Insufficient platelet inhibition and thromboembolic complications in patients with intracranial aneurysms after stent placement

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OBJECTIVE Insufficient platelet inhibition has been associated with an increased incidence of thromboembolic complications in cardiology patients undergoing percutaneous coronary intervention. Data regarding the relationship between insufficient platelet inhibition and thromboembolic complications in patients undergoing neurovascular procedures remain controversial. The purpose of this study was to assess the relationship of insufficient platelet inhibition and thromboembolic complications in patients with intracranial aneurysm undergoing stent treatment.

METHODS The authors prospectively recruited patients with intracranial aneurysms undergoing stent treatment and maintained the data in a database. MRI with diffusion-weighted sequences was performed within 24 hours of stent insertion to identify acute ischemic lesions. The authors used thromboelastography to assess the degree of platelet inhibition in response to clopidogrel and aspirin. Univariate and multivariate logistic regression analysis was used to identify potential risk factors of thromboembolic complications.

RESULTS One hundred sixty-eight patients with 193 aneurysms were enrolled in this study. Ninety-one of 168 (54.2%) patients with acute cerebral ischemic lesions were identified by diffusion-weighted MRI. In 9 (5.4%) patients with ischemic lesions, transient ischemic attack or stroke was found at discharge, and these complications were found in 11 (6.5%) patients during the follow-up period. The incidence of periprocedural thromboembolic complications increased with resistance to antiplatelet agents, hypertension, hyperlipidemia, complete occlusion, and aneurysm of the anterior circulation. The multivariate regression analysis demonstrated that the anterior circulation and adenosine diphosphate (ADP) inhibition percentage were independent risk factors of perioperative thromboembolic complications. The maximum amplitude and ADP inhibition percentage were independent risk factors for thromboembolic complications during the follow-up period.

CONCLUSIONS The ADP inhibition percentage is related to thromboembolic complications after stent placement for intracranial aneurysms. The increase of the ADP inhibition may decrease the risk of thromboembolic complications.

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KEY WORDS intracranial aneurysm; stent; cerebral infarction; antiplatelet drug resistance; platelet function test; vascular disorders

CEREBRAL infarction is one of the major disabling complications of neurovascular stent treatment. During the last decades, many studies have evaluated the safety and efficacy of the technique of stent placement for intracranial aneurysms, which demonstrated a range of 3.7%–21% thromboembolic complications.^{4,10,11,29}

Dual antiplatelet therapy (aspirin and clopidogrel) has been used as the standard protocol to decrease the inci-

dence of thromboembolic complications in patients with intracranial aneurysms undergoing stent treatment. However, many patients still experience thromboembolic complications after neurovascular intervention, despite being compliant with the standard antiplatelet medication protocol.

Previous studies have demonstrated that a low response to antiplatelet medication was associated with the

ABBREVIATIONS AA = arachidonic acid; ADP = adenosine diphosphate; DWI = diffusion-weighted imaging; ICA = internal carotid artery; MA = maximum amplitude; mRS = modified Rankin Scale; TEG = thromboelastography.

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increased incidence of thromboembolic complications in patients undergoing coronary stent placement or in patients with intracranial and extracranial vessel stenosis undergoing neurovascular stent placement.^{7,9,14,24} However, the relationship between low response to antiplatelet agents and thromboembolic complications in patients undergoing neurovascular procedures remains controversial.⁶

The purpose of this study was to assess the relationship of insufficient platelet inhibition and thromboembolic complications in patients with intracranial aneurysm undergoing stent treatment.

Methods

Patient Population

We prospectively recruited patients with intracranial aneurysm undergoing stent treatment between September 2013 and October 2014. Informed consent was obtained from all participants and the protocol was approved by our institute. Patients older than 18 years were included. The exclusion criteria were prothrombin time $> 1.5\times$ control, thrombopenia $< 80,000/\mu\text{l}$, hematocrit $< 30\%$, contraindication to aspirin or clopidogrel, glycoprotein (GP) IIb/IIIa inhibitor use before the procedure, severe liver insufficiency, patients with aortic arch or carotid stenosis, and unsuitability for MRI examination. The baseline information, including age, sex, medical history (hypertension, hyperlipidemia, diabetes, ischemic stroke, coronary artery disease, smoking), aneurysm characteristics (location, size, neck), occlusion grade, and stent type and number were recorded.

Platelet Inhibition Test

Baseline blood samples were drawn before the administration of dual antiplatelet therapy (aspirin and clopidogrel). The blood samples that were used to assess preoperative platelet inhibition were obtained immediately prior to the procedure. Blood samples (3–4 ml) were drawn from a single clean puncture of a forearm vein and collected in a 4-ml test tube (Becton-Dickinson) containing lithium heparin.

The platelet inhibition was tested using a thromboelastography (TEG) hemostasis system (Haemoscope Corp.). The TEG technology has been described previously.^{3,14} Briefly, blood clot strength is measured by the amplitude of the rotation of the pin suspended into an oscillating cup that contains the blood sample. The agonists of adenosine diphosphate (ADP) or arachidonic acid (AA) are added to measure the platelet inhibition of P2Y₁₂ receptor or cyclooxygenase pathways.

The TEG percentage platelet inhibition of AA and maximum amplitude (MA)-AA (i.e., AA-induced clot strength) were used to measure the response to aspirin; the ADP percentage inhibition and MA-ADP (ADP-induced clot strength) were used to measure the response to clopidogrel. The cutoff values of AA% $< 50\%$ and ADP% $< 30\%$ were used to define the resistance to aspirin and clopidogrel, respectively.^{3,28} The MA represents the maximum amplitude with thrombin-stimulated platelets and fibrin meshwork (the maximum clot strength).

Endovascular Procedures

Patients with unruptured aneurysms were given aspirin (100 mg/day) and clopidogrel (75 mg/day) orally for 3–5 days before the procedure. As for ruptured aneurysms, a loading dose of aspirin (300 mg) and clopidogrel (300 mg) was given at least 2 hours prior to the procedure. The endovascular procedure was performed under general anesthesia, and a bolus of heparin was administered using 3000 IU, then 1000 IU every hour. Two types of stents (Enterprise [Codman Neurovascular] and Solitaire AB neurovascular remodeling device [eV3, Inc.]) were used to treat aneurysms. Daily clopidogrel (75 mg) was maintained for 6 weeks after the procedure, and daily aspirin (100 mg) was maintained for 6 months.

Periprocedural thromboembolic complications were evaluated by both clinical examination and MRI with diffusion-weighted imaging (MRI-DWI). A baseline 3-T MRI-DWI was performed within 1 week before the procedure, and another 3-T MRI-DWI was performed on postoperative Day 1. All MR images were reviewed by a neuroradiologist.

Statistical Analysis

Categorical variables were recorded as number (percentage), and continuous variables as the mean $\pm$ SD. Analysis was carried out with unpaired t-tests, chi-square tests, Fisher exact tests, and logistic regression. A p value < 0.05 was considered statistically significant (SPSS version 17.0, SPSS Inc.).

Results

General Characteristics

One hundred sixty-eight patients with 193 intracranial aneurysms were enrolled in this study. The mean age of the patients was 54.5 ± 9.4 years (range 31–76 years), and 102 (60.7%) patients were female. Fifty-three (31.5%) patients presented with dizziness, 51 (30.4%) with headache, 28 (16.7%) with cranial nerve deficits, 19 (11.3%) with incidentally found aneurysms, and 17 (10.1%) with subarachnoid hemorrhage.

One hundred fifty-one (78.2%) aneurysms were located in the anterior circulation (57 in the ophthalmic segment of the internal carotid artery (ICA), 48 in the posterior communicating artery, 15 in the middle cerebral artery, 11 in the cavernous segment of the ICA, 10 in the anterior communicating artery, 6 in the tip of the ICA, and 4 in the anterior cerebral artery), and 42 (21.8%) aneurysms were located in the posterior circulation (27 in the vertebral artery, 12 in the basilar artery, and 3 in the posterior cerebral artery). The mean aneurysm size was 8.1 ± 5.0 mm, and the average aneurysm neck size was 4.3 ± 2.4 mm.

In total, 202 stents were placed in 168 patients, including 142 (70.3%) Enterprise stents and 60 (29.7%) Solitaire stents. In the majority of patients (80.3%) 1 stent was placed, 24 (14.3%) patients had 2 stents, and 9 (5.4%) patients had 3 stents.

The mean MA value was 63.4 ± 6.0 mm (range 43.0–78.0 mm). Fifty-eight (34.5%) patients were resistant to clopidogrel, and the mean preoperative ADP inhibition percentage was $27.5\% \pm 25.2\%$ (range 0%–100%). As for

FIG. 1. A 54-year-old patient with a 10-year history of hypertension presented with a 7-year history of dizziness. The patient had resistance to clopidogrel (ADP% 7.4%). **A:** A 3D image showing a 3.3-mm right posterior communicating artery aneurysm (arrow). **B:** Digital subtraction angiography image obtained after the procedure showing complete occlusion of the aneurysm (arrow). **C:** The patient developed left hemiparesis on postoperative Day 2. Axial MRI-DWI shows multiple thromboembolic infarctions (arrows) in the right cerebral hemisphere. The patient had a permanent disabling left hemiparesis at discharge (mRS Score 3).

aspirin, 33 (19.6%) patients were resistant, with a mean AA inhibition percentage of $77.8\% \pm 27.6\%$ (range 0%–100%).

All patients underwent MRI-DWI before and after the procedure, and in 91 (54.2%) patients new ischemic lesions were identified. All of the ischemic lesions were located in the territory of stent-treated vessels.

Most of the perioperative thromboembolic complications were silent, but 9 (5.4%) patients had ischemic clinical symptoms (6 patients had a transient neurological deficit and 3 had a permanent disability at discharge) (Fig. 1). All of these 9 patients with transient or permanent neurological deficits were resistant to clopidogrel (Table 1). Three (1.8%) periprocedural bleeding complications occurred (2 cerebral hemorrhage events occurred during the procedure and 1 occurred on postoperative Day 1); 2 of these 3 patients had a favorable clinical outcome (modified Rankin Scale [mRS] Score 1) at discharge, and the other had a permanent neurological deficit (mRS Score 3).

Comparison of Patients With and Without Perioperative Thromboembolic Complications After Stent Placement

There were no statistical differences in age and sex between the groups of patients with and without perioperative thromboembolic complications (Table 2). Thromboembolic complications were more frequently observed in patients with aneurysms in the anterior circulation. Of patients with thromboembolic complications, 88.5% (92/104) of aneurysms were in the anterior circulation, compared with 66.3% (59/89) in patients without perioperative thromboembolic complications ($p < 0.001$).

There were more completely occluded aneurysms in the thromboembolic complications group than in the group without perioperative thromboembolic complications (65.4% vs 48.3%, $p = 0.017$). A history of hypertension ($p = 0.033$) and hyperlipidemia ($p = 0.03$) were also risk factors for perioperative thromboembolic complications in univariate analysis.

The TEG test was performed in all of the enrolled pa-

TABLE 1. Characteristics of 9 patients in whom clinical ischemic events occurred after stent placement for intracranial aneurysms

Case No.	Age (yrs), Sex	Aneurysm Size (mm)	Aneurysm Location	Hypertension	Hyperlipidemia	Occlusion Grade	Event Type	Resistance to Aspirin*	Resistance to Clopidogrel*	mRS Score
1	67, M	7.0	Ophthalmic segment of ICA	Yes	Yes	Residual neck	TIA	No	Yes	2
2	52, F	25.2	Cavernous segment of ICA	No	No	Complete	TIA	No	Yes	1
3	69, F	11.0	MCA	No	Yes	Complete	TIA	No	Yes	1
4	59, M	10.3	Ophthalmic segment of ICA	No	No	Complete	TIA	No	Yes	1
5	57, M	6.8	PCA	Yes	No	Complete	TIA	No	Yes	1
6	55, F	10.1	Cavernous segment of ICA	Yes	No	Complete	TIA	No	Yes	1
7	54, M	3.3	PCoA	Yes	Yes	Complete	Infarction	No	Yes	3
8	53, M	5.5	BA	No	No	Residual neck	Infarction	Yes	Yes	3
9	47, M	3.8	Ophthalmic segment of ICA	Yes	Yes	Complete	Infarction	No	Yes	4

BA = basilar artery; MCA = middle cerebral artery; PCA = posterior cerebral artery; PCoA = posterior communicating artery; TIA = transient ischemic attack.

* Antiplatelet resistance was evaluated using a TEG test. Aspirin and P2Y₁₂ resistances were defined as aspirin and clopidogrel percentage inhibition $< 50\%$ and $< 30\%$, respectively.

TABLE 2. Comparison of baseline characteristics and clinical variables in 168 patients with and without periprocedural thromboembolic complications*

Demographic Data	No. (%) w/ Thromboembolic Complications	No. (%) w/o Thromboembolic Complications	p Value
No. of patients	91 (54.2)	77 (45.8)	
Age in yrs	54.8 ± 9.2	54.3 ± 9.7	0.72
Female	60 (65.9)	42 (54.5)	0.13
Medical history			
Hypertension	54 (59.3)	33 (42.9)	0.033
Diabetes	8 (8.8)	5 (6.5)	0.82
Brain ischemia	17 (18.7)	9 (11.7)	0.21
Hyperlipidemia	28 (30.8)	13 (16.9)	0.03
Coronary artery disease	13 (14.3)	7 (9.1)	0.30
Smoking history			0.97
Never	56 (61.5)	47 (61.0)	
Former	15 (16.5)	12 (15.6)	
Active	20 (22.0)	18 (23.4)	
Rupture	7 (7.7)	9 (11.7)	0.72
Aneurysm size	7.8 ± 4.8	8.2 ± 5.3	0.53
Aneurysm neck	4.1 ± 2.1	4.5 ± 2.8	0.67
Aneurysm location†			<0.001
Anterior circulation	92 (88.5)	59 (66.3)	
Posterior circulation	12 (11.5)	30 (33.7)	
Occlusion grade‡			0.017
Complete	68 (65.4)	43 (48.3)	
Incomplete	36 (34.6)	46 (51.7)	
Stent‡			0.62
Enterprise	75 (68.8)	67 (72.0)	
Solitaire	34 (31.2)	26 (28.0)	
Platelet inhibition			
MA	63.9 ± 6.2	62.7 ± 5.8	0.24
AA% inhibition	73.7 ± 29.8	81.5 ± 24.5	0.069
ADP% inhibition	19.0 ± 18.5	37.6 ± 28.2	<0.001
Resistance to aspirin	23 (25.3)	11 (14.3)	0.077
Resistance to clopidogrel	38 (41.8)	20 (26.0)	0.032

* Unless otherwise indicated, the values represent the number of patients (%) or the mean ± SD.

† Data represent the number of aneurysms (total 193).

‡ Data represent the number of stents (total 202).

tients to assess the extent of platelet inhibition by aspirin and clopidogrel. As shown in Table 2, the ADP inhibition was significantly lower in the thromboembolic complications group than in the group without thromboembolic complications ($p < 0.001$). The AA inhibition was lower in the group with perioperative thromboembolic complications, but was not significantly different ($p = 0.069$) (Fig. 2). The MA values were comparable in these 2 groups.

The rate of resistance to clopidogrel (ADP% < 30%) was significantly higher in the thromboembolic complications group ($p = 0.032$).

In multiple logistic regression analysis, the anterior circulation and ADP inhibition were independent risk factors for perioperative thromboembolic complications (Table 3).

Follow-Up

A total of 166 patients (98.8%) had clinical follow-up results (mean 7.8 ± 2.3 months; range 3–16 months). During the follow-up period, 2 patients experienced nonfatal intracranial hemorrhage, and 11 patients suffered thromboembolic complications related to the vascular distribution of the stent-treated parent vessel. Of the 11 patients with thromboembolic complications, 9 (81.8%) were resistant to clopidogrel.

Univariate and multivariate logistic regression were used to analyze the factors related to thromboembolic complications during the follow-up period. The factors included age, sex, medical history, characteristics of aneurysm, occlusion results, type of stent, and platelet function test results. We found that the MA and ADP inhibition percentage were independent risk factors for thromboembolic complication (Table 4).

Discussion

The major purpose of this study was to evaluate the relationship of platelet inhibition and thromboembolic complications in patients with intracranial aneurysms undergoing stent treatment. The occurrence of thromboembolic complications was found to be associated with ADP inhibition. Patients with low ADP inhibition demonstrated a higher probability of thromboembolic complications.

Kang et al. demonstrated that a higher rate of thromboembolic complications in patients with insufficient platelet inhibition,²⁰ which was similar to our results despite the use of a different endovascular procedure (coil vs stent) and antiplatelet function test (VerifyNow vs TEG). Light transmission aggregometry (LTA) is considered the gold standard in the evaluation of platelet function, but it is costly and time-consuming.²⁵ Previous studies have compared LTA and other platelet function analyzers, such as VerifyNow,^{2,13} PFA-100,¹³ and TEG,^{2,22} and showed variable results. However, Jeong et al. demonstrated a significant correlation between TEG and LTA in 730 patients treated by percutaneous coronary intervention.¹⁸ Gurbel et al. reported that the TEG MA parameters might be better than LTA in an in vivo situation because LTA ignored the important contribution of platelet-fibrin interactions to both thrombosis and hemorrhage.¹⁵

We used TEG to test the effects of antiplatelet agents, and the proportion of resistance to clopidogrel (34.5%) in our series was lower than that reported by Lee et al. (42.9%) in patients tested using VerifyNow.²¹ Our present results showed that ADP inhibition was the independently predictive factor of ischemic lesions following stent insertion, which means that P2Y₁₂ inhibitor resistance was associated with a higher risk of thromboembolic complications after stent placement.^{9,24} Similar results have also been reported in patients undergoing coronary

FIG. 2. Boxplots showing distribution of the percentage of ADP-induced (ADP%, left) and AA-induced (AA%, right) platelet inhibition tested using TEG in patients with or without cerebral infarction detected by MRI-DWI. Figure is available in color online only.

stent placement or in patients with intracranial and extracranial stenosis following stent insertion.^{7,14,24} Therefore, the ADP inhibition may be a critical factor for predicting thromboembolic complications following stent treatment, and sufficient inhibition of the platelet reactivity may reduce the occurrence of thromboembolic complications. However, sufficient inhibition of platelet reactivity may increase the risk of bleeding complications, especially for intracranial hemorrhage. Therefore, platelet inhibition must also balance the risk of thromboembolic and bleeding complications. In our previous study, we found that the TEG parameter was a predictor for acute thromboembolic complications in unruptured aneurysms undergoing stent treatment.³⁰ More studies monitoring platelet inhibition are needed to confirm a safe range for this treatment, which may reduce the risk of thromboembolic and bleeding complications.

We chose MRI-DWI to clarify the occurrence of acute stroke because this imaging technique is highly sensitive and specific in diagnosing acute ischemic stroke.^{12,27} In the present study, we found a 54.2% rate of periprocedural thromboembolic complications, including 5.4% of cases in which patients exhibited clinical symptoms, which was comparable with other studies.^{16,17} Most injuries revealed by MRI were clinically silent in our study, which might be associated with the relatively small amounts of brain affected. However, in patients with clinical syndromes, the symptoms may be caused by injuries in an eloquent region of the brain. Despite the fact that most of the thromboembolic complications were clinically silent, previous studies have demonstrated that clinically silent lesions detected by MRI-DWI might cause cognitive impairment,^{5,19} which needed to be confirmed by other long-term follow-up studies.

Several studies have shown the various causes of procedure-related embolic events, such as plaque cracking and migrating to distal cerebral vessels, and the stent itself causing embolism.^{1,23,26} All of the patients in our study presented with acute ischemic lesions in the territory of the stent-treated vessels, and one major reason may be the

dislodgement of microthrombi that arose during the stent procedure.

In the current study, we demonstrated more ischemic lesions in the territory of the parent artery of the anterior circulation, which may be associated with the more complex anatomy of the anterior circulation.

Delgado et al. reported that a history of hypertension was an independent risk factor for thromboembolic complications in patients with cerebral aneurysms undergoing treatment with Pipeline stents.⁸ In our study, we found that a history of hypertension and hyperlipidemia were risk factors for thromboembolic complications in univariate analysis, but did not have significant difference in multivariate analysis. Hypertension and hyperlipidemia were risk factors of atherosclerosis, which implies that dislodgement of the atheroma in the procedure may be the source of embolism and cause the thromboembolic complications. However, further study is needed to verify whether preoperative control of blood pressure and blood lipid levels will decrease the rate of thromboembolic complications.

Limitations of the Study

There are several limitations in our study. First, we use only TEG to measure the resistance to antiplatelet agents

TABLE 3. Results of multivariate analysis of risk factors of periprocedural thromboembolic complications

Variable	OR (95% CI)	p Value
Hypertension	1.42 (0.77–2.63)	0.26
Hyperlipidemia	1.26 (0.65–2.18)	0.22
Occlusion grade	1.39 (0.89–2.20)	0.15
Complete		
Incomplete		
Location	4.17 (1.65–10.53)	0.003
ADP inhibition	1.03 (0.59–1.79)	<0.001

TABLE 4. Risk factors for thromboembolic complications in 166 patients during the follow-up period*

Factor	No. w/ Thromboembolic Complications	No. w/o Thromboembolic Complications	Univariate Analysis		p Value	Multivariate Analysis		p Value
			OR	95% CI		OR	95% CI	
No. of patients	11	155						
Age in yrs	53.7 ± 9.6	54.6 ± 9.6	1.0	0.94–1.07	0.77	NA	NA	
Female	5 (45.5)	97 (62.6)	1.97	0.62–6.71	0.34	NA	NA	
Medical history								
Hypertension	7 (63.6)	80 (51.6)	1.64	0.46–5.832	0.44	NA	NA	
Diabetes	2 (18.2)	11 (7.1)	3.22	0.61–16.96	0.18	NA	NA	
Coronary artery disease	2 (18.2)	18 (11.6)	1.69	0.33–8.45	0.62	NA	NA	
Brain ischemia	3 (27.3)	23 (14.8)	2.15	0.53–8.71	0.38	NA	NA	
Hyperlipidemia	6 (54.5)	36 (23.2)	4.11	1.18–14.29	0.018	1.35	0.85–3.28	0.65
Aneurysm size (mm)	8.4 ± 3.4	8.2 ± 4.1	0.99	0.89–1.12	0.98	NA	NA	
Aneurysm neck (mm)	4.2 ± 2.4	4.3 ± 3.6	0.86	0.78–1.23	0.71	NA	NA	
Aneurysm location†			3.92	0.49–10.8	0.31	NA	NA	
Anterior circulation	13 (92.9)	136 (76.8)						
Posterior circulation	1 (7.1)	41 (23.2)						
Rupture	1 (7.1)	15 (8.5)	1.08	0.12–9.02	0.94	NA	NA	
Occlusion grade‡			0.98	0.32–2.94	0.97	NA	NA	
Complete	8 (57.1)	102 (57.6)						
Incomplete	6 (42.9)	75 (42.4)						
Stent‡			0.61	0.21–1.82	0.39	NA	NA	
Enterprise	9 (60)	131 (70.8)						
Solitaire	6 (40)	54 (29.2)						
Platelet function test								
MA (mm)	68.2 ± 2.8	65.8 ± 3.9	0.82	0.67–0.99	0.04	0.842	0.68–0.98	0.038
MA-ADP (mm)	54.1 ± 2.7	44.9 ± 12.5	0.81	0.67–0.97	0.02	0.763	0.59–0.97	0.022
ADP%	12.2 ± 9.1	28.6 ± 25.6	1.046	1.0–1.09	0.051	1.026	0.97–1.07	0.283
MA-AA (mm)	32.2 ± 15.5	21.9 ± 14.2	0.96	0.92–0.99	0.031	1.017	0.92–1.12	0.729
AA%	56.5 ± 30.9	78.7 ± 26.9	1.023	1.004–1.04	0.016	1.025	0.97–1.07	0.318

NA = not applicable for multivariate analysis, which was performed for the factors that were significant in univariate analysis.

* Unless otherwise indicated, the values represent the number of patients (%) or the mean ± SD.

† Data represent the number of aneurysms (total 191: 2 patients with 1 aneurysm each did not have follow-up).

‡ Data represent the number of stents (total 200: 2 patients with 1 stent each did not have follow-up).

because no other method of platelet function testing was available at our institute. Second, we could not compare the periprocedural clinical adverse events because of the low incidence.

Conclusions

Thromboembolic complications in patients with intracranial aneurysm following stent treatment were associated with ADP inhibition. Resistance to clopidogrel may increase the risk of thromboembolic complications. An adjusted antiplatelet protocol, which is based on results of the platelet function test, may reduce the rate of thromboembolic complications.

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Disclosures

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Author Contributions

Conception and design: Li, Jiang. Acquisition of data: Jiang. Analysis and interpretation of data: Yang. Drafting the article: Yang. Approved the final version of the manuscript on behalf of all authors: Li. Statistical analysis: Yang. Study supervision: Li.

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