Vital Signs, QT Prolongation, and Newly Diagnosed Cardiovascular Disease During Severe Hypoglycemia in Type 1 and Type 2 Diabetic Patients

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OBJECTIVE

To assess vital signs, QT intervals, and newly diagnosed cardiovascular disease during severe hypoglycemia in diabetic patients.

RESEARCH DESIGN AND METHODS

From January 2006 to March 2012, we conducted a retrospective cohort study to assess type 1 and type 2 diabetic patients with severe hypoglycemia at a national center in Japan. Severe hypoglycemia was defined as the presence of any hypoglycemic symptoms that could not be resolved by the patients themselves in prehospital settings.

RESULTS

A total of 59,602 cases that visited the emergency room by ambulance were screened, and 414 cases of severe hypoglycemia were analyzed. The median (interquartile range) blood glucose levels were not significantly different between the type 1 diabetes mellitus (T1DM) (*n* = 88) and type 2 diabetes mellitus (T2DM) (*n* = 326) groups (32 [24–42] vs. 31 [24–39] mg/dL, *P* = 0.59). During severe hypoglycemia, the incidences of severe hypertension (≥180/120 mmHg), hypokalemia (<3.5 mEq/L), and QT prolongation were 19.8 and 38.8% (*P* = 0.001), 42.4 and 36.3% (*P* = 0.30), and 50.0 and 59.9% (*P* = 0.29) in the T1DM and T2DM groups, respectively. Newly diagnosed cardiovascular disease during severe hypoglycemia and death were only observed in the T2DM group (1.5 and 1.8%, respectively). Blood glucose levels between the deceased and surviving patients in the T2DM group were significantly different (18 [14–33] vs. 31 [24–39] mg/dL, *P* = 0.02).

CONCLUSIONS

T1DM and T2DM patients with severe hypoglycemia experienced many critical problems that could lead to cardiovascular disease, fatal arrhythmia, and death.

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Severe hypoglycemia is a potentially life-threatening condition that can cause seizures, loss of consciousness, brain damage, and even death (1). Several studies examining diabetes mellitus have suggested that hypoglycemia may be associated with increased mortality and cardiovascular disease (2,3). In addition, some reports have indicated that hypoglycemia may be associated with a higher mortality rate among patients with critical illness or coronary heart disease (4–6). However, the available data remain insufficient to explain these observations.

Serious conditions can be anticipated during severe hypoglycemia based on previous case reports (7,8), observational studies (4–6), and small interventional studies in which patients experienced mild to moderate hypoglycemia (9,10). Moreover, recent studies have suggested an association between hypoglycemia and prolongation of the QT interval (11–13). However, various aspects of the actual conditions and complications that occur during severe hypoglycemia remain unclear.

To gain further understanding of this topic, we systematically assessed the vital signs, QT intervals, and presence of newly diagnosed cardiovascular disease during episodes of severe hypoglycemia in type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) patients.

RESEARCH DESIGN AND METHODS

We conducted a retrospective cohort study of patients with diabetes mellitus who experienced severe hypoglycemia and were transported by ambulance to the National Center for Global Health and Medicine in Tokyo, Japan, between 1 January 2006 and 31 March 2012. The eligibility criteria included a diagnosis of T1DM or T2DM and severe hypoglycemia. The exclusion criteria included cardiopulmonary arrest upon arrival. Severe hypoglycemia was defined as the presence of any hypoglycemic symptoms that could not be resolved by the patients themselves in prehospital settings and that required the medical assistance of another person after visiting the emergency room by ambulance (14). The patients' blood glucose levels were primarily measured at a central laboratory (79% [325 of 413]), although some were measured using a blood glucose meter (21% [88 of 413]). We assessed all newly diagnosed complications during episodes of severe hypoglycemia and the mortality rate as well as the patients' characteristics, vital signs, and electrocardiograms obtained upon hospital arrival. The patients' characteristics included not only general information, such as age and sex, but also the causes of the severe hypoglycemia. At least two diabetologists independently reviewed all data, including the clinical records, laboratory reports, and electrocardiograms. Disagreements between the reviewers were resolved by a third diabetologist. Diabetes mellitus was confirmed when the patient had been previously diagnosed as having diabetes mellitus or was being treated with antidiabetes medicines, and we classified the diabetes mellitus into T1DM, T2DM, or other types of diabetes mellitus. T1DM was confirmed by a previous diagnosis or the presence of antibodies to GAD, while T2DM was confirmed by a previous diagnosis or the absence of a specific cause. Multiple visits to the hospital by the same patient were analyzed as separate cases. All eligible patients in this study were followed up until they left the hospital or died. This study was approved by the institutional review board of the National Center for Global Health and Medicine.

Consciousness Level and Vital Signs

The consciousness level during an episode of severe hypoglycemia was evaluated using the Glasgow Coma Scale (GCS) score (15), which is composed of three parameters: best eye response between 1 and 4, best verbal response between 1 and 5, and best motor response between 1 and 6. The total GCS score can range from 3 to 15, with 3 being the worst and 15 being the best. The patients' body temperature, blood pressure, heart rate, and respiratory rate were also assessed. Upon arrival to our hospital, patient body temperature was measured via the rectum, axilla, or tympanic membrane, and we preferentially referred to the rectal temperature. Hypothermia was defined as a body temperature of $<35^{\circ}C$ (16). Systolic blood pressure, diastolic blood pressure, and heart rate were measured upon hospital arrival. Both the systolic and diastolic blood pressures were also checked at 1 h and 12 h after treatment initiation, provided that antihypertensive or vasopressor drugs were not used during that period. Severe hypertension was defined as a systolic blood pressure of $\geq$180 mmHg or a diastolic blood pressure of $\geq$120 mmHg (17).

Newly Diagnosed Diseases

Newly diagnosed cardiovascular disease, atrial fibrillation, and trauma during episodes of severe hypoglycemia were assessed by reviewing the medical records, laboratory data, electrocardiograms, and radiological images. Cardiovascular disease and trauma were strictly defined prior to the review. Cardiovascular disease was defined as coronary heart disease requiring treatment to achieve revascularization or as stroke confirmed radiologically by the presence of an acute lesion(s). Trauma was defined as any traumatic disease and included traumatic intracranial hemorrhage, fractures, abrasions, and bruises as a result of external pressure. The possible presence of other arrhythmias was also examined by reviewing the medical records and the electrocardiograms obtained upon arrival.

QT Intervals and Other Measurements

Upon arrival, the QT and R-R intervals for patients with severe hypoglycemia were measured using lead II with more than five consecutive beats of a 12-lead electrocardiogram by two observers who were blinded to the detailed patient characteristics (18). If the QT and R-R intervals were difficult to measure using lead II, the other limb leads were used. One corrected QT interval (QTc) was calculated using the Bazett formula: QTc = QT interval ÷ square root of the R-R interval. The Fridericia cube-root correction (QTcF) formula was also used: QTcF = QT interval ÷ cube root of the R-R interval. QTc and QTcF measurements of $\geq$0.44 s were considered abnormally prolonged, and those $\geq$0.50 s were considered highly abnormal (18,19). For cases with

atrial fibrillation, the QT intervals that followed the longest and shortest R-R intervals were measured, and then each was divided by the square root of the QTc of the preceding R-R interval (18). The average of these two values was used as the QTc. QTcF was assessed in a manner similar to that used for QTc. The QTc interval was not calculated for patients with a coupled pulse or pacemaker.

Serum creatinine and potassium levels were measured upon arrival, and the HbA_{1c} level was measured within 1 month of arrival. A serum potassium level of $<$3.5 mEq/L was considered indicative of hypokalemia. The estimated glomerular filtration rate (GFR) was calculated using the following formula, as recommended by the Japanese Society of Nephrology: estimated GFR (mL/min/1.73 m^2) = $194 \times Cre^{-1.094} \times age^{-0.287}$ ($\times$0.739 if the patient was female) (20).

Statistical Analysis

Data were abstracted and entered into the data set by three investigators (T.T., M.Ki., and R.H.). Patients were initially categorized into T1DM and T2DM groups. Data are presented as *n* (%), mean (SD), or median with the lower and upper ends of the interquartile range (IQR). Continuous variables were compared using *t* tests or Wilcoxon rank sum tests. Categorical variables were compared using χ^2 tests or Fisher exact tests. For analyses of the GCS score, body temperature, systolic blood pressure, diastolic blood pressure, and heart rate upon arrival, the subjects were divided into two groups according to a cutoff blood glucose level of 35 mg/dL (to convert blood glucose to mmol/L, multiply by 0.0555), which approximated the overall median value. *P* values of $<$0.05 according to a two-sided test were considered statistically significant for all tests. All analyses were performed using Stata software, version 11.1 (StataCorp, College Station, TX).

RESULTS

A total of 59,602 cases that visited the emergency room by ambulance were screened, and 414 cases (356 patients) with severe hypoglycemia met the criteria for inclusion in this study. The clinical characteristics of this study population upon arrival are presented in Table 1. In the T1DM (*n* = 88) and T2DM (*n* = 326) groups, the median blood glucose levels were 32 (24–42) and 31 (24–39) mg/dL, respectively. The blood glucose levels were not significantly different between the T1DM and T2DM groups. All study subjects were initially injected with glucose. The patient age in the T1DM group was significantly lower than that in the T2DM group. The prevalence of known cardiovascular disease and preexisting hypertension was significantly higher and the estimated GFR was significantly lower in the T2DM group than in the T1DM group. The duration of diabetes mellitus was not significantly different between the T1DM and T2DM groups. The HbA_{1c} levels were significantly lower in the T2DM group than in the T1DM group. In the T2DM group, the blood glucose levels in the cases with severe hypoglycemia arising from the use of sulfonylurea and from the use of insulin were 31 (25–37) mg/dL and 31 (24–40) mg/dL, respectively; these values were not significantly different (*P* = 0.81).

The consciousness level and vital signs during episodes of severe hypoglycemia are shown in Fig. 1. The median GCS scores in the T1DM and T2DM group were 12 (9–14) and 11 (7–14), respectively (Fig. 1*A*). In each group, the GCS scores of cases with a blood glucose level of $<$35 mg/dL were significantly lower than those in cases with a blood glucose level of $\geq$35 mg/dL. The body temperatures were not significantly different between the T1DM and T2DM groups, while the body temperatures of cases with a blood glucose level of $<$35 mg/dL were significantly lower than those with a blood glucose level of $\geq$35 mg/dL (Fig. 1*B*). The incidences of hypothermia in the T1DM and T2DM groups were 18.0 and 22.6%, respectively; these values were not significantly different (*P* = 0.37). The systolic blood pressure was significantly higher in the T2DM group than in the T1DM group (Fig. 1*C*), while differences between subgroups divided according to a blood glucose cutoff level of 35 mg/dL were not observed in the T1DM and T2DM groups. The diastolic blood pressure also did not differ significantly when examined according to the blood glucose levels (Fig. 1*D*). The heart rates in the T1DM and T2DM groups were 76 (66–90) and 80 (66–96) beats per minute, respectively; these parameters also did not differ significantly when examined according to the blood glucose levels.

Posttreatment changes in blood pressure are presented in Fig. 2. The systolic and diastolic blood pressures in the T2DM group at 12 h after treatment initiation were significantly lower than those upon arrival (Fig. 2*A* and *B*). In the T1DM group, the systolic and diastolic blood pressures upon arrival were not significantly different from the values at 12 h after treatment initiation.

The clinical events upon arrival and the clinical outcomes are presented in Table 2. The incidences of severe hypertension in the T1DM and T2DM groups were 19.8 and 38.8%, respectively, and the incidence in the T2DM group was significantly higher than that in the T1DM group (*P* = 0.001). Although the incidence of severe hypertension was higher among cases with preexisting hypertension than among those without preexisting hypertension, the intergroup incidence of severe hypertension was significantly different for the T1DM group (*P* = 0.02) but was not significantly different for the T2DM group (*P* = 0.17). In the T1DM and T2DM groups, the incidences of hypokalemia were 42.4 and 36.3%, respectively, while the incidences of a QTc (QTcF) of $\geq$0.44 s were 50.0 (28.1) and 59.9% (43.1%), respectively. The incidence of hypokalemia in both groups was not significantly associated with causes of severe hypoglycemia, such as the use of glucose-lowering medications and alcohol. Although QT prolongation in the T1DM and T2DM groups was not significantly associated with blood glucose levels, potassium levels, or the causes of severe hypoglycemia, significant associations were observed between QT prolongation and no cancer comorbidity or newly diagnosed atrial fibrillation in the T2DM group (Supplementary Tables 1 and 2). Further analyses of the differences between T2DM patients with a QTc of $\geq$0.50 s and those with a QTc of $<$0.44 s revealed that the incidence of newly

Table 1—Characteristics of study population upon arrival

Characteristics	T1DM	T2DM	*P*
n	88	326	
Age (years)	44.6 ± 14.3	71.4 ± 12.8	<0.001
Women	28 (31.2)	113 (34.7)	0.36
History of cardiovascular disease†	6 (6.8)	72 (22.1)	0.001
Myocardial infarction	0 (0.0)	21 (6.4)	0.01
Angina pectoris	0 (0.0)	15 (4.6)	0.04
Stroke	5 (5.7)	37 (11.4)	0.11
Preexisting disease			
Hypertension	26 (29.6)	225 (69.0)	<0.001
ARB/ACE inhibitors	15 (17.2)	131 (40.9)	<0.001
Calcium channel blockers	7 (8.0)	119 (37.2)	<0.001
Diuretics	6 (6.9)	81 (25.3)	<0.001
Atrial fibrillation	1 (1.1)	20 (6.1)	0.05
Advanced liver disease‡	0 (0.0)	14 (4.3)	0.04
Cancer (excluding hepatocellular carcinoma)§	0 (0.0)	12 (3.7)	0.06
Blood glucose (mg/dL) (*n* = 413)	32 (24–42)	31 (24–39)	0.59
HbA_{1c} (%) (*n* = 172)¶	8.3 (7.3–9.0)	6.6 (6.0–7.2)	<0.001
Duration of diabetes mellitus (years) (*n* = 253)	20 (10–29)	16 (8–24)	0.14
Treatment for diabetes mellitus			
Sulfonylurea	0 (0)	137 (43.5)	<0.001
Insulin	88 (100)	161 (51.0)	<0.001
Others	7 (7.9)	124 (39.4)	<0.001
Creatinine (mg/dL) (*n* = 374)	0.73 (0.58–0.88)	0.91 (0.67–1.52)	<0.001
Estimated GFR (mL/min/1.73 m^2) (*n* = 374)‖	86.0 (74.1–101.6)	56.2 (32.3–79.3)	<0.001
Serum potassium (mEq/L) (*n* = 391)	3.5 (3.3–3.8)	3.6 (3.2–4.1)	0.14
Causes of severe hypoglycemia			
Glucose-lowering medications	85 (96.6)	305 (93.6)	0.48
Sulfonylurea	0 (0.0)	129 (39.6)	<0.001
Insulin	85 (96.6)	156 (47.9)	<0.001
Others	0 (0.0)	20 (6.1)	0.13
Alcohol	3 (3.4)	6 (1.9)	0.40
Malnutrition	0 (0.0)	5 (1.5)	0.58
Infection**	0 (0.0)	4 (1.2)	0.58
Cancer	0 (0.0)	1 (0.3)	1.00
Others	0 (0.0)	5 (1.5)	0.58

Data are represented as *n*, *n* (%), mean ± SD, or median (IQR). T1DM: median 8.3 (7.3–9.1)% = 67 (56–76) mmoL/moL. T2DM: 6.6 (6.1–7.2)% = 49 (43–55) mmoL/moL. ARB, angiotensin II receptor blockers. SI conversion factors: To convert blood glucose to mmol/L, multiply by 0.0555; to convert creatinine to μmol/L, multiply by 88.4. †History of cardiovascular disease was defined as a history of myocardial infarction, angina pectoris, stroke, or peripheral artery disease. ‡Advanced liver disease was defined as the presence of cirrhosis or hepatocellular carcinoma. §Cancer was defined as any cancer excluding fully healed cancer and hepatocellular carcinoma. ¶HbA_{1c} level was measured at the nearest time within 1 month of arrival. ‖Estimated GFR was calculated using the following formula: estimated GFR (mL/min/1.73 m^2) = $194 \times Cre^{-1.094} \times age^{-0.287}$ (×0.739 if the patient was female). **Infection was defined as the presence of a bacterial or viral infectious disease.

diagnosed atrial fibrillation was significantly higher in patients with a QTc of ≥0.50 s (14.8 vs. 1.5%, respectively; *P* = 0.02). There were no significant differences among the other variables. Newly diagnosed cardiovascular disease occurred as a complication during an episode of severe hypoglycemia only in the T2DM group. Among the five T2DM patients with cardiovascular disease, three had cerebral infarctions, one had cerebral hemorrhage, and one had myocardial infarction requiring percutaneous coronary intervention. Although new-onset cardiovascular disease was not associated with the causes of severe hypoglycemia, such as the use of sulfonylurea and insulin, it was significantly associated with new-onset atrial fibrillation. However, all patients with newly diagnosed cardiovascular disease had no history of cardiovascular disease, preexisting hypertension, or an estimated GFR of <60 mL/min/1.73 m^2 (Supplementary Table 3). Complications of newly diagnosed atrial fibrillation only occurred in the T2DM group. Although newly diagnosed atrial fibrillation was not significantly associated with blood glucose levels upon arrival or the etiologic agents or conditions that had caused the severe hypoglycemia, patients with new-onset atrial fibrillation were not only associated with prolonged QT intervals and new-onset cardiovascular disease but also significantly older than those without new-onset atrial fibrillation (median age 79 [78–84] years vs. 72 [63–81] years; *P* = 0.01). One T2DM patient exhibited sick sinus syndrome upon arrival. However, other cases of fatal arrhythmias, such as complete atrioventricular block, ventricular

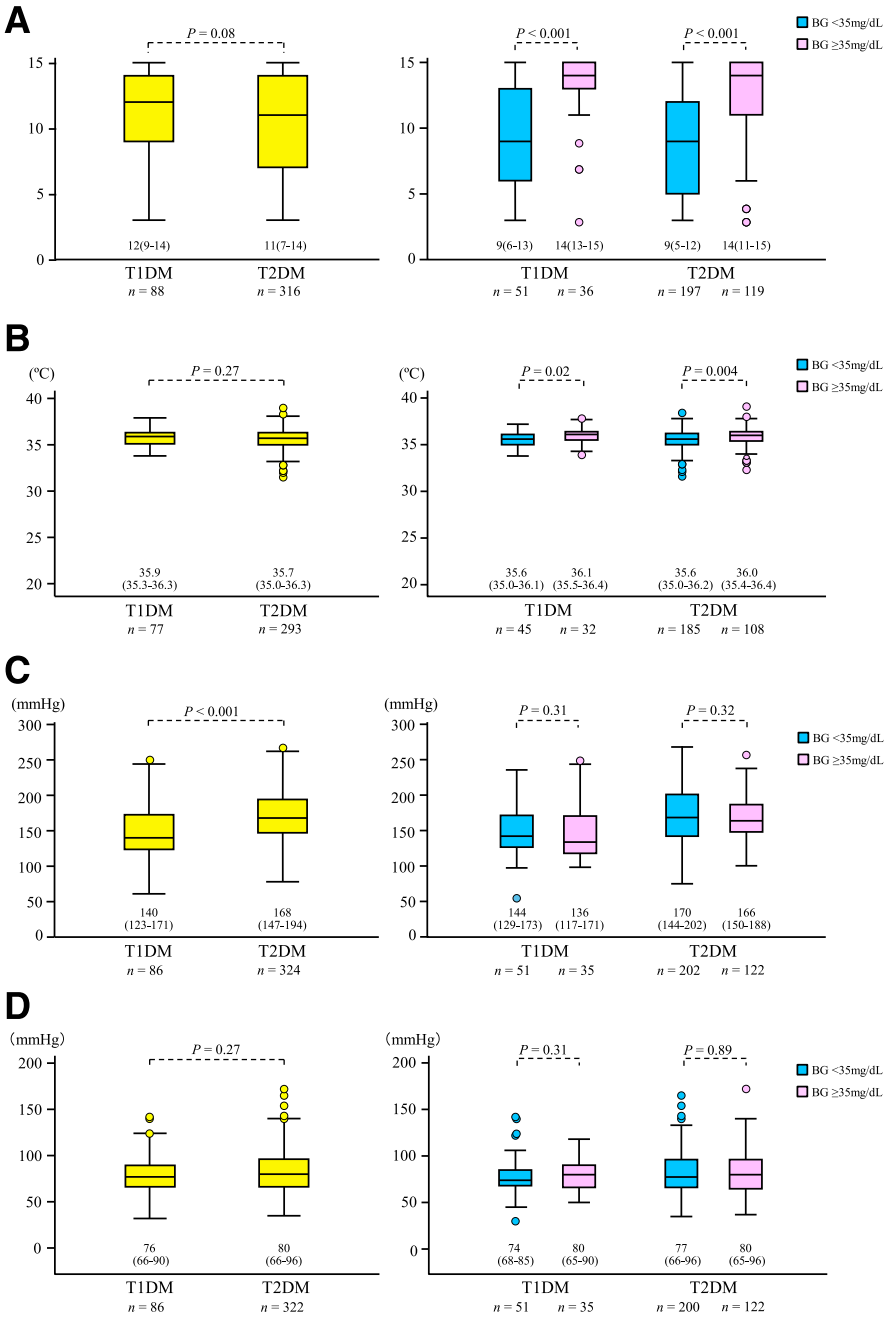

Figure 1—Consciousness level and vital signs during severe hypoglycemia upon hospital arrival. The GCS score (*A*), body temperature (*B*), systolic blood pressure (*C*), and diastolic blood pressure (*D*) are shown. To convert blood glucose to mmol/L, multiply by 0.0555. BG, blood glucose.

tachycardia, ventricular fibrillation, and torsade de pointes, were not observed in this study. More than 5% of the patients in each group suffered from trauma, and 0.6% of the T2DM group had traumatic subarachnoid hemorrhages or fractures. The incidence of trauma was not significantly different between groups and was not significantly associated with age, blood glucose levels, or etiologic agents or conditions that had caused the severe hypoglycemia. The mortality rates in the T1DM and T2DM groups were 0.0 and 1.8%, respectively. Among the six deaths in the T2DM patients, five resulted from sepsis and one resulted from multiple organ failure as a result of hepatocellular carcinoma. None of these six patients had newly diagnosed cardiovascular disease during an episode of severe hypoglycemia. The blood glucose levels between the deceased and surviving patients in the T2DM group were significantly different (18 [14–33] vs. 31 [24–39] mg/dL; $P = 0.02$). Further investigation revealed that the death of the T2DM patients was significantly associated with a comorbidity of advanced liver disease or causes of severe hypoglycemia, such as infection or cancer (Supplementary Table 4).

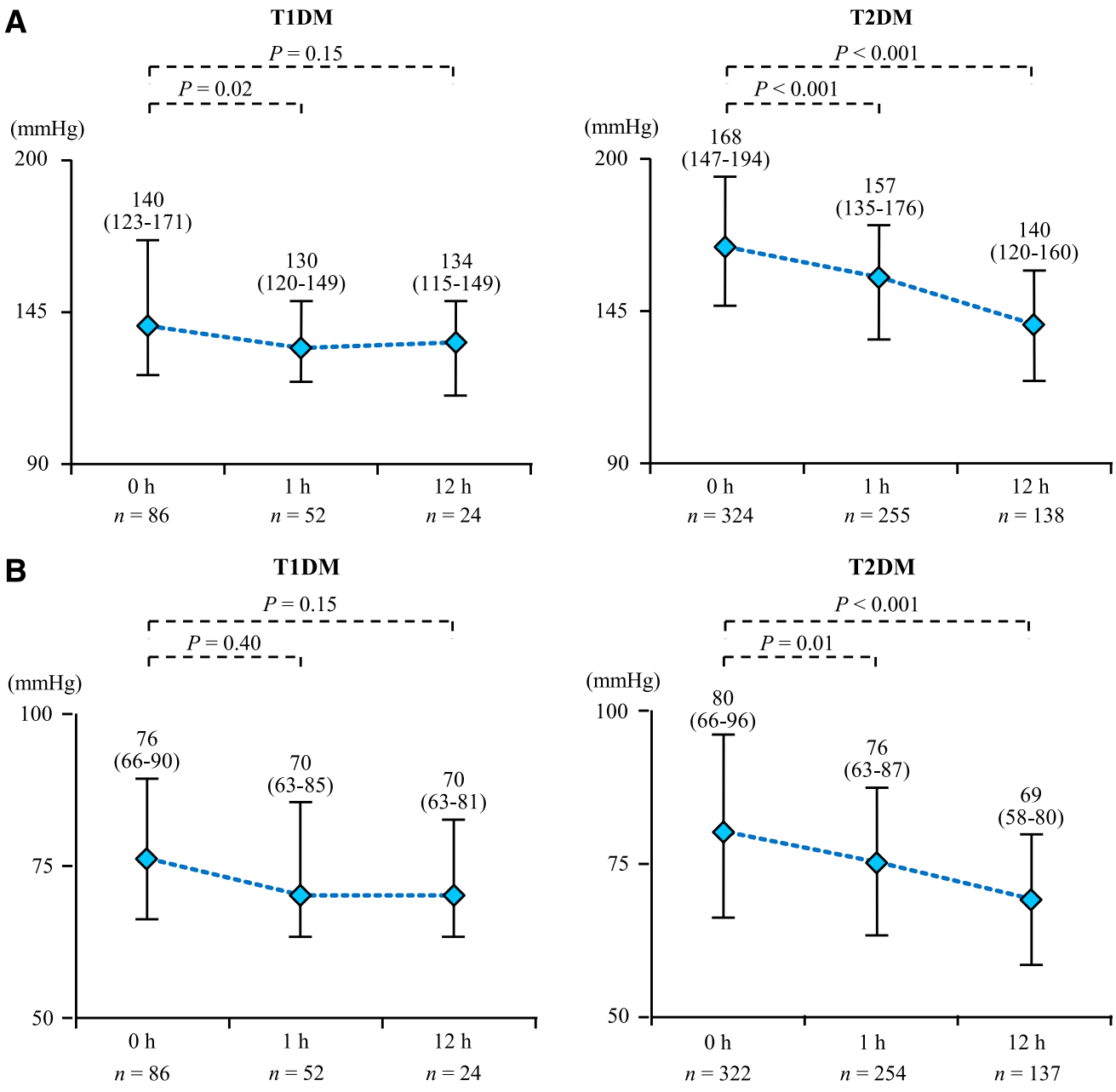

Figure 2—Posttreatment changes in blood pressure. The posttreatment changes in systolic blood pressure (*A*) and diastolic blood pressure (*B*) are shown.

CONCLUSIONS

This systematic study is, to our knowledge, the first study to report that T1DM and T2DM patients with severe hypoglycemia actually face many critical problems. Patients with severe hypoglycemia frequently exhibit hypothermia, severe hypertension, hypokalemia, QT prolongation, and other complications such as trauma. Although none of the T1DM patients with severe hypoglycemia had newly diagnosed cardiovascular disease or died, 1.5% of the T2DM patients with severe hypoglycemia experienced newly diagnosed cardiovascular disease and 1.8% died.

Hypoglycemia leads to the activation of the sympathoadrenal system and the release of counterregulatory hormones such as epinephrine and norepinephrine, resulting in hemodynamic changes (9,10). However, the blood pressure variations after severe hypoglycemic events have not been clarified. This study demonstrated that many patients with severe hypoglycemia actually exhibited severe hypertension, accompanied by a rapid drop in blood pressure after treatment. One of the reasons why the blood pressure and heart rate during severe hypoglycemia were not significantly different according to the blood glucose levels might be the profuse release of counterregulatory hormones at the level of mild to moderate hypoglycemia (21–23). Blood pressure did not significantly differ in T1DM patients

Table 2—Clinical events and outcomes in patients with severe hypoglycemia*

Event	T1DM	T2DM	*P*
n	88	326	
Severe hypertension†	17 (19.8)/86	125 (38.8)/322	0.001
Preexisting hypertension (+)‡	9 (34.6)/26	92 (41.3)/223	0.51
Preexisting hypertension (−)	8 (13.3)/60	33 (33.3)/99	0.005
Hypokalemia (mEq/L)§			
Serum potassium <3.5	36 (42.4)/85	111 (36.3)/306	0.30
Serum potassium <3.0	9 (10.6)/85	31 (10.1)/306	0.90
QT prolongation (s)			
QTc ≥0.44¶	16 (50.0)/32	100 (59.9)/167	0.29
QTcF ≥0.44‖	9 (28.1)/32	72 (43.1)/167	0.11
QTc ≥0.50	0 (0)/32	24 (14.4)/167	0.02
QTcF ≥0.50	0 (0)/32	12 (7.2)/167	0.11
Newly diagnosed complications			
Cardiovascular disease**	0 (0)/88	5 (1.5)/326	0.58
Atrial fibrillation	0 (0)/88	14 (4.3)/326	0.04
Trauma	5 (5.8)/88	19 (5.8)/326	0.95
Subarachnoid hemorrhage	0 (0)/88	2 (0.6)/326	1.00
Fracture	0 (0)/88	2 (0.6)/326	1.00
Death	0 (0)/88	6 (1.8)/326	0.34

Data are *n* (%)/total *N*. †Severe hypertension was defined as systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥120 mmHg. ‡Preexisting hypertension was confirmed when the patient was being treated with antihypertensive medication or had been previously diagnosed as having hypertension. §Serum potassium levels were measured upon arrival. ¶QTc was calculated using the Bazett formula: QTc = QT interval ÷ square root of the R-R interval. ‖QTcF was calculated using the Fridericia formula: QTcF = QT interval ÷ cube root of the R-R interval. **Cardiovascular disease was defined as coronary heart disease requiring revascularization treatment or radiologically confirmed stroke.

before and after treatment. This result might be partly attributable to the fact that T1DM patients typically experience frequent episodes of hypoglycemia and their counterregulatory response to hypoglycemia becomes blunted as a result of hypoglycemia-associated autonomic failure (22,24). For similar reasons, severe hypertension during an episode of severe hypoglycemia might not be observed as frequently in T1DM patients as in T2DM patients.

Profound hypoglycemia causes neuroglycopenic symptoms, including cognitive impairment, seizure, and coma (1), and this study suggested that the GCS scores were significantly lower in patients with lower blood glucose levels than in patients with higher blood glucose levels, even in patients with severe hypoglycemia. Although the association between hypothermia and hypoglycemia due to intracellular glycopenia has long been known (25), the body temperature of patients with severe hypoglycemia has rarely been examined in clinical settings (26). In the current study, hypothermia was often observed, particularly in patients with relatively low blood glucose levels. Hypothermia can lead to lethal outcomes and arrhythmias such as ventricular tachycardia and atrial fibrillation, which was frequently observed in the current study (16,18,27,28). Conversely, hypothermia may prevent hypoglycemia-induced neuronal death (29), and further research is needed.

The potassium levels in patients with severe hypoglycemia have not been fully investigated. This study demonstrated that many patients with severe hypoglycemia also had hypokalemia. Hyperinsulinemia, hypothermia, and the increased secretion of catecholamines might drive potassium into the cell during hypoglycemia (30,31). Because hypokalemia increases the risk of lethal arrhythmias, this condition presents another threat associated with severe hypoglycemia.

Recently, several studies have reported an association between hypoglycemia and QT prolongation (11–13), which reflects abnormal cardiac repolarization and may be a marker of increased mortality in T1DM patients (32). The results of the current study demonstrated that not only T1DM patients but also many T2DM patients exhibited an abnormal QT prolongation during severe hypoglycemia. In particular, T2DM patients frequently exhibited a highly abnormal QT prolongation during severe hypoglycemia. In addition, the association between QT prolongation and new-onset atrial fibrillation in patients with severe hypoglycemia may be supported by a recent study that revealed an association between prolonged QT interval and onset of atrial fibrillation (33). However, the causation in this study was not clear; therefore, further studies are needed. Although cardiac arrest as a result of torsade de pointes in acquired long QT syndrome is rare, such an event is potentially catastrophic (18,34).

Some previous studies have examined the relationship between hypoglycemia and cardiovascular events (2,3). However, few studies have systematically investigated whether cardiovascular events actually develop during episodes of hypoglycemia. The current study demonstrated that 1.5% of the T2DM patients with severe hypoglycemia actually exhibited new-onset cardiovascular events. Although the causality was not clear, catecholamine hypersecretion as a result of severe hypoglycemia might lead to hazardous cardiovascular stress, aggravating vascular complications

(9,10,35). In addition to the high incidence of new-onset atrial fibrillation, the T2DM patients with newly diagnosed cardiovascular disease had no history of cardiovascular disease, preexisting hypertension, or an estimated GFR of $<$60 mL/min/1.73 m^2. However, any associations among these diseases remain unclear, and further large-scale investigations are warranted. On the other hand, no cardiovascular events were observed among T1DM patients, consistent with the results reported by a recent study (36). One possible explanation is that, compared with T2DM patients, T1DM patients typically have fewer comorbidities (such as hypertension and dyslipidemia) and a weaker counterregulatory response to hypoglycemia as a result of hypoglycemia-associated autonomic failure.

Previous reports have suggested that severe hypoglycemia is associated with increased mortality (4–6). Although the mortality rates between T1DM and T2DM patients with severe hypoglycemia were not significantly different in this study, none of the T1DM patients with severe hypoglycemia died. In the current study, 1.8% of the T2DM patients with severe hypoglycemia died, and a significant association between the blood glucose levels and death was observed. Although unknown variables might exist, blood glucose levels could reflect the severity of the underlying disease in patients with severe hypoglycemia. Moreover, our study also showed that the death of T2DM patients was significantly associated with infection and cancer, resulting in severe hypoglycemia, as well as preexisting advanced liver disease. Therefore, the etiologic agents and comorbidities in patients with severe hypoglycemia might have influenced the mortality rate.

Our study had several limitations. First, this study was performed at a single national center and was limited to a specific geographical area. Therefore, large-scale studies at multiple centers throughout the world are needed to confirm the results. Second, missing data and limited samples might have influenced the results and the statistical analyses. However, few studies have investigated the detailed conditions of patients with severe hypoglycemia, and we believe that our study provides extremely important information about severe hypoglycemia. Third, coronary heart disease that did not require revascularization and ischemic changes on electrocardiograms obtained upon hospital arrival could not be sufficiently evaluated. Unfortunately, electrocardiograms obtained before the onset of severe hypoglycemia were only available for a few patients. Moreover, stroke that could not be radiologically proven might have occurred. However, the occurrence of coronary heart disease requiring revascularization and radiologically confirmed stroke in T2DM patients with severe hypoglycemia was notable. Finally, patients with prehospital cardiopulmonary arrest could not be examined. Some patients with severe hypoglycemia might have died in prehospital settings. Furthermore, considering the critical conditions of patients with severe hypoglycemia, we believe that dead-in-bed syndrome and sudden cardiac death could possibly occur (37,38).

In conclusion, this study revealed that T1DM and T2DM patients with severe hypoglycemia experienced many critical problems that could lead to cardiovascular disease, fatal arrhythmia, and death. Our results also clarified that each patient with severe hypoglycemia had different risks, depending on his or her underlying disease.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. T.T. conceived the study, designed the protocol, contributed to data collection and preparation, analyzed all data, wrote the manuscript, contributed to the interpretation of the results, and approved the final version. R.Y.-H. contributed to data collection and preparation, analyzed all data, wrote the report, contributed to the interpretation of the results, and approved the final version. H.K. and A.K. contributed to data collection and preparation, contributed to the interpretation of the results, and approved the final version. M.Ki. contributed to data collection and preparation, analyzed all data, contributed to the interpretation of the results, and approved the final version. H.N. analyzed all data, contributed to the interpretation of the results, and approved the final version. R.H. contributed to data collection and preparation, contributed to the interpretation of the results, and approved the final version. M.Ka. designed the protocol, wrote the manuscript, contributed to the interpretation of the results, and approved the final version. M.N. designed the protocol, analyzed all data, wrote the manuscript, contributed to the interpretation of the results, and approved the final version. M.N. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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