Prestroke Glucose Control and Functional Outcome in Patients With Acute Large Vessel Occlusive Stroke and Diabetes After Thrombectomy

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OBJECTIVE

To evaluate whether prestroke glucose control is associated with functional outcomes in patients with acute large vessel occlusive stroke and diabetes who underwent intra-arterial thrombectomy (IAT).

RESEARCH DESIGN AND METHODS

From the Clinical Research Center for Stroke–Korea registry, we included patients with emergent large vessel occlusive stroke with diabetes who underwent IAT between January 2009 and March 2020. The association between the HbA_{1c} level at admission and functional outcomes (modified Rankin Scale at 3 months after the index stroke) was assessed.

RESULTS

A total of 1,351 patients were analyzed. Early neurological deterioration was more common in patients with higher levels of HbA_{1c} at admission (P = 0.02 according to HbA_{1c} quintiles, P = 0.003 according to an HbA_{1c} cutoff value of 7.0%) than in those with lower HbA_{1c} levels. Higher HbA_{1c} levels at admission were significantly associated with decreased odds of favorable functional outcomes at a threshold of 7.0–7.1%. The association was consistently observed in subgroups divided according to age, sex, stroke subtype, occlusion site, degree of recanalization, thrombolysis modalities, time from symptom onset to groin puncture, and treatment period.

CONCLUSIONS

Prestroke glucose control with a target HbA_{1c} of ≤7.0% may be beneficial for neurological recovery in patients with diabetes undergoing IAT for large vessel occlusive stroke, regardless of stroke subtype, bridging intravenous thrombolysis, occlusion site, degree of recanalization, and treatment period.

Hyperglycemia during the acute stroke period is associated with infarct progression, symptomatic hemorrhage, and decreased recanalization after recombinant tissue plasminogen activator administration and, thus, results in poor functional outcomes (1–3). Higher levels of glycated hemoglobin (HbA_{1c}) increase the risk of neurological deterioration, mortality, and poor neurological recovery after ischemic stroke (4). In

patients with emergent large vessel occlusive stroke treated with endovascular recanalization therapy, both acute hyperglycemia and higher levels of HbA_{1c} were associated with decreased odds of favorable outcomes (5–8).

While these studies provided crucial information on the importance of glucose levels in stroke, most of the study populations consisted of patients without diabetes. As a result, the reference group in those studies consisted of a population without diabetes, and the effect of prestroke glucose control on clinical outcomes in patients with diabetes and ischemic stroke, especially in those with acute large vessel occlusive stroke, could not be properly evaluated.

The purpose of this study was to evaluate whether prestroke glucose control, measured by the level of HbA_{1c} at admission, is associated with functional outcomes in patients with acute large vessel occlusive stroke and diabetes after undergoing intra-arterial thrombectomy (IAT). We also evaluated whether the association is different according to each prespecified subgroup.

RESEARCH DESIGN AND METHODS

We analyzed the data of patients in the stroke registry of the Clinical Research Center for Stroke in Korea (CRCS-K). The CRCS-K is a prospective, web-based, multicenter registry of patients with stroke admitted to participating hospitals since 2008. The registry is used for the development of a stroke prevention strategy and stroke recurrence prediction model. Data regarding demographics, vascular risk factors, stroke location and angiographic findings, in-hospital management, etiology workup, laboratory results, and functional outcome were prospectively collected according to a standardized protocol (9). All participating centers obtained approval from their local institutional review boards for data collection.

We included patients with acute large vessel occlusive stroke and diabetes who underwent endovascular recanalization therapy in the participating centers between January 2009 and March 2020. Patients without information on HbA_{1c} at admission and functional outcome at 3 months were excluded.

Postthrombectomy Management of Blood Pressure and Glucose

Treating physicians at the participating centers of the CRCS-K followed guideline recommendations and expert opinion in clinical practice (10,11). Blood pressure (BP) was controlled to be $<$180/105 mmHg for 24 h after intravenous thrombolysis (IVT). After successful recanalization (thrombolysis in cerebral infarction [TICI] $\geq$2b) postmechanical thrombectomy, maintaining systolic BP (SBP) $<$140 or 160 mmHg (this level was chosen per the treating physician's discretion) was recommended to reduce the risk of reperfusion injury. Maintaining BP $<$180/105 mmHg was permitted in the event of a failed recanalization to maintain cerebral perfusion through collateral circulation. Blood glucose was controlled with a target between 140 and 180 mg/dL, and hypoglycemia was avoided ($<$60 mg/dL).

Covariates and Outcomes

The following data were obtained from the registry: *1*) age, sex, initial stroke severity, and educational level; *2*) vascular risk factors, including history of stroke, coronary heart disease, hypertension, smoking, and atrial fibrillation; *3*) stroke subtype according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria; *4*) laboratory data, including white blood cell (WBC) count, hemoglobin, platelet, total cholesterol, and BP; *5*) prior medications, including antiplatelet, anticoagulant, antihypertensive, lipid-lowering, and antidiabetic medications; *6*) treatment modalities (IAT alone vs. IAT + IVT), time from symptom onset to groin puncture, endovascular procedure time, and degree of recanalization; and *7*) functional outcomes measured by modified Rankin Scale (mRS) score at 3 months and early neurological deterioration (END), including stroke progression and symptomatic hemorrhage. A favorable functional outcome was defined as an mRS of $\leq$1 (disability free) at 3 months after the index stroke. Various functional outcomes, including mRS of $\leq$2 (functional independence) and mRS at 3 months after the index stroke, were also used in the analysis. mRS ranges from 0 to 6, with 0 indicating a lack of symptoms, 1 disability free, 2 to 3 needing some help but able to do daily activities, 4 to 5 unable to walk, or bedridden, and 6 death. END was defined as any neurological worsening within 3 weeks of the index stroke. Neurological worsening was defined as *1*) an increment of $\geq$1 on National Institutes of Health Stroke Scale (NIHSS) items 1 (level of consciousness), 5, or 6 (motor) or *2*) an increment of $\geq$2 on the NIHSS total score. Possible causes of END included stroke recurrence, stroke progression, symptomatic hemorrhagic transformation, and other; the detailed definitions of each component are described in a previous publication (9).

The study patients were classified into either five groups according to quintiles of HbA_{1c} at admission (1st quintile $\leq$6.1% [43 mmol/mol], 2nd quintile $>$6.1–6.6% [43–49 mmol/mol], 3rd quintile $>$6.6–7.1% [49–54 mmol/mol], 4th quintile $>$7.1–7.9% [54–63 mmol/mol], 5th quintile $>$7.9% [63 mmol/mol]) or two groups according to a prespecified HbA_{1c} cutoff value of 7.0% ($\leq$7.0 vs. $>$7.0% [53 mmol/mol]). The relationships between the levels of HbA_{1c} and procedure-related outcomes (procedure time and degree of recanalization) or clinical outcomes were evaluated.

Statistical Analysis

For the comparison of baseline characteristics according to HbA_{1c} levels, a χ^2 test or Fisher exact test was used for categorical variables, and independent *t* test or Mann-Whitney *U* test was used for continuous variables. Multivariable logistic regression analysis was performed to estimate the odds ratios (ORs) and 95% CIs for the association between prestroke glucose control and favorable functional outcomes. HbA_{1c} at admission was entered into the model in quintiles or as a binary variable with a threshold of 7.0% (53 mmol/mol).

A sequential regression multiple imputation method was used to impute missing values, assuming missing at random as the missing mechanism. The following were chosen as the variables affecting an occurrence of missingness: age, sex, initial NIHSS, education level, prior mRS, HbA_{1c}, stroke subtype, smoking status, risk factors (history of stroke, history of hypertension, and history of atrial fibrillation), laboratory findings (WBC, hemoglobin, platelet, total cholesterol, LDL, HDL, triglycerides, fasting serum glucose, and blood urea nitrogen), initial BP (SBP and diastolic BP), prior medication (antithrombotics, antihypertensives, lipid-lowering agents, and antidiabetic medications),

occlusion site, onset to groin puncture time, degree of recanalization, procedure time, treatment modalities, and mRS at the 3rd month. The results were obtained from imputed data with 10 iterations to achieve convergence. The goodness-of-fit was evaluated using the Hosmer-Lemeshow test. Multiplicative interaction analyses were performed to evaluate the heterogeneity of the HbA_{1c} level with reference to functional outcomes between each prespecified subgroup; the subgroups included age (<80, ≥ 80 years), sex, stroke subtype (large artery atherosclerosis, cardioembolism, other), occlusion site (anterior circulation, posterior circulation), degree of recanalization (TICI $\leq$2a, TICI $\geq$2b), thrombolysis modalities (IAT only, IAT + IVT), time from symptom onset to groin puncture ($\leq$360 min, $>$360 min), and treatment period (before 2015, after 2015). All statistical analyses were performed using Stata 13.0 software (StataCorp, College Station, TX). All tests were two-sided, and $P < 0.05$ was considered significant.

RESULTS

Among 26,646 patients with acute ischemic stroke and diabetes who visited the participating centers, 1,534 (5.8%) underwent IAT; of these, 60 patients without data on HbA_{1c} at admission and 123 without functional outcome data were excluded. As a result, 1,351 patients were included in the analysis. The median age of the patients was 72.0 years (65.0–78.0), and 777 (57.5%) were men. Overall, the patients had a median (interquartile range) NIHSS score of 14.0 (9.0–18.0), and the mean ± SD HbA_{1c} was 7.1 ± 1.4. The proportions of patients with a current smoker, quitter, and nonsmoker status were 20.1%, 13.8%, and 66.1%, respectively. The proportion of patients with diabetes diagnosed at admission was 184 (13.6%). Table 1 summarizes the baseline characteristics and variables of the patients according to HbA_{1c} levels at admission. Generally, patients with higher HbA_{1c} levels at admission were significantly younger and included a lower proportion of men than those with lower levels of HbA_{1c}. Atrial fibrillation and hypertension were less prevalent among patients with a high HbA_{1c} level. Patients with higher HbA_{1c} had a higher prevalence of large artery atherosclerosis and a lower prevalence of cardioembolism.

Table 2 shows the prevalence of END and differences in functional outcomes according to HbA_{1c} levels. END was more prevalent in patients with higher HbA_{1c} levels ($P = 0.02$ according to quintiles, $P = 0.003$ according to the cutoff value). The proportion of patients with symptomatic hemorrhage was significantly higher in those with higher quintiles of HbA_{1c} ($P = 0.033$), and stroke progression was more commonly found in patients with HbA_{1c} $>$7.0% than in those with HbA_{1c} $\leq$7.0% (20.2 vs. 15.5%, $P = 0.029$). The proportion of patients with mRS $\leq$1 was significantly lower among patients with higher HbA_{1c} ($P = 0.006$ according to quintiles, $P = 0.007$ according to the cutoff value).

Table 3 shows procedure-related outcomes according to HbA_{1c} levels. While endovascular procedure time was longer in patients with higher HbA_{1c} ($P = 0.017$ according to quintiles, $P = 0.005$ according to the cutoff value), the degree of recanalization was not significantly different according to the HbA_{1c} level.

Table 4 shows the associations between HbA_{1c} levels at admission and functional outcomes at 3 months. Compared with those in the 2nd quintile ($>$6.1–6.6% [43–49 mmol/mol]), patients in the 4th quintile ($>$7.1–7.9% [54–63 mmol/mol]) and 5th quintile ($>$7.9% [63 mmol/mol]) had a significantly lower probability of achieving the favorable functional outcome of mRS $\leq$1 after multivariable adjustment (model 2: 4th quintile OR 0.40 [95% CI 0.26, 0.63], 5th quintile 0.43 [0.28, 0.68]; model 3: 4th quintile 0.43 [0.27, 0.68], 5th quintile 0.47 [0.29, 0.75]). The probability of achieving the favorable outcome of mRS $\leq$1 was also significantly lower in the 1st quintile group (model 2: 0.56 [0.37, 0.85]; model 3: 0.59 [0.38, 0.91]). When HbA_{1c} was used as a binary variable, the probability of achieving a favorable outcome was also significantly lower in those with HbA_{1c} $>$7.0% (53 mmol/mol) compared with those with HbA_{1c} $\leq$7.0% (model 2: 0.51 [0.38, 0.69]; model 3: 0.53 [0.39, 0.72]). The analysis using patients with complete data is presented in Supplementary Table 1.

The associations among HbA_{1c} at admission, achievement of functional independence (mRS $\leq$2), and a favorable shift in mRS (ordinal) were also evaluated. Multivariable models 2 and 3 showed a significantly lower probability of achieving functional independence per mRS $\leq$2 in the 5th quintile (as quintiles) and HbA_{1c} $>$7.0% (53 mmol/mol) (as a cutoff value). The probability of achieving a favorable shift in mRS was significantly lower in the 4th and 5th quintiles (as quintiles) and HbA_{1c} $>$7.0% (53 mmol/mol) (as a cut-off value). Sensitivity analysis after excluding premorbid neurological disability (premorbid mRS $>$1) showed consistent results, with higher HbA_{1c} levels being associated with poorer functional outcomes (Supplementary Table 2).

Figure 1 shows that the influence of prestroke glucose control ($\leq$7.0 vs. $>$7.0% [53 mmol/mol]) on favorable functional outcomes was consistently observed according to prespecified subgroups, including age, sex, stroke subtype, occlusion site, degree of recanalization, thrombolysis modalities, time from symptom onset to groin puncture, and treatment period. According to the treatment modalities, such as whether bridging therapy with IVT was performed, there was no significant heterogeneity between higher HbA_{1c} and decreased odds of favorable outcomes (IAT only: OR 0.56 [95% CI 0.36, 0.87]; IVT + IAT: 0.47 [0.31, 0.73]; P for interaction = 0.586). The subgroup analyses did not reveal any significant HbA_{1c} effect modification of occlusion site (anterior circulation: 0.51 [0.37, 0.71]; posterior circulation: 0.67 [0.26, 1.73]; P for interaction = 0.594) and treatment period (before 2015: 0.37 [0.20, 0.69]; after 2015: 0.59 [0.41, 0.84]; P for interaction = 0.203). The association between prestroke glucose control and various neurological outcomes (mRS 0–2, ordinal mRS) was still consistent according to each prespecified subgroup (Supplementary Table 3).

CONCLUSIONS

Our current study showed that prestroke glucose control was associated with functional outcomes in patients with emergent large vessel occlusive stroke and diabetes who underwent IAT. Specifically, high levels of HbA_{1c} at admission were significantly associated with a decreased odds of good functional recovery regardless of the stroke subtype, occlusion site, degree of recanalization, thrombolysis modality, time from symptom onset to groin puncture,

Table 1—Baseline characteristics of the patients according to HbA_{1c} quintiles and a cutoff value of 7.0%

		HbA_{1c} quintile						HbA_{1c} cutoff		
	Total	1st (≤6.1%)	2nd (>6.1–6.6%)	3rd (>6.6–7.1%)	4th (>7.1–7.9%)	5th (>7.9%)	*P* value	≤7.0%	>7.0%	*P* value
Patients, *n*	1,351	305	281	244	259	262		796	555	
Age (years)	72 (65–78)	76 (67– 80)	73 (66–78)	72 (65–78)	72 (65–77)	68 (60–75)	<0.001	74 (66–79)	70 (62–77)	<0.001
Male sex	777 (57.5)	148 (48.5)	168 (59.8)	140 (57.4)	156 (60.2)	165 (63.0)	0.005	434 (54.5)	343 (61.8)	0.008
Initial NIHSS	14 (9–18)	14 (10–18)	15 (10–19)	14 (9–18)	13 (8–18)	13 (8–18)	0.077	14 (10–18)	13 (8–18)	<0.001
Premorbid mRS 0–1	1,133 (83.9)	240 (78.7)	245 (87.2)	211 (86.5)	224 (86.5)	213 (81.3)	0.016	667 (83.8)	466 (84.0)	0.933
Education level (years)							0.034			<0.001
0	147 (10.9)	44 (14.4)	34 (12.1)	34 (13.9)	18 (6.9)	17 (6.5)		112 (14.1)	35 (6.3)	
≤12 (high school)	1,027 (76.0)	223 (73.1)	211 (75.1)	178 (73.0)	203 (78.4)	212 (80.9)		581 (73.0)	446 (80.4)	
>12 (university)	177 (13.1)	38 (12.5)	36 (12.8)	32 (13.1)	38 (14.7)	33 (12.6)		103 (12.9)	74 (13.3)	
Risk factor										
Previous stroke	298 (22.1)	77 (25.2)	66 (23.5)	56 (23.0)	56 (21.6)	43 (16.4)	0.129	194 (24.4)	104 (18.7)	0.014
Coronary heart disease	212 (15.7)	42 (13.8)	52 (18.5)	32 (13.1)	45 (17.4)	41 (15.6)	0.365	123 (15.5)	89 (16.0)	0.772
Hypertension	1,070 (79.2)	258 (84.6)	230 (81.9)	193 (79.1)	199 (76.8)	190 (72.5)	0.006	656 (82.4)	414 (74.6)	<0.001
Smoking							0.016			<0.001
No	893 (66.1)	215 (70.5)	188 (66.9)	158 (64.8)	161 (62.2)	171 (65.3)		543 (68.2)	350 (63.1)	
Current	272 (20.1)	42 (13.8)	50 (17.8)	50 (20.5)	66 (25.5)	64 (24.4)		132 (16.6)	140 (25.2)	
Quit	186 (13.8)	48 (15.7)	43 (15.3)	36 (14.8)	32 (12.4)	27 (10.3)		121 (15.2)	65 (11.7)	
Atrial fibrillation	647 (47.9)	152 (49.8)	155 (55.2)	124 (50.8)	128 (49.4)	88 (33.6)	<0.001	414 (52.0)	233 (42.0)	<0.001
Diabetes diagnosed at admission	184 (13.6)	32 (10.5)	46 (16.4)	44 (18.0)	29 (11.2)	33 (12.6)	0.04	113 (14.2)	71 (12.8)	0.46
Occlusion site							0.151			0.046
Anterior circulation	1,176 (87.0)	271 (88.9)	251 (89.3)	215 (88.1)	215 (83.0)	224 (85.5)		705 (88.6)	471 (84.9)	
Posterior circulation	175 (13.0)	34 (11.1)	30 (10.7)	29 (11.9)	44 (17.0)	38 (14.5)		91 (11.4)	84 (15.1)	
TOAST criteria							0.003			0.001
LAD	383 (28.3)	82 (26.9)	68 (24.2)	68 (27.9)	68 (26.3)	97 (37.0)		210 (26.4)	173 (31.2)	
CE	655 (48.5)	158 (51.8)	154 (54.8)	124 (50.8)	116 (44.8)	103 (39.3)		419 (52.6)	236 (42.5)	
Others	313 (23.2)	65 (21.3)	59 (21.0)	52 (21.3)	75 (29.0)	62 (23.7)		167 (21.0)	146 (26.3)	
Laboratory findings										
WBC count ($\times 10^9$/L)	8 (7–11)	8 (6–10)	8 (6–10)	9 (7–11)	9 (7–11)	9 (7–11)	<0.001	8 (6–10)	9 (7–11)	<0.001
Hemoglobin (mg/dL)	13 (12–15)	13 (12–14)	13 (12–15)	13 (12–15)	13 (12–15)	14 (13–15)	<0.001	13 (12–15)	14 (12–15)	<0.001
Platelets ($\times 10^9$/L)	212 (172–258)	211 (168–261)	210 (172–249)	211 (169–257)	213 (167–263)	216 (183–261)	0.410	211 (169–254)	214 (176–263)	0.013
Total cholesterol (mg/dL)	151 (128–182)	149 (124–179)	148 (129–177)	149 (123–176)	152 (130–176)	163 (131–204)	<0.001	149 (126–177)	156 (131–192)	<0.001
LDL (mg/dL)	90 (69–116)	87 (69–114)	88 (68–113)	87 (66–112)	90 (69–109)	99 (73–133)	<0.001	87 (68–112)	95 (71–123)	<0.001
HDL (mg/dL)	42 (35–50)	42 (36–51)	43 (34–51)	42 (35–49)	43 (35–51)	42 (35–49)	0.699	42 (35–50)	42 (35–50)	0.938
Triglycerides (mg/dL)	102 (73–149)	96 (69–131)	101 (71–150)	103 (75–145)	102 (75–151)	114 (83–172)	<0.001	97 (71–137)	108 (80–162)	<0.001
Fasting glucose (mg/dL)	149 (119–193)	123 (105–147)	141 (116–172)	148 (123–182)	164 (127–207)	203 (158–256)	<0.001	134 (112–165)	182 (140–225)	<0.001
Initial BP										
SBP (mmHg)	142 (127–161)	140 (121–159)	145 (127–163)	145 (130–160)	148 (128–163)	144 (124–163)	0.026	140 (125–160)	146 (128–163)	0.011
DBP (mmHg)	80 (70–90)	80 (69–90)	80 (70–90)	80 (73–90)	81 (73–96)	81 (72–93)	0.002	80 (70– 90)	81 (72–94)	<0.001
IVT + IAT	628 (46.5)	128 (42.0)	131 (46.6)	122 (50.0)	128 (49.4)	119 (45.4)	0.316	362 (45.5)	266 (47.9)	0.374
Time from symptom onset to groin puncture (min)	275 (178–551)	270 (165–550)	260 (168–540)	267 (177–560)	287 (185–525)	290 (185–604)	0.631	265 (170–547)	288 (187–570)	0.011

Continued on p. 2144

Table 1—Continued

	Total	HbA_{1c} quintile					HbA_{1c} cutoff		
		1st (≤6.1%)	2nd (>6.1–6.6%)	3rd (>6.6–7.1%)	4th (>7.1–7.9%)	5th (>7.9%)	*P* value	≤7.0%	>7.0%	*P* value
Prior medication										
Antiplatelet	445 (32.9)	113 (37.0)	92 (32.7)	89 (36.5)	79 (30.5)	72 (27.5)	0.093	285 (35.8)	160 (28.8)	0.007
Anticoagulant	160 (11.8)	43 (14.1)	41 (14.6)	26 (10.7)	24 (9.3)	26 (9.9)	0.170	107 (13.4)	53 (9.5)	0.029
Antihypertension	898 (66.5)	223 (73.1)	200 (71.2)	159 (65.2)	160 (61.8)	156 (59.5)	0.002	562 (70.6)	336 (60.5)	<0.001
Lipid-lowering agent	440 (32.6)	95 (31.2)	107 (38.1)	78 (32.0)	93 (35.9)	67 (25.6)	0.023	273 (34.3)	167 (30.1)	0.105
Antidiabetic	929 (68.8)	213 (69.8)	178 (63.3)	163 (66.8)	189 (73.0)	186 (71.0)	0.127	536 (67.3)	393 (70.8)	0.175

Data are *n* (%) or median (interquartile range) unless otherwise indicated. *P* values by χ^2 test, Kruskal-Wallis test, and Wilcoxon rank sum test. CE, cardioembolism; DBP, diastolic blood pressure; LAD, large artery disease.

and treatment period. Prior studies reported the association between high HbA_{1c} and poor functional outcomes in acute ischemic stroke after endovascular thrombectomy (7,8). However, patients without diabetes were more frequently included, and HbA_{1c} levels were relatively lower in those studies. In the study by Choi et al. (7), the proportion of patients with diabetes was 37.7% with a mean HbA_{1c} level of 6.2% (44 mmol/mol). According to the most recent study by Diprose et al. (8), the proportion of patients with diabetes was 21.1%, with a median HbA_{1c} level of 5.7% (39 mmol/mol). Compared with prior studies, the current study had the highest mean HbA_{1c} level of 7.1% (54 mmol/mol), a higher rate of symptomatic hemorrhage (5.9% in the current study, 5.4% reported by Choi et al., and 4.5% reported by Diprose et al.) and a lower proportion of subjects achieving mRS 0–1 (21.3% in the current study and 24.7% reported by Choi et al.) and mRS 0–2 (33.2% in the current study, 37.6% reported by Choi et al., and 59.2% reported by Diprose et al.) at 3 months. The strong point of the current study is that the study population was confined to patients with diabetes who were enrolled from multiple participating centers, which enabled the evaluation of prestroke glucose control on clinical outcomes.

Our current study showed that higher HbA_{1c} at admission was associated with factors associated with poor clinical outcomes, such as the occurrence of END, longer procedure time, and high levels of serum cholesterol, LDL, and fasting glucose. END was more common in patients with poor prestroke glucose control. The causes of END in acute ischemic stroke include stroke progression, stroke recurrence, and reperfusion injury (12). Several mechanisms are suggested to explain the harmful effects of hyperglycemia on ischemic stroke outcomes via END. Hyperglycemia induces the evolution of an infarct by inhibiting vasodilation after recanalization therapy (13). Hyperglycemia stimulates the release of thromboxane A2 and inhibits the production of endothelium-derived nitric oxide, both of which result in vasoconstriction (14,15). Hyperglycemia aggravates reperfusion injuries by increasing the production of reactive oxygen species (ROS), proinflammatory cytokines, and lactic acid (13). ROS-related oxidative stress and proinflammatory cytokines promote inflammatory cell infiltration to the vascular endothelium and breakdown of the blood-brain barrier and lead to symptomatic intracerebral hemorrhage and cerebral edema in ischemic brain tissues (16,17). Anaerobic glycolysis increases intracellular lactate accumulation and acidosis (18). Endovascular procedure time was longer in patients with higher levels of HbA_{1c}, which may have been related to the deleterious effect of hyperglycemia on the inhibition of recanalization via the stimulation of coagulation and a reduction in both endogenous fibrinolytic activity and the activity of the administered recombinant tissue plasminogen activator (19,20). Considering that intracranial atherosclerosis-related large vessel occlusion usually requires a longer procedure time and rescue therapy (21,22), the higher proportion of large artery atherosclerosis in the poor prestroke glucose control group may explain the longer procedure time. Patients with poor prestroke glucose control had significantly higher total cholesterol, LDL, and fasting glucose, and these metabolic derangements may also have deleterious effects on functional recovery.

Contrary to prior studies that reported that the influence of high HbA_{1c} on functional recovery was more prominent among the subgroup of patients with complete recanalization (7), our study showed that such an effect of high HbA_{1c} was consistent among all the patients, regardless of the degree of recanalization. Previous studies showed that hyperglycemia at admission is inversely correlated with neurological improvement only in the patients receiving early recanalization, which implies that the detrimental effect of glucose depends on the occurrence of recanalization and the extent of penumbra tissue (23,24). Neurotoxicity induced by hyperglycemia in the acute phase may exacerbate the reperfusion injury. However, the accumulation of microvascular damage, impaired oxygenation, lactate, and intracellular acidosis and the decrement of cerebrovascular blood flow induced by chronic hyperglycemia may make the brain more vulnerable to ischemic injury and delay neurological recovery, regardless of the recanalization status (25).

The results of several clinical trials (e.g., Action to Control Cardiovascular Risk in Diabetes, Action in Diabetes and

Table 2—END occurrence and functional outcomes according to HbA_{1c} quintiles and a cutoff value of 7.0%

		HbA_{1c} quintiles						HbA_{1c} cutoff		
	Total	1st (≤6.1%)	2nd (>6.1–6.6%)	3rd (>6.6–7.1%)	4th (>7.1–7.9%)	5th (>7.9%)	*P* value	≤7.0%	>7.0%	*P* value
Patients, *n*	1,351	305	281	244	259	262		796	555	
END	360 (26.6)	61 (20.0)	76 (27.0)	63 (25.8)	82 (31.7)	78 (29.8)	0.02	188 (23.6)	172 (31.0)	0.003
Stroke progression	235 (17.4)	43 (14.1)	43 (15.3)	46 (18.9)	56 (21.6)	47 (17.9)	0.15	123 (15.5)	112 (20.2)	0.029
Symptomatic hemorrhage	80 (5.9)	9 (3.0)	22 (7.8)	11 (4.5)	16 (6.2)	22 (8.4)	0.033	39 (4.9)	41 (7.4)	0.074
mRS ≤1	288 (21.3)	55 (18.0)	77 (27.4)	62 (25.4)	44 (17.0)	50 (19.1)	0.006	190 (23.9)	98 (17.7)	0.007
mRS ≤2	448 (33.2)	95 (31.1)	99 (35.2)	90 (36.9)	88 (34.0)	76 (29.0)	0.31	278 (34.9)	170 (30.6)	0.11

Data are *n* (%) unless otherwise indicated. *P* values by χ^2 test.

Vascular Disease: Preterax and Diamicron MR Controlled Evaluation, and Veterans Affairs Diabetes Trial) showed that intensive glycemic control did not reduce cardiovascular or overall mortality and that achieving an HbA_{1c} <7% (53 mmol/mol) is generally recommended (26–28). A more stringent HbA_{1c} target of <6.5% (48 mmol/mol) might be appropriate among patients with a longer life expectancy, shorter duration of diabetes, and fewer comorbidities (29). The study by the Fukuoka Stroke Registry investigators revealed that poor prestroke glucose control (HbA_{1c} ≥6.9% [52 mmol/mol]) was associated with more neurological deterioration, less neurological improvement, and poor functional outcome (30). A study that exclusively examined patients with acute large vessel occlusive stroke after IAT also reported that the probability of achieving good functional recovery was significantly lower in those with HbA_{1c} >7.0% (53 mmol/mol) (7).

The results of our study are consistent with previous studies that prestroke glucose control with a target HbA_{1c} ≤7.0% (53 mmol/mol) may confer a benefit on neurological recovery after stroke in patients who undergo IAT. However, it should be noted that the probability of achieving nondisabling functional recovery (mRS 0–1) was significantly lower in the 1st quintile of HbA_{1c} (≤6.1% [43 mmol/mol]) compared with that in the 2nd quintile. The decreased probability of achieving a nondisabling outcome in this group was comparable with that in the higher quintile groups. The relationship between HbA_{1c} and vascular events and mortality showed a U-shaped association in several previous cohort studies, which emphasizes the necessity of including a lower threshold of HbA_{1c} (31,32). The possible causes for the lower level of HbA_{1c} in patients with diabetes include excessive control of blood glucose, restriction or poor intake of food, low hemoglobin or hemoglobinopathies, etc. Because the mean level of hemoglobin was 12.6 ± 2.2 mg/dL in the 1st quintile group, the accumulation of chronic hypoglycemia caused by improper dosing of antidiabetic medications or excessive food restriction were presumed to be a reason for the lower HbA_{1c}. Prolonged hypoglycemia could increase the risk of vascular complications by activating platelet aggregation and fibrinogen formation, increasing proinflammatory mediators (vascular cell adhesion molecule, ROS, inflammatory cytokines, and tumor necrosis factor-α), and inducing endothelial dysfunction (33). Patients with established vascular disease or arrhythmia are more susceptible to the adverse effects of hypoglycemia (34,35). In the current study, the proportion of stroke subtypes was as

Table 3—Procedure time and recanalization degree according to HbA_{1c} quintiles and a cutoff value of 7.0%

		HbA_{1c} quintiles						HbA_{1c} cutoff		
	Total	1st (≤6.1%)	2nd (>6.1–6.6%)	3rd (>6.6–7.1%)	4th (>7.1–7.9%)	5th (>7.9%)	*P* value	≤7.0%	>7.0%	*P* value
Patients, *n*	1,351	305	281	244	259	262		796	555	
Procedure time (min)	45 (27–74)	46.5 (28–80)	40 (22–70)	40.0 (26–8.5)	51.0 (35–0)	45 (28–4)	0.017	43 (25–70.5)	48 (30–8.0)	0.005
Successful recanalization (TICI ≥2b)	1,064 (78.8)	241 (79.0)	225 (80.1)	189 (77.5)	199 (76.8)	210 (80.2)	0.840	630 (79.1)	434 (78.2)	0.675
Incomplete	287 (21.2)	64 (21.0)	56 (19.9)	55 (22.5)	60 (23.2)	52 (19.8)	0.833	166 (20.9)	121 (21.8)	0.731
TICI 2b	421 (31.2)	104 (34.1)	82 (29.2)	70 (28.7)	80 (30.9)	85 (32.4)		244 (30.7)	177 (31.9)	
TICI 3	643 (47.6)	137 (44.9)	143 (50.9)	119 (48.8)	119 (45.9)	125 (47.7)		386 (48.5)	257 (46.3)	

Data are *n* (%) or median (interquartile range) unless otherwise indicated. *P* values by χ^2 test, Kruskal-Wallis test, and Wilcoxon rank sum test.

Table 4—Associations between HbA_{1c} levels at admission and functional outcome at 3 months

HbA_{1c} level	OR (95% CI)						Common OR (95% CI)		
	mRS 0–1 at 3 months			mRS 0–2 at 3 months			mRS at 3 months		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Quintile									
1st (≤6.1%)	0.58 (0.39, 0.86)	0.56 (0.37, 0.85)	0.59 (0.38, 0.91)	0.83 (0.59, 1.17)	0.83 (0.57, 1.21)	0.87 (0.58, 1.29)	0.86 (0.64, 1.14)	0.86 (0.64, 1.15)	0.91 (0.68, 1.23)
2nd (>6.1–6.6%)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
3rd (>6.6–7.1%)	0.90 (0.61, 1.33)	0.80 (0.52, 1.21)	0.84 (0.54, 1.31)	1.07 (0.75, 1.54)	0.97 (0.65, 1.43)	1.05 (0.69, 1.58)	1.05 (0.78, 1.42)	0.94 (0.69, 1.27)	0.99 (0.73, 1.35)
4th (>7.1–7.9%)	0.54 (0.36, 0.82)	0.40 (0.26, 0.63)	0.43 (0.27, 0.68)	0.95 (0.66, 1.35)	0.73 (0.49, 1.08)	0.81 (0.54, 1.22)	0.82 (0.61, 1.11)	0.63 (0.47, 0.85)	0.67 (0.49, 0.91)
5th (>7.9%)	0.62 (0.42, 0.94)	0.43 (0.28, 0.68)	0.47 (0.29, 0.75)	0.75 (0.52, 1.08)	0.49 (0.33, 0.73)	0.54 (0.35, 0.82)	0.79 (0.59, 1.06)	0.55 (0.41, 0.75)	0.59 (0.43, 0.80)
P value for overall effect	0.0069	<0.0001	0.0007	0.3159	0.0049	0.0218	0.2674	0.0002	0.0008
Cutoff									
≤7.0%	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
>7.0%	0.68 (0.52, 0.90)	0.51 (0.38, 0.69)	0.53 (0.39, 0.72)	0.82 (0.65, 1.04)	0.60 (0.46, 0.77)	0.63 (0.48, 0.83)	0.82 (0.67, 0.99)	0.62 (0.51, 0.75)	0.63 (0.52, 0.78)
P value for overall effect	0.0063	<0.0001	<0.0001	0.0993	0.0001	0.0008	0.0361	<0.0001	<0.0001

Model 1, unadjusted. Model 2, adjusted for age, sex, initial NIHSS, education level. Model 3, adjusted for age, sex, initial NIHSS, education level, ischemic stroke subtype, smoking status, history of hypertension, occlusion site, hemoglobin, total cholesterol, onset to groin puncture time, and degree of recanalization. Ref, reference.

follows: large artery atherosclerosis, 28.3%; and cardioembolism, 48.5%. Patients with large artery atherosclerosis had preexisting significant intra- or extracranial atherosclerosis, which is equivalent to established vascular disease. Most of the patients with cardioembolism had atrial fibrillation.

Our study has several limitations. Because we could not assess the status of acute glucose control during hospitalization, the effect of glucose treatment after ischemic stroke could not be analyzed. The harmful effects of prior exposure to chronic hyperglycemia may persist through epigenetic modifications (36). This metabolic memory effect could have an influence on functional recovery after stroke despite adequate glucose management during and after admission. Owing to the retrospective, registry-based observational nature of the study, the type of diabetes could not be assessed, and discriminating type 1 from type 2 was not feasible. However, the proportion of type 1 diabetes was estimated to be <5% among the total number of patients with diabetes, and the prevalence of type 1 diabetes in the entire Korean population has been shown to be small, ranging between 0.017 and 0.021% (37,38). Therefore, most of the study patients were presumed to have had type 2 diabetes. Additionally, the effect of unmeasured confounders cannot be ignored. Various factors, including socioeconomic status, premorbid cognitive function, marital status, caregiver support, and poststroke depression, could not be measured in this registry-based study and may affect functional recovery (39). Education level, which may partially reflect premorbid cognitive function and socioeconomic status, was adjusted to overcome this limitation. Education level is more closely related to functional recovery than income (40). The single-ethnicity population (East Asian) included in the current study may limit the generalizability of the findings.

In conclusion, better prestroke glucose control was associated with disability-free functional recovery in patients with diabetes receiving endovascular therapy for large vessel occlusive stroke. Prestroke glucose control with a target HbA_{1c} ≤7.0% (53 mmol/mol) may have beneficial effects on neurological recovery after stroke and subsequent IAT

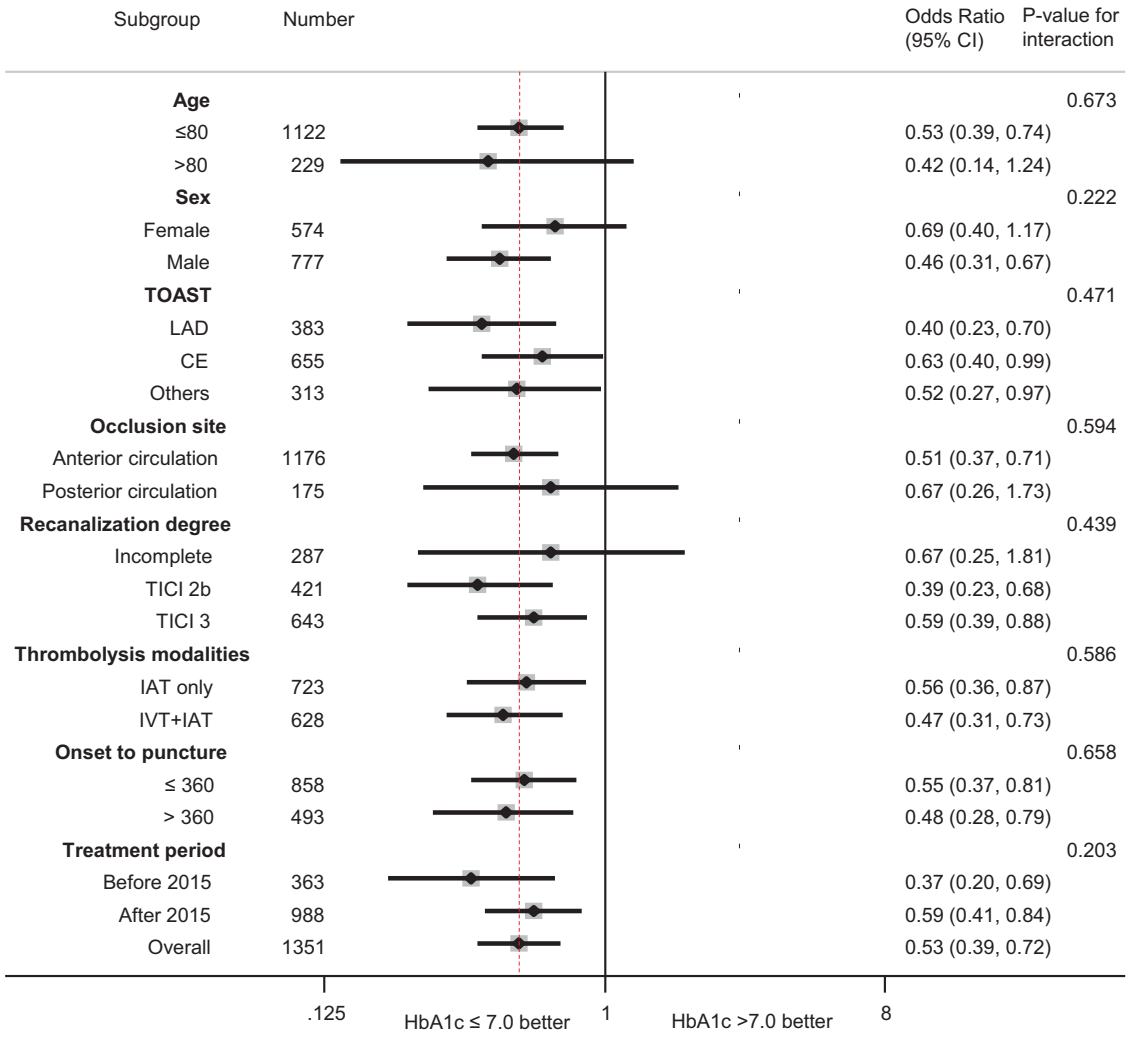

Figure 1—Influence of prestroke glucose control on neurological outcomes according to age, sex, stroke subtype, occlusion site, recanalization degree, thrombolysis modalities, time from symptom onset to groin puncture, and treatment period. CE, cardioembolism; LAD, large artery disease.

regardless of stroke subtype, bridging IVT, occlusion site, degree of recanalization, and treatment period. However, excessive glucose control with an HbA_{1c} ≤6.1% (43 mmol/mol) may reduce the chance of neurologic recovery and, therefore, should be avoided. IAT for large vessel occlusive stroke is also beneficial in diabetes. The current study emphasizes the importance of optimal prestroke glucose management among patients with diabetes to maximize the benefits of IAT.

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