Association of Thrombelastographic Parameters with Complications in Patients with Intracranial Aneurysm After Stent Placement

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■ OBJECTIVE: **A prospective trial was conducted to investigate the platelet function and association between thrombelastographic (TEG) parameters and embolic or hemorrhagic complications in patients with intracranial aneurysm undergoing stent treatment.**

■ METHODS: **Between September 2013 and June 2016, we prospectively recruited patients with intracranial aneurysm who were treated with stent-assisted coiling. TEG parameters were used to assess the platelet function before stenting procedures. The primary study end point was the onset of ischemic stroke, transient ischemic attack, or silent ischemic events in the territory of the stented artery within 6 months after the procedure. The secondary end point was assessed by bleeding events.**

■ RESULTS: **Four hundred and thirty-one patients with 453 intracranial aneurysms were enrolled. A total of 519 neurovascular stents were implanted. During the follow-up, a total of 70 primary end points (16.2%) and 59 secondary end points (13.7%) were detected. Thromboembolic complications such as symptomatic and slient ischemic complications were more frequently observed in patients with large aneurysms (>10 mm, $P = 0.01$), lower adenosine diphosphate (ADP) inhibition rate ($P < 0.0001$), and higher ADP-induced platelet-fibrin clot strength (maximum amplitude of adenosine diphosphate [MA-ADP]) ($P < 0.0001$). Besides, based on multivariate analysis, a higher ADP inhibition ratio was identified as a significant independent predictor of subsequent bleeding events ($P < 0.0001$). According to the receiver operating characteristic curve analysis, the safe range of the ADP inhibition ratio and MA-ADP of the TEG analysis were identified as 29.45%—55.4% and <46.15, respectively.**

■ CONCLUSIONS: **The ADP inhibition ratio and MA-ADP of TEG analysis were associated with subsequent cerebral ischemic events and intracranial or extracranial bleeding events in patients with intracranial aneurysm after stent treatment.**

Key words
- Antiplatelet drug resistance
- Intracranial aneurysms
- Stent
- Thrombelastographic parameters

Abbreviations and Acronyms
AA: Arachidonic acid
ADP: Adenosine diphosphate
ADP%: Inhibition ratio of ADP
AUC: Area under the curve
CI: Confidence interval
LTA: Light transmission aggregometry
MA: Maximum amplitude
MA-AA: Maximum amplitude of arachidonic acid
MA-ADP: Maximum amplitude of adenosine diphosphate
OR: Odds ratio
ROC: Receiver operating characteristic curve
TEG: Thromboelastography

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INTRODUCTION

Stent treatment technology has emerged as a viable and preferable method for wide-necked, complex-shaped, and dissecting intracranial aneurysms.[1] Neurovascular stents not only protect coils to protrude into the parent artery, but also create a mesh for endothelialization.[2,3] Several studies have demonstrated that cerebral infarction is one of the major disabling complications (range, 3.7%—21%) of neurovascular stent treatment.[4-7] Dual antiplatelet therapy (100 mg of aspirin and 75 mg of clopidogrel daily) has been used as the standard protocol to decrease the incidence of thromboembolic complications in intracranial aneurysms that are treated with stents. However, there is great variability in the activation of the antiplatelet drugs (especially clopidogrel). A portion (7%—40%) of patients with high on-treatment platelet reactivity during the standard antiplatelet preparation had it occur in thromboembolic events.[8-11] Therefore, platelet function testing may be necessary. As a monitoring technique for global hemostasis, thromboelastography (TEG) (model 5000 [Haemoscope Corp., Skokie, Illinois, USA]) has been widely used to assess clot formation and test the inhibitory response of antiplatelet agents.[12,13]

The literature has focused on the efficiency of TEG in monitoring platelet function among patients with acute coronary syndrome or ischemic stroke undergoing stent placement.[13-15] Compared with studies of cardiovascular disease or cerebral ischemic stroke, there are few reports referring to the use of TEG in intracranial aneurysms. Yang et al.[4,12] demonstrated the effectiveness of TEG with the inhibition ratio of ADP (ADP%) and maximum amplitude of adenosine diphosphate (MA-ADP) (ADP-induced clot strength). Besides, the experience of individualized antiplatelet therapy and standard predictors of drug efficiency have not been well investigated. In this study, we sought to identified the association of TEG parameters with subsequent ischemic and bleeding complications in patients with intracranial aneurysm treated with neurovascular stents, and to measure the safe range of TEG platelet mapping assay.

METHODS

Patient Population

We prospectively recruited patients with intracranial aneurysm undergoing stent treatment between September 2013 and June 2016. All patients gave written informed consent to participate. The privacy of patients was strictly protected. The protocol of this study was approved by our ethics committee. Inclusion criteria were as follows: 1) 18—80 years of age, 2) wide-necked or dissecting intracranial aneurysm, and 3) treatment with neurovascular stent. Exclusion criteria included the following: 1) treatment with anticoagulants, thrombolytic agents, and other antiplatelet drugs within 2 weeks; 2) acute ruptured aneurysm; 3) use of tirofiban during the procedure; 4) severe cardiovascular disease or cerebral ischemic stroke; 5) significant coagulopathy; 6) severe hepatic or renal dysfunction, malignant disease, chronic inflammatory disease, or an infectious condition at study entry; and 7) missing the clinical follow-up. The baseline demographic information, including age, sex, clinical presentation, cerebrovascular risk factors (smoking and drinking history, diabetes, hypertension, and hypercholesterolemia), and aneurysm characteristics (location, size, and occlusion grade), were recorded.

Dual Antiplatelet Regimen

All recruited patients received standard dual antiplatelet therapy (clopidogrel: 75 mg/d; aspirin: 100 mg/d) for at least 3 days before stent placement. After the endovascular procedure, patients were given clopidogrel (75 mg/d) for 2 months and aspirin (100 mg/d) for at least 6 months.

Platelet Function Testing

Platelet function testing was available in all patients. The baseline blood samples were drawn before the administration of standard dual antiplatelet therapy (aspirin and clopidogrel). To assess preoperative platelet inhibition, the secondary blood samples were collected immediately prior to procedures. The TEG hemostasis system was used to test platelet inhibition. The agonists of adenosine diphosphate (ADP) and arachidonic acid (AA) were added to measure the platelet inhibition of the P2Y12 receptor and cyclooxygenase pathways. The maximum amplitude (MA) represents the MA with thrombin-stimulated platelets and fibrin meshwork (maximum clot strength). The ADP% and MA-ADP (ADP-induced clot strength) were used to measure the response to clopidogrel. The inhibition ratio of AA and maximum amplitude of arachidonic acid (MA-AA) (AA-induced clot strength) measured the aspirin effect.

Endovascular Procedures

Endovascular procedures were performed under general anesthesia. During procedures, a bolus of heparin was administered using 3000 IU, and then 1000 IU/h. Three types of stents (LVIS [MicroVention, Inc.], Enterprise [Codman Neurovascular, Raynham, Massachusetts, USA], and Solitaire AB [ev3 Neurovascular, Irvine, California, USA]) were used to treat aneurysms. The occlusion grade was assessed for every aneurysm by the 3-point Raymond-Roy Scale (complete occlusion, neck remnant, and residual sac) combining with the stent alone. We considered the residual neck (<2 mm or Raymond-Roy Scale class II) as the near-complete occlusion.

Clinical End Points

The primary end point was the incidence of cerebral ischemic events during the 6-month follow-up. The ischemic events included symptomatic ischemic complications, such as a newly developed transient ischemic attack or permanent ischemic infarctions within the period of antiplatelet therapy, and clinically silent acute thromboembolic phenomena, which was in the territory of the stented vessel, as represented by diffusion restriction on post-procedural diffusion-weighted imaging. All magnetic resonance imaging was independently reviewed by 2 neuroradiologists. The secondary end point was defined as the bleeding events which presented as the intracranial hemorrhage or any hemorrhage outside the cranium that appeared once patients received antiplatelet therapy and remitted as long as they stopped treatment. If an end point was secondary to the other end point, we identified the first one as the clinical end point that was needed by research.

Statistical Analysis

Data are presented as mean ± SD or expressed in terms of frequency and percentage. Analyses of independent sample *t* tests and χ^2 tests or Mann-Whitney rank-sum tests were used to test for differences among groups for continuous and categorical variables, respectively. Receiver operating characteristic curve (ROC) analysis was performed to identify the best discriminatory level of ADP% or AA inhibition ratio, MA-ADP, and MA-AA associated with the cerebral ischemic events and bleeding events. Univariate and multivariate logistic regression analysis was used to evaluate the significance of variables concerning the cerebral ischemic

Table 1. Characteristics of the Study Population

Characteristics	Value	%
Age (years)		
Range	18–79	
Mean ± SD	53.8 ± 9.6	
Sex		
Female	278	64.5
Male	153	35.5
Hemorrhagic history	53	12.3
Hypertension	202	46.9
Hyperlipidemia	38	8.8
Diabetes mellitus	33	7.7
Smoker	100	23.2
Alcohol intake	76	17.6
Location		
Anterior circulation	366	80.8
Posterior circulation	87	19.2
Aneurysm size		
≥10 mm	128	28.3
<10 mm	325	71.7
Aneurysm type		
Saccular	348	76.8
Dissecting	67	14.8
Fusiform or anomalous	38	8.4
Occlusion grade		
Complete	302	66.7
Near complete	105	23.2
Partial complete	15	3.3
Stent alone	31	6.8
Stent type		
Enterprise	306	58.9
LVIS	126	24.3
Solitaire AB	87	16.8

Values are number of patients or as otherwise indicated.

events and bleeding events occurring during the follow-up period. $P < 0.05$ was considered statistically significant. The statistical analysis was performed by SPSS 17.0 software (SPSS Inc., Chicago, Illinois, USA).

RESULTS

General Characteristics

Four hundred and thirty-one patients with 453 intracranial aneurysms were enrolled. A total of 519 neurovascular stents were implanted. In most patients (n = 361, 83.7%) 1 stent was placed; 55 patients (12.8%) had 2 stents, and 15 patients (3.5%) had at least 3 stents. There were 278 women (64.5%) and 153 men

Table 2. Comparison of Baseline Characteristics and Clinical Variables in 431 Cases with and without Ischemic Events

Demographic Data	Ischemic Group (n = 70; 16.2%)	Nonischemic Group (n = 361; 83.8%)	*P* Value
Age	54.7 ± 9.9	53.7 ± 9.5	0.384
Female	52 (74.3)	226 (62.6)	0.076
Medical history			
Hypertension	40 (57.1)	162 (44.9)	0.067
Hyperlipidemia	5 (7.1)	33 (9.1)	0.656
Diabetes mellitus	3 (4.3)	30 (8.3)	0.329
Rupture	7	46	0.562
Aneurysm location			0.742
Anterior circulation	58	308	
Posterior circulation	12	75	
Aneurysm size			0.01
≥10 mm	29	99	
<10 mm	41	284	
Aneurysm type			0.126
Saccular	55	293	
Dissecting	6	61	
Fusiform or anomalous	9	29	
Occlusion grade			0.249
Complete	44	258	
Near complete	17	88	
Partial complete	5	10	
Stent alone	4	27	
Stent type			0.725
Enterprise	50	256	
LVIS	24	102	
Solitaire AB	13	74	
Platelet inhibition			
ADP%	18.8 ± 15.7	39.0 ± 25.7	<0.0001
MA-ADP	53.0 ± 10.9	42.8 ± 14.8	<0.0001
AA%	82.4 ± 28.2	84.1 ± 22.2	0.611
MA-AA	20.5 ± 14.9	18.0 ± 13.8	0.176

Data are shown as mean ± SD, number of patients (%), number of patients, or as otherwise indicated.
ADP%, percentage inhibition of adenosine diphosphate; MA-ADP, maximum amplitude of adenosine diphosphate; AA%, percentage inhibition of arachidonic acid; MA-AA, maximum amplitude of arachidonic acid.

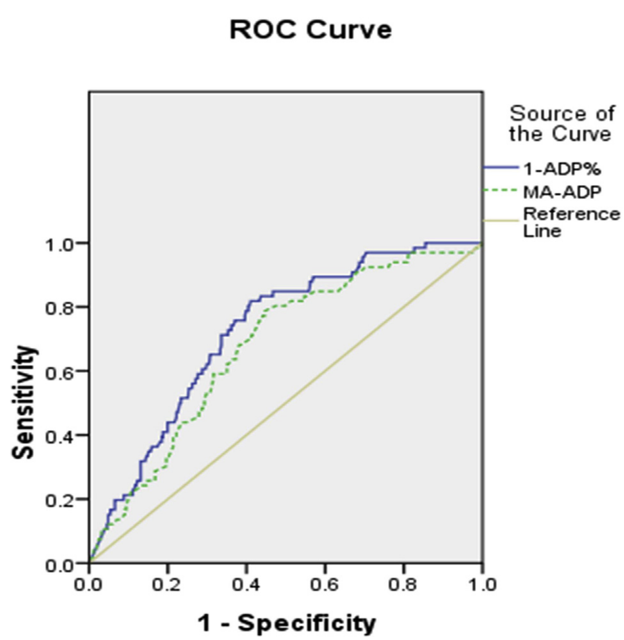

Figure 1. Receiver operating characteristic curve for percentage inhibition of adenosine diphosphate and maximum amplitude of adenosine diphosphate in cerebral ischemic events. ADP%, percentage inhibition of adenosine diphosphate; MA-ADP, maximum amplitude of adenosine diphosphate; ROC, receiver operating characteristic curve.

(35.5%), and the mean age ranged from 18 to 79 years (mean ± SD, 53.8 ± 9.6 years). The patient characteristics and aneurysm features are listed in **Table 1**.

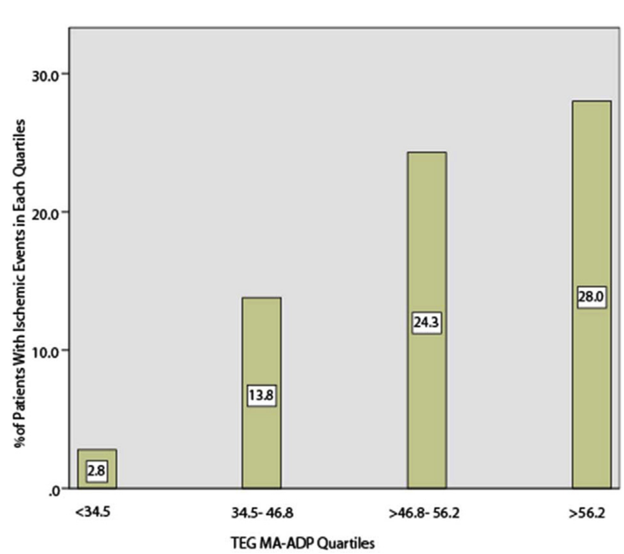

Figure 2. Quartile distribution of cerebral ischemic events for thromboelastography maximum amplitude of adenosine diphosphate. MA-ADP, maximum amplitude of adenosine diphosphate; TEG, thromboelastography.

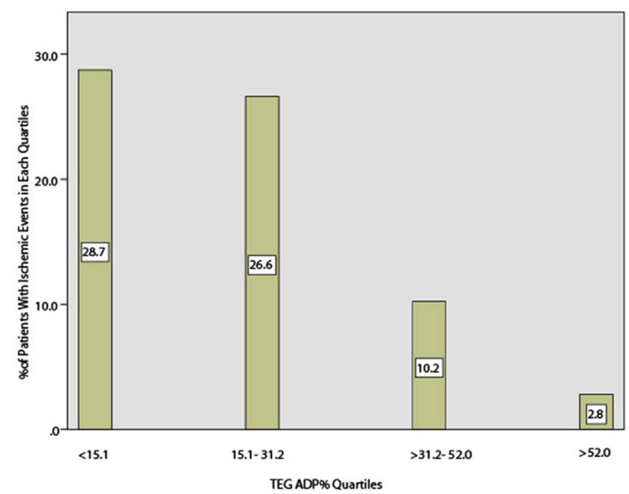

Figure 3. Quartile distribution of cerebral ischemic events for thromboelastography percentage inhibition of adenosine diphosphate. ADP%, percentage inhibition of adenosine diphosphate; TEG, thromboelastography.

Ischemic Events Occurrence

During a mean clinical follow-up of 424.5 ± 290.7 days (range, 1–1147 days), 70 primary end point events (16.2%), including 24 (5.6%, 24/431) symptomatic ischemic complications and 46 (10.6%, 46/431) silent ischemic events, were detected. Fifty-three ischemic events (75.7%) occurred within 7 days of stenting procedures and 17 (24.3%) occurred after 7 days.

There were no statistical differences in age, sex, medical history, hemorrhagic history, aneurysm type, occlusion grade, and stent type between the nonischemic group and cerebral ischemic events group. Thromboembolic complications were more frequently observed in patients with large aneurysms ($P = 0.01$), lower ADP% ($P < 0.0001$), and higher MA-ADP ($P < 0.0001$) (**Table 2**). In contrast, no significant differences were found in the AA inhibition ratio and MA-AA between the ischemic group and nonischemic group. The association of platelet function parameters and ischemic events was assessed with ROC analysis. The results showed that the ADP% (area under the curve [AUC] of inverted ADP% [1 − ADP%], 0.724; 95% confidence interval [CI], 0.665–0.784; $P < 0.0001$) and MA-ADP (AUC, 0.676; 95% CI, 0.61–0.741; $P < 0.0001$) had good predictive value of cerebral ischemic events (**Figure 1**). After the adjustment for analysis of the sensitivity and specificity of different ADP% and MA-ADP tangent points, the cutoff point of MA-ADP was 46.15 with a specificity of 55.3% and for ADP% it was 29.45% with a specificity of 59.0%. Quartile analysis also demonstrated a higher incidence of ischemic events in the higher quartiles of MA-ADP (**Figure 2**). For the ADP%, higher quartiles were associated with a lower incidence of ischemic events (**Figure 3**). According to the univariate logistics regression analysis using the ROC cut point, MA-ADP ($P < 0.0001$; OR, 6.072; 95% CI, 3.153–11.693), ADP% ($P < 0.0001$; OR, 7.719; 95% CI, 3.922–15.191), and aneurysm size (diameter >10 mm) ($P = 0.011$; OR, 1.985; 95% CI, 1.172–3.361) were associated with cerebral ischemic events. On multivariate

Table 3. Risk Factors of Cerebral Ischemic Events After Embolization Procedures

	Univariate Logical Regression Analysis			Multivariate Logical Regression Analysis		
Variables	**OR**	**95% CI**	***P* Value**	**OR**	**95% CI**	***P* Value**
Age	0.962	0.546—1.695	0.894	-	-	-
Sex	0.698	0.416—1.173	0.175	-	-	-
Hypertension	1.638	0.977—2.746	0.061	-	-	-
Hyperlipidemia	0.765	0.288—2.032	0.59	-	-	-
Diabetes mellitus	0.494	0.147—1.666	0.256	-	-	-
Aneurysm size	1.985	1.172—3.361	0.011	1.473	0.771—2.816	0.241
Aneurysm location	1.323	0.661—2.649	0.43	-	-	-
Aneurysm morphology	1.042	0.701—1.549	0.84	-	-	-
Type of stents	0.917	0.68—1.238	0.573	-	-	-
Complete occlusion	1.04	0.769—1.406	0.80	-	-	-
ADP% <29.45%	7.719	3.922—15.191	<0.0001	4.722	1.642—13.585	0.004
MA-ADP >46.15	6.072	3.153—11.693	<0.0001	0.601	0.217—1.664	0.327

OR, odds ratio; CI, confidence interval; ADP%, percentage inhibition of adenosine diphosphate; MA-ADP, maximum amplitude of adenosine diphosphate.

logistics analysis, ADP% was the independent risk predictor of ischemic events ($P = 0.004$; OR, 4.722; 95% CI, 1.642—13.585) (Table 3). Kaplan-Meier event-time curves depicted the occurrence of cerebral ischemic end points and indicated the association of these events with parameters by a cutoff point of ADP% 29.45 (Figure 4) and MA-ADP 46.15 (Figure 5).

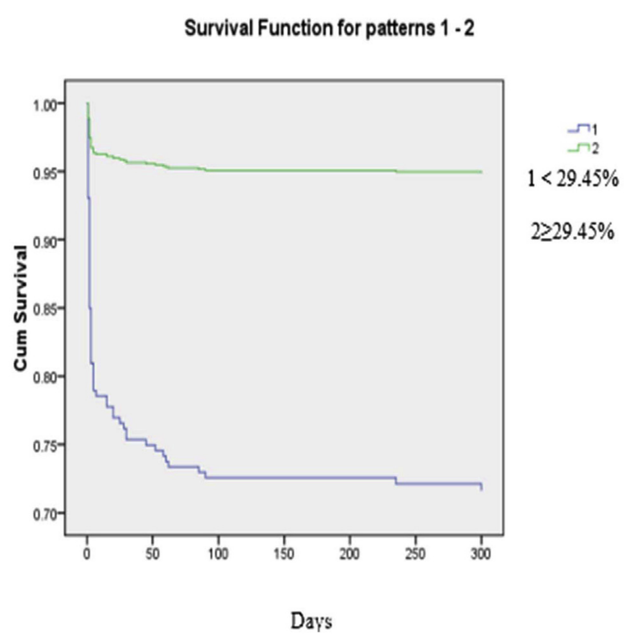

Figure 4. Survival function: Kaplan-Meier event time curves demonstrated the association between ischemic events and platelet function parameters, which was identified by percentage inhibition of adenosine diphosphate, with a cutoff point of 29.45%. Cum, cumulative.

Bleeding Events

Fifty-nine patients experienced bleeding events, which consisted of 15 intracranial hemorrhages (25.4%) and 44 hemorrhages

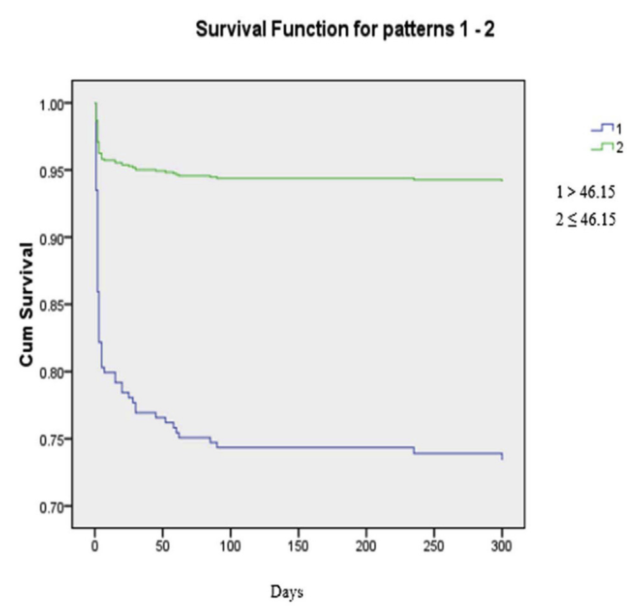

Figure 5. Survival function: Kaplan-Meier event time curves demonstrated the association between ischemic events and platelet function parameters, which was identified by maximum amplitude of adenosine diphosphate with a cutoff point of 46.15. Cum, cumulative.

Table 4. Comparison of Baseline Characteristics Between Bleeding and Nonbleeding Groups

Demographic Data	Bleeding Group (n = 59; 13.7%)	Nonbleeding Group (n = 372; 86.3%)	*P* Value
Age	54.1 ± 9.3	53.8 ± 9.7	0.791
Female	37 (62.7)	241 (64.8)	0.771
Medical history			
Hypertension	29 (49.2)	173 (46.5)	0.779
Hyperlipidemia	7 (11.9)	52 (13.9)	0.456
Diabetes mellitus	2 (3.4)	31 (8.3)	0.206
Platelet inhibition			
ADP%	60.7 ± 27.2	31.8 ± 22.8	<0.0001
MA-ADP	31.8 ± 15.6	46.4 ± 13.5	<0.0001
AA%	88.7 ± 23.5	83.0 ± 25.9	0.112
MA-AA	16.2 ± 14.4	18.8 ± 13.9	0.198

Data are mean ± SD, number of patients (%), or as otherwise indicated.
ADP%, percentage inhibition of adenosine diphosphate; MA-ADP, maximum amplitude of adenosine diphosphate; AA%, percentage inhibition of arachidonic acid; MA-AA, maximum amplitude of arachidonic acid.

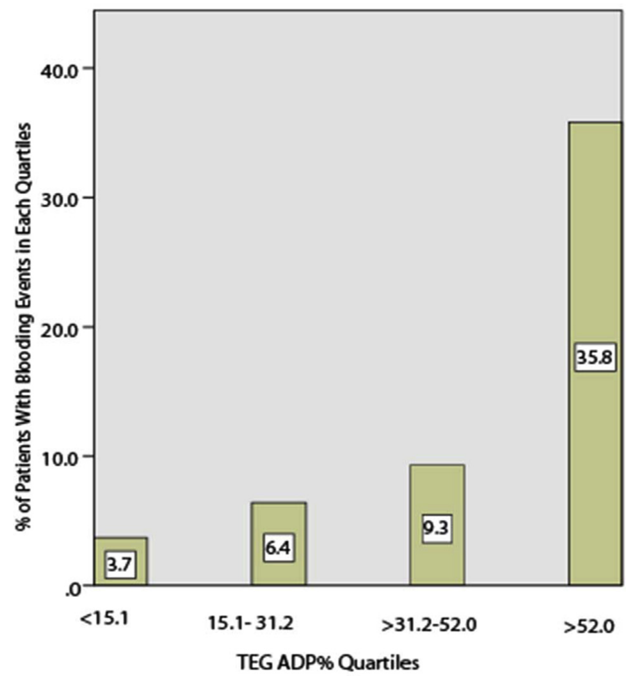

Figure 6. Quartile distribution of bleeding events for thromboelastography percentage inhibition of adenosine diphosphate. ADP%, percentage inhibition of adenosine diphosphate; TEG, thromboelastography.

outside the cranium (74.6%). Thirty of the bleeding events (50.8%) occurred within 7 days after the stenting procedures, and the remaining 29 cases (49.2%) occurred between 7 days and 6 months of follow-up.

There were significant statistical differences between the bleeding events group and nonbleeding events group on ADP% (60.7 ± 27.2 vs. 31.8 ± 22.8, P < 0.0001) and MA-ADP (31.8% ± 15.6% vs. 46.4% ± 13.5%, P < 0.0001), respectively. No significant differences were found in the AA inhibition ratio (P = 0.112) and MA-AA (P = 0.198) referring to bleeding events between these 2 groups (**Table 4**). Quartile analysis also showed a higher incidence of bleeding events in the higher quartiles of ADP % (**Figure 6**). For MA-ADP, lower quartiles were associated with a higher incidence of bleeding events (**Figure 7**). ROC analysis was used to assess the association of platelet function parameters and bleeding events. According to the adjustment of the sensitivity and specificity of different platelet function parameters, ADP% (AUC, 0.633; 95% CI, 0.545–0.722; P = 0.005) and MA-ADP (AUC, 0.395; 95% CI, 0.311–0.479; P = 0.026) had the better predictive value of bleeding events (**Figure 8**). The cutoff point of ADP% was identified as 55.4% with a specificity of 80.3%. The proportion of patients with ADP% >55.4% was 22.3% (96/431). The incidence of bleeding events in patients with ADP% >55.4% was significantly higher than in patients with ADP% ≤55.4% (39.6% vs. 6.3%, respectively; P < 0.0001). Based on univariate logistics regression analysis, ADP% >55.4% (P < 0.0001; OR, 9.796; 95% CI, 5.365–17.887) was associated with bleeding events (**Table 5**). The association of bleeding events with parameters (ADP% >55.4%) was demonstrated by Kaplan-Meier event-time curves (**Figure 9**).

Among these bleeding events, 15 cases (25.4%, 15/59) were intracranial hemorrhages, which were detected with computed tomography scan after embolization procedures. The results of univariate logistics regression analysis indicated that ADP% >55.4% (P = 0.006; OR, 4.26; 95% CI, 1.504–12.068) might played a role in the occurrence of intracranial hemorrhage (**Table 6**).

DISCUSSION

Ischemic and hemorrhagic complications of stent placement technology cannot be ignored. Lee et al.[16] reported a 13.8% procedural complication rate. In other studies, the ischemic complication rate ranged from 4% to 28%.[17-19] The ischemic complications in our study were consistent with small microemboli causing small vessel occlusions because all these lesions were detected in the perfusion territory of the parent artery. There were multiple theoretical sources for embolic events during endovascular treatment of aneurysms, such as the stent itself functioning as a thrombotic nidus, preexisting thrombus, or fresh clot migrating distally during the procedure. A study referring to neurovascular stent placement demonstrated that oral antiplatelet drug resistance might be associated with thromboembolic events.[11] Sufficient inhibition of the platelet reactivity could reduce the occurrence of thromboembolic complications after stent treatment. However, excessive inhibition of platelet reactivity might increase the risk of bleeding complications.[4] Therefore,

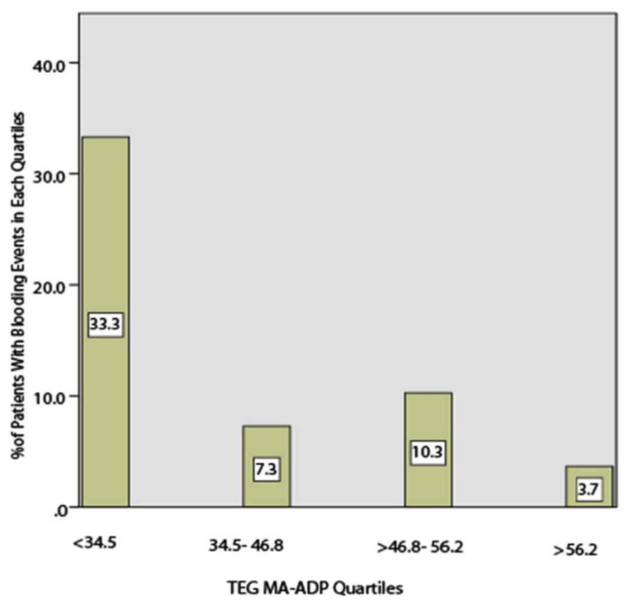

Figure 7. Quartile distribution of bleeding events for thromboelastography maximum amplitude of adenosine diphosphate. MA-ADP, maximum amplitude of adenosine diphosphate; TEG, thromboelastography.

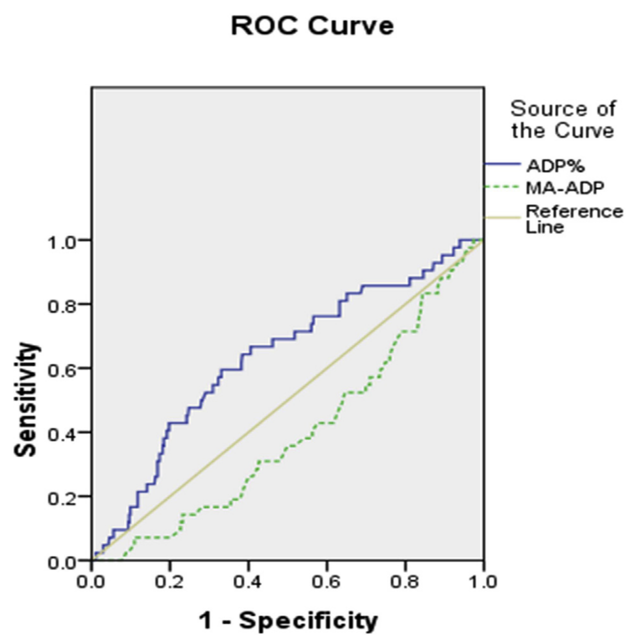

Figure 8. Receiver operating characteristic curve for percentage inhibition of adenosine diphosphate and maximum amplitude of adenosine diphosphate in bleeding events. ADP%, percentage inhibition of adenosine diphosphate; MA-ADP, maximum amplitude of adenosine diphosphate; ROC, receiver operating characteristic curve.

platelet inhibition must balance the risk of thromboembolic and bleeding complications.

Several platelet function tests have been used to assess the responsiveness of patients with cardiovascular disease to clopidogrel or aspirin.[20] Different tests might provide various parameters for the prevalence of antiplatelet drug resistance.[21] Compared with light transmission aggregometry (LTA), which was considered the previous criterion standard for evaluating platelet function, TEG was not time consuming and relatively inexpensive.[22] Besides, The TEG MA parameters measure the strength of a clot as a direct function of the maximum dynamic properties of fibrin platelet binding via GPIIb/IIIa and the platelet contractile system. Gurbel et al.[13] demonstrated that the TEG MA parameters might be better than LTA in in vivo situations because LTA ignored the important contribution of platelet-fibrin interactions to both thrombosis and hemorrhage. A study referring to patients undergoing percutaneous coronary intervention reported that thrombin MA >72 mm was considered to be a high risk factor for predicting ischemic events occurrence.[23] However, in our previous study, thrombin MA was not significantly associated with ischemic events and could be explained by the fact that only 8.7% of patients (4/46) had a thrombin MA >72 mm.[12] Because of the easier formation of stable thrombus with stronger platelet-fibrin clot strength, the higher MA-ADP level meant that the patients tended to suffer from adverse effects such as intrastent stenosis and accordingly ischemic stroke. Yao et al.[24] also demonstrated that a higher tertile of MA was related to stroke severity in the acute phase, indicated by higher National Institutes of Health Stroke Scale score on admission and longer in-hospital stay. Delgado Almandoz et al.[25] found that patients both under- or overresponsive to clopidogrel therapy were more likely to experience clinically evident thrombosis and hemorrhage. Rafiq et al.[26] indicated that MA-ADP >69 mm could be associated with a significantly increased incidence of 30-day ischemic stroke (17.2% vs. 6.6%, $P = 0.019$) in a total of 200 patients undergoing coronary artery bypass graft surgery. In this study, our ROC and quartiles analyses showed that ischemic events after neurovascular stenting

Table 5. Risk Factors of Bleeding Events After Embolization Procedures

	Univariate Logical Regression Analysis		
Variables	**OR**	**95% CI**	***P* Value**
Age	1.073	0.59—1.951	0.817
Sex	1.094	0.619—1.932	0.757
Hypertension	1.112	0.642—1.926	0.705
Hyperlipidemia	0.537	0.27—1.068	0.076
Diabetes mellitus	0.386	0.09—1.657	0.20
Smoking	0.926	0.478—1.793	0.819
Alcohol	0.946	0.456—1.964	0.882
ADP% >55.4%	9.796	5.365—17.887	<0.0001

OR, odds ratio; CI, confidence interval; ADP%, percentage inhibition of adenosine diphosphate.

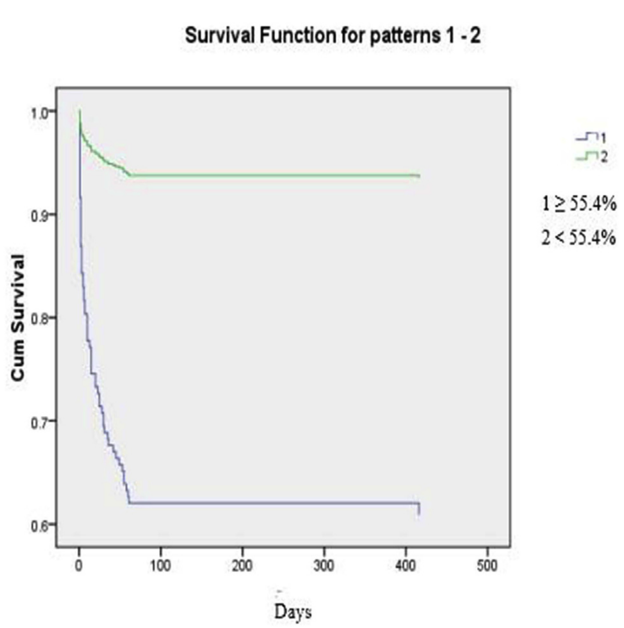

Figure 9. Survival function: Kaplan-Meier event time curves demonstrated the association between bleeding events and platelet function parameters, which was identified by percentage inhibition of adenosine diphosphate, with a cutoff point of 55.4%. Cum, cumulative.

commonly occurred in the patients who were detected with ADP% <29.45% and MA-ADP >46.15, suggesting higher quartiles of MA-ADP and lower quartiles of ADP% may need more aggressive antiplatelet therapy. Additionally, the aneurysm size, especially a size of at least 10 mm, conferred higher risk of procedural thromboembolism after the stent placement according to our univariate analysis. We hypothesized the cause was the disturbed flow across the aneurysm neck with ingress and egress through the stent lumen. The finding was similar with the Heller et al. data.[27] Johnson et al.[28] also demonstrated that large aneurysms were associated with more total complications and trended toward having more major complications after stent-assisted coiling. In summary, large aneurysms accompanied with lower ADP% or higher MA-ADP should be carefully reviewed because of the risk of intra- or postoperative ischemic complications.

Theoretically, the most important risk that could threaten patients by doubling the clopidogrel maintenance dosage is hemorrhagic accidents.[29] A prolonged usage of dual antiplatelet therapy, as recommended by the cardiology guideline, might not be applied for patients with intracranial aneurysm. Therefore, a higher ADP% (>55.4%), which is equal to the efficacy of high-dose antiplatelet drugs, might be considered as the platelet overinhibition and could increase the risk of the systemic bleeding events as excluding the intraoperative fault. After adjustment of the data, the safe range of ADP% was identified as 29.45%–55.4% and MA-ADP of the TEG was <46.15 in patients with intracranial aneurysms treated by stent placement.

Table 6. Risk Factors of Cerebral Hemorrhage Events (n = 15)

	Univariate Logical Regression Analysis		
Variables	**OR**	**95% CI**	***P* Value**
Age	2.184	0.775–6.156	0.14
Sex	0.124	0.16–1.95	0.065
Hypertension	0.992	0.353–2.78	0.987
Hyperlipidemia	2.721	0.733–10.103	0.135
Diabetes mellitus	0.857	0.109–6.729	0.883
Aneurysm size	0.575	0.16–2.074	0.398
Aneurysm location	1.586	0.351–7.167	0.549
Aneurysm morphology	0.559	0.297–1.052	0.071
Type of stents	0.677	0.387–1.185	0.172
Complete occlusion	1.007	0.554–1.831	0.982
ADP% >55.4%	4.26	1.504–12.068	0.006

OR, odds ratio; CI, confidence interval; ADP%, percentage inhibition of adenosine diphosphate.

Limitations

There are some limitations in our study. First, we only used TEG to measure the resistance to antiplatelet agents because no other method of platelet function testing was available in our center. In the next step, we will try to introduce some popular and relatively advanced platelet function testing technologies, such as VerifyNow (Accumetrics, San Diego, California, USA). Second, because of the shortage of patients, we excluded the patients who were treated with flow diverters. Third, in our cohort, the relatively lower rate of intracranial hemorrhage complications (only 15 cases) might be prone to bias of evaluating the predictive efficiency of TEG parameters.

CONCLUSIONS

ADP% and MA-ADP of TEG analysis were associated with subsequent cerebral ischemic events and intracranial or extracranial bleeding events in patients with intracranial aneurysms after stent treatment. The quantitative assessment of ADP% and MA-ADP could be identified as modified investigations of personalized antiplatelet treatment.

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