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Pre-stroke glycemic control is associated with early neurologic deterioration in acute atrial fibrillation-related ischemic stroke

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ABSTRACT

Background: It has been suggested that AF-related ischemic stroke (IS) that is accompanied by atherosclerotic burden have poorer outcomes. The aim of this study was to investigate the importance of pre-stroke glycemic control (PSGC) on the early neurologic deterioration (END) of patients with acute AF-related IS.

Methods: We retrospectively recruited 121 patients with AF-related IS who also had Diabetes mellitus (DM). The HbA1C level was measured in all subjects. END was defined as an increase in the National Institute of Health Stroke Scale (NIHSS) score of 4 NIHSS points within 7 days of symptom onset compared to the initial NIHSS score.

Results: In this study, 20.7% (25 patients) were classified as having a poor PSGC status with a HbA1C level above 8.0%. In the univariate analysis, a poor PSGC status ($p < 0.01$), smoking ($p = 0.01$), severe neurologic deficits at admission ($p = 0.01$), and a larger size of ischemic lesions on DWI ($p < 0.01$) were associated with the occurrence of END. In the multivariate model, a poor PSGC status ($p = 0.02$) and larger size of ischemic lesions on MRI ($p < 0.01$) were independent predictors of END in acute AF-related IS.

Conclusion: The HbA1c level upon admission was independently associated with significant prediction of END in acute AF-related IS.

1. Introduction

Atrial fibrillation (AF) is the most common cause of cardioembolism (CE), [1] accounting for 77% of the high-risk cardiac sources of embolism in ischemic stroke (IS). AF-related IS exhibits higher recurrence and mortality than other IS types [2].

Unlike other etiologies of CE, AF is significantly influenced by the presence of systemic atherosclerosis, which initiates ischemic events. Recently, the presence of carotid plaques has been associated with an increased risk of ischemic stroke in individuals with AF [3]. Additionally, several studies reported an increase in CHADS2/CHA2DS2-VASc scores, indicating that the presence of systemic atherosclerosis was related to high mortality and poor outcomes in patients who experienced AF-related IS [4,5]. It suggested that the atherosclerotic burden might contribute to the progression of neuronal damage in acute AF-related IS. The presence of diabetes mellitus is an important factor in the progression of atherosclerosis. Several studies have demonstrated that a poor pre-stroke glycemic control (PSGC) state is associated with short- [6,7] and long-term outcomes after acute IS [8,9], regardless of the subtype [10].

Early neurologic deterioration (END) is a significant event encountered in acute IS, and the predictive factors of END have not yet been fully elucidated [11,12]. Recently, a poor PSGC state in patients with acute ischemic stroke has been shown to be associated with the occurrence of END [6,7]. The aforementioned studies were primarily performed in non-cardioembolic IS, such as those affecting the penetrating artery or brainstem infarctions. However, until now, it has been unclear whether the PSGC status might be a critical predictor of the presence of END in AF-related IS.

The aim of this study was to investigate the importance of PSGC in the early neurologic deterioration of patients with acute AF-related IS.

2. Methods

From January 2013 to December 2015, we retrospectively recruited AIS patients (within 24 h after their ischemic events) who were registered in the Dong-A University Stroke registry. In this study, we selected patients with CE based on TOAST classification [13] with MRI

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Table 1
Baseline characteristics of patients according to level of HbA1C.

		Total	HbA1C			p-Value
			6.0–6.9	7.0–7.9	≥ 8.0	
Total		121	73 (60.3)	23 (19.0)	25 (21.0)	
Sex	Male	61 (50.4)	31 (51.0)	12 (20.0)	18 (30.0)	0.04
	Female	60 (50.0)	42 (70.0)	11 (18.3)	7 (11.7)	
Age (yr)	Mean ± std	73.3 ± 8.6	74.4 ± 9.0	71.2 ± 7.5	72.2 ± 8.0	0.23
	Median (IQR)	74.0 (51.0–92.0)	75.0 (51.0–92.0)	73.0 (54.0–83.0)	73.0 (58.0–86.0)	0.20
	≤ 69	40 (33.1)	20 (50.0)	11 (28.0)	9 (23.0)	0.40
	70–79	54 (45.0)	34 (63.0)	8 (15.0)	12 (22.2)	
	≥ 80	27 (22.3)	19 (70.4)	4 (15.0)	4 (15.0)	
Hypertension	No	28 (23.1)	17 (61.0)	4 (14.3)	7 (25.0)	0.69
	Yes	93 (77.0)	56 (60.2)	19 (20.4)	18 (19.4)	
Smoking	No	107 (88.4)	67 (63.0)	20 (19.0)	20 (19.0)	0.27
	Yes	14 (12.0)	6 (43.0)	3 (21.4)	5 (36.0)	
Old_CAD	No	107 (88.4)	64 (60.0)	19 (18.0)	24 (22.4)	0.33
	Yes	14 (12.0)	9 (64.3)	4 (29.0)	1 (7.1)	
Old CVA	No	112 (93.0)	66 (59.0)	21 (19.0)	25 (22.3)	0.28
	Yes	9 (7.4)	7 (78.0)	2 (22.2)	0 (0.0)	
t-PA	No	80 (66.1)	45 (56.3)	15 (19.0)	20 (25.0)	0.25
	Yes	41 (34.0)	28 (68.3)	8 (19.5)	5 (12.2)	
Initial BP	Mean ± std	131.8 ± 21.4	133.0 ± 20.7	128.7 ± 24.6	131.2 ± 21.1	0.70
	Median (IQR)	130.0 (80.0–190.0)	130.0 (100.0–190.0)	120.0 (100.0–190.0)	130.0 (80.0–190.0)	
Initial NIHSS (quartile)	Mean ± std	9.38 ± 7.42	8.63 ± 6.61	9.91 ± 8.10	11.08 ± 8.89	0.34
	Median (IQR)	8.0 (0.0–28.0)	7.0 (0.0–26.0)	8.0 (0.0–25.0)	12.0 (0.0–28.0)	0.55
	≤ 2	28 (23.1)	15 (54.0)	7 (25.0)	6 (21.4)	0.41
	3–8	34 (28.1)	23 (68.0)	5 (15.0)	6 (18.0)	
	9–14	27 (22.3)	20 (74.1)	3 (11.1)	4 (15.0)	
	15–28	32 (26.4)	15 (47.0)	8 (25.0)	9 (28.1)	
Serum glucose (mg/dl) (quartile)	Mean ± std	158.83 ± 60.80	142.47 ± 45.01	159.78 ± 50.95	205.72 ± 83.19	< 0.01
	Median (IQR)	143.0 (66.0–461.0)	134.0 (77.0–272.0)	143.0 (66.0–260.0)	208.0 (73.0–461.0)	< 0.01
	≤ 117	31 (26.0)	23 (74.2)	4 (13.0)	4 (13.0)	< 0.01
	> 117–143	30 (25.0)	20 (67.0)	8 (27.0)	2 (7.0)	
	> 143–193	30 (25.0)	21 (70.0)	4 (13.3)	5 (17.0)	
	> 193	30 (25.0)	9 (30.0)	7 (23.3)	14 (47.0)	
LDL (mg/dl) (quartile)	Mean ± std	99.98 ± 36.08	102.56 ± 37.38	88.13 ± 25.94	103.46 ± 39.27	0.22
	Median (IQR)	99.5 (31.0–218.0)	102.0 (31.0–218.0)	81.0 (41.0–129.0)	96.5 (35.0–194.0)	0.31
	≤ 75	29 (24.2)	18 (62.1)	8 (28.0)	3 (10.3)	0.29
	> 75–99	31 (26.0)	15 (48.4)	6 (19.4)	10 (32.3)	
	> 99–119	31 (26.0)	20 (65.0)	6 (19.4)	5 (16.1)	
	> 199	29 (24.2)	20 (69.0)	3 (10.3)	6 (21.0)	
New AF	No	49 (40.5)	34 (69.4)	6 (12.2)	9 (18.4)	0.47
	Yes	72 (59.5)	39 (54.2)	17 (23.6)	16 (22.2)	
END	No	105 (87.0)	68 (65.0)	21 (20.0)	16 (15.2)	< 0.01
	Yes	16 (13.2)	5 (31.3)	2 (13.0)	9 (56.3)	
Size of DWI (CC) (quartile)	Mean ± std	40.31 ± 59.71	32.12 ± 51.34	34.38 ± 56.57	69.70 ± 76.47	0.02
	Median (IQR)	11.3 (0.0–270.0)	8.8 (0.0–241.4)	9.5 (0.0–200.0)	55.4 (0.2–270.0)	0.02
	≤ 2.61	31 (26.0)	21 (68.0)	6 (19.4)	4 (13.0)	0.18
	> 2.61–11.28	30 (25.0)	20 (67.0)	7 (23.3)	3 (10.0)	
	> 11.29–60.00	31 (26.0)	19 (61.3)	5 (16.1)	7 (23.0)	
	> 60.00	29 (24.0)	13 (45.0)	5 (17.2)	11 (38.0)	

Old CAD: previous history of coronary artery diseases, old CVA - previous history of cerebrovascular accident, initial BP - initial measurement of blood pressure at emergency room, LDL - low density lipoprotein, new AF - newly diagnosed atrial fibrillation after admission, END - early neurologic deterioration, DWI - diffusion weighted images.

screening. Additionally, we excluded patients with valvular heart disease among those patients with CE. For the purpose of the study, only the patients with an established diagnosis of DM at the time of hospital admission were included; DM was defined according to patients' self-reported histories or based on the use of a hypoglycemic drug or insulin.

For each patient, we recorded their age, sex, and the presence of vascular risk factors. A quantitative determination of plasma HbA1c (%) using high-performance liquid chromatography was performed for all patients as a PSGC parameter.

The stroke mechanism categories were classified using acute stroke treatment classification of the modified Trial of Org 10,172 in Acute Stroke Treatment. The local ethics review board approved this study.

Stroke severity was assessed by the National Institutes of Health Stroke Scale (NIHSS), which was performed in the emergency room. We measured NIHSS at 24 h, 72 h, and 7 days after admission and at discharge. Early neurological worsening was defined as an increase in the NIHSS score of ≥ 4 NIHSS points within 7 days of symptom onset compared to the initial NIHSS score. In patients with END, we took follow up images, including brain CT or MRI, to identify their causes.

2.1. MR imaging and analysis

MRI (1.5 T, Signa Echospeed Superconducting Imaging System; General Electric Medical Systems, Milwaukee, Wl, USA) images included T1, axial fluid-attenuated inversion recovery (FLAIR), three-dimensional time-of-flight MR angiography, axial diffusion-weighted imaging (DWI), and axial perfusion-weighted imaging (PWI). DWI was performed using echo-planar imaging (EPI) techniques. The edge of the DWI abnormality was visually identified using the trace of the diffusion coefficient, and regions of interest (ROIs) were outlined using a pixel-wise method.

Table 2
Univariate and multivariate analysis for an occurrence of END.

		Univariate		Multivariate	
		OR (95% CI)	p-Value	OR (95% CI)	p-Value
Constant				0.01 (0.00–0.07)	< 0.01
Sex	Male	1.00 (ref.)			
	Female	0.41 (0.13–1.27)	0.12		
Age (yr)	≤ 69	1.00 (ref.)			
	70–79	0.71 (0.21–2.38)	0.58		
	≥ 80	0.99 (0.25–3.88)	0.98		
Hypertension	No	1.00 (ref.)			
	Yes	0.89 (0.26–3.01)	0.85		
Smoking	No	1.00 (ref.)		1.00 (ref.)	
	Yes	4.85 (1.38–17.07)	0.014	4.42 (1.03–23.27)	0.05
Old CAD	No	1.00 (ref.)			
	Yes	0.47 (0.06–3.88)	0.48		
Old CVA	No	1.00 (ref.)			
	Yes	0.81 (0.09–6.93)	0.845		
t-PA	No	1.00 (ref.)			
	Yes	0.87 (0.28–2.70)	0.81		
New AF	No	1.00 (re.)			
	Yes	1.56 (0.54–4.49)	0.42		
Initial BP	≤ 130	1.00 (ref.)			
	> 130	1,01 (0.98–1.03)	0.52		
Initial NIHSS (median)	≤ 8	1.00 (ref.)		1.00 (ref.)	
	≥ 9	5.56 (1.49–20.67)	0.01	1.58 (0.14–4.02)	0.63
Serum glucose (quartile)	≤ 143	1.00 (ref.)		1.00 (ref.)	
	> 143	1.83 (0.62–5.41)	0.27	1.75 (0.14–4.02)	0.73
LDL (quartile)	≤ 99	1.00 (ref.)			
	> 99	0.63 (0.21–1.89)	0.41		
HbA1C	< 7.0	1.00 (ref.)		1.00 (ref.)	
	7.0–8.0	1.30 (0.23–7.17)	0.77	0.82 (0.08–8.68)	0.87
	> 8.0	7.65 (2.26–25.95)	< 0.01	6.72 (1.29–35.00)	0.02
DWI	(Continuous)	1.02 (1.01–1.03)	< 0.01	1.02 (1.01–1.03)	< 0.01
Number of observations used	121				
Likelihood ratio χ^2 (p-value)	30.829 (0.000)				
R^2; max-rescaled R^2	0.225; 0.415				

Significance variable selection from pre-univariate analysis.
Old CAD: previous history of coronary artery diseases, old CVA - previous history of cerebrovascular accident, initial BP - initial measurement of blood pressure at emergency room, LDL - low density lipoprotein, new AF - newly diagnosed atrial fibrillation after admission, END - early neurologic deterioration, DWI - diffusion weighted images.

2.2. Statistical analysis

All statistical analyses were performed using SAS 9.2. Categorical variables are represented as counts and relative frequencies, and numeric variables are represented as the mean ± standard deviation or median (Interquartile range, IQR).

We arbitrarily classified the study population into 3 groups according to their PSGC status as follows: good (6.0% ≤ HbA1c ≥ 6.9%), fair (7.0% ≤ HbA1c ≥ 7.9%) and poor (HbA1c ≥ 8.0%). The clinical characteristics among the PSGC groups were compared by logistic regression analysis, analysis of variance, or the Wilcoxon rank sum test.

To determine the independent factors that affect the occurrence of END in patients, a multivariate model was created using a backward elimination method, and the probability threshold for removal was set at 0.10. The ORs were also adjusted for the factors that affected the response variable. A p-value < 0.05 was considered statistically significant.

3. Results

During the observation period, 1986 acute IS patients were enrolled in our stroke registry. Among those patients, 466 patients were classified with CE. Of these patients, we selected 400 patients with acute AF-related IS after excluding other potential causes of CE, such as valvular heart diseases or acute MI. Finally, we enrolled 121 patients with acute AF-related IS who were diagnosed with DM at admission. Their mean age was 73.3 ± 8.6 years, and the median NIHSS was 8.0 (0.0–28.0). Among 121 subjects, 49 patients were taking anticoagulants upon diagnosis of AF, while the remaining 72 were newly diagnosed with AF after admission. Of the 121 enrolled patients, 25 patients (20.7%) exhibited poor PSGC (HbA1c ≥ 8.0%). Table 1 shows comparisons of the clinical, laboratory and radiologic findings according to their PSGC status. In the poor PSGC group, the neurologic severity expressed by NIHSS and frequency of END was significantly higher than in the good and fair PSGC groups. Regarding the size of ischemic lesions on DWI, those patients with a poor PSGC status (69.7 ± 76.5 CC, p = 0.02) had significantly larger lesions than those with a good (34.4 ± 56.6 CC) or fair (32.1 ± 51.3 CC) PSGC status.

During the 7-day observation period following ischemic events, 13.2% (16 patients) experienced END. Of those 16 patients with an END, 9 patients had stroke progression, 2 hemorrhagic transformation, and 1 early stroke recurrence. The prevalence of END in patients with poor PSGC status (9/25 patients, p < 0.01) was significantly higher than in patients with good (5/73 patients) an fair (2/23 patients) PSGC statuses.

In the univariate analysis, poor PSGC status (OR, 7.65; CI, 2.26–25.95; p < 0.01), smoking (OR, 4.85; CI 1.38–17.07; p = 0.01), severe neurologic deficit measured by NIHSS at admission (OR, 5.56; CI 1.49–20.67; p = 0.01), and larger size of ischemic lesions on DWI (OR, 1.02; CI, 1.01–1.033; p < 0.01) were associated with the occurrence of END. To determine the independent factors associated with the occurrence of END, a multivariate model was created using a backward elimination method, and the probability threshold for removal was set at 0.1 (Table 2). Smoking (OR4.42; CI, 1.03–23.27; p = 0.05), poor PSGC status (OR, 6.72; CI, 1.29–35.00; p = 0.02) and larger size of the ischemic lesions on DWI (OR, 1.02; CI, 1.01–1.03; p < 0.01) were

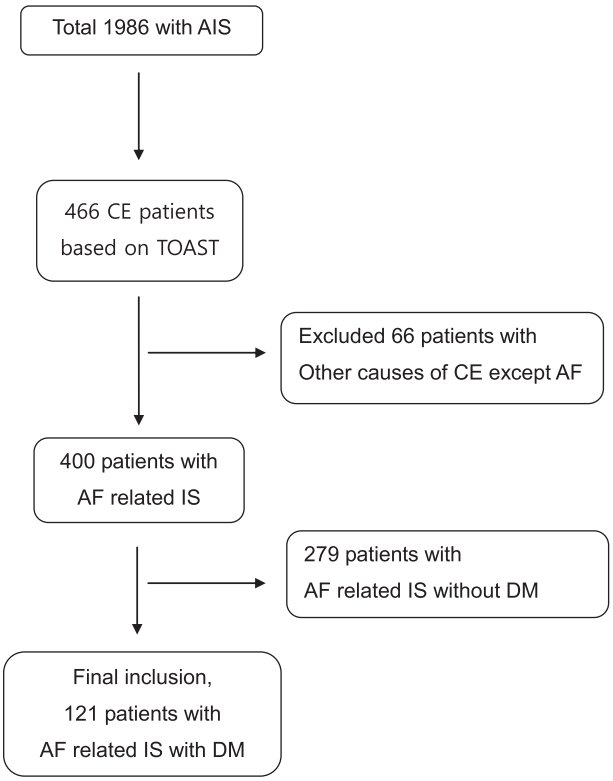

Fig. 1. Flow chart of the selection process of study subjects.

independent predictors for the occurrence of END in acute AF-related IS.

4. Discussion

In this study, the prevalence of END was 13.2% in patients with acute AF-related IS. Previous studies showed that its prevalence varies between 13 and 38% [14]. The proportion of patients with neurologic deterioration was slightly lower in the present study compared with previous reports. However, the incidences varied based on the chosen definition and characteristics of the populations used in each study. We investigated END alone in patients with CE caused by AF. It has been suggested that progression is most common in patients with large artery occlusive disease and least common in those with CE stroke [15], which is in agreement with our study.

Worsening of acute stroke has been correlated with high blood pressure, elevated serum glucose levels, ischemic lesions in the carotid artery territory, the stroke subtype of atherothrombotic infarctions and branch atheromatous disease (BAD), and high NIHSS [16]. Unlike our findings, many studies have indicated that an elevated initial glucose level was a powerful indicator for END after acute IS [17]. We were unable to fully explain this discrepancy, but we were able to suggest several possible causes. In previous studies of END in acute IS with DM, the initial glucose level was not an independent predictor for its occurrence [18]. We hypothesized that its influences on the occurrence of END might have been weakened in acute IS with DM. Supporting this, a meta-analysis investigating the impact of serum glucose levels on stroke outcomes also failed to show an association between the admission glucose levels and outcomes in DM patients [19].

We also noted differences in the methods used to check glucose levels in each study. Many studies on the relationship between hyperglycemia and neurologic outcomes after IS performed serial measurements of the glucose levels using a specialized continuous glucose monitoring system. In this study, we measured single casual glucose levels instead of performing continuous glucose monitoring. A previous report insisted that, in people with diabetes, clinicians should not rely on a single-point glucose estimate when assessing the independent impact of hyperglycemia on stroke outcomes because this value grossly underestimates the true glycemic profile [18]. Therefore, to predict the short- and long-term outcomes after stroke, it would be more suitable to monitor the state of pre-stroke glycemic control in DM patients. From this view point, the glycosylate hemoglobin A1, which reflects the average glycaemia over the previous 6–8 weeks, is a useful tool for predicting vascular damage and complications in diabetic patients [20,21].

A previous study showed that unregulated HbA1C levels detected on admission in patients with penetrating artery infarction [6] or brainstem infarction [7] are predictive of END. Based on the above findings, we hypothesized that poorly controlled diabetes may directly affect the process of neurologic deterioration in an adverse manner by causing AF-related IS (Fig. 1).

The mechanism by which poor glycemic control before onset is associated with END after acute AF-related IS has been unclear. We hypothesized that many mechanisms acted together to provoke END in AF-related IS with uncontrolled DM. Basically, poor PSGC status leads to larger ischemic lesions on DWI [6] as well as severe neurologic deficits [8] after acute IS. In this study, the size of ischemic lesions on DWI was much larger in the group with poorly controlled PSGC than in the other groups. Similar to previous studies of END after acute IS, severe and large ischemic lesions are associated with a higher chance of END occurrence after AIS. We believe that poor PSGC status might promote large ischemic lesions in patients with AF, which might have induced higher END in the poor PGSC group than in the good or fair PSGC groups in this study. The cause of larger ischemic lesions in AF-related IS patients with poorly controlled PSGC is multifactorial. Poorly controlled DM upregulates matrix metalloproteinase (MMP) and proteolytic activity [22]. The enhanced activity is involved in thrombogenesis in AF, which can cause a large cardioembolic stroke [23]. Additionally, the increased MMP activity promotes brain-blood barrier damage and leakage of serum components, [22] resulting in a higher chance of neurologic deterioration after acute IS. Additionally, chronic uncontrolled hyperglycemia that affects the structure and function of the vascular bed could hamper the blood supply to the salvageable penumbra and subsequently increase the susceptibility of ischemic regions to permanent neuronal damage.

In this study, the presence of smoking was a significant factor for the occurrence of END in AF-related IS, after adjusting for several confounding factors. We cannot precisely explain the effects of smoking on END after AF-related IS. Smoking itself induces the activation and release of inflammatory cells, increases acute phase protein or pro-inflammatory cytokines, causes hemostatic as well as coagulation disturbances and consequently leads to vascular vulnerability or endothelial damage in AF patients [24]. Therefore, we readily presumed that smoking might contribute to the occurrence of END after AF-related IS. However, more detailed studies will be required to confirm this.

Although this study provides some meaningful results, there remain some limitations. Because this was not a prospective study, we cannot rule out selection bias. Furthermore, it will be necessary to recruit a larger study population to confirm the study results. Additionally, we were not able to collect information about the onset of DM or the types of medications being used for glycemic control.

In conclusion, a poor PSGC state is associated with the occurrence of END in acute AF-related IS. This result suggests, as in atherothrombotic IS, that a poor PSGC state (HbA1C $>$ 8.0%) may serve as a useful predictor of short-term outcomes in cardioembolic IS.

Disclosures

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Otsuka Korea, Bayer Korea, ESAI-Korea, Daewoong Pharmaceutical Co. Ltd., Daichi Sankyo, Pfizer, Sanofi-Aventis Korea, AstraZeneca Korea; has served as a consultant or scientific advisory board for Bayer Korea, Boehringer Ingelheim Korea and Pfizer Korea; and has received lecture honoraria from AstraZeneca Korea, Bayer Korea, Novatis Korea, Ostuka Korea, Pfizer Korea, and Daichi Sankyo Korea (modest).

All authors report that they have no conflicts of interest to report.

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