



# Hypoglycemia at Admission in Patients With Acute Myocardial Infarction Predicts a Higher 30-Day Mortality in Patients With Poorly Controlled Type 2 Diabetes Than in Well-Controlled Patients

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## OBJECTIVE

We aimed to evaluate the association between hypoglycemia at admission and 30-day mortality in patients with acute myocardial infarction (AMI) and to determine whether these associations differed according to diabetes-control status in AMI patients with diabetes.

## RESEARCH DESIGN AND METHODS

We analyzed the prognostic significance of hypoglycemia and hyperglycemia in 34,943 AMI patients with or without type 2 diabetes from two AMI registries: the Korea Acute Myocardial Infarction Registry (KAMIR) and the Korea Working Group on Myocardial Infarction (KorMI).

## RESULTS

The patients were divided into five groups according to serum-glucose levels at admission: <3.9 mmol/L (<70 mg/dL); 3.9–7.72 mmol/L (70–139 mg/dL); 7.78–11.06 mmol/L (140–199 mg/dL); 11.11–14.39 mmol/L (200–259 mg/dL); and ≥14.44 mmol/L (≥260 mg/dL). The 30-day mortality rates in the lowest and highest glucose groups were higher than those in other groups; the lowest glucose group had the highest mortality for patients with type 2 diabetes, after adjusting for multiple factors. We also extracted and compared four subgroups from the patients with type 2 diabetes, based on hemoglobin A1c and serum-glucose levels at admission: group A, <6.5% (48 mmol/mol) and <3.9 mmol/L; group B, <6.5% (48 mmol/mol) and ≥11.11 mmol/L; group C, ≥8% (64 mmol/mol) and <3.9 mmol/L; and group D, ≥8% (64 mmol/mol) and ≥11.11 mmol/L. Group C had the highest 30-day mortality rate among the groups.

## CONCLUSIONS

These data suggest that hypoglycemia at admission affects clinical outcomes differently in AMI patients with type 2 diabetes depending on the diabetes-control status.

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Hyperglycemia is a well established predictor of mortality in patients with acute myocardial infarction (AMI) with or without diabetes (1–3). However, many clinical studies have failed to show that the intensive management of hyperglycemia provides specific mortality benefit to the hospitalized patients with AMI (4–6). Because intensive glucose control increases the risk of severe hypoglycemia (7), there have been consistent questions about whether hypoglycemia induces cardiovascular (CV) disease, thus leading to the dilution of the potential benefit of intensive glucose control in high-risk patients.

A frequently suggested but unconfirmed mechanism by which hypoglycemia might lead to fatality during CV events is QT interval prolongation on an electrocardiogram. This phenomenon seems to be precipitated by increased levels of circulating catecholamines and hypokalemia (8,9), although a recent study demonstrated that hypokalemia does not play an important role in the development of QT prolongation during severe hypoglycemia (10). Other possible mechanisms have also been listed: hemodynamic changes caused by increased sympathetic activity, platelet activation and aggregation, a rise in factor VIII and von Willebrand factor levels, and increases in the circulating levels of interleukins, cytokines, markers of endothelial dysfunction including endothelin-1, and reactive oxygen species (7,11). More complicating is that hypoglycemia might be a sign of vulnerability to CV morbidity and mortality, as well as other grave diseases (12–14). Therefore, because hypoglycemia can be a cause, a marker of severity, and an aggravating factor in AMI patients (7,15), understating hypoglycemia during an AMI event has important clinical relevance for the management of AMI and stress hyperglycemia.

Several studies have shown that hypoglycemia increased the mortality rates in AMI patients with or without diabetes (3,16,17), whereas others studies disagreed (1,4,18,19). The different results might arise from heterogeneities in the study protocols, such as admission or postadmission hypoglycemia; spontaneous or insulin treatment-related hypoglycemia; in-hospital or long-term mortality; different degrees

or definitions of hypoglycemia or target goals for glycemic control during the hospitalization period; and diabetic or nondiabetic subjects (16–18).

Although hypoglycemia at admission was shown to predict death at 30 days in patients with AMI (3,17), it is unclear whether postadmission hypoglycemia or insulin therapy-induced hypoglycemia consistently increases mortality during hospitalization in AMI patients (17,20).

Additionally, diabetes and its control status may differentially affect the death rate in AMI patients who present with admission hypoglycemia. Although there have been a few reports that admission hypoglycemia is more strongly associated with higher mortality in AMI patients with diabetes than in nondiabetic subjects (17,21), no studies have addressed whether admission hypoglycemia in AMI patients with diabetes has different effects on mortality depending on the level of diabetes control before admission.

In the current study, we aimed to evaluate the association between admission hypoglycemia and 30-day mortality in AMI patients and to determine whether these associations differed according to the preadmission diabetes-control status in AMI patients with type 2 diabetes mellitus.

## RESEARCH DESIGN AND METHODS

These data were obtained from the Korea Acute Myocardial Infarction Registry (KAMIR) and the Korea Working Group on Myocardial Infarction (KorMI), which are prospective multicenter, observational registries designed to study the current epidemiology of hospital management and AMI outcomes in Korea. KAMIR (2005–2008;  $n = 11,062$ ) and KorMI (2008–2012;  $n = 23,881$ ) contain ~1 year of clinical follow-up data regarding primary percutaneous coronary interventions (PCIs) in 53 community and university hospitals, as described previously (22,23). The registries include patients suffering from AMI, including both ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction. AMI was diagnosed if the patients met the following criteria: 1) at least one positive cardiac biochemical marker of necrosis (including creatine kinase MB and troponin I and T); and 2) typical symptoms

compatible with AMI and/or new or presumed new ST-segment elevation of at least 1 mm at any location or a new left bundle-branch block on the index or subsequent electrocardiogram (22,23). These registries were supported by KorMI, shared with many community and university hospitals, and used similar treatment protocols based on the American College of Cardiology/American Heart Association guidelines (24). We merged the two registries to maximize the statistical power. After the KAMIR registry, there were some protocol amendments to the KorMI registry, including regular laboratory measurements (at 6, 12, 24, and 36 months) and long-term follow-up scheduled for up to 3 years. These study protocols were reviewed and approved by the Institutional Review Board at each participating center. All KorMI participants provided written informed consent.

The database is comprehensive and includes demographic features, medical history, clinical characteristics, laboratory findings, clinical performance, and angiographic findings. Blood samples without lipid profiles were collected at admission or before PCI. Overnight fasting blood was drawn for lipid measurements.

We divided the total cohort into two groups, the type 2 diabetes mellitus and nondiabetic groups. Type 2 diabetes was defined by the patient-reported history (medical treatment, age of diabetes onset  $\geq 30$  years, and the absence of a history of ketoacidosis), medical records, or by a hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) level  $\geq 6.5\%$  (48 mmol/mol) in patients with no history of diabetes, no features of diabetic ketoacidosis, and an age  $\geq 30$  years. We then stratified each group into five subgroups (groups 1–5) according to the serum-glucose level at admission:  $<3.9$  mmol/L ( $<70$  mg/dL); 3.9–7.72 mmol/L (70–139 mg/dL); 7.78–11.06 mmol/L (140–199 mg/dL); 11.11–14.39 mmol/L (200–259 mg/dL); and  $\geq 14.44$  mmol/L ( $\geq 260$  mg/dL).

We also extracted and compared four subgroups of patients with type 2 diabetes, based on the HbA<sub>1c</sub> and serum-glucose levels at admission: group A,  $<6.5\%$  (48 mmol/mol) and  $<3.9$  mmol/L ( $<70$  mg/dL); group B,  $<6.5\%$  (48 mmol/mol) and  $\geq 11.11$  mmol/L ( $\geq 200$  mg/dL); group C,  $\geq 8.0\%$  (64 mmol/mol) and  $<3.9$  mmol/L ( $<70$

mg/dL); and group D,  $\geq 8.0\%$  (64 mmol/mol) and  $\geq 11.11$  mmol/L ( $\geq 200$  mg/dL). We defined serum-glucose levels  $< 3.9$  mmol/L ( $< 70$  mg/dL) as hypoglycemia and  $\geq 11.11$  mmol/L ( $\geq 200$  mg/dL) as hyperglycemia; HbA<sub>1c</sub>  $< 6.5\%$  (48 mmol/mol) was defined as a well-controlled diabetes, and HbA<sub>1c</sub>  $> 8\%$  (64 mmol/mol) was defined as a poorly controlled diabetes.

The primary study outcome was 30-day all-cause mortality. Mortality was assessed during sentinel hospitalization using chart reviews and 30 days after presentation with AMI using mortality registry data.

### Statistical Analysis

The continuous variables were expressed as the mean  $\pm$  SEM and analyzed with Student *t* test and an ANOVA. Categorical variables were expressed as numbers (percent) and compared with  $\chi^2$  test or Fisher exact test as appropriate. The cumulative incidence of adverse events was estimated according to the Kaplan-Meier method, and the significance level was assessed with the log-rank test. We performed a Cox proportional hazards regression analysis to find independent factors related to mortality in AMI patients and to compare survival in AMI patients after adjusting for multiple factors. Cox proportional hazards regression analyses were performed to estimate the hazard ratios (HRs) and associated 95% CIs. Statistical significance was assumed at  $P < 0.05$ . The statistical analysis was performed with SPSS version 18.0 (SPSS Inc., Chicago, IL).

## RESULTS

### Clinical Characteristics of Study Patients

All patients had AMI that was properly managed with medication, thrombolysis, and/or PCIs according to American College of Cardiology/American Heart Association guidelines (24,25). We divided a total of 34,943 patients into two groups, the type 2 diabetic ( $n = 20,714$ ) and nondiabetic groups ( $n = 14,229$ ). The baseline clinical characteristics of the study subjects are shown in Table 1. The mean ages were 64.1 years for the type 2 diabetic group and 63.3 years for the nondiabetic group. The first treatment was primary PCI in 90.26% of the nondiabetic group and

**Table 1—Baseline characteristics of the study subjects ( $n = 34,943$ )**

	Nondiabetic ( $n = 14,229$ )	Type 2 diabetic ( $n = 20,714$ )	<i>P</i> value
Age (years)	63.31 $\pm$ 0.47	64.09 $\pm$ 0.08	<0.001
Sex (female)	44.71%	37.25%	0.001
BMI (kg/m <sup>2</sup> )	23.73 $\pm$ 0.03	23.89 $\pm$ 0.03	<0.001
sBP (mmHg)	128.51 $\pm$ 0.28	128.48 $\pm$ 0.26	0.910
dBp (mmHg)	78.77 $\pm$ 0.24	78.13 $\pm$ 0.23	<0.001
HbA <sub>1c</sub> (%)	5.75 $\pm$ 0.01	7.76 $\pm$ 0.02	<0.001
HbA <sub>1c</sub> (mmol/mol)	39.45 $\pm$ 0.11	61.32 $\pm$ 0.46	<0.001
Glucose (mmol/L)	7.92 $\pm$ 0.04	10.52 $\pm$ 0.03	<0.001
Creatinine ( $\mu$ mol/L)	99.58 $\pm$ 1.36	114.72 $\pm$ 1.17	<0.001
TGs (mmol/L)	1.44 $\pm$ 0.01	1.49 $\pm$ 0.01	0.001
HDL cholesterol (mmol/L)	1.16 $\pm$ 0.005	1.15 $\pm$ 0.003	0.005
LDL cholesterol (mmol/L)	3.01 $\pm$ 0.010	2.95 $\pm$ 0.009	<0.001
hsCRP (mg/L)	3.11 $\pm$ 0.06	3.78 $\pm$ 0.07	<0.001
Killip class			<0.001
I	71.47%	72.81%	
II	13.49%	14.44%	
III	9.54%	7.31%	
IV	5.49%	5.44%	
Hypertension	52.23%	48.57%	<0.001
Smoking	40.68%	43.27%	<0.001
Previous MI	7.94%	6.13%	<0.001
HF	2.56%	1.67%	<0.001
PAD	1.11%	0.54%	<0.001
CVA	7.62%	6.37%	<0.001
Statin	65.19%	73.85%	<0.001
Aspirin	14.89%	13.40%	<0.001
Clopidogrel	4.89%	5.80%	<0.001
Hypertension treatment	89.44%	89.38%	0.478
$\beta$ -Blocker	9.07%	7.39%	<0.001
ACE inhibitor/ARB	94.085%	94.82%	0.101
CCB	10.85%	8.75%	<0.001
Nitrate	5.23%	3.42%	<0.001
Thrombolysis	3.61%	6.69%	<0.001
Primary PCI	90.26%	79.87%	<0.001

ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

in 79.87% of the type 2 diabetic group. Thrombolysis was performed in 3.61% of the nondiabetic group and in 6.69% of the type 2 diabetic group. Conservative treatment was administered to 10.68% of the type 2 diabetic group and 3.75% of the nondiabetic group. The 30-day mortality rate was higher in the nondiabetic group (4.09%) than in the type 2 diabetic group (3.70%;  $P < 0.05$ ).

Additionally, age, BMI, systolic blood pressure (sBP), heart rate, HDL cholesterol, Killip classification, known hypertension, known peripheral artery disease (PAD), cerebrovascular accident (CVA), LDL cholesterol, high-sensitivity C-reactive protein (hsCRP), admission serum-glucose level, and serum creatinine

were also shown to affect the 30-day mortality. After adjusting for the above-mentioned factors and sex, hypertension medication, dyslipidemia, diastolic blood pressure (dBp), the use of aspirin and statins, total cholesterol, triglycerides (TGs), previous history of MI, and known heart failure (HF), the 30-day mortality was higher in patients with type 2 diabetes compared with patients without diabetes.

### The 30-Day Mortality of AMI Patients Showed a U-Shaped Relationship With Serum-Glucose Levels at Admission

The entire cohort of 34,943 patients was divided into five groups according to the serum-glucose levels at admission:  $< 3.9$

mmol/L (<70 mg/dL;  $n = 409$ , group 1); 3.9–7.72 mmol/L (70–139 mg/dL;  $n = 15,215$ , group 2); 7.78–11.06 mmol/L (140–199 mg/dL;  $n = 10,316$ , group 3); 11.11–14.39 mmol/L (200–259 mg/dL;  $n = 4,173$ , group 4); and  $\geq 14.44$  mmol/L ( $\geq 260$  mg/dL;  $n = 4,139$ , group 5). The 30-day mortality rates of the five glucose groups were 13.93, 3.08, 5.09, 7.40, and 14.87% in groups 1, 2, 3, 4, and 5, respectively. The 30-day mortality rates showed a U-shape distribution according to the glucose levels at admission in not only the entire AMI patient cohort (Fig. 1A), but also both the nondiabetic and type 2 diabetic groups (Fig. 1B). The clinical characteristics of each of the five glucose subgroups of AMI patients with type 2 diabetes and without diabetes are presented in Supplementary Tables 1 and 2. It is worth noting that nondiabetic patients in group 5 more frequently had a Killip class  $>II$  compared with the patients in other glucose groups (Supplementary Table 2). Regarding group 5, the group with the highest glycemic level, the 30-day mortality rates were 26.39% for the patients without diabetes and 12.14% for the patients with type 2 diabetes, with a significant difference between the nondiabetic and type 2 diabetic patients ( $P < 0.001$ ).

Next, we compared the 30-day mortality rates among the five groups using Cox proportional hazards regression models after adjusting for multiple factors, including age, sex, BMI, hypertension, hypertensive medication use, dyslipidemia, sBP, dBP, Killip class, aspirin use, statin use, hsCRP, smoking, total

cholesterol, TGs, HDL cholesterol, LDL cholesterol, serum creatinine, PAD, CVA, previous MI, and HF. We defined group 2 (serum glucose 3.9–7.72 mmol/L) as the reference group because this group had the lowest 30-day mortality rate among the five groups. After adjusting for multiple factors, group 1, the group with hypoglycemia, showed the highest 30-day mortality (HR 2.157 [95% CI 1.222–3.807];  $P = 0.008$ ). Group 5, the group with severe hyperglycemia, also had increased 30-day mortality (HR 1.869 [95% CI 1.416–2.468];  $P < 0.001$ ). However, the 30-day mortality rates of groups 3 and 4 were similar to that of group 2.

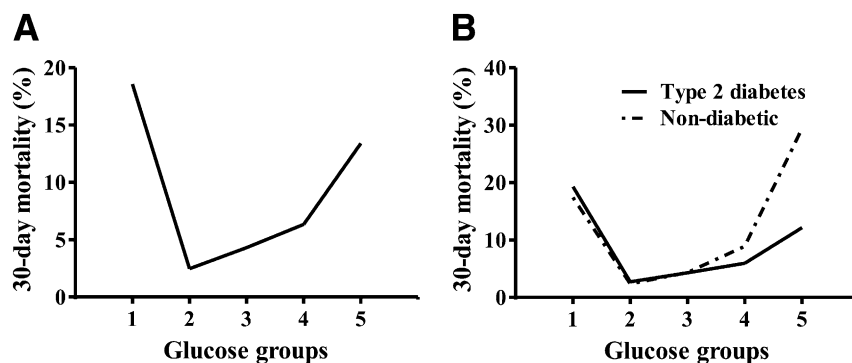
The trends in the 30-day mortality rates of the five subgroups from both the nondiabetic and type 2 diabetic groups were similar to those observed in the total patient cohort. The HRs for groups 1 and 5 were 4.777 (95% CI 2.090–10.918;  $P < 0.01$ ) and 2.548 (95% CI 1.624–4.000;  $P < 0.01$ ), respectively, in the nondiabetic group, and 2.866 (95% CI 1.564–5.250;  $P < 0.01$ ) and 1.616 (95% CI 1.222–2.141;  $P < 0.01$ ), respectively, in the type 2 diabetic group.

#### Both Hypoglycemia and Hyperglycemia Are Independent Predictors of 30-Day Mortality in AMI Patients

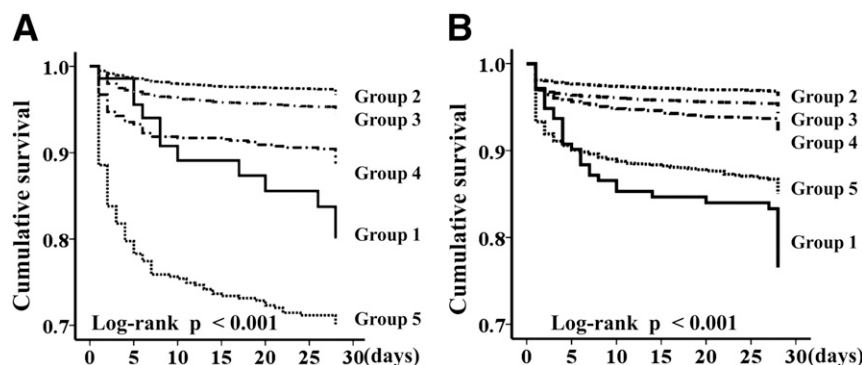
After adjusting for multiple factors, we performed a multivariate Cox proportional hazards regression analysis to identify the independent factors associated with 30-day mortality in the nondiabetic and type 2 diabetic AMI patients (Supplementary Table 3). Both

hypoglycemia (<3.9 mmol/L) and hyperglycemia ( $\geq 14.44$  mmol/L) were strong independent factors associated with 30-day mortality in both AMI patient groups. The risk associated with hypoglycemia was comparable to that associated with Killip class level. In addition to glycemic parameters, other previously well-known factors, including older age, lower sBP, a high Killip class ( $\geq III$ ), CVA history, and a higher hsCRP level were risk factors related to higher 30-day mortality in both AMI patient groups. Furthermore, in the nondiabetic AMI group, HF and PAD were significant risk factors related to 30-day mortality. In patients with type 2 diabetes, a previous MI, no aspirin use, and higher creatinine levels were additional independent factors associated with higher 30-day mortality.

We analyzed the 30-day cumulative survival with a Cox proportional hazards regression model (Fig. 2A and B). After adjusting for age, sex, BMI, hypertension, hypertensive medication use, dyslipidemia, sBP, dBP, Killip class, aspirin use, statin use, hsCRP, smoking, total cholesterol, TGs, HDL cholesterol, LDL cholesterol, serum creatinine, PAD, CVA, previous MI history, and HF, both hypoglycemia (<3.9 mmol/L) and hyperglycemia (groups 4 and 5) at admission were shown to decrease cumulative survival in the nondiabetic AMI group (Fig. 2A). However, in patients with type 2 diabetes, hypoglycemia (<3.9 mmol/L) had a more prominent effect than hyperglycemia on the 30-day cumulative survival rate after AMI events. Furthermore, in patients with



**Figure 1**—The 30-day mortality rates of the five glucose-based groups among the total AMI patient cohort ( $n = 34,943$ ) (A) and the AMI patients with ( $n = 20,714$ ) and without type 2 diabetes ( $n = 14,229$ ) (B). The five glucose subgroups of AMI patients were categorized according to the admission serum-glucose levels, as follows: group 1, <3.9 mmol/L (<70 mg/dL); group 2, 3.9–7.72 mmol/L (70–139 mg/dL); group 3, 7.78–11.06 mmol/L (140–199 mg/dL); group 4, 11.11–14.39 mmol/L (200–259 mg/dL); and group 5,  $\geq 14.44$  mmol/L ( $\geq 260$  mg/dL).



**Figure 2**—Cumulative survival curves according to the admission glucose levels in nondiabetic AMI patients (A) and AMI patients with type 2 diabetes (B). The five glucose groups are described in Fig. 1 and RESEARCH DESIGN AND METHODS.

type 2 diabetes, only severe hyperglycemia (group 5) was shown to decrease the 30-day cumulative survival after AMI events (Fig. 2B).

Additionally, we analyzed the association between HbA<sub>1c</sub> and cumulative survival 30 days after AMI events in patients with type 2 diabetes. HbA<sub>1c</sub> was not associated with 30-day cumulative survival after AMI events in these patients (data not shown). Similarly, no such association was observed in the total patient cohort (data not shown).

#### Hypoglycemia at Admission in Patients With AMI Predicts a Higher 30-Day Mortality in Patients With Poorly Controlled Type 2 Diabetes Than in Well-Controlled Patients

To determine the effects of the diabetes-control status before the AMI event and admission hypoglycemia on mortality in AMI patients with type 2 diabetes, we classified these patients into

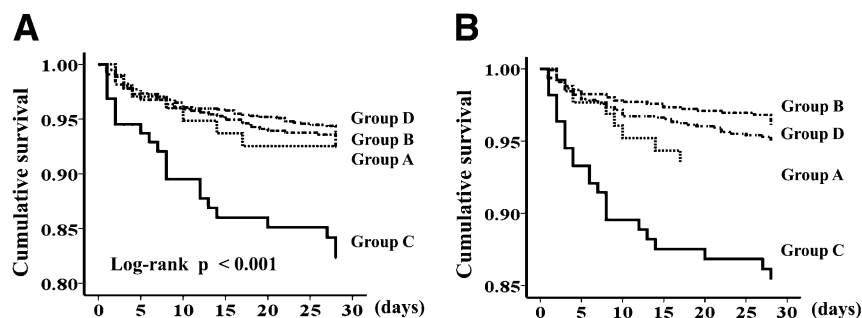
four selected subgroups, based on the HbA<sub>1c</sub> and serum-glucose levels at admission: the well-controlled diabetic and admission hypoglycemic group (group A), with HbA<sub>1c</sub> <6.5% (48 mmol/mol) and serum glucose <3.9 mmol/L (<70 mg/dL); the well-controlled diabetic and admission hyperglycemic group (group B), with HbA<sub>1c</sub> <6.5% (48 mmol/mol) and serum glucose ≥11.11 mmol/L (200 mg/dL); the poorly controlled diabetic and admission hypoglycemic group (group C), with HbA<sub>1c</sub> ≥8.0% (64 mmol/mol) and serum glucose <3.9 mmol/L (<70 mg/dL); and the poorly controlled diabetic and admission hyperglycemic group (group D), with HbA<sub>1c</sub> ≥8.0% (64 mmol/mol) and serum glucose ≥11.11 mmol/L (200 mg/dL). The clinical characteristics of these four specific subgroups are presented in Supplementary Table 4. No differences in blood pressure, HDL, hsCRP, HF, and the use of aspirin,

ACE inhibitors, angiotensin receptor blockers, or β-blockers were observed among the groups. However, many other factors differed significantly among four groups.

We first used the Kaplan-Meier method (Fig. 3A) to compare cumulative survival among the four specific groups, followed by a Cox proportional hazards regression analysis (Fig. 3B), to compare the independent cumulative survival after adjusting for multiple factors. Interestingly, group C showed a markedly decreased 30-day cumulative survival in both analyses (Fig. 3A and B). After adjusting for multiple factors, group A also showed a decreased 30-day cumulative survival rate in comparison with the two hyperglycemic groups (groups B and D; Fig. 3B).

#### CONCLUSIONS

In the current study, we observed that both hypoglycemia and hyperglycemia



**Figure 3**—The effects of admission hypoglycemia and the preadmission diabetes-control status on 30-day cumulative survival in AMI patients with type 2 diabetes. Kaplan-Meier survival estimates (A) and the Cox proportional hazards regression analysis (B) after adjusting for age, sex, BMI, hypertension, hypertensive medication use, dyslipidemia, sBP, dBP, Killip class, aspirin use, statin use, hsCRP, smoking, total cholesterol, TGs, HDL cholesterol, LDL cholesterol, serum creatinine, PAD, CVA, previous MI history, and HF. We classified the AMI patients with type 2 diabetes according to the HbA<sub>1c</sub> and serum-glucose levels at admission as follows: group A, HbA<sub>1c</sub> <6.5% (48 mmol/mol) and serum glucose <3.9 mmol/L (<70 mg/dL); group B, HbA<sub>1c</sub> <6.5% (48 mmol/mol) and serum glucose ≥11.11 mmol/L (≥200 mg/dL); group C, HbA<sub>1c</sub> ≥8.0% (64 mmol/mol) and serum glucose <3.9 mmol/L (<70 mg/dL); and group D, HbA<sub>1c</sub> ≥8.0% (64 mmol/mol) and serum glucose ≥11.11 mmol/L (≥200 mg/dL).

at admission were associated with increased 30-day mortality in AMI patients with or without type 2 diabetes. In particular, admission hypoglycemia in patients with poorly controlled type 2 diabetes (indicated by a higher HbA<sub>1c</sub> level) was associated with a markedly decreased 30-day survival rate after an AMI event. However, the HbA<sub>1c</sub> level alone was not associated with the risk of 30-day mortality in AMI patients with type 2 diabetes.

Several studies have shown that hypoglycemia in AMI patients was associated with increased short- or long-term mortality (16,17,26,27). Our findings are consistent with those of previous studies in which admission hypoglycemia was a predictor of 30-day mortality in AMI patients with diabetes (17). Additionally, many previous studies have shown a J- or U-shaped relationship between glycemia and 30-day mortality in patients with AMI (3,16,17,26). Depending on study protocols, the definition of hypoglycemia and the grouping of the study patients have been different (28). Most studies used a lower cutoff level between 3.33 and 4.44 mmol/L as the definition of hypoglycemia (1,3,17). We observed the most prominent difference in 30-day mortality when we categorized our patients as having hypoglycemia if their serum-glucose level was <3.9 mmol/L. Previous data have consistently indicated that in AMI patients without diabetes, admission blood-glucose levels higher than the euglycemic level are associated with increased short-term mortality after an AMI event; however, the serum-glucose level associated with the lowest early mortality in AMI patients with type 2 diabetes seems to differ according to study population, stage of diabetes, diabetes complications, and comorbid states (28,29). Studies have shown that even euglycemic levels of serum glucose (for example, <7 mmol/L) may be associated with increased early mortality in AMI patients with type 2 diabetes (28,29). However, in the current study, for the group with serum-glucose levels between 3.9 and 7.72 mmol/L (70–139 mg/dL) at admission, the 30-day mortality rate after an AMI event was comparable for the nondiabetic patients and the patients with type 2 diabetes. In contrast to the significant association between admission serum-glucose level

and early mortality, no such association between HbA<sub>1c</sub> and mortality was observed in a large cohort of AMI patients with diabetes (30). Our results also showed that HbA<sub>1c</sub> alone was not associated with 30-day mortality in AMI patients with type 2 diabetes.

It is well known that admission hyperglycemia is associated with increased mortality in patients with AMI (17,19,26,31,32). Although some studies have suggested that hyperglycemia is associated with greater short- or long-term mortality in AMI patients without diabetes than in AMI patients with type 2 diabetes (2,31), others have reported that the risk was similar between the patient groups (33,34). In the current study, hyperglycemia (serum glucose  $\geq 14.44$  mmol/L or  $\geq 260$  mg/dL) was associated with an increased risk of 30-day mortality in both the nondiabetic and type 2 diabetic groups, with a greater increase in 30-day mortality in the nondiabetic AMI patients. The reason for this higher mortality rate in nondiabetic AMI patients with admission hyperglycemia, compared with their diabetic counterparts, is not clear, but such a trend has been previously reported (28,29). A greater degree of stress might be required for a nondiabetic patient to achieve the same hyperglycemic state as a diabetic counterpart (35). In line with this speculation, our results showed that the nondiabetic patients in glucose group 5 more frequently had a Killip class >II compared with the patients in other glucose groups.

Furthermore, the unadjusted 30-day mortality was higher in patients without diabetes than in patients with type 2 diabetes in the current study. However, after adjusting for multiple factors, the 30-day mortality was higher in patients with type 2 diabetes compared with nondiabetic patients. Although diabetes has been shown to predict long-term mortality after AMI in many previous studies, some studies, including KAMIR (36) and a similar Japanese registry study (37), have suggested that diabetes did not increase short-term mortality (28,32) because of recent progress in treatment, especially the development of PCI.

The most important finding in the current study, we believe, is that hypoglycemia in AMI patients with poorly

controlled type 2 diabetes was associated with the highest 30-day mortality among the subgroups, which also included hypoglycemic patients with well-controlled diabetes, hyperglycemic patients with well-controlled diabetes, and hyperglycemic patients with poorly controlled diabetes. An explanation for this finding has remained elusive. However, this finding suggests that the avoidance of hypoglycemia in poorly controlled high-risk patients is extremely important.

Several pathways might mediate the adverse effects of hypoglycemia on outcomes in AMI patients, including sympathetic activation, hypokalemia, QT prolongation, platelet activation and prothrombotic activity, increased inflammation and cytokine levels, endothelial dysfunction, and oxidative stress (7,10,11). In particular, hyperglycemia after hypoglycemia was shown to cause more severe pathophysiologic changes than those observed during recovery to euglycemia, for a so-called “reperfusion-like effect” (38,39). These pathologic processes might be more relevant to patients with poorly controlled diabetes if they also have micro- or macrovascular complications (40). Additionally, acute hyperglycemia itself prevents ischemic preconditioning in patients with AMI who are undergoing reperfusion (28). Thus, in theory, ischemia-reperfusion injuries in patients with AMI could be further complicated by glucose-reperfusion after hypoglycemia. This agrees with our finding that hypoglycemia in AMI patients with poorly controlled diabetes was associated with highly unfavorable outcomes.

This study had several limitations. First, there is a possibility that other residual confounding factors were not excluded completely because the registries that were used were AMI but not diabetes oriented. Second, the number of patients who experienced hypoglycemia at admission for AMI was relatively small compared with the number of patients with hyperglycemia, and detailed information regarding diabetes control and hypoglycemia is lacking. Third, the long-term effects of hypoglycemia on mortality were not determined in the current study. It is not known how long the pathophysiologic changes persist following each episode of acute hypoglycemia. Further studies are required to fully understand the

long-term effects of hypoglycemia on the CV system and other organ systems.

In conclusion, hypoglycemia in AMI patients with or without type 2 diabetes is a more important factor related to 30-day mortality than was previously thought. In particular, hypoglycemia in AMI patients with poorly controlled diabetes is associated with increased mortality compared with patients with well-controlled diabetes.

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