

Association of Prestroke Glycemic Control With Vascular Events During 1-Year Follow-up

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Abstract

Background and Objectives

We evaluated the association between admission glycated hemoglobin (HbA1c) and subsequent risk of composite vascular events, including stroke, myocardial infarction (MI), and vascular death, in patients with acute ischemic stroke and diabetes.

Methods

Patients who had a TIA or an acute ischemic stroke within 7 days of symptom onset and diabetes were included in a retrospective cohort design using the stroke registry of the Clinical Research Center for Stroke in Korea. The association between admission HbA1c and composite vascular events, including stroke, MI, and vascular death, during 1-year follow-up was estimated using the Fine-Gray model. The risk of composite vascular events according to the ischemic stroke subtype was explored using fractional polynomial and linear-quadratic models.

Results

Of the 18,567 patients, 1,437 developed composite vascular events during follow-up. In multivariable analysis using HbA1c as a categorical variable, the risk significantly increased at a threshold of 6.8%–7.0%. The influence of admission HbA1c level on the risk of composite vascular events was pronounced particularly among those in whom fasting glucose at admission was ≤ 130 mg/dL. The optimal ranges of HbA1c associated with minimal risks for composite vascular events were lowest for the small vessel occlusion subtype (6.6 [95% confidence interval [CI], 6.3–6.9]) compared to the large artery atherosclerosis (7.3 [95% CI, 6.8–7.9]) or the cardioembolic subtype (7.4 [95% CI, 6.3–8.5]).

Discussion

In patients with ischemic stroke and diabetes, the risks of composite vascular events were significantly associated with admission HbA1c. The optimal range of admission HbA1c was below 6.8%–7.0% and differed according to the ischemic stroke subtype.

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Glossary

CI = confidence interval; CRCS-K = Clinical Research Center for Stroke in Korea; DM = diabetes mellitus; ED = emergency department; FP = fractional polynomial; HbA1c = glycated hemoglobin; HR = hazard ratio; MI = myocardial infarction; TOAST = Trial of Org 10172 in Acute Stroke Treatment.

More than 420 million patients have diabetes mellitus (DM) and the prevalence of DM has increased from 4.7% in 1980 to 8.5% in 2014.¹ DM increases the risk of first-ever stroke by 1.5–4.0-fold and that of recurrent stroke by 2.1–5.6-fold.^{2,3} Poor glucose control is associated with increased risk of atherosclerosis, increases in the carotid intima–media thickness, coronary heart disease, and atrial fibrillation, which are related to vascular events.^{4,5}

Glycated hemoglobin (HbA1c) indicates the average glucose level over 3 months and is widely used as a representative index for DM control. Current guidelines recommend maintaining a target level of HbA1c <7.0%, while a less stringent HbA1c target is recommended in patients with established vascular disease, old age, longstanding DM, or limited life expectancy.⁶ Intensive glucose control with a target HbA1c level of <6.5% was shown to reduce the risk of microvascular events, while the risk of macrovascular complications was significantly increased when HbA1c >7.0% was used as a threshold.⁷ Current guidelines focus on identifying the characteristics of patients who may benefit more from intensive glucose control, but studies regarding the beneficial effects of intensive glucose control according to specific disease entities are lacking.

Higher levels of HbA1c are associated with an increased risk of first-ever stroke. However, there is a lack of evidence regarding the optimal target level of HbA1c that minimizes the risk of cardiovascular events in patients with acute ischemic stroke. Moreover, ischemic stroke consists of several subtypes with different pathomechanisms, including large artery atherosclerosis, small vessel occlusion, cardioembolism, and other demonstrated causes such as coagulation disorder and nonatherosclerotic vasculopathies⁸; as such, the effect of prestroke glucose control on cardiovascular events may be different according to the ischemic stroke subtypes. Pre-morbid neurologic status and treatment-related factors (e.g., history of endovascular recanalization therapy, prior adherence to antidiabetic medication) may also have an influence on the association.

The purpose of the current study was to investigate and further delineate the association between HbA1c at admission and the subsequent risk of composite vascular events, including stroke, myocardial infarction (MI), and vascular death, in patients with acute ischemic stroke and DM. The influence of prestroke glucose control on cardiovascular events according to the ischemic stroke subtypes was also evaluated.

Methods

Data Source and Study Population

We reviewed the medical records of patients in the stroke registry of the Clinical Research Center for Stroke in Korea (CRCS-K) who had been admitted for treatment between January 2011 and July 2019. The CRCS-K is a prospective, nationwide, multicenter registry designed to establish the basis for the development of stroke prevention strategies and provide epidemiologic and clinical data on stroke and its care in Korea.⁹

Patients with a history of DM and TIA or acute ischemic stroke within 7 days after stroke onset were included in the analysis and those without data on HbA1c level at admission were excluded. From the registry, we collected data regarding demographics including age, sex, and body mass index; stroke subtype according to Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification; initial stroke severity and vascular risk factors including history of stroke, hypertension, DM, dyslipidemia, smoking, atrial fibrillation, and coronary heart disease; radiographic data including the presence and degree of cerebral artery stenosis; laboratory data including HbA1c, fasting glucose, lipid profile, and platelet count; and functional outcome at 3 months. Diabetes is defined as previous diagnosis of type I or II diabetes, fasting blood glucose ≥ 126 mg/dL, or HbA1c $\geq 6.5\%$. HbA1c was measured on the day of the emergency department (ED) visit. The fasting glucose was measured 8–10 hours after the last meal, likely the day after visiting the ED or the day of admission.

Study Outcomes

The primary end point was composite vascular event and the secondary end point was the recurrence of stroke during 1-year follow-up. Composite vascular events included stroke, MI, and vascular death. MI was defined as the presence of at least 2 of the following: symptoms of cardiac ischemia, elevation in cardiac enzymes, and changes in ECGs that are indicative of MI. Vascular death was defined as death occurring during hospitalization or after discharge due to stroke recurrence, MI, heart failure, or death without obvious nonvascular causes.¹⁰ The event outcomes were prospectively captured during hospitalization and at 1 year after the index stroke at the outpatient clinic or through telephone interviews with patients or their caregivers using structured questionnaires.¹¹

HbA1c was analyzed as a continuous or prespecified categorical variable. The patients were classified according to HbA1c quintiles, 5 groups according to HbA1c levels

(i.e., <6.0, ≥6.0–<7.0, ≥7.0–<8.0, ≥8.0–<9.0, ≥9.0), or 3 groups according to HbA1c levels (i.e., <6.5, ≥6.5–<7.0, ≥7.0). To evaluate the influence of acute hyperglycemia along with HbA1c, the patients were categorized into 6 groups: HbA1c <6.5 and fasting glucose ≤130, HbA1c <6.5 and fasting glucose >130, HbA1c ≥6.5–<7.0 and fasting glucose ≤130, HbA1c ≥6.5–<7.0 and fasting glucose >130, HbA1c ≥7.0 and fasting glucose ≤130, and HbA1c ≥7.0 and fasting glucose >130.

Statistical Analysis

Clinical characteristics were compared using the χ^2 test or Fisher exact test for categorical variables and independent *t* test or Mann-Whitney *U* test for continuous variables. The cumulative incidence of each outcome was compared according to the HbA1c level. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of HbA1c level with outcome events over 1 year were calculated using the Fine-Gray model. Other causes of death were the competing risks for composite vascular events and all-cause death for stroke recurrence. The covariates used in multivariable adjustments were age, sex, stroke severity, medical history (stroke or TIA, hypertension, coronary heart disease, atrial fibrillation, smoking status), hemoglobin, total cholesterol, creatinine clearance, initial systolic and diastolic blood pressure, cerebral artery atherosclerosis (≥50% or <50%), history of endovascular recanalization therapy, and ischemic stroke subtype. Sensitivity analyses that included patients without admission HbA1c data were performed after imputations using a sequential regression multiple imputation method.

The prespecified subgroups included age (≥80 or <80), sex, ischemic stroke subtype (large artery atherosclerosis, small vessel occlusion, cardioembolism, other determined, undetermined), cerebral artery atherosclerosis (≥50% or <50%), history of endovascular recanalization therapy, prior antidiabetic medication, premorbid neurologic status (modified Rankin Scale ≤3 or >3), and fasting glucose at admission (>130 or ≤130 mg/dL). Multiplicative interaction analyses between each variable and HbA1c were performed.

The relationship between HbA1c level and adjusted HRs for composite vascular events according to the ischemic stroke subtype was plotted using fractional polynomial (FP) and linear-quadratic curves. The level of HbA1c with the smallest HR for the outcomes was calculated from both the estimated FP model and the linear-quadratic model. The HbA1c level at which the first derivative of the FP model was equal to 0 was regarded as the minimum point of the FP curve. The optimal HbA1c for the linear-quadratic model was $-b/2a$, where “a” is a coefficient of quadratic term and “b” is a coefficient of the first-order term for the model. The proportional hazards assumption was evaluated based on the Schoenfeld residuals. Nonlinearity was evaluated using restricted cubic spline regression. All analyses were performed using Stata version 14.1 (StataCorp.). All tests were 2-sided, and *p* values less than 0.05 were considered statistically significant.

Standard Protocol Approvals, Registrations, and Patient Consents

All participating centers obtained approval from their local institutional review boards for data collection. Written informed consent was obtained from patients or their caregivers.

Data Availability

The data that support the findings of this study are available from the corresponding author on reasonable request.

Results

Among the 66,353 patients in the stroke registry, 21,094 had DM. After excluding patients with hemorrhagic stroke (*n* = 1,660) or missing information on HbA1c (*n* = 855) or event outcomes (*n* = 12), 18,567 were finally included in the analysis. The median age was 70.0 (interquartile range, 61.0–71.0) and 59.5% were male. The mean HbA1c was 7.5 (SD 0.96). The proportion of patients with the ischemic stroke subtype was the highest in large artery atherosclerosis (7,644 [41.2%]), followed by undetermined etiology (3,842 [20.7%]), cardioembolism (3,395 [18.3%]), small vessel occlusion (3,326 [17.9%]), and other determined etiology (360 [1.9%]). The baseline characteristics of the patients according to the HbA1c quintiles are presented in Table 1.

During 1-year follow-up, 1,437 patients developed the composite vascular events and 954 patients developed stroke. Table 2 shows the HRs for composite vascular events and stroke recurrence according to HbA1c levels as a continuous or categorical variable. Multivariable-adjusted HRs for 1 unit increase of HbA1c on admission were 1.04 (1.01, 1.07) for composite vascular events and 1.02 (0.99, 1.06) for stroke recurrence. Multivariable-adjusted HRs according to HbA1c quintiles at admission were 1.09, 1.27, 1.38, and 1.21 for composite vascular events, and 0.98, 1.25, 1.43, and 1.12 for stroke recurrence. Compared with the first HbA1c quintile (≤6.2), the third (>6.8–≤7.5), fourth (>7.5–≤8.7), and fifth quintiles (>8.7) had significantly higher HRs for composite vascular events after multivariable adjustment (1.27 [95% CI, 1.08–1.50], 1.38 [95% CI, 1.1–1.64], and 1.21 [95% CI, 1.02–1.45], respectively). The risk of stroke recurrence was significantly higher in the third (1.25 [95% CI, 1.02–1.53]) and fourth quintiles (1.43 [95% CI, 1.17–1.76]) compared with the first quintile. Adjusted HRs according to prespecified ranges of HbA1c (≥6.0–<7.0, ≥7.0–<8.0, ≥8.0–<9.0, ≥9.0) vs HbA1c <6.0 were 1.16, 1.31, 1.40, and 1.27 for composite vascular events and 1.08, 1.29, 1.46, and 1.14 for stroke recurrence, respectively. Higher levels of HbA1c (>7.0) were associated with an increased risk of composite vascular events compared with HbA1c <6.0. Adjusted HRs according to another prespecified range of HbA1c (<6.5, ≥6.5–<7.0, and ≥7.0) showed that HbA1c ≥7.0 was associated with a significantly higher HR for both

Table 1 Baseline Characteristics of Study Patients According to Glycated Hemoglobin (HbA1c) Quintiles

	Total (n = 18,567)	1st quintile (≤6.2) (n = 3,929)	2nd quintile (>6.2–≤6.8) (n = 3,985)	3rd quintile (>6.8–≤7.5) (n = 3,714)	4th quintile (>7.5–≤8.7) (n = 3,392)	5th quintile (>8.7) (n = 3,547)	p Value
Age, y	70.0 (61.0–77.0)	74.0 (66.0–80.0)	72.0 (64.0–78.0)	71.0 (63.0–77.0)	69.0 (60.0–76.0)	64.0 (55.0–73.0)	<0.001
Male sex	11,046 (59.5)	2,225 (56.6)	2,351 (59.0)	2,178 (58.6)	2,085 (61.5)	2,207 (62.2)	
Initial NIHSS	4.0 (1.0–7.0)	4.0 (2.0–10.0)	3.0 (1.0–8.0)	3.0 (1.0–7.0)	3.0 (1.0–7.0)	4.0 (2.0–6.0)	<0.001
Risk factors							
Previous stroke	4,624 (24.9)	1,171 (29.8)	1,006 (25.2)	919 (24.7)	803 (23.7)	725 (20.4)	<0.001
Coronary heart disease	2,112 (11.4)	445 (11.3)	516 (12.9)	414 (11.1)	387 (11.4)	350 (9.9)	0.001
HT	14,603 (78.7)	3,306 (84.1)	3,207 (80.5)	2,914 (78.5)	2,634 (77.7)	2,542 (71.7)	<0.001
New onset DM	2,361 (12.7)	406 (10.3)	678 (17.0)	512 (13.8)	314 (9.3)	451 (12.7)	<0.001
Smoking	7,011 (37.8)	1,283 (32.7)	1,442 (36.2)	1,383 (37.2)	1,335 (39.4)	1,568 (44.2)	<0.001
AF	3,431 (18.5)	944 (24.0)	905 (22.7)	713 (19.2)	495 (14.6)	374 (10.5)	<0.001
Laboratory findings							
Hb	13.5 (12.2–14.8)	13.1 (11.6–14.4)	13.5 (12.2–14.7)	13.4 (12.1–14.7)	13.6 (12.3–14.9)	14.1 (12.7–15.4)	<0.001
Total cholesterol	163 (135–196)	156 (130–184)	161 (133–190)	163 (134–192)	164 (137–197)	180 (147–217)	<0.001
LDL	99 (75–128)	93 (71–118)	97 (73–125)	98 (74–125)	100 (76–130)	112 (83–143)	<0.001
Triglyceride	117 (85–166)	98 (73–137)	110 (82–155)	119 (87–165)	127 (93–179)	138 (100–200)	<0.001
Initial blood pressure, mm Hg							
SBP	146 (130–164)	142 (128–160)	145 (130–162)	145 (130–164)	148 (130–167)	150 (130–170)	<0.001
DBP	80 (72–92)	80 (70–90)	80 (72–90)	80 (72–92)	82 (74–94)	84 (74–96)	<0.001
Cerebral artery stenosis ≥50%	8,472 (45.6)	1,852 (47.1)	1,833 (46.0)	1,741 (46.9)	1,511 (44.5)	1,535 (43.3)	0.003
Endovascular treatment	1,184 (6.4)	296 (7.5)	293 (7.4)	259 (7.0)	204 (6.0)	132 (3.7)	<0.001
Prior medications							
Statin	5,141 (27.7)	1,031 (26.2)	1,222 (30.7)	1,063 (28.6)	975 (28.7)	850 (24.0)	<0.001
Anti-diabetic medication	13,460 (72.5)	2,766 (70.4)	2,808 (70.5)	2,771 (74.6)	2,656 (78.3)	2,459 (69.3)	<0.001
Previous mRS >3	755 (4.2)	314 (8.2)	124 (3.2)	122 (3.4)	104 (3.1)	91 (2.6)	<0.001
mRS at 3 months	2.0 (1.0–4.0)	2.0 (1.0–4.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	<0.001

Abbreviations: AF = atrial fibrillation; DBP = diastolic blood pressure; DM = diabetes mellitus; HT = hypertension; mRS = modified Rankin Scale; LDL = low-density lipoprotein; NIHSS = NIH Stroke Scale; SBP = systolic blood pressure. Values are median (interquartile range) or n (%).

the composite vascular event (1.27 [95% CI, 1.12–1.44]) and stroke recurrence (1.28 [95% CI, 1.10–1.49]) compared with HbA1c <6.5. As baseline characteristics were significantly different between patients with and without admission HbA1c data (eTable 1, links.lww.com/WNL/B513), we performed a sensitivity analysis that included patients without HbA1c data. The results of sensitivity analysis were consistent, showing that higher HbA1c levels (>6.8%–7.0%) were associated with an increased risk of composite vascular events and stroke recurrence (eTable 2, links.lww.com/WNL/B514).

The effect of fasting glucose at admission on the association between HbA1c and composite vascular events was analyzed (Table 3). Compared with the reference group (HbA1c <6.5, fasting glucose ≤130 mg/dL), patients with the same level of HbA1c but a higher level of fasting serum glucose (>130 mg/dL) had a significantly higher risk of composite vascular events (1.44 [95% CI, 1.16–1.78]). Among the patients with HbA1c ≥6.5–<7.0, only those with fasting serum glucose >130 mg/dL had a significantly higher risk of composite vascular events compared with the reference group (1.44 [95% CI, 1.15–1.79]). HbA1c levels higher than 7.0 were

Table 2 Hazard Ratios (95% Confidence Intervals) for Composite Vascular Events and Stroke Recurrence According to Glycated Hemoglobin

	1st quintile (≤6.2)	2nd quintile (>6.2–≤6.8)	3rd quintile (>6.8–≤7.5)	4th quintile (>7.5–≤8.7)	5th quintile (>8.7)	p Value for overall effect
Composite vascular event	Reference	1.09 (0.93–1.28)	1.27 (1.08–1.50)	1.38 (1.17–1.63)	1.21 (1.02–1.45)	0.001
Stroke recurrence	Reference	0.98 (0.80–1.21)	1.25 (1.02–1.53)	1.43 (1.17–1.76)	1.12 (0.90–1.40)	<0.001
	<6.0	≥6.0–<7.0	≥7.0–<8.0	≥8.0–<9.0	≥9.0	p Value for overall effect
Composite vascular event	Reference	1.16 (0.99–1.37)	1.31 (1.10–1.56)	1.40 (1.15–1.72)	1.27 (1.04–1.55)	0.006
Stroke recurrence	Reference	1.08 (0.87–1.33)	1.29 (1.03–1.60)	1.46 (1.14–1.87)	1.14 (0.89–1.46)	0.009
	<6.5	≥6.5–<7.0	≥7.0	Overall p value		
Composite vascular event	Reference	1.14 (0.97–1.34)	1.27 (1.12–1.44)	<0.001		
Stroke recurrence	Reference	1.06 (0.86–1.28)	1.28 (1.10–1.49)	0.005		

Adjusted by age, sex, stroke severity, medical history (stroke, hypertension, coronary heart disease, atrial fibrillation, smoking status), hemoglobin, total cholesterol, creatinine clearance, initial systolic and diastolic blood pressure, cerebral arteries atherosclerosis (≥50% or <50%), history of endovascular recanalization therapy, history of antidiabetic medication, and ischemic stroke subtype.

associated with increased risks of composite vascular events compared with the reference group regardless of the fasting serum glucose level (fasting glucose ≤130, 1.39 [95% CI, 1.14–1.69]; fasting glucose >130, 1.46 [95% CI, 1.24–1.71]).

The effects of prestroke glucose control on composite vascular events and stroke recurrence were consistent with respect to age (<80, ≥80), sex, stroke subtype, presence of cerebral artery atherosclerosis (≥50%, <50%), history of endovascular recanalization therapy, and premorbid neurologic status (Figures 1 and 2). However, there was a significant interaction between composite vascular events and fasting glucose level at admission; the HR of composite vascular events per 1 unit increase of HbA1c was 1.09 in patients with fasting glucose ≤130 mg/dL compared with 0.99 in those with fasting glucose >130 mg/dL (*p* interaction = 0.003). There was a marginally significant interaction between stroke recurrence and history of antidiabetic medication; the HRs of stroke recurrence per 1 unit increase of HbA1c in patients with and without prior antidiabetic medication were 1.05 and 0.96 (*p* interaction = 0.022), respectively, while the HRs of composite vascular events in patients with and without prior

antidiabetic medication were 1.06 and 0.99, respectively (*p* interaction = 0.06).

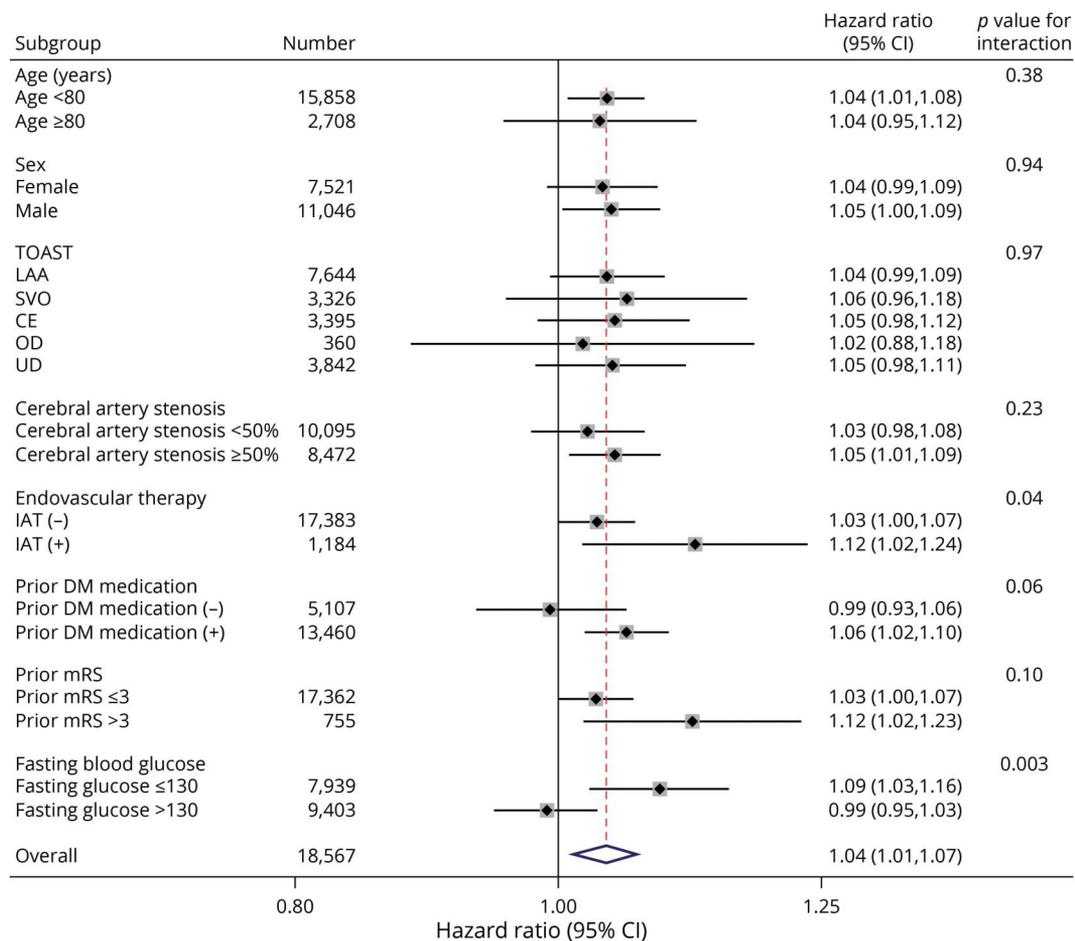
The relationship between the risk of composite vascular events and HbA1c at admission was plotted and the fitted curves are presented in Figure 3. According to the FP model, the optimal range of HbA1c associated with a minimum cardiovascular risk was the lowest for small vessel occlusion (6.6 [95% CI, 6.3–6.9]), followed by large artery atherosclerosis (7.3 [95% CI, 6.8–7.9]) and cardioembolism (7.4 [95% CI, 6.3–8.5]) (Table 4). Similarly, the linear-quadratic model showed that the HbA1c associated with a minimum cardiovascular risk was the lowest for small vessel occlusion (6.6 [95% CI, 5.6–7.7]), followed by large artery atherosclerosis (7.4 [95% CI, 6.8–8.0]) and cardioembolism (8.0 [95% CI, 5.1–10.8]). In patients with cerebral artery atherosclerosis ≥50%, the HbA1c with the lowest risk was 8.8 (95% CI, 8.3–9.2) in the FP model and 8.8 (95% CI, 8.3–9.2) for in the linear-quadratic model; in patients with cerebral artery atherosclerosis <50%, the HbA1c with the lowest risk was 7.8 (95% CI, 7.5–8.0) in the FP model and 8.2 (95% CI, 7.9–8.6) in the linear-quadratic model.

Table 3 Hazard Ratios (95% Confidence Intervals) for Composite Vascular Events and Stroke Recurrence According to Glycated Hemoglobin (HbA1c) and Fasting Glucose (FG) at Admission

	HbA1c <6.5, FG ≤ 130	HbA1c <6.5, FG > 130	6.5 ≤ HbA1c < 7.0, FG ≤ 130	6.5 ≤ HbA1c < 7.0, FG > 130	HbA1c ≥7.0, FG ≤ 130	HbA1c ≥7.0, FG > 130	p Value for overall effect
Composite vascular event	Reference	1.44 (1.16–1.78)	1.18 (0.94–1.49)	1.44 (1.15–1.79)	1.39 (1.14–1.69)	1.46 (1.24–1.71)	<0.001
Stroke recurrence	Reference	0.98 (0.73–1.32)	1.08 (0.83–1.42)	1.01 (0.75–1.36)	1.35 (1.09–1.69)	1.21 (1.00–1.47)	0.06

Adjusted by age, sex, stroke severity, medical history (stroke, hypertension, coronary heart disease, atrial fibrillation, smoking status), hemoglobin, total cholesterol, creatinine clearance, initial systolic and diastolic blood pressure, cerebral arteries atherosclerosis (≥50% or <50%), history of endovascular recanalization therapy, history of antidiabetic medication, and stroke subtype.

Figure 1 Composite Vascular Events According to the Prespecified Subgroups



CE = cardioembolic; CI = confidence interval; DM = diabetes mellitus; IAT = intraarterial thrombosis; LAA = large artery atherosclerosis; mRS = modified Rankin Scale; OD = other determined; SVO = small vessel occlusion; TOAST = Trial of ORG 10172 in Acute Stroke Treatment; UD = undetermined.

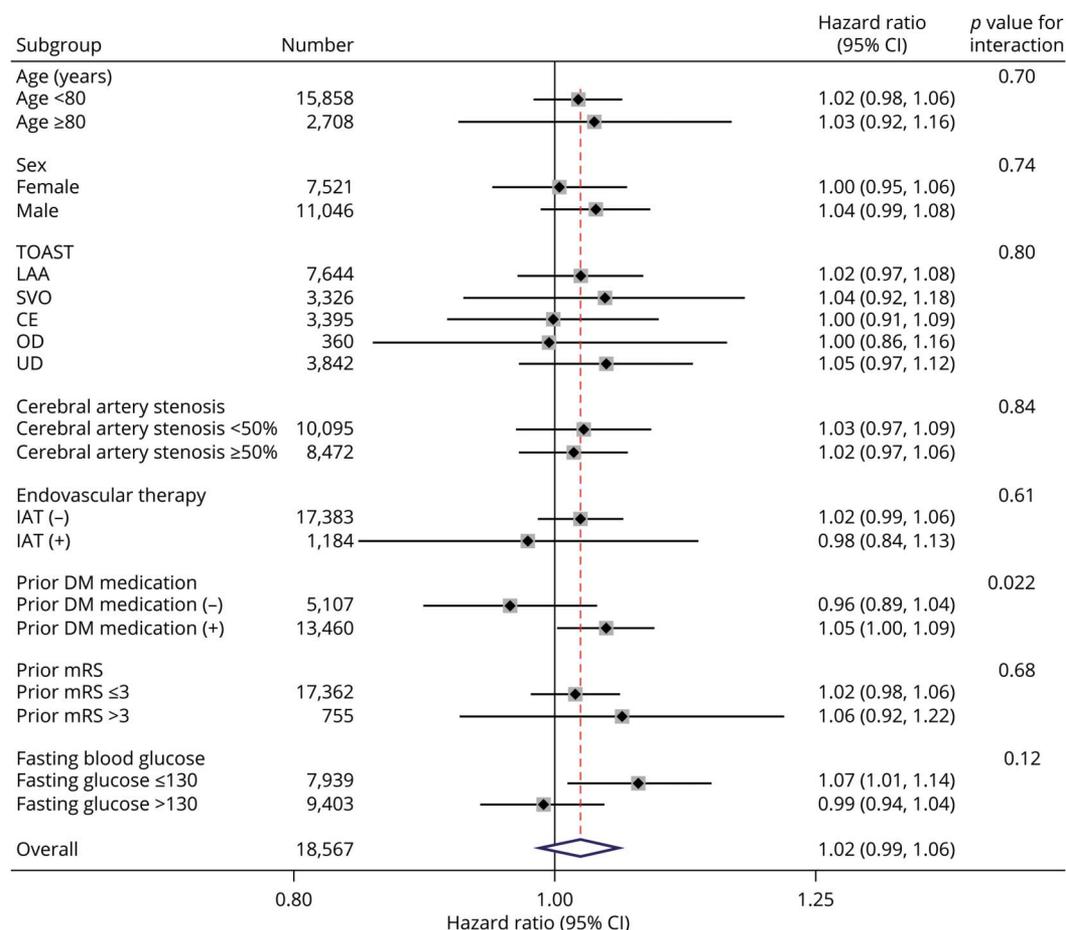
Discussion

Our study showed that prestroke glycemic control is associated with the subsequent risk of composite vascular events during 1-year follow-up in patients with acute ischemic stroke and DM. The risk of cardiovascular events significantly increased above the HbA1c threshold of 6.8%–7.0% as a categorical variable. The influence of HbA1c at admission on the risk of composite vascular events was particularly pronounced among those in whom fasting glucose level at admission was well-controlled (≤ 130 mg/dL). The optimal range of HbA1c that minimized the risk of vascular events was different according to the ischemic stroke subtype, with the small vessel occlusion subtype showing the lowest range. Lastly, the optimal level of HbA1c was higher among those with significant cerebral artery atherosclerosis than in those without.

The relationship between HbA1c and cardiovascular risk in patients with ischemic stroke, especially among patients with cerebral artery atherosclerosis $\geq 50\%$, seemed not much different from other established vascular diseases.¹² However,

the optimal range of HbA1c was different according to the ischemic stroke subtype. Ischemic stroke with small vessel occlusion subtype was more likely to benefit from intensive prestroke glucose control as the inflection point of the fractional polynomial plot was 6.6% in small vessel occlusion compared with 7.3% in large artery atherosclerosis. Cerebral small vessel disease involves the brain's small perforating arterioles, capillaries, and venules, which leads to various lesions including white matter hyperintensities, microbleeds, and microinfarct.¹³ Pathologically, the small-vessel occlusion subtype may be considered as a disease entity that is partway between the microvascular and macrovascular complications of DM.^{14,15} Also, a previous study showed that recurrent strokes were twice as likely to be presented with the same subtype as index stroke in small vessel occlusion.¹⁶ The result from the current study is in agreement with the previous reports that lowering the target level of HbA1c from 7% to 6% confers an additional benefit for preventing microvascular complications of DM, provided that the target can be safely achieved without hypoglycemia. Thus, more intense glycemic control may be warranted to reduce the risk of recurrent small vessel occlusion.

Figure 2 Stroke Recurrence According to the Prespecified Subgroups

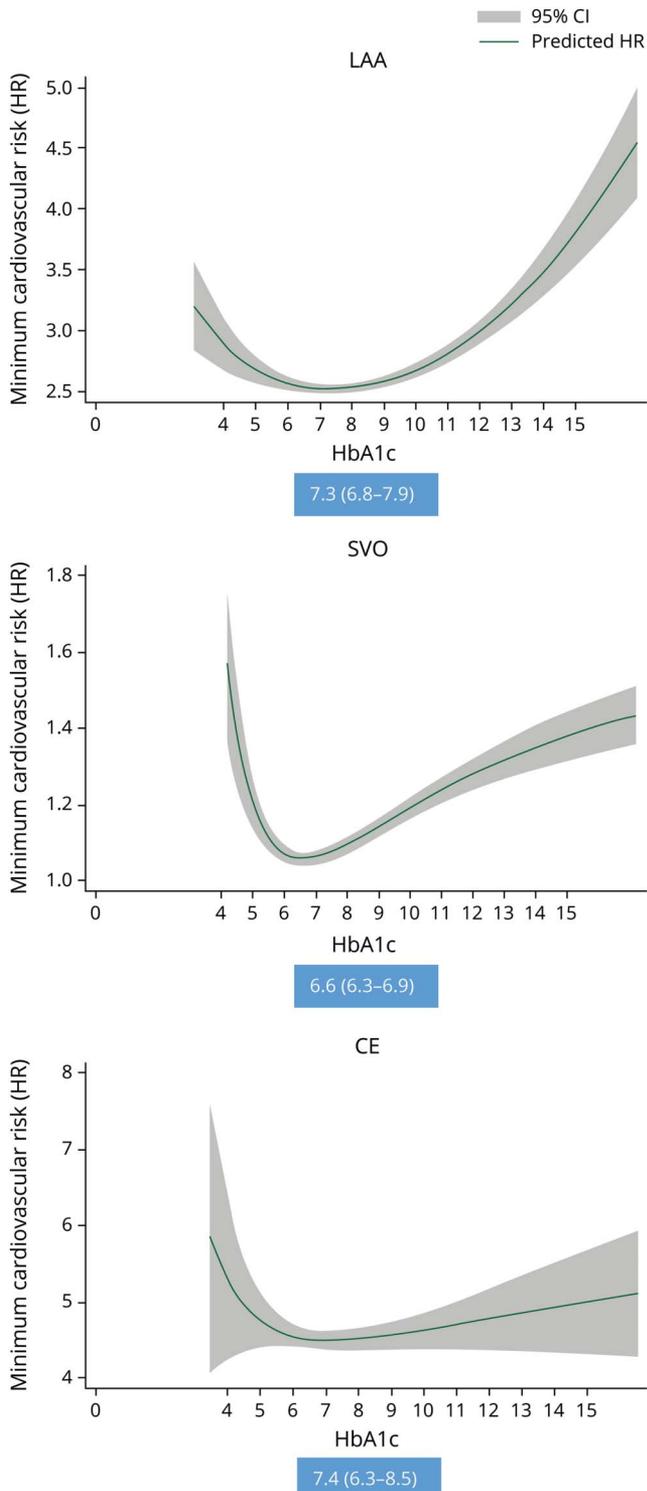


CE = cardioembolic; CI = confidence interval; DM = diabetes mellitus; IAT = intraarterial thrombosis; LAA = large artery atherosclerosis; mRS = modified Rankin Scale; OD = other determined; SVO = small vessel occlusion; TOAST = Trial of ORG 10172 in Acute Stroke Treatment; UD = undetermined.

Less stringent glucose control may be justified in patients with significant cerebral artery atherosclerosis, who showed the lowest risk for cardiovascular disease at an HbA1c level more than 8%. Ischemic stroke with significant cerebral artery atherosclerosis could be considered as a manifestation of advanced macrovascular complications in which the risk of hypoglycemia outweighs the additional benefit from strict glucose control. Meanwhile, the risk of cardiovascular disease was not notably decreased by prestroke glucose control, but steeply increased at HbA1c levels lower than 7.4% in cardioembolism, suggesting that preventing hypoglycemia may be more important than hyperglycemia control in such patients. Atrial fibrillation is one of the most important causes of cardioembolic stroke, and its prevalence increases with age, affecting more than 10% of individuals above 80 years of age. In the current study, patients with cardioembolism had the highest mean age (72.9 ± 10.1). Strict glucose control needs to be avoided in those with cardioembolic ischemic stroke to prevent the adverse events associated with hypoglycemia. An individualized glucose control strategy depending on the ischemic stroke subtypes is required.

Our results showed that acute hyperglycemia additionally increases the risk of cardiovascular events in patients with ischemic stroke and DM. Acute hyperglycemia at admission (>130 mg/dL) additionally increased the risk of subsequent composite vascular events even in patients with HbA1c below 7.0. Discordance of HbA1c and fasting glucose was found in almost 25% of patients with type 2 DM.¹⁷ Old age, elevated body mass index, male sex, fatty liver, and prolonged DM history were associated with high fasting glucose and normal HbA1c values.¹⁷ Increased cardiovascular risk among the patients with this discordance may be attributed to these characteristics. In addition, wide fluctuation of glucose may also increase the risk of microvascular complications, macrovascular complications, and mortality resulting from oxidative stress and frequent hypoglycemic insults.¹⁸ The influence of HbA1c at admission on the risk of composite vascular events was particularly pronounced among those in whom fasting glucose at admission was ≤ 130 mg/dL. We speculated that the harmful effect of acute hyperglycemia may mitigate the association between high HbA1c and vascular outcome. The relatively higher proportion of new onset diabetes among patients with fasting glucose at admission

Figure 3 Optimal Glycated Hemoglobin (HbA1c) Level for Minimizing the Risk of Composite Vascular Events



CE = cardioembolic; CI = confidence interval; HR = hazard ratio; LAA = large artery atherosclerosis; SVO = small vessel occlusion.

>130 mg/dL compared with those with fasting glucose at admission \leq 130 mg/dL (13.8% vs 12.5%, $p = 0.02$) may be another reason for the nonsignificant association between HbA1c and composite vascular events.

Table 4 Optimal Ranges of Glycated Hemoglobin According to Fractional Polynomial and Linear-Quadratic Models

	Fractional polynomial	Linear-quadratic
Total	8.6 (8.3–8.9)	8.8 (8.5–9.1)
Large artery atherosclerosis	7.3 (6.8–7.9)	7.4 (6.8–8.0)
Small vessel occlusion	6.6 (6.3–6.9)	6.6 (5.6–7.7)
Cardioembolism	7.4 (6.3–8.5) ^a	8.0 (5.1–10.8)
Cerebral artery stenosis \geq50%	8.8 (8.3–9.2)	8.8 (8.3–9.2)
Cerebral artery stenosis $<$50%	7.8 (7.5–8.0)	8.2 (7.9–8.6)

Data shown are hazard ratios (95% confidence intervals).

^a Cubic polynomial.

The stroke registry used in this study employs an MRI-based algorithm for classifying the subtype of acute stroke, which utilizes recently developed stroke imaging tools such as diffusion-weighted imaging, high-resolution vessel wall imaging, and the results of recanalization therapy.¹⁹ Thus, this study has an advantage that the ischemic stroke subtype classification may be more reliable than that using the traditional TOAST classification.

The current study has a limitation that only the HbA1c measurements at admission were used in the analysis and follow-up measurements of HbA1c were not available. The association between HbA1c at admission and subsequent cardiovascular disease may not reflect the effort on glycemic control during follow-up. Yet the deleterious effects of poor glycemic control can last despite adequate control afterward. The long-lasting effect of prior hyperglycemia exposure, called metabolic memory, can be induced by epigenetic modifications.²⁰ It may persist long after the termination of hyperglycemic stimuli and result in diabetic microvascular and macrovascular complications.²¹ Considering that covert infarcts are common in the elderly,²² the incidence of recurrent lacunar infarcts may be underestimated as we did not perform MRI routinely without clinical symptoms. The relatively short follow-up period and the inclusion of a single ethnicity may limit the generalizability of the study results.

The risks of composite vascular events and stroke recurrence were associated with prestroke glucose control in patients with ischemic stroke and DM. The optimal range of admission HbA1c with a minimum risk for composite vascular events and stroke recurrence was estimated to be between 6.8% and 7.0% and were notably different according to the ischemic stroke subtype. More stringent glucose control may be justified in patients with stroke with small vessel occlusion subtype, which is consistent with the current recommendation for preventing the microvascular complications of DM.

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Appendix (continued)

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