

## ORIGINAL RESEARCH

# Differential Effects of Admission Hemoglobin A<sub>1c</sub> by Estimated Glomerular Filtration Rate Stages on Mortality in Acute Ischemic Stroke and Diabetes

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**BACKGROUND:** The relationship between admission hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) levels, estimated glomerular filtration rate (eGFR) stages, and early outcomes may provide key insights into the need for individualized glycemic control based on kidney function in patients with ischemic stroke and diabetes.

**METHODS:** We analyzed data from a multicenter, nationwide, prospective stroke registry in South Korea, including patients with ischemic stroke within 7 days of onset and diabetes. Admission HbA<sub>1c</sub> levels (prestroke glycemic status) were categorized as <6.0%, 6.0% to 7.0%, 7.0% to 8.0%, and ≥8.0%. eGFR stages were classified from stage 1 to stage 5 based on the Kidney Disease: Improving Global Outcomes 2021 guidelines. The primary outcome was 3-month all-cause mortality. Cox proportional hazards models were performed and an interaction term between eGFR stages and HbA<sub>1c</sub> groups was included to evaluate potential effect modification.

**RESULTS:** A total of 27 496 patients (age, 69.6±11.4 years; men, 60.3%) were included. The 3-month cumulative all-cause mortality rates differed significantly by admission HbA<sub>1c</sub> levels: 8.9% in HbA<sub>1c</sub> <6.0% versus 5.3% in HbA<sub>1c</sub> ≥8.0%. In adjusted analyses, while no association between HbA<sub>1c</sub> <6.0% and mortality was observed among eGFR stages, higher HbA<sub>1c</sub> levels (7.0%–8.0% in eGFR stages 1, 3, and 5, and ≥8.0% in stages 2 and 5) were significantly associated with increased mortality risk. Notably, in stage 4, there was no significant association between HbA<sub>1c</sub> and mortality (*P*=0.027 for interaction).

**CONCLUSIONS:** The association between admission HbA<sub>1c</sub> and 3-month mortality varied among eGFR stages. These findings suggest that eGFR stage may need to be considered when tailoring glycemic control strategies in patients with ischemic stroke and diabetes.

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**Key Words:** acute ischemic stroke ■ diabetes ■ eGFR ■ hemoglobin A<sub>1c</sub> ■ renal function

## CLINICAL PERSPECTIVE

### What Is New?

- In patients with acute ischemic stroke and diabetes, the association between admission hemoglobin A<sub>1c</sub> levels and 3-month mortality varied significantly among estimated glomerular filtration rate stages.
- Higher hemoglobin A<sub>1c</sub> levels (≥7.0%) were associated with increased mortality, particularly in patients with preserved or moderately impaired renal function, while the association was attenuated in advanced chronic kidney disease stages.

### What Are the Clinical Implications?

- Glycemic control strategies in patients with diabetes who experience stroke might be tailored based on renal function; individualized management may help optimize early outcomes after stroke.

## Nonstandard Abbreviations and Acronyms

|                         |                                                   |
|-------------------------|---------------------------------------------------|
| <b>CKD-EPI</b>          | Chronic Kidney Disease Epidemiology Collaboration |
| <b>CRCS-K</b>           | Clinical Research Center for Stroke-Korea         |
| <b>HbA<sub>1c</sub></b> | hemoglobin A <sub>1c</sub>                        |
| <b>KDIGO</b>            | Kidney Disease: Improving Global Outcomes         |
| <b>NIHSS</b>            | National Institutes of Health Stroke Scale        |
| <b>RMST</b>             | restricted mean survival time                     |
| <b>TOAST</b>            | Trial of Org 10172 in Acute Stroke Treatment      |

**P**atients with stroke and diabetes face a higher risk of recurrent stroke, increased mortality, and generally poor outcomes compared with those without diabetes.<sup>1,2</sup> While previous clinical studies have indicated that intensive glucose-lowering treatment may not necessarily improve outcomes in acute ischemic stroke,<sup>3</sup> uncontrolled diabetes at the time of stroke occurrence is likely to negatively affect stroke outcomes.<sup>4</sup> In addition, prestroke glycemic status is considered to

be an important factor associated with outcomes in patients with ischemic stroke and diabetes.<sup>4,5</sup>

Reduced estimated glomerular filtration rate (eGFR) in patients with stroke is well known to increase the risk of adverse outcomes, including mortality.<sup>6–8</sup> Diabetes is a common and leading cause of chronic kidney disease (CKD) and renal failure.<sup>9</sup> However, managing diabetes in patients with CKD is highly complex, and glycemic targets need to be individualized for each patient. Currently, there are limited data and few clinical trials addressing the ideal glucose targets in patients with CKD stage ≥3. Despite the lack of robust evidence regarding optimal hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) levels in these patients, the recently updated Kidney Disease: Improving Global Outcomes (KDIGO) guideline recommends a broad HbA<sub>1c</sub> target range of <6.5% to <8.0% for patients with diabetes and CKD who are not undergoing kidney replacement therapy.<sup>10</sup>

Moreover, the impact of HbA<sub>1c</sub> on outcomes in patients with ischemic stroke who have diabetes, particularly in relation to eGFR stage or the presence of CKD, remains largely unknown. Interestingly, there appears to be an interaction between diabetes status and eGFR in determining outcomes after stroke.<sup>11</sup>

Therefore, we aimed to investigate the relationship between admission HbA<sub>1c</sub> at a granular level, eGFR stages, and outcomes in patients with acute ischemic stroke with diabetes. Understanding these relationships may improve prediction of outcomes in patients with ischemic stroke and diabetes.

## METHODS

### Participants

This study analyzed data from the CRCS-K (Clinical Research Center for Stroke-Korea) registry, a nationwide collection of consecutive patients with acute stroke or transient ischemic attack admitted to 20 academic hospitals in South Korea. Comprehensive methodological details about the CRCS-K registry have been previously documented.<sup>12,13</sup> We identified patients with acute cerebrovascular events admitted between January 2011 and April 2023 (N=99 791). We included patients with acute ischemic stroke occurring within 7 days of onset and diabetes among the patients with acute cerebrovascular events. Exclusions comprised those lacking information on serum creatinine (or eGFR), HbA<sub>1c</sub>, and glucose levels on admission. 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 participant anonymity and minimal risk to the participants. The data used in this study are available on 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 were prospectively collected as previously described.<sup>12,13</sup> HbA<sub>1c</sub> levels (prestroke glycemic status) were measured during the initial fasting period postadmission and arbitrarily categorized as <6.0%, 6.0% to 7.0%, 7.0% to 8.0%, and ≥8.0%. Although the general target for glycemic control in patients with diabetes is HbA<sub>1c</sub> <7.0%, lower HbA<sub>1c</sub> levels have paradoxically been associated with worse outcomes in some studies,<sup>14,15</sup> and thus the 6.0% to 7.0% range was selected as the reference group. The cut-points at 7.0% and 8.0% were further stratified to reflect the more lenient glycemic targets commonly recommended for older adults or frail patients, including those with renal impairment.<sup>16,17</sup> This granular categorization was intended to capture potential heterogeneity in optimal glycemic targets among varying patient conditions.

eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation (2021) formula, based on creatinine levels, age, and sex collected from blood tests on admission. The stages of eGFR were categorized as follows: stage 1 with eGFR ≥90 mL/min per 1.73 m<sup>2</sup>, stage 2 with eGFR 60 to 89 mL/min per 1.73 m<sup>2</sup>, stage 3 with eGFR 30 to 59 mL/min per 1.73 m<sup>2</sup>, stage 4 with eGFR 15 to 29 mL/min per 1.73 m<sup>2</sup>, and stage 5 with eGFR ≤15 mL/min per 1.73 m<sup>2</sup>.<sup>18</sup> The normal kidney function range was defined as stage 1 or 2. Stage 3 was considered as mild (3a; 45–60 mL/min per 1.73 m<sup>2</sup>) to moderate (3b; 30–45 mL/min per 1.73 m<sup>2</sup>) kidney damage, stage 4 as severe kidney damage, and stage 5 as renal failure. Ischemic stroke subtypes were classified using TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria, refined with additional data from modern imaging studies.<sup>19,20</sup>

## Outcomes

The primary outcome was all-cause mortality within 3 months, as prestroke glycemic status and eGFR stage were predominantly associated with increased risk of all-cause mortality.<sup>21,22</sup> The secondary outcomes included a composite of recurrent stroke (either

hemorrhagic or ischemic), myocardial infarction (MI), and all-cause mortality, as well as the individual outcomes of recurrent stroke (either ischemic or hemorrhagic) and MI.

Vascular events were prospectively observed during hospitalization and during a 3-month follow-up period after the qualifying event via routine clinic visits or telephone interviews performed by dedicated nurses or physicians with a predefined protocol. To ensure the accuracy of the outcome captured and to minimize inter-interviewer discrepancy, a set of uniform structured questionnaires was used by trained personnel. Detailed definitions of the outcome events and methods of outcome capture used in the current study are described in previous reports.<sup>12,13</sup>

## Statistical Analysis

Baseline characteristics and outcomes were compared among each HbA<sub>1c</sub> group using  $\chi^2$ , ANOVA, or Kruskal–Wallis tests according to the type of variable. The missing values were addressed with single imputation using the sequential regression method (also known as chained equations method). The following parameters had missing data and the proportion of missing values was as follows: height (1.1%), weight (1.3%), hemoglobin (0.2%), platelet count (0.3%), and white blood cell count (0.2%).

Differences in 3-month outcome event probabilities among the HbA<sub>1c</sub> groups were analyzed using log-rank test in all patients as well as in patients stratified by eGFR stage. In addition, comparison between the HbA<sub>1c</sub> 6.0% to 6.9% group and the other HbA<sub>1c</sub> groups were performed by comparing event rates at 3 months using z-test. In unadjusted analysis, the z-test used the Greenwood formula for variance, which is based on the Kaplan–Meier method. In adjusted analysis, the z-test was performed using the direct adjusted survival probability at 3 months and its standard error calculated from Cox model. Hazard ratios (HRs) and 95% CIs for 3-month all-cause mortality were analyzed using the Cox proportional hazards model. Adjustments were made for the following predetermined variables with clinically relevant associations with the outcome variables: age, sex, body mass index, NIHSS score, history of stroke, history of coronary artery diseases, hypertension, dyslipidemia, atrial fibrillation, prior antiplatelet use, prior statin use, hemoglobin, glucose, low-density lipoprotein cholesterol, systolic blood pressure, large artery steno-occlusion, reperfusion therapy, and TOAST stroke subtypes. Multicollinearity among covariates was assessed using variance inflation factors, and no significant multicollinearity was detected (all variance inflation factors <2.5). The modifying effect of eGFR stages on the relationships between HbA<sub>1c</sub> group and 3-month all-cause mortality was explored

by separately introducing an interaction term of eGFR stages and HbA<sub>1c</sub> groups into the models. Given the violation of the proportional hazards assumption, we performed a post hoc restricted mean survival time (RMST) analysis up to 3 months to provide a robust comparison of survival outcomes among groups. The RMST represents the expected survival time within a fixed period and is less sensitive to nonproportional hazards. RMST ratios were calculated to compare relative survival times between HbA<sub>1c</sub> groups.<sup>23</sup>

Statistical significance was generally determined considering 2-sided *P* values <0.05 indicative of significance. Given the known insensitivity of interaction testing, evidence of heterogeneity was considered present with *P* values ≤0.10. Statistical analyses were performed with R software using the “rms” package version 3.6.0 (R Foundation for Statistical Computing) and SAS version 9.4 (SAS Institute Inc.).

## RESULTS

### General Characteristics

A total of 27 496 patients (mean age, 69.6±11.4 years; men, 60.3%) met the eligibility criteria and were analyzed for this study. The median National Institutes of Health Stroke Scale (NIHSS) score was 4 (interquartile range, 1–7). The mean HbA<sub>1c</sub> level and glucose level on admission was 7.5±1.7% and 187.0±83.1 mg/dL, respectively. The eGFR stages are as follows: 38.5% (n=10 585) in stage 1, 37.5% (n=10 322) in stage 2, 17.8% (n=4 894) in stage 3, 3.2% (n=875) in stage 4, and 3.0% (n=820) in stage 5. For HbA<sub>1c</sub> levels, 12.3% (n=3 394) of patients had levels ≤6.0%, 34.7% (n=9 531) had levels between 6.0% and 6.9%, 23.7% (n=6 517) had levels between 7.0% and 7.9%, and 29.3% (n=8 054) had levels ≥8.0%. Demographic and clinical characteristics of the eGFR stages and HbA<sub>1c</sub> groups are shown in Table 1 and Table S1. Compared with the HbA<sub>1c</sub> <6.0% group, the higher HbA<sub>1c</sub> groups were more likely to be men, have a prestroke modified Rankin Scale of 0 or 1, be current smokers, and have a large artery atherosclerosis subtype, and were less likely to have a history of stroke, hypertension, atrial fibrillation, prior antihypertensive use, or a cardioembolism subtype.

### Outcomes

The follow-up duration was a mean±SD of 88.9±8.8 days and 97.1% of the study patients completed 3 months of follow-up. The 3-month cumulative incidences of all-cause mortality, the composite of stroke, MI and all-cause mortality, recurrent stroke, and MI were 6.2%, 9.4%, 3.7%, and 0.4%, respectively.

The 3-month cumulative incidences of all-cause mortality and the composite outcome of recurrent stroke, MI, and all-cause mortality showed significant

differences based on HbA<sub>1c</sub> levels. The lowest HbA<sub>1c</sub> (<6.0%) was associated with the highest incidences of all-cause mortality and composite of stroke, MI, and all-cause mortality (8.9% and 11.4%, respectively), while the highest HbA<sub>1c</sub> (≥8.0%) was associated with the lowest incidences (5.3% and 9.0%, respectively). In contrast, the cumulative incidence of recurrent stroke was higher with elevated HbA<sub>1c</sub> levels: 3.4% for HbA<sub>1c</sub> <6.0% and 4.1% for HbA<sub>1c</sub> ≥8.0% (*P*=0.04) (Table 2; Table S2). No significant differences in MI incidence were observed among HbA<sub>1c</sub> levels (Table S2).

### HbA<sub>1c</sub> Levels and Outcomes According to eGFR Stages

Within eGFR stages, the highest rates of 3-month all-cause mortality were observed in the lowest HbA<sub>1c</sub> group (<6.0%) in the eGFR stage 1 group (4.9%), while the lowest rates of all-cause mortality were observed in the highest HbA<sub>1c</sub> group (≥8.0%) in the eGFR stage 1 group (2.8%). Significant differences in 3-month all-cause mortality by HbA<sub>1c</sub> levels were similarly observed among eGFR stages 1 to 4 but not in stage 5 (Table 2; Figure 1). Secondary outcome event rates including 3-month composite of stroke, MI, and all-cause mortality and 3-month recurrent stroke are shown in Figure S2. In unadjusted analyses, the HbA<sub>1c</sub> <6.0% group was significantly associated with higher all-cause mortality (HR, 1.56 [95% CI, 1.35–1.79] in all patients; HR, 1.54 [95% CI, 1.11–2.13] in stage 1; HR, 1.43 [95% CI, 1.13–1.81] in stage 2; and HR, 1.43 [95% CI, 1.10–1.86] in stage 3) compared with the HbA<sub>1c</sub> 6.0% to 7.0% group, while higher HbA<sub>1c</sub> groups showed no significant associations among eGFR stages. In addition, no significant associations of HbA<sub>1c</sub> groups with all-cause mortality were observed in eGFR stages 4 and 5.

After adjustments of relevant variables, the significant associations of all-cause mortality with low HbA<sub>1c</sub> (<6.0%) disappeared among eGFR stages, but higher HbA<sub>1c</sub> levels (HbA<sub>1c</sub> 7.0% to 8.0% in eGFR stages 1 and 3, and ≥8.0% in eGFR stages 2 and 5), compared with the HbA<sub>1c</sub> 6.0% to 7.0% group, were significantly associated with increased risk of 3-month all-cause mortality. However, in stage 4, there was no significant association between HbA<sub>1c</sub> levels and 3-month all-cause mortality (Figure 2). A significant interaction between eGFR stages and HbA<sub>1c</sub> groups was identified (*P*=0.027 for interaction) (Table S3). The stage-specific estimates in Figure 2 and Table S3 were derived from the overall model that included the interaction effect between stage and HbA<sub>1c</sub> group, rather than from separate subgroup analyses.

To address violations of the proportional hazards assumption, RMST analyses were conducted and detailed results are provided in Tables S4 and S5. In the adjusted RMST analysis, an RMST ratio >1 indicates

**Table 1. General Characteristics of Patients According to HbA<sub>1c</sub> Levels**

|                              | HbA <sub>1c</sub> <6.0% | 6.0% to 7.0% | 7.0% to 8.0% | ≥8.0%       | P value* | P for trend† |
|------------------------------|-------------------------|--------------|--------------|-------------|----------|--------------|
| No.                          | 3394                    | 9531         | 6517         | 8054        |          |              |
| Age, y                       | 73.4±11.1               | 71.5±10.6    | 69.8±10.7    | 65.5±11.9   | <0.001   | <0.001       |
| Men                          | 1875 (55.2)             | 5686 (59.7)  | 3949 (60.6)  | 5075 (63.0) | <0.001   | <0.001       |
| Arrival within 24 h          | 2416 (71.2)             | 6597 (69.2)  | 4344 (66.7)  | 5022 (62.4) | <0.001   | <0.001       |
| Pre-mRS 0 to 1               | 2510 (74.0)             | 8038 (84.3)  | 5564 (85.4)  | 6994 (86.8) | <0.001   | <0.001       |
| BMI                          | 23.2±3.6                | 24.2±3.5     | 24.4±3.5     | 24.3±3.6    | <0.001   | <0.001       |
| NIHSS, median (IQR)          | 4 (2–10)                | 4 (1–8)      | 3 (1–7)      | 3 (2–6)     | <0.001   | <0.001       |
| Medical history              |                         |              |              |             |          |              |
| History of TIA               | 57 (1.7)                | 179 (1.9)    | 114 (1.7)    | 130 (1.6)   | 0.599    | 0.399        |
| History of stroke            | 1016 (29.9)             | 2569 (27.0)  | 1607 (24.7)  | 1767 (21.9) | <0.001   | <0.001       |
| History of CAD               | 425 (12.5)              | 1234 (12.9)  | 846 (13.0)   | 864 (10.7)  | <0.001   | <0.001       |
| History of PAD               | 47 (1.4)                | 115 (1.2)    | 65 (1.0)     | 91 (1.1)    | 0.355    | 0.216        |
| Current smoking              | 548 (16.1)              | 1921 (20.2)  | 1515 (23.2)  | 2393 (29.7) | <0.001   | <0.001       |
| AF                           | 892 (26.3)              | 2168 (22.7)  | 1247 (19.1)  | 972 (12.1)  | <0.001   | <0.001       |
| Hypertension                 | 2898 (85.4)             | 7790 (81.7)  | 5134 (78.8)  | 5904 (73.3) | <0.001   | <0.001       |
| Dyslipidemia                 | 1138 (33.5)             | 3980 (41.8)  | 2768 (42.5)  | 3352 (41.6) | <0.001   | <0.001       |
| Medication history           |                         |              |              |             |          |              |
| Prior antiplatelet           | 1291 (38.0)             | 3746 (39.3)  | 2479 (38.0)  | 2625 (32.6) | <0.001   | <0.001       |
| Prior statin                 | 976 (28.8)              | 3306 (34.7)  | 2174 (33.4)  | 2311 (28.7) | <0.001   | <0.001       |
| Prior antihypertensive       | 2412 (71.1)             | 6573 (69.0)  | 4227 (64.9)  | 4428 (55.0) | <0.001   | <0.001       |
| Prior antidiabetic           | 2370 (69.8)             | 6710 (70.4)  | 5006 (76.8)  | 5739 (71.3) | <0.001   | 0.001        |
| Large artery steno-occlusion |                         |              |              |             | <0.001   | <0.001       |
| No                           | 1519 (44.8)             | 4331 (45.4)  | 3012 (46.2)  | 3742 (46.5) |          |              |
| Mild                         | 269 (7.9)               | 808 (8.5)    | 575 (8.8)    | 852 (10.6)  |          |              |
| Significant                  | 623 (18.4)              | 1824 (19.1)  | 1328 (20.4)  | 1758 (21.8) |          |              |
| Occlusion                    | 983 (29.0)              | 2568 (26.9)  | 1602 (24.6)  | 1702 (21.1) |          |              |
| TOAST                        |                         |              |              |             | <0.001   | <0.001       |
| LAA                          | 1156 (34.1)             | 3649 (38.3)  | 2635 (40.4)  | 3714 (46.1) |          |              |
| SVO                          | 510 (15.0)              | 1580 (16.6)  | 1203 (18.5)  | 1641 (20.4) |          |              |
| Cardioembolism               | 846 (24.9)              | 2055 (21.6)  | 1221 (18.7)  | 1003 (12.5) |          |              |
| Other cause                  | 94 (2.8)                | 199 (2.1)    | 130 (2.0)    | 170 (2.1)   |          |              |
| Undetermined                 | 788 (23.2)              | 2048 (21.5)  | 1328 (20.4)  | 1526 (18.9) |          |              |
| Reperfusion therapy          |                         |              |              |             | <0.001   | <0.001       |
| No                           | 2791 (82.2)             | 7933 (83.2)  | 5530 (84.9)  | 7130 (88.5) |          |              |
| IVT                          | 273 (8.0)               | 742 (7.8)    | 461 (7.1)    | 485 (6.0)   |          |              |
| EVT                          | 214 (6.3)               | 512 (5.4)    | 287 (4.4)    | 253 (3.1)   |          |              |
| IV+EVT                       | 116 (3.4)               | 344 (3.6)    | 239 (3.7)    | 186 (2.3)   |          |              |
| In-hospital treatment        |                         |              |              |             |          |              |
| Statin                       | 2869 (84.5)             | 8400 (88.1)  | 5767 (88.5)  | 7299 (90.6) | <0.001   | <0.001       |
| Antihypertensive             | 1722 (50.7)             | 4884 (51.2)  | 3315 (50.9)  | 4021 (49.9) | 0.372    | 0.170        |
| Antidiabetic                 | 1532 (45.1)             | 5859 (61.5)  | 4775 (73.3)  | 6094 (75.7) | <0.001   | <0.001       |
| Laboratory findings          |                         |              |              |             |          |              |
| WBC count                    | 8.2±3.6                 | 8.3±3.1      | 8.6±3.8      | 8.8±3.1     | <0.001   | <0.001       |
| Hemoglobin                   | 12.6±2.4                | 13.3±2.0     | 13.4±2.1     | 13.9±2.1    | <0.001   | <0.001       |
| Platelet count               | 218.5±82.4              | 226.8±76.5   | 231.2±72.4   | 238.0±72.4  | <0.001   | <0.001       |
| Low-density lipoprotein      | 93.1±35.5               | 96.8±36.8    | 99.6±38.6    | 110.4±44.3  | <0.001   | <0.001       |
| Creatinine                   | 1.34±1.56               | 1.12±1.01    | 1.17±1.24    | 1.12±1.06   | <0.001   | <0.001       |

(Continued)

**Table 1. Continued**

|         | HbA <sub>1c</sub> <6.0% | 6.0% to 7.0% | 7.0% to 8.0% | ≥8.0%       | P value* | P for trend† |
|---------|-------------------------|--------------|--------------|-------------|----------|--------------|
| Glucose | 135.1±47.1              | 154.3±50.6   | 183.1±61.5   | 250.8±100.4 | <0.001   | <0.001       |
| eGFR    | 71.9±27.8               | 76.2±24.3    | 76.6±25.3    | 80.2±26.4   | <0.001   | <0.001       |
| SBP     | 146.9±27.7              | 148.6±27.3   | 150.4±27.7   | 152.8±29.1  | <0.001   | <0.001       |

Values are expressed as number (percentage) and mean±SD, unless otherwise indicated. AF indicates atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; EVT, endovascular thrombectomy; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; IQR, interquartile range; IVT, intravenous thrombolysis; LAA, large artery atherosclerosis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PAD, peripheral artery disease; SBP, systolic blood pressure; SVO, small vessel occlusion; TIA, transient ischemic attack; TOAST, Trial of Org 10172 in Acute Stroke Treatment; and WBC, white blood cell.

\*P value by  $\chi^2$  test, ANOVA, or Kruskal-Wallis test.

†P value by Cochran-Armitage trend, Cochran-Mantel-Haenszel, or linear contrasts test in ANOVA.

that the mean survival time up to 3 months was longer in the target group than in the reference group, whereas an RMST ratio <1 reflects a shorter mean survival time.

**Table 2. Event Rates of All-Cause Mortality Within 3 Months in Each HbA<sub>1c</sub> Group According to the eGFR Stages**

| eGFR stages  | HbA <sub>1c</sub> , % | Event rates within 3 mo, % (95% CI) | P value |
|--------------|-----------------------|-------------------------------------|---------|
| All patients |                       |                                     | <0.001  |
|              | <6.0                  | 8.9 (7.9–9.9)                       |         |
|              | 6.0–7.0               | 5.8 (5.3–6.3)                       |         |
|              | 7.0–8.0               | 6.4 (5.8–7.0)                       |         |
|              | ≥8.0                  | 5.3 (4.8–5.8)                       |         |
| Stage 1      |                       |                                     | 0.006   |
|              | <6.0                  | 4.9 (3.6–6.2)                       |         |
|              | 6.0–7.0               | 3.2 (2.6–3.8)                       |         |
|              | 7.0–8.0               | 3.8 (3.0–4.6)                       |         |
|              | ≥8.0                  | 2.8 (2.3–3.4)                       |         |
| Stage 2      |                       |                                     | 0.001   |
|              | <6.0                  | 8.0 (6.5–9.5)                       |         |
|              | 6.0–7.0               | 5.6 (4.9–6.3)                       |         |
|              | 7.0–8.0               | 5.1 (4.2–6.0)                       |         |
|              | ≥8.0                  | 5.6 (4.8–6.5)                       |         |
| Stage 3      |                       |                                     | 0.007   |
|              | <6.0                  | 12.8 (10.2–15.3)                    |         |
|              | 6.0–7.0               | 9.1 (7.8–10.5)                      |         |
|              | 7.0–8.0               | 11.6 (9.8–13.5)                     |         |
|              | ≥8.0                  | 8.9 (7.3–10.5)                      |         |
| Stage 4      |                       |                                     | 0.030   |
|              | <6.0                  | 22.5 (15.8–29.1)                    |         |
|              | 6.0–7.0               | 15.3 (11.0–19.6)                    |         |
|              | 7.0–8.0               | 17.0 (11.4–22.5)                    |         |
|              | ≥8.0                  | 11.1 (7.2–15.1)                     |         |
| Stage 5      |                       |                                     | 0.499   |
|              | <6.0                  | 13.6 (8.6–18.6)                     |         |
|              | 6.0–7.0               | 10.3 (6.3–14.3)                     |         |
|              | 7.0–8.0               | 14.5 (9.6–19.4)                     |         |
|              | ≥8.0                  | 14.4 (9.4–19.3)                     |         |

P value by log-rank test.

eGFR indicates estimated glomerular filtration rate; and HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>.

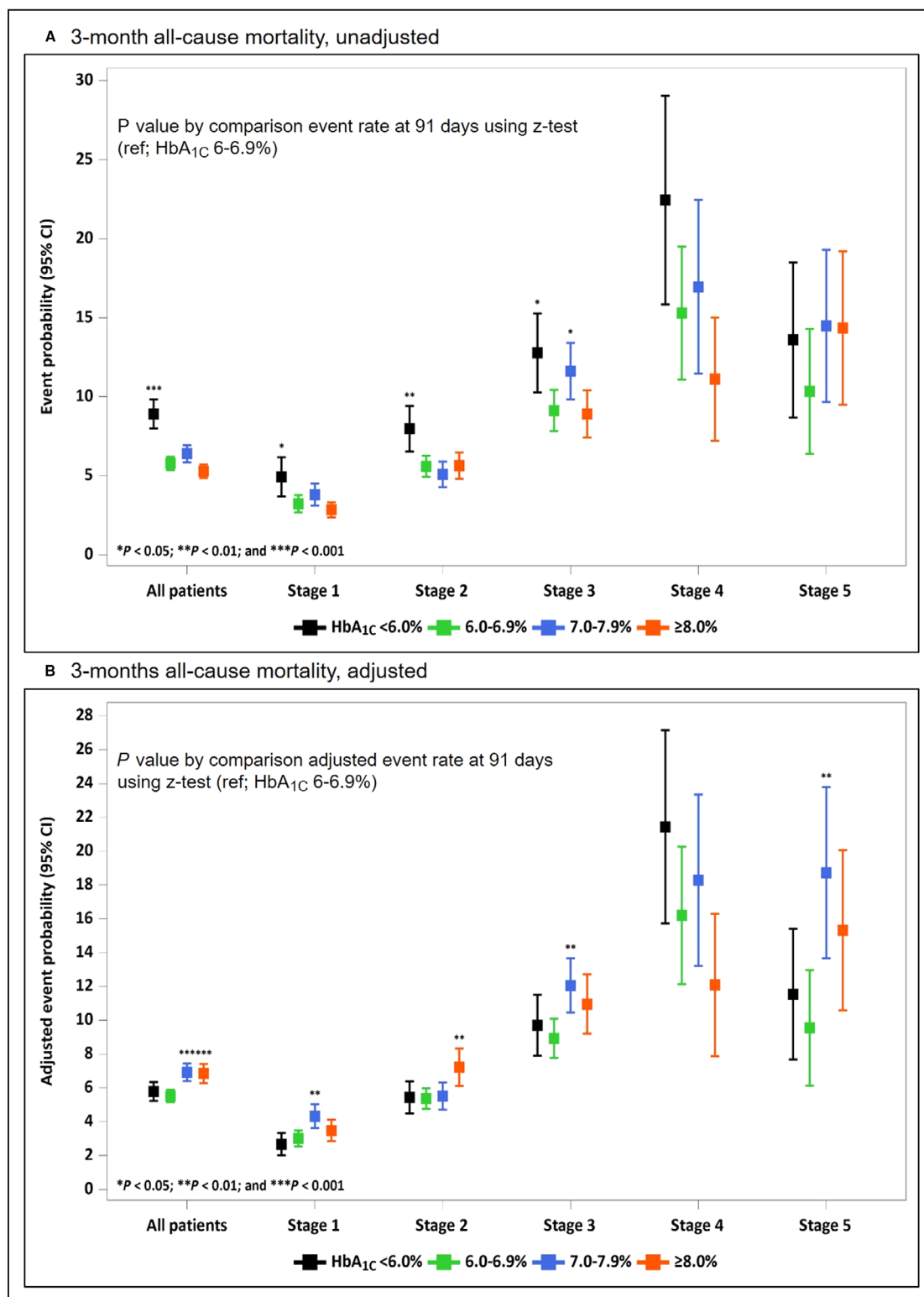
The direction of the adjusted RMST ratio was consistent with that of the adjusted HR for the HbA<sub>1c</sub> groups; however, statistical significance may differ between the 2 measures.

The associations between 3-month recurrent stroke, the composite outcome of stroke, MI, and all-cause mortality, and MI with HbA<sub>1c</sub> groups according to eGFR stages is presented in [Tables S6 through S8](#) and [Figure S3](#). Although the relationship between higher HbA<sub>1c</sub> levels and outcomes was complex among the eGFR stages, no significant association was observed between HbA<sub>1c</sub> levels and 3-month outcomes in eGFR stage 4.

## DISCUSSION

In this study, we analyzed a large stroke registry of >27 000 patients with acute ischemic stroke and diabetes, demonstrating that the relationship between admission HbA<sub>1c</sub> levels and 3-month all-cause mortality varies among eGFR stages. Notably, in eGFR stage 4, admission HbA<sub>1c</sub> levels were not significantly associated with 3-month all-cause mortality and composite of stroke, MI, and all-cause mortality, whereas in other stages, admission HbA<sub>1c</sub> levels between 7.0% and 8.0% or ≥8.0% were linked to a heightened risk of 3-month all-cause mortality and composite of stroke, MI, and all-cause mortality. In addition, the absolute risk of 3-month all-cause mortality increased consistently with higher eGFR stages. These findings suggest that the impact of prestroke glycemic status on early all-cause mortality may differ depending on eGFR stage, highlighting the need for individualized glycemic targets in patients with ischemic stroke and diabetes.

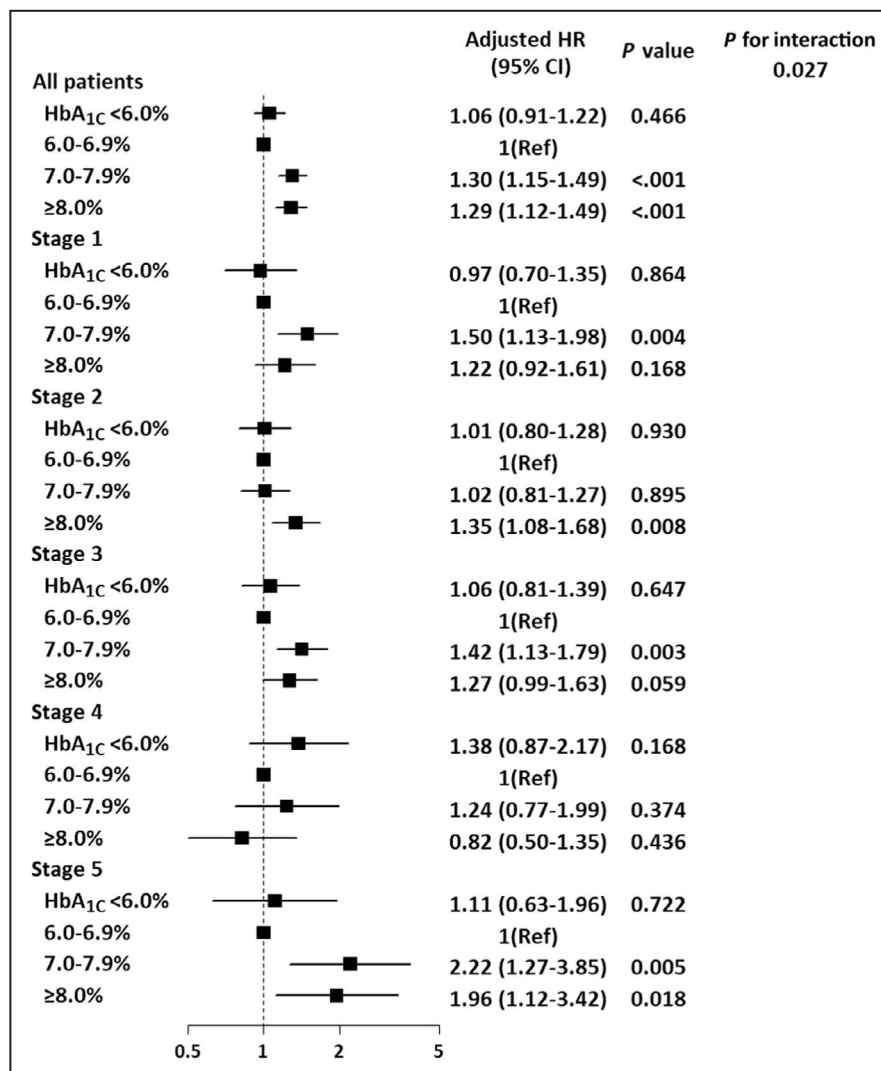
Our study found that patients with admission HbA<sub>1c</sub> <6.0% had the highest 3-month early all-cause mortality rate, regardless of eGFR stage. This may be attributed to these patients being older and more likely to have a history of stroke, atrial fibrillation, large vessel occlusion, and higher NIHSS scores, suggesting that they represent a frailer population. After adjusting for relevant variables, the significant association between admission HbA<sub>1c</sub> <6.0% and 3-month all-cause mortality disappeared.



**Figure 1. Event rates of all-cause mortality within 3 months according to the HbA<sub>1c</sub> levels by eGFR stages.** (A), Unadjusted rates and (B) adjusted rates. eGFR indicates estimated glomerular filtration rate; and HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>.

Therefore, the unadjusted analysis showing the highest 3-month all-cause mortality rates in the admission HbA<sub>1c</sub> <6.0% group does not necessarily imply that maintaining

or treating to achieve HbA<sub>1c</sub> <6.0% increases the risk of all-cause mortality in patients with ischemic stroke and diabetes.



**Figure 2.** Forest plots for 3-month all-cause mortality in all patients and by eGFR stages.

eGFR indicates estimated glomerular filtration rate; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; and HR, hazard ratio.

In addition, patients with CKD often experience anemia, which can influence HbA<sub>1c</sub> levels.<sup>24</sup> Low hemoglobin levels may contribute to reduced HbA<sub>1c</sub> levels, potentially leading to an underestimation of glycemic control in these patients. Moreover, in patients with impaired renal function, the accuracy of HbA<sub>1c</sub> measurements may be influenced by multiple factors beyond anemia. These include erythropoiesis-stimulating agent therapy, iron supplementation, recent blood transfusions, and the accumulation of uremic toxins, which can result in the formation of carbamylated hemoglobin.<sup>25–29</sup> Such alterations may interfere with specific assay methodologies, leading to either overestimation or underestimation of true glycemic control. In addition, chronic inflammation commonly seen in CKD may affect red blood cell lifespan and glycation rates. Since these confounding factors were not fully

accounted for in our study, the interpretation of HbA<sub>1c</sub>-based results, particularly in patients with advanced CKD, should be approached with caution.

In contrast, after adjusting for relevant variables, higher admission HbA<sub>1c</sub> groups showed a significantly increased risk of 3-month all-cause mortality and composite of stroke, MI, and all-cause mortality. These findings align with previous studies highlighting the impact of prestroke glycemic status on stroke prognosis and further suggest that glycemic status might be an important prognostic factor,<sup>4,21</sup> particularly when considering eGFR stages. However, unlike eGFR stage, admission HbA<sub>1c</sub> levels do not appear to have a linear relationship with prognosis,<sup>21</sup> which may explain the challenges in determining an optimal target glycemic status in stroke with diabetes. This study suggests that clinical trials attempting a uniform target

HbA<sub>1c</sub> management approach might face difficulties in achieving success in stroke with diabetes. However, as our study is retrospective, factors such as glycemic control after stroke and other treatments may have influenced the outcomes.

Our findings provide supportive evidence that worsening eGFR stages are a critical factor in increasing the risk of all-cause mortality, with absolute rates of 3-month all-cause mortality rising from eGFR stage 1 to stage 4, regardless of HbA<sub>1c</sub> levels. However, in clinical practice, glycemic status may hold greater clinical relevance depending on the eGFR stage in patients with stroke who have diabetes, as glycemic management is more actionable than modifying eGFR. Our study found that among patients with renal impairment (eGFR stages 3–5), the relationship between admission HbA<sub>1c</sub> levels and 3-month mortality varied by eGFR stages. Specifically, in stage 4 (severe kidney damage), HbA<sub>1c</sub> levels were not associated with an increased risk of 3-month mortality. In contrast, in stages 3 (moderate kidney damage) and 5 (renal failure), HbA<sub>1c</sub> levels >8% at admission were associated with an increased risk of 3-month all-cause mortality, by 27% and 96%, respectively. These findings suggest that, in patients with moderate kidney damage (stage 3), the impact of HbA<sub>1c</sub> on mortality is similar to that observed in individuals with normal kidney function. However, in severe kidney damage (stage 4), eGFR levels or other related variables may play a more critical role in mortality, potentially outweighing the influence of HbA<sub>1c</sub> levels.

It is also important to note that the context of renal failure was distinct from severe kidney damage. In clinical practice, patients with CKD who progress to renal failure or require dialysis appear to have prognoses that differ from those with severe CKD.<sup>30,31</sup> Managing glycemic control in the presence of CKD adds complexity, requiring careful selection of medications and individualized glycemic targets according to the CKD stages.<sup>32,33</sup> Currently, there are insufficient data and trials regarding the ideal glucose target in patients with eGFR stage 3 or worse. Ultimately, this study underscores that both reduced eGFR and elevated HbA<sub>1c</sub> are associated with worse vascular outcomes in patients with diabetes and stroke. Notably, from normal eGFR (1 or 2) to moderate kidney damage (eGFR 3), the management of HbA<sub>1c</sub> may be an important factor in reducing the risk of all-cause mortality in patients with stroke and diabetes. This suggests that glycemic control remains an important consideration for patients up to eGFR stage 3.

Our study analyzed prospective data from >27 000 patients with stroke and diabetes, allowing for a granular assessment of eGFR stages and admission HbA<sub>1c</sub> levels. Despite the complex relationship observed, our detailed exploration yielded meaningful insights. However, several important limitations should be

acknowledged. First, since our analysis was limited to patients with stroke and diabetes, there is a potential for index event bias.<sup>34</sup> Second, we did not distinguish between type 1 and type 2 diabetes, and data on diabetes medications and follow-up HbA<sub>1c</sub> levels were not available. While these factors might influence long-term outcomes, we focused on 3-month outcomes to specifically examine the impact of prestroke glycemic status. Third, our study has the limitation of classifying patients into eGFR-based stages without distinguishing between CKD and acute kidney injury. Although acute kidney injury can occur in the setting of acute ischemic stroke, most cases were presumed to be CKD, and this uncertainty may have influenced the results. Fourth, given the violation of the proportional hazards assumption in certain analyses, the interpretation of HRs may be limited. However, we sought to mitigate this issue by conducting RMST analyses, which offer a valid alternative for comparing survival outcomes without relying on the proportional hazards assumption (Tables S4 and S5). Fifth, because the proportion of missing data was very low (<2%), we employed single imputation; nevertheless, we acknowledge that multiple imputation would be more appropriate in settings with higher levels of missingness. Last, as our study was conducted within a Korean population, inherent limitations exist regarding generalizability, as regional characteristics may affect the applicability of our findings to other populations.

In conclusion, our study demonstrated that 3-month all-cause mortality increased significantly with higher eGFR stages. However, the effect of admission glycemic status on mortality varied among eGFR stages. In patients with normal to moderate kidney damage (eGFR stages 1–3), higher admission HbA<sub>1c</sub> levels were associated with an increased hazard for 3-month all-cause mortality. In contrast, among patients with severe kidney damage (stage 4), no significant association was observed between HbA<sub>1c</sub> levels and mortality. Our findings suggest that eGFR stage may need to be considered when tailoring glycemic control strategies in patients with stroke and diabetes. Given the retrospective nature of our study, prospective studies are warranted to validate these findings and clarify the impact of individualized glycemic management after stroke based on kidney function.

## ARTICLE INFORMATION

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## Disclosures

None.

## Supplemental Material

Tables S1–S8

Figures S1–S3

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