercise (yes)	0.90 (0.89–0.92)	< 0.0001
Urban place	1.07 (1.05–1.09)	< 0.0001
Low economic status (Q1)	0.99 (0.97–1.01)	0.218
Hypertension	1.39 (1.36–1.42)	< 0.0001
Congestive heart failure	2.57 (2.49–2.66)	< 0.0001
Myocardial infarction	1.55 (1.48–1.63)	< 0.0001
Ischemic stroke	1.32 (1.28–1.36)	< 0.0001
End-stage renal disease	2.85 (2.51–3.23)	< 0.0001
Insulin use	1.51 (1.46–1.55)	< 0.0001
Sulfonylurea use	1.07 (1.05–1.09)	< 0.0001
Hyperthyroidism	1.35 (1.30–1.41)	< 0.0001