Collagen-Induced Platelet Aggregates, Diabetes, and Aspirin Therapy Predict Clinical Outcomes in Acute Ischemic Stroke

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Background: Aggregation of platelets is a trigger for additional development of larger thrombi. This study aimed to identify factors that may affect platelet aggregability and their role in clinical outcomes in acute ischemic stroke. *Methods:* Consecutive acute ischemic stroke patients (n = 352) who were transferred within 24 hours after its onset were enrolled. Peripheral venous blood was sampled to measure platelet aggregability and other parameters. *Results:* Mean values of spontaneous small-sized platelet aggregates and collagen- or adenosine diphosphate (ADP)-induced large-sized aggregates were elevated in acute ischemic stroke. In atherothrombotic stroke (n = 178), collagen and ADP-induced large-sized aggregates were positively correlated with HbA1c, respectively. High incidence of the modified Rankin Scales (mRS) 5-6 at discharge was associated with diabetes complication (odds ratio [OR] 8.77, 95% confidence interval [CI] 1.32-57.56). The proportion of patients who were functionally independent (the mRS 0-2) at discharge was lower in the middle tertile of collagen and ADP-induced large-sized aggregates than their low tertile (OR 2.46, 95% CI 1.09-5.58; OR 2.43, 95% CI 1.05-5.59, respectively). Prestroke administration of aspirin recovered the proportion of independence at discharge (OR 0.25, 95% CI 0.06-0.99), and ameliorated incidence of the mRS 5-6. On logistic regression analysis, diabetes, HbA1c, collagen-induced large-sized aggregates, and prestroke administration of aspirin remained independent predictors of clinical outcomes in atherothrombotic stroke. In cardioembolic and lacunar stroke, no relations with clinical outcomes were found. *Conclusions:* High plasma level of HbA1c is involved in enhanced platelet aggregability in acute atherothrombotic stroke patients, and prestroke administration of aspirin may be beneficial to clinical outcomes.

Key Words: Spontaneous microaggregation of platelets—stroke—prognosis—albumin—modified Rankin scale

Introduction

Stroke is the third leading cause of death and is the major cause of disability in adults.[1,2] One of the specific treatment shown to improve outcome in patients with acute ischemic stroke is intravenous tissue plasminogen activator, but the therapeutic benefit of this treatment declines in the first few hours after stroke onset.[3] Aspirin has been used as a primary and a secondary strategy to prevent cardiovascular events including ischemic stroke in diabetic and nondiabetic individuals. Meta-analysis of large scale collaborative trials suggests that a low dose of aspirin should be used as a primary prevention strategy

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with diabetes that is at high risk for cardiovascular diseases.[4] In Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) trial[5] and the median 10-year follow-up of the JPAD trial and the JPAD2 study,[6] long-term therapy with low-dose aspirin did not affect cardiovascular events in Japanese patients with type 2 diabetes mellitus. However, whether these findings are broadly applicable to other patient populations remains uncertain. Early antiplatelet therapy is a cornerstone in the prevention of recurrent ischemic stroke and transient ischemic attacks (TIAs), although the responsiveness to antiplatelet medications varies among patients. The importance of very early treatment in both acute ischemic stroke and TIA has been further established in a recent time-course analysis of existing randomized trials.[7]

An important role of platelet macro- and microaggregation in systemic and brain circulation was demonstrated in patients with stroke and diabetes after the creation of a laser LS system for microaggregates.[8-10] Macroaggregation of platelets was formed after stimulation with collagen and adenosine diphosphate (ADP), whereas spontaneous microaggregation of platelets (SMAP) was formed under no stimulation with exogenous agonists which is frequently observed in stroke and diabetic patients.[11-13] Macro- and microaggregation of platelets is a trigger for additional development of larger thrombi leading to vascular occlusions, but its role in the disease pathogenesis and clinical outcomes in acute ischemic stroke remains to be determined. To detect high risk patients for thrombus formation, we enrolled the patients who were admitted to Hirosaki stroke and rehabilitation center after suffering from stroke in this study. We analyzed platelet aggregabilities and various parameters in acute stroke patients to reveal factors related to increased platelet aggregability. Furthermore, we investigated the relationship between platelet aggregability and clinical outcomes.

Methods

Study Patients

The protocol of the present study was approved by the ethics committee of the Hirosaki stroke and rehabilitation center, and informed consent was obtained from all patients or families. A total of 352 consecutive acute ischemic (only atherothrombotic, lacunar, and cardioembolic) stroke patients from April 2015 through March 2017 who were transferred to emergency room of the center within 24 hours after stroke onset were enrolled. The reason for limitation of a 24-hour window after stroke was to collect patients before receiving initial medical treatment to acute ischemic stroke. Indeed, no patients had undergone acute therapy until arrival to our center, because they were directly transferred to our center after confirmation of stroke attack. They underwent head computed tomography scan and magnetic resonance imaging, and the peripheral venous blood was sampled for the measurement of biochemical parameters before any treatments at arrival to the emergency room. NIHSS scale was assessed at admission and 1 week later to estimate stroke severity, and modified Rankin Scales (mRS) before stroke onset, at admission and discharge were scored (Table 1).

Table 1 shows clinical profiles of stroke patients. The types of 352 ischemic strokes were atherothrombotic stroke (n = 178), lacunar stroke (n = 60), and cardioembolic

Table 1. *Patients profile*

	Total (n = 352)	Atherothrombotic stroke (n = 178)	Cardioembolic stroke (n = 114)	Lacunar stroke (n = 60)
Age (years)	74 ± 12 (45-96)	74 ± 12 (45-90)	74 ± 12 (46-96)	74 ± 12 (46-88)
Height (cm)	158 ± 11 (130-185)	158 ± 11 (130-185)	158 ± 11 (130-184)	158 ± 11 (140-176)
Body weight (kg)	59 ± 12 (31-97)	59 ± 12 (31-90)	58 ± 12 (32-97)	59 ± 12 (41-93)
BMI	23 ± 4 (15-36)	23 ± 4 (16-36)	23 ± 4 (15-31)	23 ± 4 (17-35)
Gender (M/W)	213/139	109/69	67/47	37/23
<mRS (Admission)>				
0/1/2 (n)	21/49/65	13/28/32	6/9/14	2/12/19
3/4/5/6 (n)	31/127/46/0	20/61/17/0	7/47/29/0	4/19/0/0
<mRS (Discharge)>				
0/1/2 (n)	62/123/64	27/68/37	17/28/17	18/27/10
3/4/5/6 (n)	24/40/24/9	13/24/4/2	10/13/20/7	1/3/0/0
<Risk factor>				
Diabetes	106	67	20	19
Hypertension	283	147	86	50
Dyslipidemia	249	139	74	36
Atrial fibrillation	117	14	100	3
Congestive heart failure	32	4	27	1
Smoking	90	52	14	24
Alcohol	121	65	35	21

Abbreviations: mRS, modified Rankin Scales.

stroke (n = 114). Age, gender, and incidence of risk factors such as hypertension, dyslipidemia, and diabetes did not differ among the type of stroke. At admission, some stroke patients had been already administered aspirin (100 mg/day, n = 19, 4, and 7), thienopyridine (clopidogrel at 75-150 mg/day or ticlopidine at 100-200 mg/day, n = 14, 5, and 9), cilostazol (100-200 mg/day, n = 6, 0, and 1), and combined medicine (n = 6, 0, and 1) to prevent cardiovascular diseases in atherothrombotic, lacunar, and cardioembolic strokes, respectively.

At admission, 29 patients (atherothrombotic 7, lacunar 0, and cardioembolic stroke 22) received intravenous administration of tissue plasminogen activator in our hospital, and most of the patients were received conventional therapies such as antithrombotic and antiradical injections. The atherothrombotic or lacunar stroke patients were administered antiplatelet medicines, whereas the cardioembolic stroke patients were received direct oral anticoagulants during the course of observation.

Detection of Platelet Aggregates

Light intensities of small (9-25 μn), medium (25-50 μm), and large (50-70 μm)-sized platelet aggregates were measured by the laser light scattering aggregometer (model PA-200C; Kowa, Tokyo, Japan) immediately after sampling the peripheral venous blood. Briefly, platelet-rich plasma (PRP) was obtained from blood collected into sodium citrate (14 μmol/l) by centrifugation at 155 *g* for 12 minutes at room temperature, and the density of platelets in PRP was adjusted to 300,000 of platelets per microliter. We usually selected one reading of light scattering in PRP with 1 test, but in some cases, double sampling of 1 venous blood sample was performed in order to detect variability of the measurement on repetition. Platelet aggregation was determined by measuring the light scattering intensity on a PA-200 aggregometer. Platelet aggregates were observed under low shear stress conditions at a stirring speed of 1000 rpm (26 dyn/cm^2) without stimulation by an exogenous agonist or with stimulation by ADP at 2 μM or collagen at 1 μg/mL. The data were recorded as a 2-dimensional graph showing the change in total light intensity over time, expressed as a cumulative summation at 10-second intervals of scattered light intensity and the number of particles corresponding to that intensity in terms of particle size (volts × counts per second). The degree of platelet aggregates was described by the area under the curve of each detection line for 7 minutes. Area under the curve data were expressed as $\times 10^5$ particles.

We checked a number of factors that may have influenced collagen and ADP-induced large-sized platelet aggregates and SMAP. None of them were correlated with the time interval after stroke, the presence or absence of atherosclerotic diseases, and risk factors for atherosclerosis, suggesting that the timing of blood sampling may not influence the values of ADP-induced and collagen induced large platelet aggregates and SMAP if they are measured within 24 hours after stroke onset. Good reproducibility was found by double sampling of PRP.

Statistical Analysis

All results are expressed as mean ± standard deviation. Differences between groups were examined for statistical significance using analysis of variance. Relationships between 2 continuous variables were assessed by a regression analysis using the Pearson correlation coefficient and multivariate Cox regression analysis. Differences in items were analyzed by Chi-square test or Fisher's exact probability test. The level of significance was less than 0.05.

Results

Interaction Between Platelet Aggregation and Biochemical Parameters

Mean values (mV × count × min) of SMAP and collagen- or ADP-induced large-sized aggregates were 8.2 ± 1.2, 31.5 ± 10.4, and 47.7 ± 22.9 × 10^6 in ischemic stroke patients (n = 352), respectively. Values of age-matched control subjects (n = 343, mean age 71 years) complicated with 45%-10% of hypertension, dyslipidemia, diabetes, and smoking were 6.4 ± 7.6, 26.8 ± 14.2, and 40.7 ± 26.8 × 10^6, respectively. All of 3 kinds of platelet aggregability were elevated in acute ischemic stroke, and no difference was found among 3 types of ischemic strokes.

Table 2 shows the correlation of platelet aggregability with various items in patients with atherothrombotic, cardioembolic, and lacunar strokes. In atherothrombotic stroke, ADP-induced large-sized platelet aggregates tended to increase when HbA1c was increased (r = .13, P = .08). Collagen-induced large-sized platelet aggregates were correlated with HbA1c positively (r = .17, $P < .05$). In cardioembolic stroke, by univariate analysis, collagen-induced large-sized platelet aggregates were correlated with plasma albumin, triglyceride (TG), high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol positively, and with alanine transaminase negatively. Multivariable Cox regression analysis revealed that plasma TG was an independent predictor of collagen-induced large-sized platelet aggregability. In lacunar stroke, SMAP was correlated with plasma albumin negatively (r = −.29, P = .03).

Figure 1 demonstrated 4 correlation diagrams between ADP-induced large-sized platelet aggregates and HbA1c in atherothrombotic stroke (A), between collagen-induced large-sized platelet aggregates and HbA1c in atherothrombotic stroke (B), between collagen-induced large-sized platelet aggregates and TG in cardioembolic stroke (C), and between SMAP and albumin in lacunar stroke (D).

Table 2. *Correlation coefficient (r value) of univariate analysis between platelet aggregation and various items*

	Atherothrombotic stroke			Cardioembolic stroke			Lacunar stroke		
	SMAP	ADP	Collagen	SMAP	ADP	Collagen	SMAP	ADP	Collagen
Age	.03	.05	.03	.03	.10	.07	.04	.18	.04
Height	.01	.08	.02	.02	.08	.14	.07	.08	.10
Body weight	.09	0	.07	.02	.05	.07	.04	.02	.15
BMI	.13	.07	.10	.04	.01	.03	.01	.02	.11
SBP	.01	.06	0	.06	.15	.08	.14	.10	.2
DBP	.08	.05	.16	.09	.07	.18	.06	.01	.18
HR	.14	.05	.12	.03	.07	.14	.04	.07	.16
KT	.11	.12	.08	.10	.10	.11	.10	.01	.15
Alb	.09	.03	.18	.08	.12	.26*	.29*	.04	.23
TG	.03	.02	.05	.10	.11	.34*	.04	.12	.06
HDL-C	.13	.01	.10	.08	.07	.30*	.12	.11	.21
LDL-C	.16	.03	.05	.10	.11	.21*	.08	.11	.23
Cr	.01	.03	.03	.16	.21	.06	.05	.01	.23
T-Bil	.05	.04	.04	.03	.11	.01	.14	.10	.06
ALT	.12	.01	.05	.05	.12	.24*	.10	.13	.19
AST	.11	.08	.04	.07	.15	.09	.11	.10	.24
HbA1c	.01	.13+	.17*	.08	0	.13	.15	.01	.01
BNP	.23	.11	.01	.01	.01	.09	.09	.12	.02

Abbreviations: ADP, ADP-induced large-sized platelet aggregation; Alb: albumin; BNP, brain natriuretic peptide; Collagen, collagen-induced large sized platelet aggregation; Cr, creatinine; DBP, diastolic blood pressure; HR, heart rate; KT, korper temperature; SBP: systolic blood pressure; SMAP, spontaneous formation of platelet microaggregation; TG, triglyceride.

*$P < 0.05$.

+$P < 0.1$.

Platelet Aggregability and Clinical Outcomes in Acute Ischemic Stroke

Figure 2 shows the relationship between platelet aggregability and clinical outcomes. Disability was analyzed using the mRS, ranging from 0 (no symptoms) to 6 (death) with categories 0 through 2 collapsed into 1 category of functional independence and categories 3, 4, 5 (severe disability) and 6 collapsed into 1 category of disability or death. In atherothrombotic stroke, the proportion of patients who were functionally independent (score 0-2 on the mRS) was similar at admission among the first (low) through third (high) tertiles of collagen-induced large-sized aggregates. However, the proportion of patients achieving independence was lower at discharge in the second (middle) tertile of collagen-induced large-sized aggregates than the first (low) tertile of collagen-induced large-sized aggregates ($P < .05$ by Chi-square test; odds ratio [OR] 2.46, 95% confidence interval [CI] 1.09-5.58; relative risk [RR] 1.90, 95% CI 1.06-3.47) (Fig 2a). These relationships were also observed in ADP-induced large-sized aggregates in patients with atherothrombotic stroke ($P < .05$ by Chi-square test; OR 2.43, 95% CI 1.05-5.59; RR 1.91, 95% CI 1.04-3.61; Fig 2b). Frequency of aspirin and/or thienopyridine administration was similar among each tertile of collagen-induced and ADP-induced platelet aggregation. Being consistent with a positive correlation between HbA1c and collagen-induced large-sized platelet aggregates, complication of diabetes (n = 67) was associated with high incidence of the mRS 5 or 6 at discharge ($P < .05$ by Chi-square test; OR 8.77, 95% CI 1.32-57.56; Fig 2c). However, the proportion of patients achieving independence was higher at discharge in atherothrombotic stroke patients who were already administered aspirin before onset (n = 25) compared with those without aspirin (both $P < .05$ by Chi-square test; OR 0.25, 95% CI 0.06-0.99; RR 0.31, 95% CI 0.08-0.99; Fig 2d). These relations were not found in prestroke administration of P2Y12 antagonists, and cardioembolic and lacunar strokes.

When poor outcome was defined as higher scores of the mRS, logistic regression analysis identified the following independent predictors for clinical outcome: diabetes ($P < .001$), HbA1c ($P = .009$), collagen-induced large-sized aggregates ($P = .038$), and prestroke administration of aspirin ($P = .021$) in acute atherothrombotic stroke patients.

Discussion

The major findings of this study are discussed further. In atherothrombotic stroke patients, collagen, and ADP-induced large-sized aggregates were positively correlated with HbA1c. The proportion of patients who were functionally independent was lower at discharge in the middle tertile of collagen and ADP-induced large-sized aggregates than the low tertile of aggregates in patients with atherothrombotic stroke. In contrast, it was higher in patients with atherothrombotic stroke who were already administered aspirin before onset compared with those without aspirin. These relations on clinical outcomes were not found in cardioembolic and lacunar strokes.

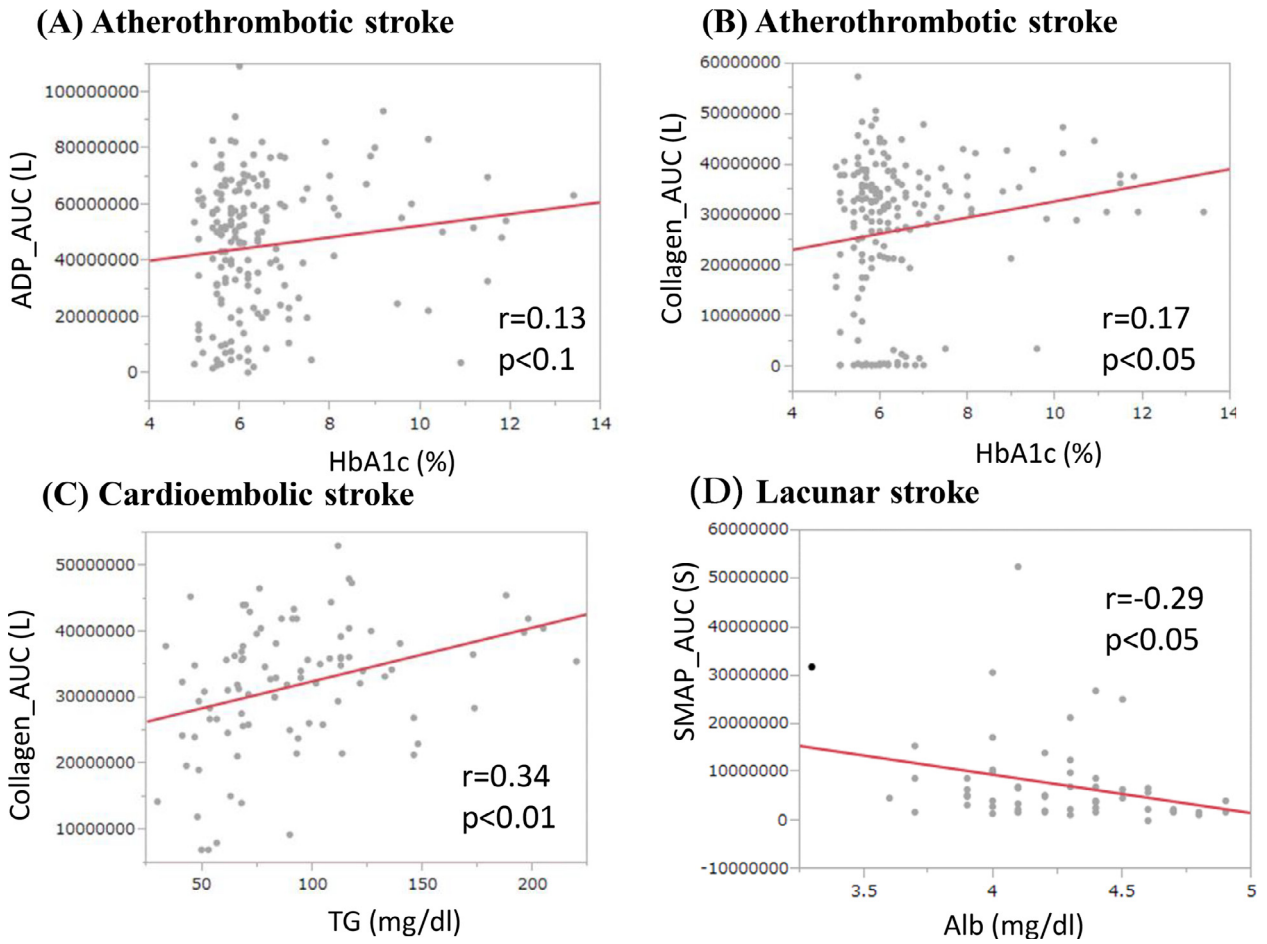

Figure 1. *Correlation diagrams between ADP-induced large-sized platelet aggregation and HbA1c in atherothrombotic stroke (A), between collagen-induced large-sized platelet aggregation and HbA1c in atherothrombotic stroke (B), between collagen-induced large-sized platelet aggregation and TG in cardioembolic stroke (C), and between SMAP and albumin in lacunar stroke (D).*

Factors Influencing Platelet Aggregation in Acute Atherothrombotic Stroke

We analyzed factors influencing platelet aggregability in acute ischemic stroke patients, and found that HbA1c was positively correlated with collagen- and ADP-induced large-sized platelet aggregates in atherothrombotic stroke, but not in cardioembolic stroke. This difference is thought to be based on distinct pathogenesis; collagen- and ADP-induced large-sized platelet aggregates are a trigger for additional development of larger thrombi leading to vascular occlusions in atherothrombotic stroke, whereas coagulants formation is due to atrial fibrillation in cardioembolic stroke.

Patients with type 2 diabetes mellitus were shown to have increased platelet aggregation in response to multiple concentrations of collagen and ADP compared to non-diabetic patients.[14] In diabetic children, the ratio between the polyunsaturated and saturated fatty acids in the TG fraction was reported to be negatively correlated to the maximal aggregation after 10 mg/l collagen stimulation,[15] suggesting that diabetes-related lipid impairment may be associated with 1 possible pathophysiology why patients with high HbA1c had high collagen-induced platelets aggregation. By intensive glucose control, ADP-induced platelet aggregation was shown to be reduced in diabetic patients in a subanalysis of the CHIPS Study.[14] Since insulin could modulate platelet activation through its receptor IRS-1,[16] the benefit of an intensive insulin therapy may be due to not only the P2Y12-ADP dependent pathway but also the P2Y12-ADP independent pathway. The superiority of P2Y12 antagonist over aspirin is controversial in atherosclerotic stroke. A recent prespecified exploratory subgroup analysis of the SOCRATES clinical trial demonstrated the superiority of ticagrelor, a P2Y12 antagonist, over aspirin in stroke/TIA patients with ipsilateral atherosclerotic stenosis.[17] In the COMPRESS study, there was no significant difference between combination medication consisting of clopidogrel and aspirin and aspirin alone in patients with acute ischemic stroke of the large artery atherosclerosis type according to the TOAST classification.[18] An analogous result was shown in the CHANCE-subgroup study in which the addition of clopidogrel to aspirin did not significantly alter the risk of recurrent stroke in patients.[19] In the present study,

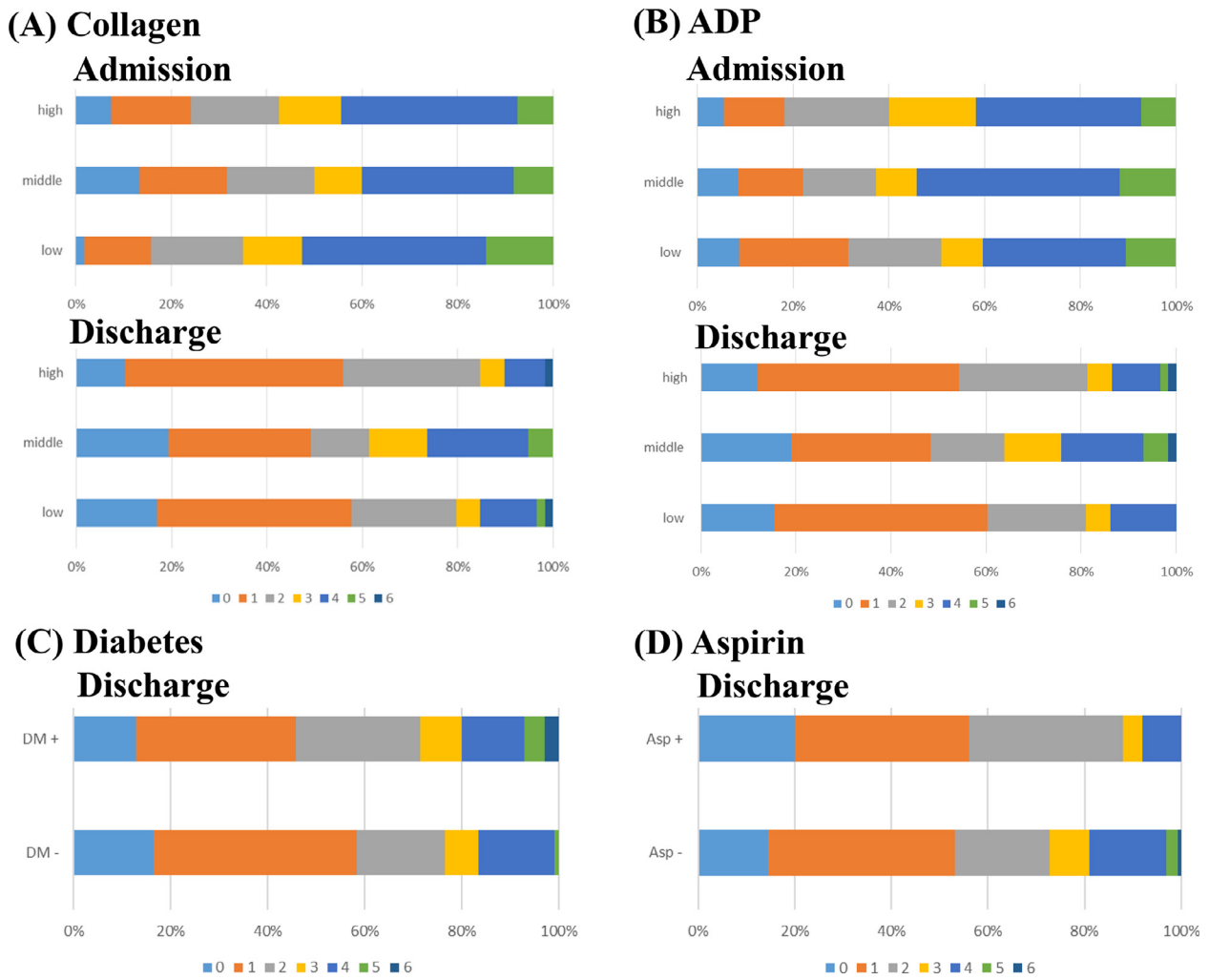

Figure 2. *Factors influencing modified Rankin Scales (mRS). (A) The mRS distribution of atherothrombotic stroke patients in tertiles of collagen-induced large-sized platelets aggregates at admission and discharge. (B) The mRS distribution of atherothrombotic stroke patients in tertiles of ADP-induced large-sized platelets aggregates at admission and discharge. (C) The mRS distribution of atherothrombotic stroke patients with or without diabetes at discharge. Diabetes − n = 111, Diabetes + n = 67. (D) The mRS distribution of atherothrombotic stroke patients with or without pre-stroke administration of aspirin. Aspirin − n = 153, Aspirin + n = 25.*

prestroke administration of P2Y12 antagonists did not affect clinical outcomes.

We investigated the relationship between collagen- or ADP-induced large-sized platelet aggregates to clinical outcomes, and found that the proportion of patients achieving independence was lower at discharge in the middle but not high tertile of collagen- and ADP-induced large-sized aggregates than the low tertile of collagen- and ADP-induced large aggregates. The reason why high tertile of platelet aggregates had less proportion of patients achieving independence must be due to preadministration of aspirin and/or P2Y12 antagonists. We, therefore, performed logistic regression analysis and showed diabetes, HbA1c, collagen-induced large-sized aggregates, and prestroke administration of aspirin as independent predictors for clinical outcomes. Platelet hyperreactivity to agonists' stimulation was already shown to be a marker for prognosis in patients with myocardial infarction.[20] To our knowledge, this study first showed that collagen- and ADP-induced large-sized platelet aggregates within 24 hours after stroke onset could predict clinical outcomes in acute atherothrombotic stroke patients.

It is intriguing that complication of diabetes was associated with high incidence of the mRS 5 or 6 at discharge in atherothrombotic stroke, but the proportion of patients who were functionally independent (score 0-2 on the mRS) was higher at discharge in the patients who were already administered aspirin before onset compared with those without aspirin. Previous JPAD trial investigated the effects of low-dose aspirin on primary prevention of cardiovascular events in patients with type 2 diabetes, and showed that low-dose aspirin as primary prevention did not reduce the risk of cardiovascular events.[5]

However, the combined end point of fatal coronary events and fatal cerebrovascular events occurred in 1 patient (stroke) in the aspirin group and 10 patients (5 fatal myocardial infarctions and 5 fatal strokes) in the nonaspirin group (hazard ratio, 0.10; 95% CI, 0.01-0.79; $P = .0037$). In the median 10-year follow-up of the JPAD trial and the JPAD2 study, long-term therapy with low-dose aspirin did not affect cardiovascular events in Japanese patients with type 2 diabetes mellitus and without preexisting atherosclerotic cardiovascular disease.[6] Whether these findings are broadly applicable to other patient populations remains uncertain, with international trials presently underway evaluating the utility of low-dose aspirin for primary cardiovascular prevention in patients with type 2 diabetes mellitus.

The present study provided a possibility that low-dose aspirin might fail to prevent stroke onset but could improve clinical outcomes in acute atherothrombotic stroke. When aspirin was already administrated before stroke onset to prevent cardiovascular diseases, clinical outcomes was better in acute atherothrombotic stroke. Thus, it is likely that very early antiplatelet therapy is important not only to prevent recurrent ischemic stroke and TIAs but also to have beneficial clinical outcomes in atherothrombotic stroke.

Factors Influencing Platelet Aggregation in Acute Cardioembolic or Lacunar Stroke

Plasma TG was correlated positively with collagen-induced large-sized platelet aggregates in cardioembolic stroke, and plasma albumin was correlated negatively with SMAP in lacunar stroke.

Concerning the association between lipids and platelet aggregability, lipid-lowering drugs, such as ezetimibe and simvastatin, were shown to decrease ADP and collagen-induced platelet aggregation.[21] Cholesterol depletion impairs microtubule ring formation and aggregate size, besides diminishing the extent of the open canalicular system and collagen-induced platelet ATP release.[22] Plasma low-density lipoprotein cholesterol contributes to a prothrombotic risk via enhanced platelet reactivity.[20] The influence of lipid emulsions on platelet function is a controversial issue: some studies describe an impediment of the platelet aggregation after an intravenous infusion of TGs[23] or after consuming high-linoleic acid diets.[24] Other studies had not found an influence of lipid emulsions containing n-3 fatty acid on platelet function[25,26] or after a diet with high linoleic acid versus high oleic acid.[27] Furthermore, previous studies showed that dietary intervention with oil rich fish reduces platelet-monocyte aggregation in man.[28] Overall, TG may accelerate platelet aggregability but some kinds of fatty acids such as n-3 fatty acid inhibit it.

Low serum albumin was shown to be an independent predictor for in-hospital mortality, severity of stroke, and clinical outcomes in patients with acute ischemic stroke.[29-32] However, ALIAS part 2 findings showed no clinical benefit of 25% albumin in patients with ischemic stroke.[33] P2Y12 receptor is associated with SMAP formation.[34] Therefore, antiplatelet therapy with P2Y12 receptor antagonists or cilostazol was reported to attenuate SMAP formation in type 2 diabetic patients who had an insufficient platelet response to aspirin.[12] However, prestroke administration of P2Y12 antagonists did not affect clinical outcomes in acute ischemic stroke. Recently, hyporesponse to clopidogrel was demonstrated in polymorphisms of the CYP2C19 gene. CYP2C19*2 could cause low active clopidogrel metabolite levels and might be associated with a low response to clopidogrel.[35,36] In a recent meta-analysis, it was found that the recurrent stroke or TIA risk was significantly higher in patients with high on treatment platelet reactivity, also known as nonresponders, and that its prevalence after clopidogrel administration was 27%.[37] Reticulated platelets also have garnered interest as a plausible explanation for hyporesponse to clopidogrel.[38]

In conclusion, high plasma level of HbA1c is involved in enhanced platelet aggregability in acute atherothrombotic stroke patients, and prestroke administration of aspirin may be beneficial to clinical outcomes.

Study Limitations

The present study had some limitations. It was unable to ascertain whether or not stroke onset is secondary to activated platelet profile because of the nature of the cross-sectional study. The present study also could not address whether or not enhanced platelet aggregability increases the frequency of stroke onset. The majority of stroke patients showed an altered profile of platelet activation including ADP- and collagen-induced platelet aggregation and SMAP. Given the growing concern over cardiovascular consequences in patients, further follow-up and intervention studies are needed to establish whether ADP- and collagen-induced platelet aggregation and SMAP is involved in stroke and a therapeutic target to prevent it.

Disclosures

None.

Conflict of Interest

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2019.05.021.

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