Original Contribution

Use of Platelet Function Testing Before Pipeline Embolization Device Placement

A Multicenter Cohort Study

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Background and Purpose—Thromboembolic complications constitute a significant source of morbidity after neurointerventional procedures. Flow diversion using the pipeline embolization device for the treatment of intracranial aneurysms necessitates the use of dual antiplatelet therapy to reduce this risk. The use of platelet function testing before pipeline embolization device placement remains controversial.

Methods—A retrospective review of prospectively maintained databases at 3 academic institutions was performed from the years 2009 to 2016 to identify patients with intracranial aneurysms treated with pipeline embolization device placement. Clinical and radiographic data were analyzed with emphasis on thromboembolic complications and clopidogrel responsiveness.

Results—A total of 402 patients underwent 414 pipeline embolization device procedures for the treatment of 465 intracranial aneurysms. Thromboembolic complications were encountered in 9.2% of procedures and were symptomatic in 5.6%. Clopidogrel nonresponders experienced a significantly higher rate of thromboembolic complications compared with clopidogrel responders (17.4% versus 5.6%). This risk was significantly lower in nonresponders who were switched to ticagrelor when compared with patients who remained on clopidogrel (2.7% versus 24.4%). In patients who remained on clopidogrel, the rate of thromboembolic complications was significantly lower in those who received a clopidogrel boost within 24 hours pre-procedure when compared with those who did not (9.8% versus 51.9%). There was no significant difference in the rate of hemorrhagic complications between groups.

Conclusions—Clopidogrel nonresponders experienced a significantly higher rate of thromboembolic complications when compared with clopidogrel responders. However, this risk seems to be mitigated in nonresponders who were switched to ticagrelor or received a clopidogrel boost within 24 hours pre-procedure. **(*Stroke*. 2017;48:00-00. DOI: 10.1161/STROKEAHA.116.015308.)**

Key Words: aneurysm ■ clopidogrel ■ complications ■ pipeline embolization device ■ platelet function test ■ responders ■ thromboembolic ■ ticagrelor

Thromboembolic complications are the most common cause of morbidity after neurointerventional procedures.[1,2] The risk of these complications is particularly high after the placement of an intra-arterial flow diverter such as the pipeline embolization device (PED). The PED is the only US Food and Drug Administration–approved flow-diverting stent for the treatment of intracranial aneurysms and works to remodel the parent artery by providing a scaffold for endothelization, ultimately excluding the aneurysm from circulation. Unique to the PED is a 3- to 5-fold increase in surface coverage area as compared with other stents designed for intracranial use. The 30% to 35% surface-area cobalt chromium/platinum tungsten stent can cause platelet activation and acts as a nidus for thrombosis and subsequent thromboembolic stroke. Although this risk is reduced by the use of dual antiplatelet therapy, the most efficacious regimen is not known. Gupta et al[3] surveyed neurointerventionalists in the United States and found that almost all practitioners used a combination of aspirin and clopidogrel as the initial treatment regimen. Although both of these medications are generally well tolerated and widely available, clopidogrel resistance or nonresponsiveness is an emerging concern. The current understanding of the clinical implications of this pharmacodynamic phenomenon is largely extrapolated from the cardiology

Received August 31, 2016; final revision received February 10, 2017; accepted February 20, 2017.

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Guest Editor for this article was Michael Brainin, MD.

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literature, with relatively little data guiding neurointerventional procedures. Despite up to half of patients demonstrating an inadequate response to clopidrogrel,[4] the use of platelet function test before PED placement remains controversial.[3,5,6] Moreover, only half of neurointerventionalists in the United States switch nonresponders to another antiplatelet agent (eg, ticagrelor or prasugrel).[3]

In this study, we present a large multicenter cohort of intracranial aneurysm patients treated with a PED with a focus on thromboembolic complications and clopidogrel responsiveness.

Methods

A retrospective review of prospectively maintained databases at 3 academic institutions in the United States was performed from the years 2009 to 2016 to identify patients with intracranial aneurysms treated with flow diversion using a PED. Inclusion criteria consisted of all adult (age ≥18 years) patients with an intracranial aneurysm treated with PED placement. Both ruptured and unruptured aneurysms were included; all aneurysm morphologies (ie, saccular, dissection, fusiform, and blister) and intracranial locations were included. The following information was collected: patient demographics, aneurysm characteristics, platelet function test results, antiplatelet regimen, procedural details, complications, and angiographic and functional outcomes. Institutional review board approval was obtained at all 3 centers.

Procedure Details

Patients received aspirin 325 mg daily and clopidogrel 75 mg daily for 3 to 14 days before the intervention, an accepted duration to achieve maximal steady state of 50% to 60% platelet inhibition.[7–9] The last dose of clopidogrel was given the morning of platelet function testing. Platelet function testing was routinely performed using whole-blood lumi-aggregometer, light transmission aggregometry, or VerifyNow. Clopidogrel nonresponders were identified based on established cutoff values at the individual institutions and were guided by manufacturer recommendations. Whole-blood lumi-aggregometry was performed on the CHRONO-LOG Model 700 and uses impedance (or electric resistance) as the method of measuring platelet aggregation. The change in resistance after agonist administration is measured and quantified in ohms; an increase in impedance is directly proportional to the mass of the platelet aggregate. The response pattern is compared with established norms provided by the manufacturer; >6 Ω after administration of ADP is regarded as a clopidogrel nonresponder. Light-transmission aggregometry measures light transmission as a surrogate of platelet aggregation. Platelet aggregation decreases the optical density of the solution, allowing more light to pass through the solution. Platelet aggregation >50% of the maximum in 2 runs of 5 μmol/L ADP was considered clopidogrel nonresponsive. VerifyNow is a simple and rapid bedside platelet function test that uses whole-blood samples and light transmission to quantify platelet aggregation; these results are reported as $P2Y_{12}$ reaction units (PRU) when evaluating clopidogrel. Patients with PRU value >208 were considered clopidogrel nonresponders. If a patient was identified as a clopidogrel responder, the clopidogrel was continued. If a patient was identified as a clopidogrel nonresponder, the choice to continue on same dose clopidogrel, administer a one-time 600-mg clopidogrel boost within 24 hours pre-procedure, or switch to ticagrelor was at the discretion of the interventionalist performing the procedure. Patients undergoing treatment of a ruptured aneurysm were treated urgently (within 24–48 hours of presentation) and received a loading dose of aspirin 650 mg and clopidogrel 600 mg before the intervention. Patients underwent local anesthesia with sedation or general anesthesia at the discretion of individual institutions, and all patients were anticoagulated with heparin throughout the procedure. Activated clotting time was used to guide heparin administration intraprocedurally, with a target of 250 to 300; typical dosing consisted of a 3000 to 5000 U bolus at the beginning of the procedure, with hourly dosing of 1000 U. The type of the guide catheter and micro catheter used for PED deployment was at the discretion of the individual institutions. The deployment and apposition of the PED to the vessel wall were documented using fluoroscopy. Dual antiplatelet therapy was continued for at least 3 months after the procedure and aspirin indefinitely thereafter.

Complications and Outcomes

Thromboembolic complications occurring from the date of the procedure up to last follow-up were included. Intraprocedural thromboembolic complications were identified on digital subtraction angiography as thrombus formation, slow filling of a previously normally filling vessel, or vessel dropout. Intraprocedural thromboembolism was treated at the discretion of the interventionalist performing the procedure and could include additional antiplatelet medication (ie, eptifibatide or abciximab), anticoagulation, thrombolytics, mechanical thrombectomy, or observation. Postprocedural thromboembolic complications were identified using a combination of clinical and radiographic findings. Postprocedural imaging was performed at the discretion of the individual institutions and was only obtained because of clinical concern. Routine screening for clinically silent ischemic strokes was not performed. Postprocedural imaging obtained to detect an ischemic stroke could include any combination of a noncontrast computed tomography, computed tomographic angiography, or magnetic resonance imaging. Only ischemic strokes in the territory of the treated vessel were included. An ischemic complication was considered symptomatic if the patient reported symptoms attributable to thromboembolism or demonstrated signs attributable to thromboembolism; this includes transient or resolving signs and symptoms.

Hemorrhagic complications were identified intraoperatively as contrast extravasation on digital subtraction angiography or on postprocedure imaging obtained because of clinical concern. Hemorrhagic complications occurring from the time of the procedure up until last follow-up were included. Hemorrhages were counted as symptomatic if the patient reported symptoms or demonstrated signs attributable to a hemorrhage. In contrast to ischemic complications, all vascular territories and arterial puncture sites were included.

Angiographic outcome was assessed using digital subtraction angiography, magnetic resonance angiography, or computed tomographic angiography. Aneurysm occlusion after PED treatment was categorized as complete (100%), near complete (90%–99%), or partial (<90%) occlusion. Functional outcome was assessed using the modified Rankin Scale at the last follow-up.

Statistical Analysis

Statistical analysis was performed using SPSS 21.0 (IBM Corp, Armonk, NY). In univariable analysis, variables were compared between groups by Mann–Whitney test for numeric variables and χ^2 test for categorical variables. Statistical significance was defined as $P<0.05$. Multivariable logistic regression was performed on candidate predictor variables that were significant on univariable analysis to identify variables independently associated with thromboembolic and hemorrhagic complications after controlling for potential confounders. Efforts to account for interactions and collinearity between variables were undertaken. Kaplan–Meier curves were designed to compare the rate of thromboembolism-free procedures overtime between different antiplatelet regimens.

Results

Patients and Aneurysm Characteristics

Four hundred and 2 patients (median age, 58 years; male-to-female ratio, 1:4.7) underwent 414 PED procedures for the treatment of 465 intracranial aneurysms. Multiple aneurysms were present in 43.2% of procedures, although not all were treated using PED. Current history of diabetes mellitus and

chronic renal failure was identified in 7% and 4.8% of procedures, respectively. The pretreatment modified Rankin Scale score was 0 to 2 in 94.9% of procedures and 3 to 5 in 5.1%.

The majority of aneurysms were located along the internal carotid artery (82.8%), followed by the posterior circulation (13.3%). Saccular aneurysms accounted for 68.2% of all aneurysms. The median aneurysm maximal diameter was 7.6 mm. A daughter sac was present in 24.9%. Acute aneurysmal subarachnoid hemorrhage (<2 weeks) was present in 3.1% of procedures at the time of treatment. Previous endovascular treatment had been performed in 8.2% of aneurysms and previous clipping in 2.8% (Table 1).

Treatment Outcome

The majority of procedures used a single PED (77.1%), whereas ≥3 PEDs were placed in 6.3% of procedure. Pretreatment platelet function testing was performed in 96.4% of procedures; 28.8% were identified as clopidogrel nonresponders. Of the nonresponders, 32.2% were switched to ticagrelor, and 67.8% remained on clopidogrel. Among nonresponders who remained on clopidogrel, 65.4% received a one-time boost dose of clopidogrel (600 mg) pre-procedure. All patients treated with clopidogrel received daily dosing of 75 mg. There was no significant difference in the status of clopidogrel responsiveness among patients with diabetes mellitus (P=0.4) or chronic renal failure (P=0.79) compared with patients with neither of the diseases.

At a median angiographic follow-up of 13.2 months (mean, 19.1 months), complete occlusion was achieved in 79.8% of aneurysms. Retreatment was performed in 5.6% of aneurysms. Last follow-up modified Rankin Scale score improved in 32.3% and worsened in 10.2%; this includes patients presenting with aneurysmal subarachnoid hemorrhage. Thromboembolic complications were encountered in 9.2% of procedures and were symptomatic in 5.6%. Hemorrhagic complications were encountered in 3.4% of procedures and were symptomatic in 1.9%. The mortality rate was 1.8%; mortality was related to preprocedural aneurysmal subarachnoid hemorrhage in 0.5%, ischemic stroke in 0.5%, postprocedural hemorrhage in 0.3%, and unrelated causes in 0.5% (Table 2).

Predictors of Thromboembolic Complications

Larger maximal aneurysm diameter was associated with a higher rate of thromboembolism (P=0.025). Patients and treatment characteristics, including the number of PEDs used, had no significant correlation with thromboembolic complications (Table 3).

Effect of Antiplatelet Therapy on the Rate of Thromboembolic and Hemorrhagic Complications

There was no significant difference in the rate of thromboembolic complications (P=0.33) or hemorrhagic complications (P=0.479) between clopidogrel responders as detected by the 3 platelet function tests. Clopidogrel nonresponders experienced a significantly higher rate of thromboembolic complications when compared with clopidogrel responders (17.4% versus 5.6%; P=0.0002). This difference was even greater in clopidogrel nonresponders who remained on the same dose of clopidogrel when compared with clopidogrel

Table 1. Baseline Characteristics

Parameter	Number
No. of patients	402
No. of procedure	414
No. of aneurysms	465
Sex, n (%)	
Female	341 (82.4)
Male	73 (17.6)
Age range, y (median)	58 (18–82)
Smoking, n (%)	107 (25.8)
Multiple aneurysms, n (%)	179 (43.2)
Diabetes mellitus, n (%)	29 (7)
Chronic renal failure, n (%)	20 (4.8)
Pretreatment mRS score, n (%)	
0–2	393 (94.9)
3–5	21 (5.1)
Location, n (%)	
ICA	385 (82.8)
Petrous	10 (2.1)
Cavernous	77 (16.6)
Paraophthalmic	249 (53.5)
Posterior communicating	40 (8.6)
Anterior choroidal	5 (1.1)
Carotid bifurcation	4 (0.9)
Anterior communicating	2 (0.4)
ACA	4 (0.9)
MCA	12 (2.6)
Posterior circulation	62 (13.3)
Aneurysm shape, n (%)	
Saccular	317 (68.2)
Fusiform	122 (26.2)
Blister	12 (2.6)
Dissection	14 (3)
Measurements, mm (median; range)	
Maximal diameter*	7.6 (1–60)
Daughter sac, n (%)	116 (24.9)
Subarachnoid hemorrhage, n (%)	
Acute (<2 wk)	13 (3.1)
Remote (>2 wk)	36 (8.7)
Previous treatment, n (%)	
Endovascular	38 (8.2)
Surgery	13 (2.8)
Both	5 (1.1)

ACA indicates anterior cerebral artery; ICA, internal cerebral artery; MCA, middle cerebral artery; and mRS, modified Rankin Scale.

*Data were not available for 15 aneurysms.

Table 2. Treatment Outcomes

Parameter	Number
No. of pipelines, n (%)	
1	319 (77.1)
2	69 (16.7)
≥3	26 (6.3)
Platelet function test, n (%)	
Yes	399 (96.4)
No	15 (3.6)
Type of platelet function test, n (%)	
Whole-blood lumi-aggregometer	56 (14)
Light-transmission aggregometry	117 (29.3)
VerifyNow	226 (56.7)
Clopidogrel responder, n (%)	
Yes	284 (71.2)
No	115 (28.8)
Nonresponders' treatment, n (%)	
Switch to ticagrelor	37 (32.2)
No switch	78 (67.8)
Nonresponders maintained on clopidogrel, n (%)	
Clopidogrel boost (600 mg) within 24 h	51 (65.4)
No clopidogrel boost, n (%)	27 (34.6)
Last angiographic follow-up, mo (median)*	13.2 (1–83)
Follow-up occlusion*, n (%)	
Complete (100%)	303 (79.8)
Near complete (90%–99%)	24 (6.3)
Partial (<90%)	53 (13.9)
Retreatment	
Endovascular	26 (5.6)
Follow-up mRS score, n (%)†	
0–2	368 (93.6)
3–5	18 (4.6)
6 (death)	7 (1.8)
Change in mRS score, n (%)†	
Improved	127 (32.3)
No change	226 (57.5)
Worsened	40 (10.2)
Complications, n (%)	
Thromboembolic	38 (9.2)
Symptomatic	23 (5.6)
Hemorrhagic	14 (3.4)
Symptomatic	9 (2.2)

mRS indicates modified Rankin Scale.
*Data were not available for 85 procedures.
†Data were not available for 21 procedures.

Table 3. Predictors of Thromboembolic Complications

Parameter	No Complications (n=376)	Complications (n=38)	*P* Value
Age, y (median; range)	58 (18–82)	54 (29–82)	0.366
Sex, n (%)			0.754
Female	309 (90.6)	32 (9.4)	
Male	67 (91.8)	6 (8.2)	
Smoking, n (%)			0.647
Yes	96 (89.7)	11 (10.3)	
No	280 (91.2)	27 (8.8)	
Multiple aneurysms, n (%)			0.883
Yes	163 (91.1)	16 (8.9)	
No	213 (90.6)	22 (9.4)	
Diabetes mellitus, n (%)			0.37
Yes	25 (86.2)	4 (13.8)	
No	351 (91.2)	34 (8.8)	
Chronic renal failure, n (%)			0.51
Yes	19 (95)	1 (5)	
No	357 (90.6)	37 (9.4)	
Pretreatment mRS score, n (%)			0.955
0–2	357 (90.8)	36 (9.2)	
3–6	19 (90.5)	2 (9.5)	
Location, n (%)			0.528
ICA	278 (91.7)	25 (8.3)	
Pcom	31 (93.9)	2 (6.1)	
Acom	2 (100)	0	
ACA	3 (75)	1 (25)	
MCA	10 (83.3)	2 (16.7)	
Posterior circulation	52 (86.7)	8 (13.3)	
Aneurysm shape, n (%)			0.497
Saccular	246 (91.4)	23 (8.6)	
Fusiform	107 (88.4)	14 (11.6)	
Blister	9 (90)	1 (10)	
Dissection	14 (100)	0	
Measurements, mm (median)			
Maximal diameter*	8.2 (1.6–60)	11 (2–44.5)	0.024
Daughter sac, n (%)			0.283
Yes	99 (93.4)	7 (6.6)	
No	276 (89.9)	31 (10.1)	
Subarachnoid hemorrhage, n (%)			0.964
No	331 (90.7)	34 (9.3)	
Acute (<2 wk)	12 (92.3)	1 (7.7)	
Remote (>2 wk)	33 (91.7)	3 (8.3)	

(*Continued*)

Table 3. Continued

Parameter	No Complications (n=376)	Complications (n=38)	*P* Value
Previous treatment, n (%)			0.154
No	326 (90.1)	36 (9.9)	
Yes	50 (96.2)	2 (3.7)	
Treatment, n (%)			
Number of pipelines			0.479
1	292 (91.5)	27 (8.5)	
2	62 (89.9)	7 (10.1)	
≥3	22 (84.6)	4 (15.4)	

ACA indicates anterior cerebral artery; Acom, anterior communicating artery; ICA, internal carotid artery; MCA, middle cerebral artery; mRS, modified Rankin Scale; and Pcom, posterior communicating artery.

*Data were not available for 15 procedures.

responders (51.9% versus 5.6%; *P*<0.0001). Considering only clopidogrel nonresponders, patients who were switched to ticagrelor had a significantly lower rate of thromboembolic complications compared with patients who remained on clopidogrel (2.7% versus 24.4%; *P*=0.004), even after controlling for aneurysm maximal diameter using multivariable analysis (odds ratio, 0.085; 95% confidence interval, 0.011–0.672; *P*=0.019; Figure 1). In nonresponders who remained on clopidogrel, the rate of thromboembolic complications was lower in those who received a clopidogrel boost within 24 hours pre-procedure when compared with those who did not (9.8% versus 51.9%; *P*=0.00004). Although there was a trend in nonresponders who were switched to ticagrelor toward a lower rate of thromboembolic complications compared with those who were maintained on clopidogrel and received a clopidogrel boost (2.7% versus 9.8%), the difference did not reach statistical significance (*P*=0.25). Additionally, there was no significant difference in the thromboembolic rate between clopidogrel responders and nonresponders who were switched to ticagrelor (5.6% versus 2.7%; *P*=0.41). On Kaplan–Meier curve, there was a statistically significant difference in the rate of thromboembolism-free procedures overtime among the 4 groups (clopidogrel responders, clopidogrel nonresponders who remained on their dose, clopidogrel nonresponders who received a boost of clopidogrel, and clopidogrel nonresponders who were switched to ticagrelor; *P*<0.0001). This difference continued to increase ≤20 months post-procedure (Figure 2). There was no significant difference in the hemorrhagic complications between groups (Table 4).

Discussion

In this study, we report a multicenter cohort that evaluates the use of platelet function testing before PED placement for the treatment of intracranial aneurysms. Clopidogrel nonresponders experienced a significantly higher rate of thromboembolic complications when compared with clopidogrel responders. This rate was significantly lower in nonresponders who were switched to ticagrelor when compared with those who remained on clopidogrel. In nonresponders who remained on clopidogrel, the rate of thromboembolic complications was significantly lower in those who received a clopidogrel boost within 24 hours pre-procedure. This study is unique in its ability to compare known clopidogrel nonresponders who

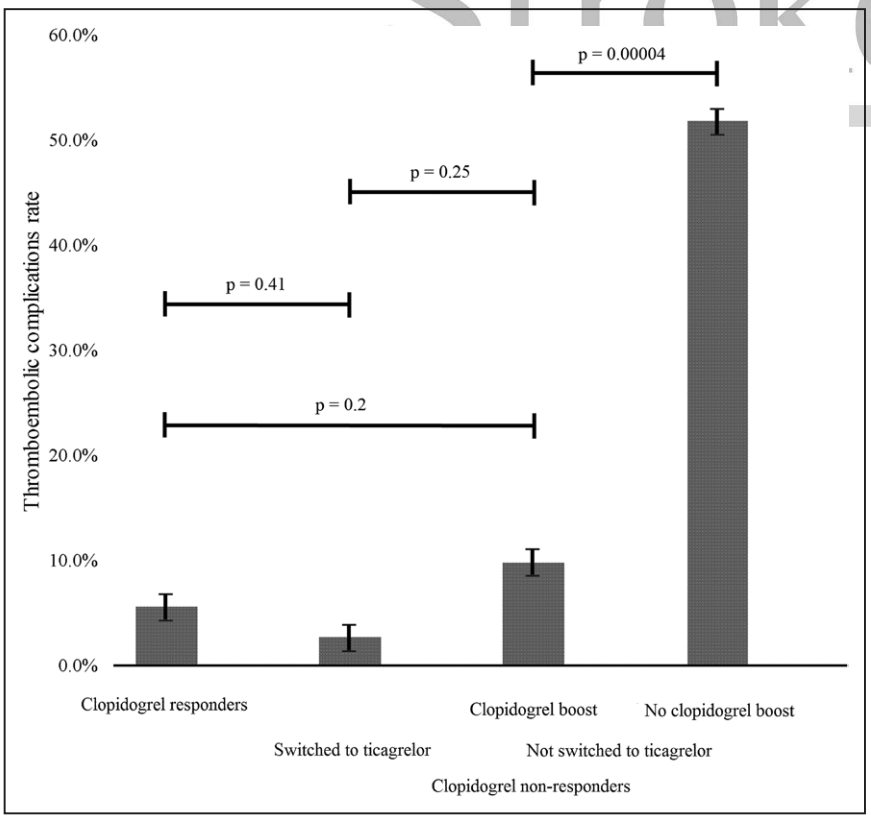

Figure 1. Rate of thromboembolic complication in clopidogrel responders compared with nonresponders.

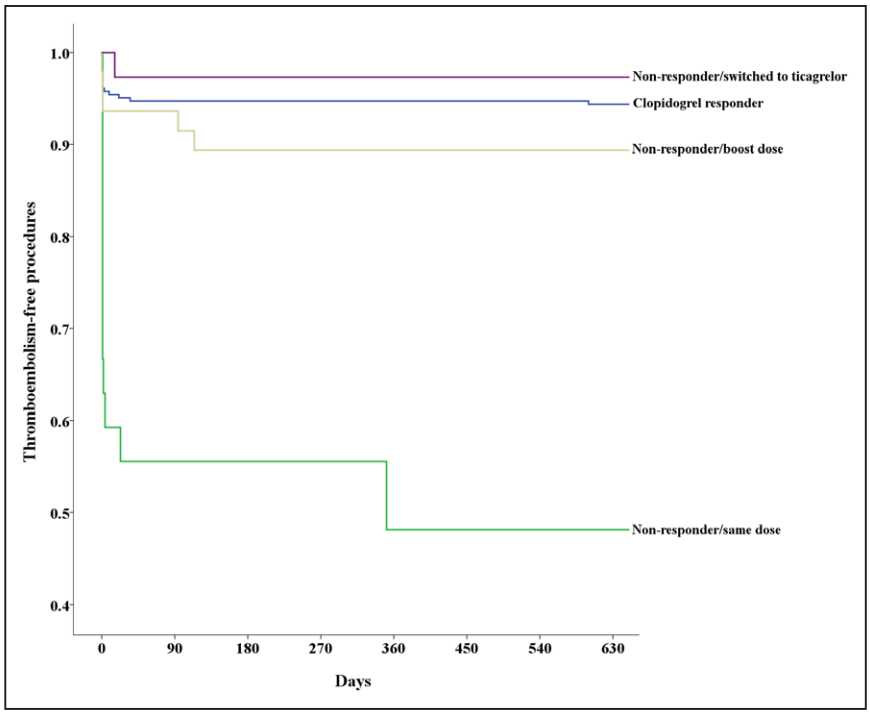

Figure 2. Kaplan–Meier curve comparing the time of occurrence of thromboembolism between different treatment regimens, including clopidogrel responders, clopidogrel nonresponders who remained on their dose, clopidogrel nonresponders who received a boost of clopidogrel, and clopidogrel nonresponders who were switched to ticagrelor.

remained on clopidogrel to a group of nonresponders who were subsequently transitioned to an alternative antiplatelet regimen or boosted with additional clopidogrel.

Thromboembolic Complications

Coil embolization alone for the treatment of intracranial aneurysms is associated with significant rates of recanalization, particularly in large complex aneurysms.[10–12] In an effort to improve aneurysm obliteration rates, especially large or wide-necked aneurysms, stent-assisted coiling[13–15] and flow diversion techniques have been developed.[16–19] These metallic high-surface-area devices can be complicated by thromboembolism, which is the most frequent cause of periprocedural morbidity.[15,19–22] Flow-diverting stents, such as the PED, are designed to remodel the vessel lumen by providing a scaffold for endothelialization while diverting blood flow away from the aneurysm. These unique mechanisms of action require a high-surface-coverage ratio with the potential for platelet activation and thrombus formation. Thromboembolic complications have been reported in 4% to 9% of PED cases, which is comparable to the overall rate in the current series.[17,18,23–25] To minimize this risk, dual antiplatelet therapy is implemented pre-procedure and continued for at least 3 months post-procedure. The standard antiplatelet regimen consists of aspirin and clopidogrel; yet, an emerging body of literature suggests that a significant minority of patients do not respond to clopidogrel.[4,23,26–28] This had led to the development and use of preprocedure platelet function testing to assess for clopidogrel responsiveness to tailor the dual antiplatelet therapy on individualized basis. Perhaps the largest experience with clopidogrel responsiveness and platelet function testing can be found in the cardiology literature where tailoring dual antiplatelet therapy based on platelet function testing for coronary stenting has produced mixed results and remains a controversial topic.[29–34] However, the use of these tests has not been established in the setting of PED placement for the treatment of intracranial aneurysms, and considerable controversy surrounds their efficacy.[35,36]

After intracranial aneurysm treatment with the PED, age (≥65 years), larger aneurysm size (≥10 mm), longer procedure time (>116 minutes), and deployment of multiple PEDs have been correlated with a higher rate of symptomatic thromboembolic complications and consequently a higher mortality rate.[25,35,37] Additionally, Daou et al[24] identified PRUs in excess of 240 as a risk factor for thromboembolic complications of any type, whereas PRUs >150 were associated with cerebral thromboembolic complications. An intermediate cutoff value of >208 has been associated with an increased rate of symptomatic thromboembolic complications in the GRAVITAS trial (Gauging Responsiveness With A VerifyNow P2Y12 Assay: Impact on Thrombosis and Safety).[38] Although such a prospective study does not yet exist in the neuroendovascular literature, this cutoff has proven safe in patients undergoing PED placement.[25] These findings suggests that clopidogrel nonresponders, or even hyporesponders, are at an increased risk for thromboembolic complications after PED placement. Although these studies are suggestive, they were limited by a lack of a control group without therapeutic adjustments based on the preoperative PRU. The present study overcomes this limitation and reaches a similar conclusion.

Inadequate response to clopidogrel has been detected in up to half of patients.[4] The variability in response is attributed to differences in active metabolite generation caused by inconsistent absorption, functional variability in CYP isoenzyme activity, and drug–drug interactions.[39] In the present study, clopidogrel nonresponders represented 28.8% of the study population. Although there was a significantly higher rate of nonresponders with shorter duration of dual antiplatelet therapy, the overall rate is comparable to what is reported in the literature.[29–34,40] Alternative treatment strategies including increasing clopidogrel dose or the use of a more potent $P2Y_{12}$

Table 4. Effect of Antiplatelet Therapy on the Rate of Thromboembolic and Hemorrhagic Complications

Parameter		Thromboembolic				Hemorrhagic		
				P Value				
		Yes	No	Univariable	Multivariable*	Yes	No	*P* Value
Platelet function test, n (%)								
Yes		36 (9)	363 (91)	0.57	…	14 (3.5)	385 (96.5)	0.46
No		2 (3.3)	13 (86.7)			0	15 (3.5)	
Clopidogrel responder, n (%)								
Yes		16 (5.6)	268 (94.4)	0.0002	OR, 0.23; 95% CI, 0.1–0.5; *P*=0.0001	9 (3.2)	275 (96.8)	0.56
No		20 (17.4)	95 (82.6)			5 (4.3)	110 (95.7)	
Clopidogrel responders per platelet function test, n (%)								
Whole-blood lumi-aggregometer		2 (6.7)	28 (93.3)	0.33	…	1 (3.3)	29 (96.7)	0.48
Light transmission aggregometry		2 (2.4)	80 (97.6)			1 (1.2)	81 (98.8)	
VerifyNow		12 (7)	160 (93)			7 (4.1)	165 (95.9)	
Nonresponders' treatment, n (%)								
Switch to ticagrelor		1 (2.7)	36 (97.3)	0.004	OR, 0.085; 95% CI, 0.011–0.672; *P*=0.019	0	37 (100)	0.11
No switch		19 (24.4)	59 (75.6)			5 (6.4)	73 (93.6)	
Nonresponders maintained on clopidogrel, n (%)								
Clopidogrel boost (600 mg) within 24 h		5 (9.8)	46 (90.2)	0.00004	OR, 0.11; 95% CI, 0.03–0.36; *P*=0.0003	1 (2)	50 (98)	0.06
No clopidogrel boost		14 (51.9)	13 (48.1)			4 (14.8)	23 (85.2)	
Comparison groups, n (%)								
A	Clopidogrel responders	16 (5.6)	268 (94.4)	0.41	…	9 (3.2)	275 (96.8)	0.25
	Nonresponders switched to ticagrelor	1 (2.7)	36 (97.3)			0	37 (100)	
B	Clopidogrel responders	16 (5.6)	268 (94.4)	0.2	…	9 (3.2)	275 (96.8)	0.69
	Nonresponders/not switched; clopidogrel boost (600 mg)	5 (9.8)	46 (90.2)			1 (2)	50 (98)	
C	Nonresponders switched to ticagrelor	1 (2.7)	36 (97.3)	0.25	…	0	37 (100)	0.43
	Nonresponders/not switched; clopidogrel boost (600 mg)	5 (9.8)	46 (90.2)			1 (2)	50 (98)	

CI indicates confidence interval; and OR, odds ratio.
*After controlling for aneurysm maximal diameter.

antagonist are used by some clinicians in these situations.[41,42] However, little data exist to guide this therapeutic substitution in the cerebrovascular literature.

Clopidogrel nonresponders experienced a significantly higher rate of thromboembolic complications when compared with clopidogrel responders (17.4% versus 5.6%; *P*=0.0002). This rate was significantly lower in nonresponders who were switched to ticagrelor when compared with those who remained on clopidogrel (2.7% versus 24.4%; *P*=0.004). In nonresponders who remained on clopidogrel, the rate of thromboembolic complications was significantly lower in those who received a clopidogrel boost within 24 hours pre-procedure when compared with those who did not (9.8% versus 51.9%; *P*=0.00004). These findings lend supports to the use of platelet function testing before PED placement. Additionally, the study demonstrates that initiating alternative antiplatelet strategies in patients identified as clopidogrel nonresponders may reduce thromboembolic complications without increasing the risk of hemorrhagic complications.

Limitations

The primary limitations of the current study include its retrospective design and variability in the management of patients across centers. Retrospective studies are subject to incomplete data sets, selection bias, and unidentified confounders. The inclusion of multiple institutions improves the generalizability of the findings but introduces variability in patient management. The difference in management strategies among the 3 institutions, including preprocedural antiplatelet regimens and timing of drug administration, may affect stroke rates, and outcome variability existed in the duration of clopidogrel administration before platelet function testing ranging from 3 to 14 days; it is possible that some patients, especially those at the lower end of this range, had not achieved steady-state platelet inhibition at the time of testing. Even if the reason for nonresponsiveness is a short duration of clopidogrel administration, initiating alternative antiplatelet regimen as if they are truly nonresponders (ie, CYP2C19 polymorphisms) may be the safest approach. Choice of platelet function test and

their respective cutoff values were based on protocols intrinsic to each institution in accordance with manufacturer recommendations. Postprocedure imaging to detect silent ischemic strokes was not routinely obtained. There was also a variation in the treatment strategy for intraprocedural thrombosis. Although this reflects common clinical practice, it introduced the possibility of underestimating ischemic stroke rates. This risk is assumed to be evenly distributed among groups and therefore was not expected to impact the results. Finally, although this is the largest study to date exploring the topic, it may be underpowered for evaluation of clinical outcomes.

Conclusions

In patients undergoing PED placement for the treatment of intracranial aneurysms, clopidogrel nonresponders experienced a significantly higher rate of thromboembolic complications when compared with clopidogrel responders. However, this risk seems to be mitigated in nonresponders who were switched to the alternative $P2Y_{12}$ antagonist, ticagrelor, or received a clopidogrel boost within 24 hours pre-procedure. Identifying clopidogrel nonresponders and initiating an alternative antiplatelet regimen may reduce thromboembolic complications associated with PED treatment of intracranial aneurysms.

Disclosures

Dr Siddiqui is a consultant to Covidien. Dr Levy receives an honorarium for training and lectures for Covidien; is a national PI for Covidien – SWIFT Prime trials; is a shareholder for Intratech Medical, Ltd, and NeXtGen Biologics; is a consultant for Pulsar Vascular; is a AIS clinical advisor for Stryker; is a member of advisory board for NeXtGen Biologics and MEDX; and gives carotid training for physicians in Abbott Vascular. The other authors report no conflicts.

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Stroke
Journal of the American Heart Association

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Stroke. published online April 14, 2017;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628