Received: 30 August 2024 | Accepted: 8 December 2024

DOI: 10.1111/ene.70004

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

Influence of prestroke glycemic status on outcomes by age in patients with acute ischemic stroke and diabetes mellitus

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Funding information
the Korea National Institute of Health (KNIH) research project, Grant/Award Number: 2023-ER-1006-01; the Chonnam National University Hospital Biomedical Research Institute, Grant/Award Number: BCRI24042

Abstract

Background: This study aimed to explore the association between admission HbA1c and the risk of 1-year vascular outcomes stratified by age group in patients with acute ischemic stroke (AIS) and diabetes mellitus (DM).

Methods: This study analyzed prospective multicenter data from patients with AIS and DM. Admission HbA1C were categorized as:≤6.0%, 6.1%–7.0%, 7.1%–8.0%, and >8.0%. Age was analyzed in categories:≤55 years, 56–65 years, 66–75 years, 76–85 years, and >85 years. The primary outcome was 1-year composite of stroke, MI, and all-cause mortality. The modifying effect of age on the relationships between HbA1c and 1-year primary outcome was explored by Cox proportional hazards model.

Results: A total of 16,077 patients (age 69.0 ± 12.4 years; 59.4% males) were analyzed in this study. Among patients ≤55 years, the hazard ratio (HR) of the 1-year primary outcomes increased with an HbA1C > 8.0% (adjusted HR 1.39[1.13–1.70]). For patients aged 56–65 and 66–75, the highest HRs were observed for an HbA1c of 7.1–8.0% (aHRs; 1.21 [1.01–1.46] and 1.22 [1.05–1.41], respectively). In the 85+ age group, the highest HR occurred for HbA1c ≤ 6.0% (aHR 1.47 [0.98–2.19]). The HbA1c 8.0% showed evident age-dependent heterogeneity in the post hoc HR plots.

Conclusion: Our study revealed that in patients with AIS and diabetes under 55, higher admission hbA1c was associated with an increased risk of the 1-year primary outcome, while in patients aged over 85, lower HbA1c value (≤6.0%) may be associated with an increased risk of vascular events. The results of our study suggest the age-stratified,

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heterogeneous associations between admission HbA1c and 1-year vascular outcomes in patients with AIS and diabetes.

KEYWORDS
acute ischemic stroke, age, diabetes, glycated hemoglobin (hbA1c), prestroke glycemic status

INTRODUCTION

Diabetes mellitus (DM) is a significant risk factor for stroke in the general population and for vascular events after acute ischemic stroke or transient ischemic attack (TIA). [1, 2] In patients with ischemic stroke and diabetes, admission HbA1c levels have been linked to 1-year vascular events and 3-month functional outcomes. [3, 4] However, clinical trials have not demonstrated a benefit of intensive glucose control on early recurrent stroke or functional outcomes in these patients [5, 6].

The European or American stroke guidelines suggest maintaining HbA1c below 7.0% in patients with ischemic stroke, [7, 8] but emphasize that targets should be individualized based on age and patient-specific factors. [8] However, age-specific HbA1c targets for stroke patients are not well-defined, and research in this area remains limited. Guidelines for diabetes management generally recommend an HbA1c target of 7%–8%, or even 8%–9% for elderly individuals with limited life expectancy or significant comorbidities, to reduce the risk of hypoglycemia. [9, 10] Notably, the risk of vascular events associated with diabetes is higher in younger adults than in older adults. [11, 12] Previous studies have often categorized age groups simply as <65 years versus ≥65 years, lacking detailed granularity. Given that ischemic stroke and TIA patients are typically older and have preexisting vascular conditions, the impact of prestroke glycemic control on stroke prognosis may vary by age.

This study aims to explore the association between admission HbA1c levels and the risk of subsequent vascular events, stratified by age, in patients with ischemic stroke and diabetes. By classifying patients into more specific age and HbA1c groups, we seek to identify potential variations in outcomes across different age groups.

MATERIALS AND METHODS

Subjects

In this study, we analyzed data from the Clinical Research Center for Stroke-Korea (CRCS-K) registry, a nationwide collection of consecutive acute stroke or transient ischemic attack (TIA) patients admitted to 18 academic hospitals in South Korea. Comprehensive methodological details about the CRCS-K registry have been previously documented. [13, 14] We identified patients who were admitted to these hospitals between January 2011 and November 2019 for acute cerebrovascular events ($n = 69{,}670$). We included patients with acute ischemic stroke occurring within 48 h of onset and DM among the patients with acute cerebrovascular events. Those with uncommon stroke etiology (other etiology subtype) and those lacking information on HbA1c and glucose levels at admission were excluded. A detailed patient selection flowchart is shown in Figure S1.

ETHICS STATEMENT

Clinical information was collected from the CRCS-K registry with approval from the local institutional review boards of all the participating centers. A waiver for informed consent was provided because of study subject anonymity and minimal risk to the participants. The data used in this study are available upon reasonable request following the submission of a legitimate academic research proposal to be assessed by the CRCS-K steering committee.

Data collection

Demographic, clinical, imaging, and laboratory information was prospectively collected. According to the American Diabetes Association (ADA) criteria, [15] DM is generally defined as: (1) FPG ≥126 mg/dL (7.0 mmol/L), (2) 2-h PG ≥200 mg/dL (11.1 mmol/L) during an OGTT, (3) HbA1C >6.5%, or (4) in the presence of classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL. In our study, we defined DM based on a preexisting history of DM/glucose-lowering treatment or an admission HbA1C >6.5%. We did not use OGTT or FPG on admission for new DM diagnosis, as hyperglycemia can occur in the acute phase of ischemic stroke. HbA1c was measured during the initial post-admission fasting period and classified into four categories: ≤6.0%, 6.1–7.0%, 7.1%–8.0%, and >8.0%. Age was analyzed as both a continuous variable and a categorical variable, with the latter being classified into five categories: ≤55 years, 56–65 years, 66–75 years, 76–85 years, and >85 years. Ischemic stroke subtypes were classified using the Trial of Org 10,172 in Acute Stroke Treatment (TOAST) criteria and refined with additional data from modern imaging studies [16, 17].

Outcomes

The primary outcome was a composite of major vascular events outcomes, including recurrent stroke (either hemorrhagic or ischemic), myocardial infarction (MI) and all-cause mortality, within 1 year of admission. The secondary outcomes included the following individual vascular outcomes: (a) all-cause mortality, (b) stroke (either ischemic or hemorrhagic), (c) MI, and (d) hemorrhagic stroke. Detailed definitions

of the vascular outcome events and methods of outcome identification used in the current study are described in the Supplemental Methods and previous reports. [13, 14] In addition, to differentiate between all-cause mortality and index stroke-related mortality, we performed a sensitivity analysis excluding all death within 30 days after index stroke, that is, likely related to the index event.

Statistical analysis

Baseline characteristics and outcomes were compared among the HbA1c groups using the chi-square test, ANOVA, or Kruskal–Wallis test according to the type of variable. The event probability of 1-year vascular outcomes according to HbA1c group in all patients combined and by age subgroup was calculated using the Kaplan–Meier method, and the log-rank test was performed to analyze differences among the groups. In addition, comparisons between the HbA1c 6.1%–7.0% group and the other HbA1c groups were performed using the log-rank test with Dunnett's method for multiple comparisons. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) for 1-year vascular outcomes were analyzed using a Cox proportional hazards model. Adjustments were made for the following predetermined variables with clinically relevant associations with the outcome variables: age, sex, BMI, NIHSS score, history of stroke, history of coronary artery diseases, HTN, dyslipidemia, atrial fibrillation, prior antiplatelet use, prior statin use, glucose, LDL-C, creatinine, systolic blood pressure, large-artery steno-occlusion, and TOAST stroke subtypes. The modifying effect of age group on the relationships between HbA1c group and primary vascular outcomes was explored by separately introducing an interaction term of age groups and HbA1c groups into the models. *E*-values were calculated to assess the potential contribution of unmeasured confounders for each of the models. [18] The *E*-value estimates the minimum magnitude of association that would be required between an unmeasured confounder and both the exposure and outcome, conditional on measured covariates, to overcome the statistically significant effect observed in a study where residual confounding is a potential problem [18].

The dichotomized HbA1c values were analyzed post hoc in relation to the 1-year primary outcome according to age (continuous variable), comparing HbA1c >8.0% to ≤8.0% and ≤6.0% to >6.0%. Hazard ratio plots were generated for a clearer understanding of the associations. In predefined subgroup analyses, we explored the outcome of interest in patients stratified by sex (male or female), stroke severity (minor [NIHSS 0–4], moderate [5–10], or severe [>10]), subtypes according to the Trial of ORG 10172 in Acute Stroke Treatment classification, history of hypertension (present or absent), and prestroke mRS score (0–1 or >1). Statistical significance was generally indicated by two-sided *p*-values <0.05. Given the known insensitivity of interaction testing, *p*-values ≤0.10 were considered to indicate evidence of heterogeneity. Statistical analyses were performed with R software using the "rms" package (version 3.6.0, R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

General characteristics

A total of 16,077 patients (mean age = 69.0 ± 12.4 years; 59.4% males) met the eligibility criteria and were included in this study. The median NIHSS score was 4 (IQR 2–9). The mean HbA1c and glucose levels at admission were 7.4 ± 1.6% and 184.6 ± 79.9 mg/dL, respectively. The age distribution was as follows: 14.9% were aged 55 years or younger, 20.6% were aged 56–65 years, 30.1% were aged 66–75 years, 28.8% were aged 76–85 years, and 5.6% were aged over 85 years. For HbA1c, 14.1% of patients had values at or below 6.0%, 38.0% of patients had values between 6.1% and 7.0%, 22.0% had values between 7.1% and 8.0%, and 25.9% had values exceeding 8.0%. The demographic and clinical characteristics stratified by HbA1c group are shown in Table 1. Compared to patients in the HbA1c ≤6.0% group, patients in the higher HbA1c groups were more likely to be male; have a prestroke mRS score of 0–1; be a current smoker; and have a large-artery atherosclerosis (LAA) subtype, while they were less likely to have a history of stroke, HTN, atrial fibrillation, prior antiplatelet therapy, prior statin therapy, prior antihypertensive therapy, or the cardioembolism (CE) subtype.

Outcomes

The mean follow-up duration was 311 ± 108 days, and 89.6% of the study participants completed 1 year of follow-up. The 1-year cumulative incidences of the composite of stroke, MI, and all-cause mortality did not show a significant trend across HbA1c groups ($P_{trend} = 0.92$) (Table 2). However, all-cause mortality exhibited a significant decreasing trend with increasing HbA1c values ($P_{trend} < 0.001$) (Table S1). The HbA1c ≤6.0% and 6.1%–7.0% groups had fewer stroke events at 1 year (17.1% and 17.7%, respectively), while the 7.1%–8.0% and >8.0% groups had higher rates of stroke at 1 year (20.4% and 19.8%, respectively) ($P_{trend} = 0.002$) (Table S2). No significant differences were observed in the 1-year cumulative incidence of MI or hemorrhagic stroke across HbA1c groups in any of the patients (Table S3).

Age subgroups and outcomes

Differences in the 1-year primary outcome based on HbA1c values were observed in the ≤55 years age group but not in the other age categories (Table 2). Among those ≤55 years of age, the 1-year primary outcome significantly increased with increasing HbA1c ($P_{trend} = 0.007$). Conversely, in patients aged over 55 years, the 1-year cumulative incidence of all-cause mortality did not significantly decrease with increasing HbA1c (Table S1). For stroke, a significant increase in the 1-year cumulative incidence was observed with higher HbA1c values in the ≤55 years and 76–85 years age groups

TABLE 1 General characteristics of the subjects according to their glycated hemoglobin (HbA1c) values at admission.

	HbA1c ≤6.0	HbA1c 6.1–7.0	HbA1c 7.1–8.0	HbA1c >8.0	*p*-Value[a]	P_{trend}[b]
N	*n* = 2267	*n* = 6109	*n* = 3533	*n* = 4168		
Age	68.8 ± 12.4	68.8 ± 12.4	69.3 ± 12.3	69.1 ± 12.3	0.20	0.18
Male	1259 (55.5)	3556 (58.2)	2113 (59.8)	2628 (63.1)	<0.001	<0.001
Arrival within 24 h	1948 (85.9)	5179 (84.8)	2978 (84.3)	3376 (81.0)	<0.001	<0.001
Pre-mRS 0–1	1731 (76.4)	5179 (84.8)	3033 (85.8)	3569 (85.6)	<0.001	<0.001
BMI	23.3 ± 3.5	24.1 ± 3.5	24.3 ± 3.5	24.2 ± 3.5	<0.001	<0.001
NIHSS, med (IQR)	5 (2–12)	4 (2–10)	4 (2–8)	4 (2–7)	<0.001	<0.001
Medical history						
History of TIA	40 (1.8)	129 (2.1)	64 (1.8)	73 (1.8)	0.51	0.47
History of stroke	662 (29.2)	1488 (24.4)	842 (23.8)	862 (20.7)	<0.001	<0.001
History of CAD	274 (12.1)	727 (11.9)	437 (12.4)	414 (9.9)	0.002	0.01
History of PAD	25 (1.1)	60 (1.0)	30 (0.8)	42 (1.0)	0.80	0.71
Smoking status						
Nonsmoker	1530 (67.5)	3991 (65.3)	2223 (62.9)	2362 (56.7)	<0.001	<0.001
Current smoker	393 (17.3)	1271 (20.8)	822 (23.3)	1282 (30.8)		
Ex-smoker	235 (10.4)	572 (9.4)	316 (8.9)	337 (8.1)		
Recently quit	109 (4.8)	275 (4.5)	172 (4.9)	187 (4.5)		
AF	651 (28.7)	1608 (26.3)	738 (20.9)	548 (13.1)	<0.001	<0.001
HTN	1918 (84.6)	4765 (78.0)	2676 (75.7)	2997 (71.9)	<0.001	<0.001
Dyslipidemia	748 (33.0)	2232 (36.5)	1335 (37.8)	1509 (36.2)	0.003	0.04
DM type						
Known DM	2058 (90.8)	4213 (69.0)	2837 (80.3)	3412 (81.9)	<0.001	0.020
Newly diagnosed DM	209 (9.2)	1896 (31.0)	696 (19.7)	756 (18.1)		
Medication history						
Prior antiplatelet use	866 (38.2)	2206 (36.1)	1250 (35.4)	1247 (29.9)	<0.001	<0.001
Prior statin use	588 (25.9)	1708 (28.0)	951 (26.9)	1006 (24.1)	<0.001	0.004
Prior antihypertensive use	1609 (71.0)	3989 (65.3)	2188 (61.9)	2238 (53.7)	<0.001	<0.001
Prior antidiabetic use	1584 (69.9)	3534 (57.8)	2461 (69.7)	2750 (66.0)	<0.001	<0.001
LASO						
No	971 (42.8)	2705 (44.3)	1601 (45.3)	1892 (45.4)	<0.001	<0.001
Mild, <50%	162 (7.1)	495 (8.1)	311 (8.8)	462 (11.1)		
Significant, >50%	420 (18.5)	1032 (16.9)	648 (18.3)	849 (20.4)		
Occlusion	714 (31.5)	1877 (30.7)	973 (27.5)	965 (23.2)		
TOAST						
LAA	761 (33.6)	2240 (36.7)	1358 (38.4)	1878 (45.1)	<0.001	<0.001
SVO	357 (15.7)	979 (16.0)	664 (18.8)	862 (20.7)		
CE	623 (27.5)	1547 (25.3)	746 (21.1)	589 (14.1)		
UD	526 (23.2)	1343 (22.0)	765 (21.7)	839 (20.1)		
Reperfusion therapy						
None	1786 (78.8)	4858 (79.5)	2876 (81.4)	3571 (85.7)	<0.001	<0.001
IVT	246 (10.9)	649 (10.6)	338 (9.6)	359 (8.6)		
EVT	128 (5.6)	312 (5.1)	150 (4.2)	129 (3.1)		
IV + EVT	107 (4.7)	290 (4.7)	169 (4.8)	109 (2.6)		
In-hospital treatment						
Statins	1915 (84.5)	5262 (86.1)	3041 (86.1)	3727 (89.4)	<0.001	<0.001
Antihypertensives	1106 (48.8)	2988 (48.9)	1743 (49.3)	2020 (48.5)	0.90	0.81
Antidiabetics	1020 (45.0)	3332 (54.5)	2463 (69.7)	3044 (73.0)	<0.001	<0.001

TABLE 1 (Continued)

	HbA1c ≤6.0	HbA1c 6.1–7.0	HbA1c 7.1–8.0	HbA1c >8.0	*p*-Value[a]	P_{trend}[b]
Laboratory findings						
WBC	8.2 ± 3.6	8.5 ± 3.2	8.7 ± 3.1	8.9 ± 3.1	<0.001	<0.001
Hemoglobin	12.8 ± 2.2	13.4 ± 2.0	13.5 ± 2.0	13.9 ± 2.1	<0.001	<0.001
Platelet count	222.1 ± 83.5	228.9 ± 79.7	231.2 ± 71.3	237.1 ± 71.0	<0.001	<0.001
LDL-C	96.9 ± 34.6	102.8 ± 37.8	104.3 ± 38.6	113.1 ± 42.7	<0.001	<0.001
Creatinine	1.26 ± 1.42	1.07 ± 0.89	1.15 ± 1.21	1.09 ± 0.98	<0.001	<0.001
Glucose	135.5 ± 44.8	155.1 ± 49.3	187.0 ± 63.9	252.5 ± 96.5	<0.001	<0.001
SBP, mmHg	146.7 ± 27.6	148.0 ± 27.3	150.5 ± 28.2	151.8 ± 29.1	<0.001	<0.001

[a]*p*-value determined by the chi-square test, ANOVA or Kruskal–Wallis test.

[b]*p*-value determined by the Cochran-Armitage trend test, Cochran–Mantel–Haenszel test or linear contrasts in ANOVA.

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; CE, cardioembolism; EVT, endovascular thrombectomy; HTN, hypertension; IVT, intravenous thrombolysis; LAA, large-artery atherosclerosis; LASO, large-artery steno-occlusion; LDL-C, low-density lipoprotein cholesterol; mRS, modified Rankin Scale; NIHSS, National Institutes of Stroke Scale; PAD, peripheral artery disease; SBP, systolic blood pressure; SVO, small vessel occlusion; TIA, transient ischemic attack; TOAST, Trials of Org 10,172 in Acute Stroke Treatment; UD, undetermined etiology; WBC, white blood cell.

(P_{trend} < 0.001 and 0.05, respectively) (Table S2). Comparisons of vascular events within 1 year among different HbA1C groups according to age group are shown in Figures S2 and S3. Table S3 presents one-year incidence of MI and hemorrhagic stroke. Sensitivity analysis excluding all death within 30 days after index stroke, likely related to the index stroke, are shown in Table S4.

Interaction testing revealed heterogeneity by age subgroup in the relationship between HbA1c values and vascular events (Table 3). Kaplan–Meier cumulative incidence plots of the primary outcome within 1 year by age subgroup (Figure 1) illustrate distinct patterns based on HbA1c and age subgroups. Among patients aged 55 years or younger, the relative risk increased when HbA1c exceeded 8.0% (unadjusted HR 1.40 [1.16–1.71] and adjusted HR 1.39 [1.13–1.70]). For patients aged 56–65 years and 66–75 years, the highest relative risk was observed for those with an HbA1c value in the middle category (7.1%–8.0%), with adjusted HRs of 1.21 [1.01–1.46] and 1.22 [1.05–1.41], respectively. In the 85+ age group, the highest relative risk occurred for those with an HbA1c value in the lowest category (unadjusted HR 1.57 [1.05–2.34], adjusted HR 1.47 [0.98–2.19]), as shown in Figure 2.

The *E*-values for unmeasured confounders were calculated for the adjusted HRs of the study populations. The adjusted HR point estimates of 1.01, 1.05, and 1.11 for the 1-year primary vascular outcome in all patients in the HbA1c subgroup corresponded to *E*-values of 1.09, 1.22 and 1.36, respectively (Table 3). *E*-values for the adjusted HRs of the 1-year secondary vascular outcomes are shown in Tables S5–S8.

Associations of HbA1C groups with 1-year stroke incidence by age groups are shown in Table S5, Figures S2 and S3. The associations of HbA1c with 1-year vascular outcomes by age subgroup are detailed in Figure S4 (unadjusted analysis), Figure 2 (adjusted analysis), and Tables S6–S8.

Hazard ratio plots based on dichotomized HbA1c values (≤6.0% vs. >6.0% and >8.0% vs. 8.0% or less) for the 1-year primary outcome are shown in Figure 3 and Figure S5. The plots show a significant interaction of age (age cut-off; ≤51 years and ≥85 years) with an HbA1c >8.0% ($P_{interaction}$ = 0.008, Figure 3) but not with an HbA1c ≤6.0% ($P_{interaction}$ = 0.73, Figure S5).

Subgroup analysis

There were no significant interactions between any of the 5 predefined age subgroups and the HbA1c group (Figure S6).

DISCUSSION

In our analysis of a large registry of more than 16,000 acute ischemic stroke patients with diabetes, we identified age-dependent variations in the impact of prestroke glycemic status on the 1-year composite of stroke, MI, and all-cause mortality. Specifically, for stroke patients with diabetes aged 55 years or younger, high HbA1c values (>8.0%) at admission were associated with increased risks of the 1-year composite of stroke, MI, all-cause mortality and individual stroke events. However, in the elderly population over 75 years of age, HbA1c values at admission that were above the range of 6.1%–7.0% were not significantly associated with the composite risk of stroke, MI, and all-cause mortality within 1 year. These findings highlight the age-specific associations of prestroke glycemic status with vascular outcomes in ischemic stroke patients with DM.

Previous observational studies have consistently shown that elevated HbA1c values upon admission are associated with an increased risk of stroke recurrence and mortality across various stroke subtypes. [4, 19] However, other studies have shown that admission hyperglycemia had varying impacts on outcomes depending on the stroke subtype. [20] Interestingly, research on individuals in the general population highlights that modifiable risk factors, including obesity,

TABLE 2 One-year primary outcome and glycated hemoglobin values according to age group.

Age group	HbA1c values	Primary outcomes within 1-year: No. of events/ No. of patients	Primary outcomes within 1-year: Event rate (%) at 1 year (95% CI)[a]	P_{trend}[b]
All patients	≤6.0%	590/2267	27.4 (25.5–29.3)	0.92
	6.1–7.0%	1490/6109	25.4 (24.2–26.5)	
	7.1–8.0%	930/3533	27.4 (25.9–28.9)	
	>8.0%	1034/4168	25.6 (24.2–27.0)	
≤55 year	≤6.0%	91/348	27.7 (22.8–32.6)	0.01
	6.1–7.0%	225/953	24.5 (21.7–27.3)	
	7.1–8.0%	119/501	24.7 (20.8–28.6)	
	>8.0%	184/590	32.2 (28.4–36.1)	
56–65 year	≤6.0%	127/463	28.7 (24.4–32.9)	0.49
	6.1–7.0%	297/1263	24.5 (22.1–27.0)	
	7.1–8.0%	194/711	28.3 (24.9–31.7)	
	>8.0%	204/876	24.0 (21.1–26.8)	
66–75 year	≤6.0%	181/683	27.7 (24.2–31.1)	0.63
	6.1–7.0%	460/1824	26.4 (24.3–28.4)	
	7.1–8.0%	302/1056	29.9 (27.0–32.7)	
	>8.0%	310/1282	24.9 (22.5–27.3)	
76–85 year	≤6.0%	154/653	25.3 (21.8–28.8)	>0.99
	6.1–7.0%	440/1740	26.2 (24.1–28.3)	
	7.1–8.0%	260/1052	25.7 (22.9–28.4)	
	>8.0%	286/1180	25.1 (22.6–27.7)	
>85 year	≤6.0%	37/120	32.1 (23.5–40.7)	0.22
	6.1–7.0%	68/329	21.3 (16.8–25.8)	
	7.1–8.0%	55/213	27.8 (21.5–34.2)	
	>8.0%	50/240	21.5 (16.2–26.8)	

[a]Based on Kaplan–Meier estimates.

[b]*p*-value determined by the log-rank test for trend.

hypertension, and diabetes, had a more substantial impact and relative risk reduction in younger individuals than in older individuals. [12] The Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS) further revealed age-related differences, indicating a greater risk of stroke associated with diabetes in adults aged <65 years than in those aged ≥65 years. [21] However, despite the prevalence of older age and comorbidities in stroke patients, limited research has explored the age-specific prognostic implications of prestroke glycemic status. Our study addressed this gap by revealing the significant interaction effect of age and HbA1c at admission on 1-year vascular outcomes in patients with acute ischemic stroke and diabetes. Among patients aged ≤55 years, those with HbA1c greater than 8.0% at admission were 40% more likely to experience the 1-year composite of stroke, MI, and all-cause mortality, as well as 1-year stroke, than those with an HbA1c of 6.1–7.0%. Intriguingly, up to the age of 75, an HbA1c of 7.1–8.0% at admission was associated with a greater risk of the 1-year composite of stroke, MI, and all-cause mortality and individual stroke events than an HbA1c of 6.1–7.0%. These findings suggest that a well-controlled prestroke glycemic status below an HbA1c <7.0% might be more effective for preventing recurrent stroke in stroke patients with diabetes, especially those under 75 years old (particularly under 55 years). Furthermore, an HbA1c of 8.0% at admission showed evident age-dependent heterogeneity in the post hoc hazard ratio plots (Figure 3). Below the age cut-off point of 51 years, there was an increase in the HR for the 1-year primary outcome, while for those aged 85 years and above, there was a trend toward decreasing risk. The 6.5% cut-off for HbA1C as a diagnostic criterion for diabetes mellitus has been widely validated in adult populations and is supported by guidelines for its use across most age groups. [22] However, it is important to note that the physiological changes associated with very old age, including altered glucose metabolism and higher prevalence of comorbidities, may warrant reconsideration of whether this threshold is universally appropriate. While recent ADA clinical guidelines support using HbA1C, FPG, or 2-h PG to screen for diabetes in children and adolescents, [23] there is limited evidence specific to very old age groups. Further research is needed to determine whether age-specific adjustments to the HbA1C cut-off, or alternative diagnostic criteria, might be necessary for this population to improve accuracy and clinical outcomes.

In the overall population, our study revealed a notable trend: as admission HbA1c values decreased, 1-year event rates of mortality increased, while 1-year event rates of stroke increased. Consequently, there was less pronounced difference in the 1-year composite vascular event rates according to the HbA1c at admission. Previous studies have suggested that in elderly individuals, the risk of mortality might be greater due to the potential dangers of hypoglycemia associated with intensive glucose lowering. [24–26] In our study, across all age groups, mortality rates were numerically greater for the ≤6.0% HbA1c subgroup than for the >8.0% HbA1c subgroup. Lower HbA1c values in older patients may indicate a potentially frailer condition, such as poor nutritional status, sarcopenia, or chronic diseases. It is possible that in elderly individuals, a lower HbA1c value may be associated with an increased risk of episodes of hypoglycemia, and several clinical and preclinical studies have indicated that exposure to hypoglycemia increases the risk of cardiovascular events. [27, 28] Many experts currently argue that the benefits of intensive control of macrovascular disease are likely limited to younger patients with recent-onset diabetes and without established vascular disease. [9, 10] These considerations underscore the importance of individualizing glycemic control strategies, accounting for both age and overall health status, to optimize patient outcomes. However, unfortunately, our study did not implement glucose-lowering therapy, which prevents us from confirming whether lower HbA1c is associated with hypoglycemia. Additionally, data on the incidence of severe hypoglycemia were not available for the study population, and we could not explore the relationship between hypoglycemia and stroke risk for each HbA1c category.

Our study analyzed the relationship between prestroke glycemic status and outcomes in patients with ischemic stroke and diabetes. Therefore, we could not discern the impact of DM control following the index stroke event. However, the survival curve revealed that the first month showed a notably high occurrence of stroke events and a

TABLE 3 Associations of glycated hemoglobin with the 1-year primary outcome by age group.

	HbA1c	Unadjusted HR (95% CI)	*p*	P_{int}	Adjusted HR (95% CI)	*p*	P_{int}	*E*-value
All patients	≤6.0%	1.07 (0.97–1.17)	0.18	0.006	1.01 (0.92–1.11)	0.81	0.005	1.09
	6.1–7.0%	1 (Ref)			1 (Ref)			
	7.1–8.0%	1.10 (1.01–1.19)	0.03		1.11 (1.03–1.21)	0.01		1.36
	>8.0%	1.02 (0.94–1.11)	0.58		1.05 (0.95–1.15)	0.35		1.22
≤55 year	≤6.0%	1.12 (0.88–1.43)	0.37		1.05 (0.83–1.35)	0.67		1.22
	6.1–7.0%	1 (Ref)			1 (Ref)			
	7.1–8.0%	1.02 (0.81–1.27)	0.88		1.00 (0.80–1.25)	0.99		1.00
	>8.0%	1.40 (1.16–1.71)	<0.001		1.39 (1.13–1.70)	0.001		1.82
56–65 year	≤6.0%	1.18 (0.96–1.45)	0.13		1.14 (0.93–1.41)	0.21		1.42
	6.1–7.0%	1 (Ref)			1 (Ref)			
	7.1–8.0%	1.19 (0.99–1.43)	0.06		1.21 (1.01–1.46)	0.04		1.54
	>8.0%	0.99 (0.83–1.19)	0.94		1.04 (0.86–1.25)	0.71		1.20
66–75 year	≤6.0%	1.06 (0.89–1.26)	0.52		1.00 (0.84–1.19)	0.97		1.00
	6.1–7.0%	1 (Ref)			1 (Ref)			
	7.1–8.0%	1.17 (1.01–1.35)	0.04		1.22 (1.05–1.41)	0.01		1.56
	>8.0%	0.96 (0.83–1.11)	0.57		0.99 (0.85–1.15)	0.91		1.09
76–85 year	≤6.0%	0.91 (0.76–1.09)	0.31		0.85 (0.71–1.02)	0.08		1.48
	6.1–7.0%	1 (Ref)			1 (Ref)			
	7.1–8.0%	0.97 (0.84–1.14)	0.74		0.99 (0.85–1.15)	0.89		1.19
	>8.0%	0.95 (0.82–1.10)	0.48		0.98 (0.84–1.14)	0.77		1.13
>85 year	≤6.0%	1.57 (1.05–2.34)	0.03		1.47 (0.98–2.19)	0.06		1.94
	6.1–7.0%	1 (Ref)			1 (Ref)			
	7.1–8.0%	1.27 (0.89–1.82)	0.18		1.25 (0.87–1.78)	0.23		1.61
	>8.0%	1.00 (0.69–1.44)	>0.99		0.97 (0.67–1.40)	0.87		1.17

Note: Adjusted for the following variables: age, sex, BMI, history of stroke, history of CAD, HTN, dyslipidemia, AF, prior antiplatelet therapy, prior statin use, glucose, LDL-C, creatinine, SBP, LASO, and TOAST subtypes. P for interaction between age group and HbA1c group.

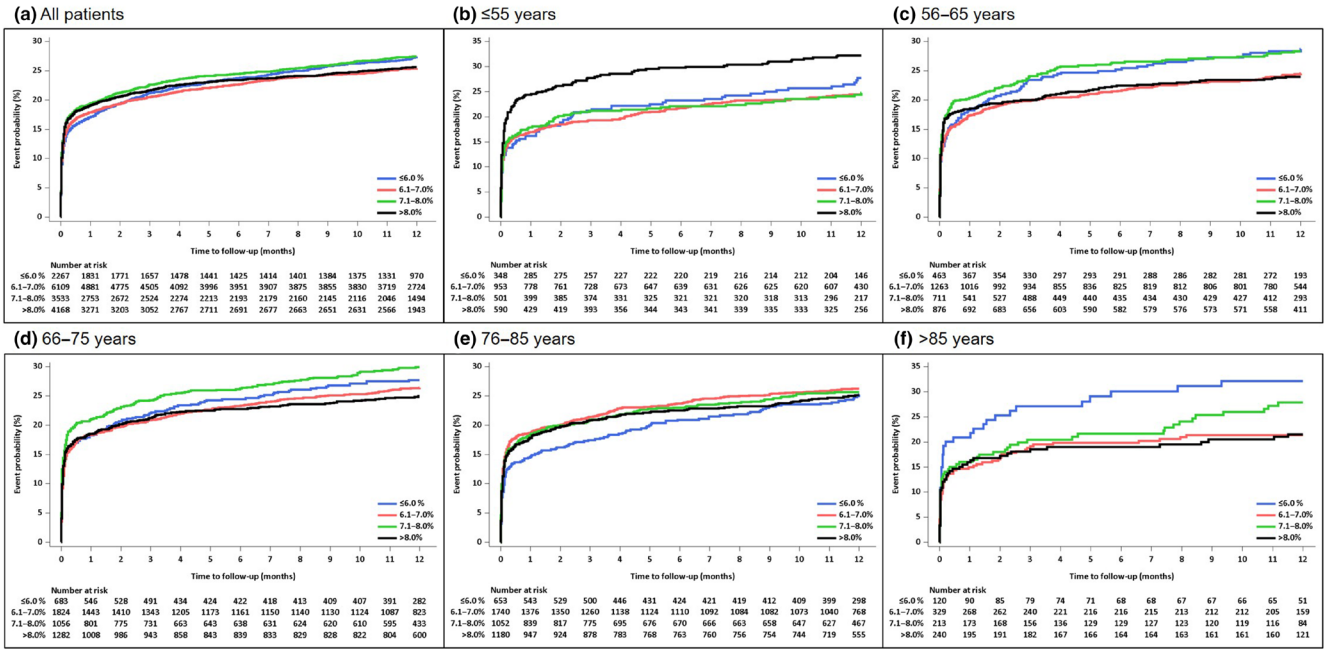

FIGURE 1 Kaplan–Meier survival curves for the 1-year primary outcome by age group.

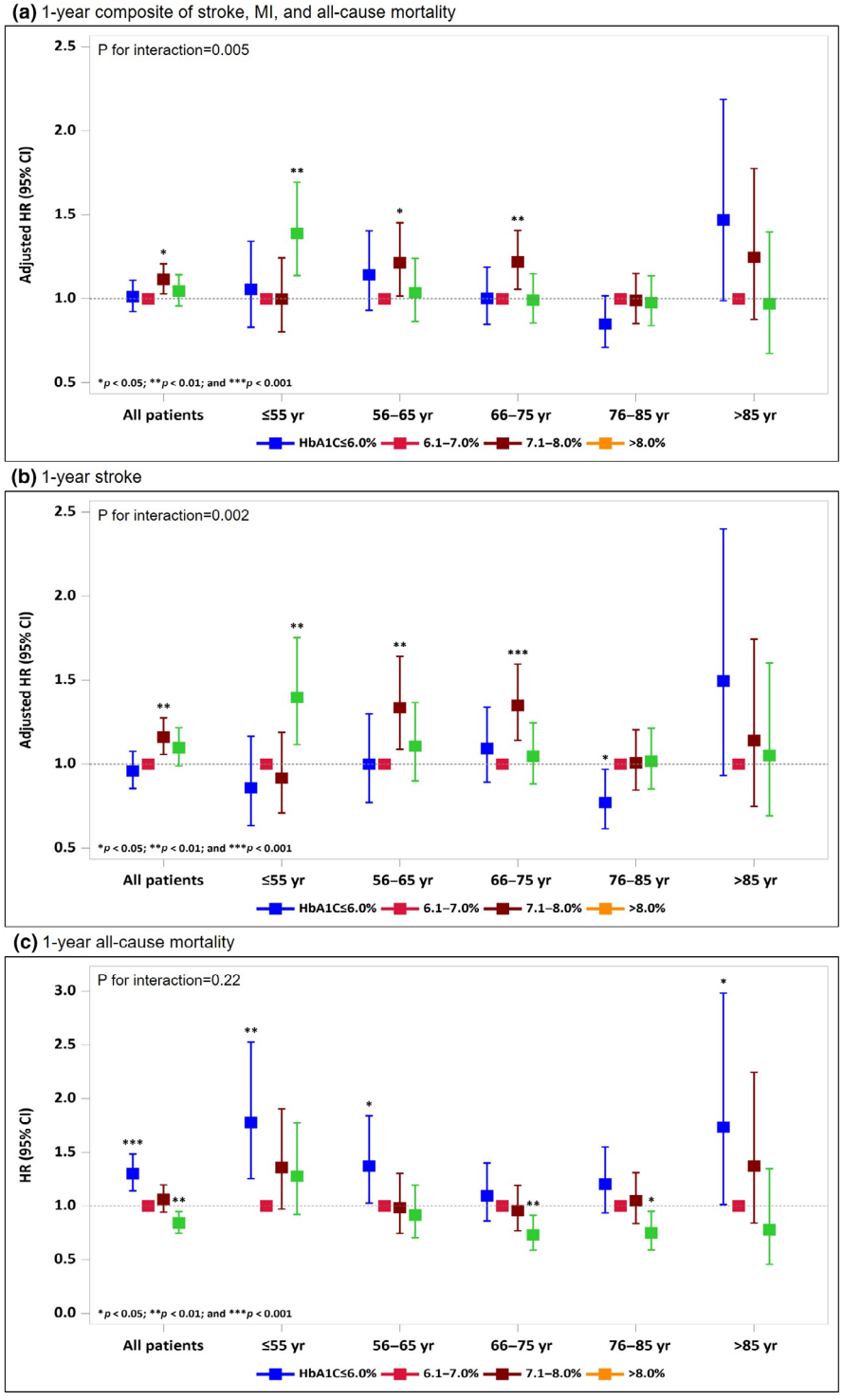

FIGURE 2 Associations between glycated hemoglobin and 1-year vascular outcomes, including (a) primary outcome, (b) stroke, and (c) all-cause mortality, stratified by age in an adjusted analysis.

composite of stroke, MI, and all-cause mortality, suggesting the potential significance of prestroke glycemic status. Perhaps prestroke glycemic status may influence early recurrent stroke events, while mortality appears to be less influenced by prestroke glycemic status. A long-term study may be necessary to further explore these relationships.

Among patients older than 55 years, patients with an HbA1c value >8.0% at admission did not have an increased risk of stroke or composite events compared to those with lower HbA1c values (for example, 7.1–8.0%). One possible explanation is that the intensity of antidiabetic treatment may vary based on prestroke glycemic status at admission. Another hypothesis is that only patients with better overall health survive, and they experience stroke without significant consequences, which is a form of collider stratification bias. [29] However, additional research is required to provide support for our findings on the complex relationship between age and HbA1c at admission.

Our study has several limitations. First, information on previous diabetes management and duration, which are important factors in

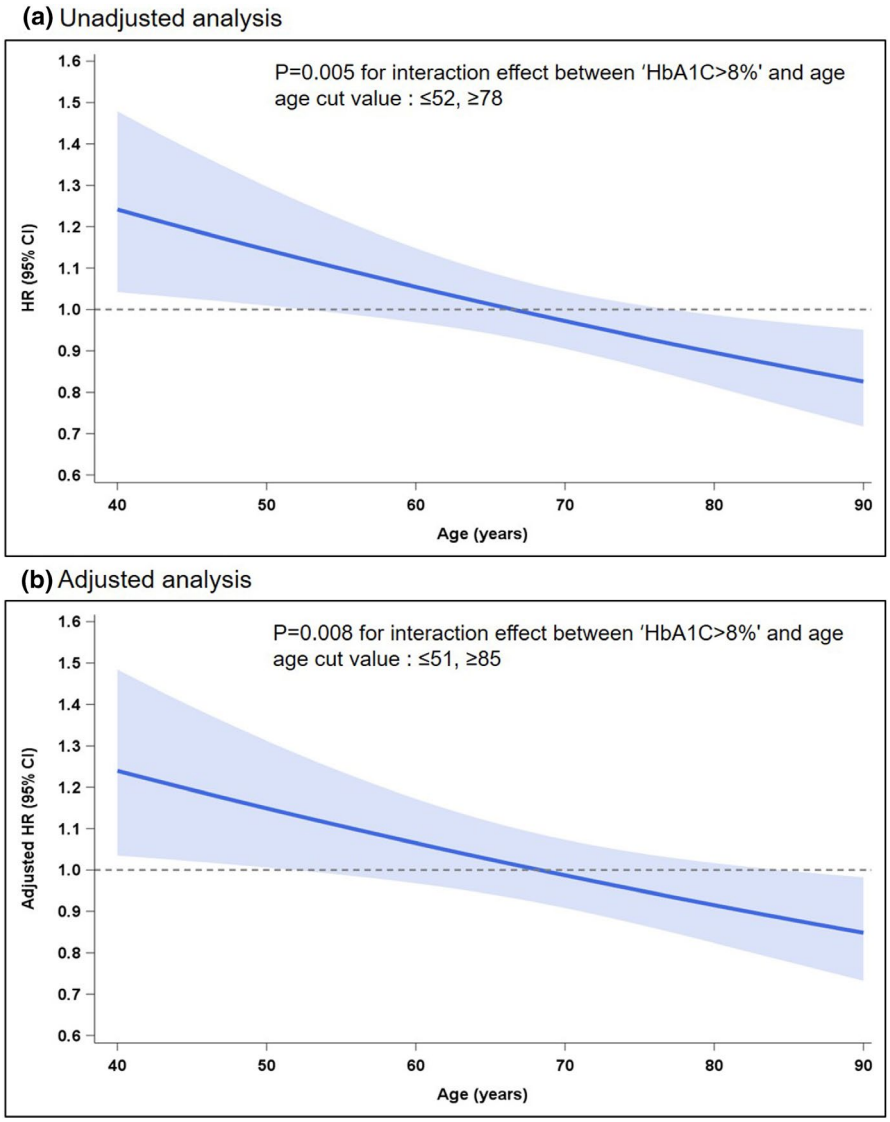

FIGURE 3 Hazard ratio plots of HbA1c >8.0% (vs. 8.0% or less) for 1-year primary outcome according to age (a) unadjusted and (b) adjusted analyses.

prognosis, was lacking. Additionally, we did not distinguish between newly diagnosed patients with diabetes and those with preexisting treated diabetes. Second, as this study focused on prestroke glycemic status, we cannot exclude the possibility that in-hospital and discharge treatments may have influenced outcomes. The results seem to be too complex to be applied in clinical practice. The reason of such complexity stems from the fact that both hypoglycemia and hyperglycemia are detrimental for stroke survivors, and essential information about glycemic control such as medication profile and duration of treatment had not been included in the study. Third, despite multiple adjustments, unmeasured confounders might have influenced the findings. However, *E*-values were calculated as a sensitivity analysis to determine the likelihood that an unmeasured confounder would negate the observed relationships between the HbA1c group and 1-year primary outcomes stratified by age group. These estimates are relatively low, ranged from 1.00 to 1.94 (Table 3), indicated that little unmeasured confounding would be needed to explain away the effect estimates. Forth, as a retrospective analysis, our study has inherent limitations. Moreover, its applicability is limited to individuals living in Korea, affecting its generalizability. However, data on a large population of individuals with acute ischemic stroke and diabetes were analyzed in this study, and HbA1c and age were examined at granular levels. Importantly, there was an intricate relationship between HbA1c and age.

In conclusion, our study revealed that in patients under 55 years of age with acute ischemic stroke and diabetes, an increase in admission HbA1c is associated with an elevated risk of a poor 1-year primary vascular outcome. Conversely, in those aged over 75 years, the impact of HbA1c at admission on outcomes was less pronounced and in patients aged over 85 years, lower HbA1c values may tend to be associated with an increased risk of vascular events, suggesting that in patients with ischemic stroke and DM, associations of admission HbA1c and outcomes might be age-specific. These findings provide a basis for future research to optimize diabetes control in acute ischemic stroke patients with diabetes.

AUTHOR CONTRIBUTIONS

Study concept and design: JT Kim. Acquisition of data: JT Kim, H Kim, BJ Kim, J Kang, KJ Lee, JM Park, K Kang, SJ Lee, JG Kim, JK Cha,

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ACKNOWLEDGMENTS

The authors have nothing to report.

FUNDING INFORMATION

This research was supported by the Korea National Institute of Health (KNIH) research project (No. 2023-ER-1006-01). This study was supported by a grant (BCRI24042) from the Chonnam National University Hospital Biomedical Research Institute.

CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Clinical information was collected from the CRCS-K registry with approval from the local institutional review boards of all the participating centers including Chonnam National University Hospital.

INFORMED CONSENT

A waiver for informed consent was provided because of study subject anonymity and minimal risk to the participants.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Kim J-T, Lee JS, Kim H, et al. Influence of prestroke glycemic status on outcomes by age in patients with acute ischemic stroke and diabetes mellitus. *Eur J Neurol*. 2025;32:e70004. doi:10.1111/ene.70004