Management of antiplatelet therapy in patients undergoing neuroendovascular procedures

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Neuroendovascular techniques for treating cerebral aneurysms and other cerebrovascular pathology are increasingly becoming the standard of care. Intraluminal stents, aneurysm coils, and other flow diversion devices typically require concomitant antiplatelet therapy to reduce thromboembolic complications. The variability inherent with the pharmacodynamic response to common antiplatelet agents such as aspirin and clopidogrel complicates optimal selection of antiplatelet agents by clinicians. This review serves to discuss the literature related to antiplatelet use in neuroendovascular procedures and provides recommendations for clinicians on how to approach patients with variable response to antiplatelet agents, particularly clopidogrel.

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KEY WORDS aneurysm; clopidogrel; intracranial stenosis; platelet reactivity; vascular disorders

NEUROVASCULAR techniques are increasingly becoming the standard for the treatment of intracranial aneurysms and other cerebrovascular pathology. Stent and flow diversion techniques are often used, requiring peri- and postprocedural medical therapy, in particular antiplatelet medications, to minimize complications. Adequately trained operators and appropriate facilities are still relatively limited across the US; thus, many of these procedures are primarily performed at regional referral centers. The intent of this review is to introduce clinicians to the role of antiplatelet pharmacotherapy in preventing complications during and after various types of neuroendovascular interventions. The current dependence on complicated antiplatelet regimens and the variability in patient-specific response has led to the increased use of platelet function testing to determine the optimal dose and choice of medication. The role of platelet function testing and the use of agents for thromboembolic rescue in this paradigm will also be reviewed.

Neuroendovascular Therapeutics

Coil embolization, most commonly known for its role in the treatment of cerebral aneurysms, is the process by

which a series of small (typically 0.010–0.018-inch) platinum coils are passed through a catheter into the lumen of an aneurysm to occlude it, thereby preventing rupture of the aneurysm. These coils are procoagulant by nature, with a high surface area, leading to early thrombosis and ultimately formation of vascular collagenous scar tissue.^{10,11} The use of antiplatelet therapy in the periprocedural period is common due to the significant risk of thromboembolic events, as high as 12.5% in 1 large study, although this must be weighed among other hemorrhagic risk factors, especially in the setting of a ruptured aneurysm.⁵² While stent-assisted coiling has allowed for the endovascular treatment of lesions once deemed “uncoilable,” the stents pose a risk for thrombosis through perturbation of the endothelium and release of procoagulant factors into the blood, as well as by providing a lattice on which thrombi may form. Mocco et al. demonstrated a 4% risk of thromboembolic events with stent-assisted coiling; however, 1% were intraprocedural and immediately corrected, while all others were associated with interruption of periprocedural dual antiplatelet therapy (DAT).⁴²

Aside from being a structural adjunct, some intracranial stents have been developed to treat aneurysms alone by way

ABBREVIATIONS ACS = acute coronary syndrome; ARU = aspirin reaction unit; CYP = cytochrome P450; DAT = dual antiplatelet therapy; DWI = diffusion-weighted imaging; GRAVITAS = Gauging Responsiveness with a VerifyNow P2Y12 assay: Impact on Thrombosis and Safety; HTPR = high on-treatment platelet reactivity; LTA = light/optical transmission aggregometry; LTPR = low on-treatment platelet reactivity; PCI = percutaneous coronary intervention; PED = Pipeline embolization device; PRU = P2Y12 reaction unit.

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of diverting blood flow away from the body of the lesion and permitting natural thrombosis and inflammatory pathways to allow the aneurysm to resolve over time. Thrombosis rates with the Pipeline embolization device (PED; ev3 Neurovascular) have tended to be higher than non-flow-diverting stents, with thrombosis rates ranging from 8% to 12%, even when combined with DAT.^{14,32,38} The 6-month incidence of in-stent stenosis has reportedly ranged from 3.5% to 16%.¹² Because of these issues, significant interest has developed in the neurointerventional community regarding the optimization of antiplatelet therapy.

Platelet Function

Platelets contribute to the development of both hemostasis and thrombosis as part of the normal physiological response. In clinical practice, extreme conditions causing increased or decreased platelet reactivity may predict adverse clinical events, such as ischemia or bleeding, and therefore evidence of increased or decreased platelet reactivity may be noteworthy in some patients. Historically, patients at high risk for thrombotic events included patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI). In a similar fashion, patients undergoing cerebrovascular procedures are also at high risk for thromboembolic or ischemic events. Consequently, DAT is initiated to prevent thromboembolic events, but the risk for thromboembolic events remains in some patients. This increased risk is likely due to differences in stent dynamics when comparing intracranial and coronary stents, as well as high interpatient pharmacological variability with antiplatelet medications, mainly with clopidogrel therapy. The major limitation with clopidogrel therapy is the incomplete activation of its parent compound due to genetic polymorphism, drug-drug interactions, or clinical factors known to increase platelet reactivity. This phenomenon is known as high on-treatment platelet reactivity (HTPR).⁶³ Conversely, low on-treatment platelet reactivity (LTPR) may also be observed with clopidogrel or other P2Y₁₂ receptor antagonist therapy due to either a genetic polymorphism or the high potency of antiplatelet effects. HTPR and LTPR with P2Y₁₂ receptor antagonist therapy have been associated with ischemic and bleeding complications, respectively.^{7,68}

Incomplete or excess bioactivation of clopidogrel has been implicated in high or low platelet reactivity, respectively, with genetic polymorphism of cytochrome P450 (CYP) isoenzymes 2C19, 3A4, 3A5, 2C9, 1A2, 2B6, paroxonase 1, and ATP-binding cassette efflux transporter.³⁰ This led the FDA to revise the prescribing information for clopidogrel in 2010 to include a boxed warning to inform clinicians regarding the potentially detrimental clinical effects of “poor metabolizers” in patients undergoing PCI. There are more than 25 known variant alleles of CYP2C19, but CYP2C19*2 is the most commonly occurring loss-of-function allele.^{59–61} It occurs with high frequency among different ethnic groups, i.e., 12% in Caucasians, 15% in African Americans, and 29%–35% in Asians. Reduced or absent activity is also observed with alleles *3–*8, which are found in less than 1% of all ethnic groups, except for Asians, where *3 is found in 2%–9% of the population.⁶⁰

Other significant mutations to note are functional activity allele *1 and increased activity allele *17. The degree of CYP2C19 function depends on the genotype, whether it is homozygous or heterozygous alleles, as it will determine whether a patient is an ultrarapid metabolizer (e.g., *1/*17, *17/*17), extensive metabolizer (e.g., *1/*1), intermediate metabolizer (e.g., *1/*2, *1/*3, *2/*17), or poor metabolizer (e.g., *2/2, *2/*3, *3/*3). Patients who are ultrarapid metabolizers and poor metabolizers are of clinical importance and are identified in 5%–30% of all populations and 2%–15% of all populations (specifically 2%–5% of Caucasians and African Americans, and 15% of Asians), respectively. Observational cohort studies and meta-analyses to date involving patients with ACS undergoing PCI have characterized the increased incidence of major adverse cardiac events, especially stent thrombosis, in patients who were categorized as poor metabolizers (*2 carrier, *1*2, *2*2). Conversely, an increased incidence of bleeding was demonstrated in patients who were categorized as ultrarapid metabolizers (*17 carrier).³⁰ Paré et al. reported conflicting results on clinical outcomes of CYP2C19 genetic variations in patients with ACS without ST-segment elevation (Clopidogrel in Unstable Angina to Prevent Recurrent Events [CURE] trial) and in patients with atrial fibrillation (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events [ACTIVE] A trial); however, the study is limited by the low incidence of metabolizer phenotypes.⁴⁹

The American Heart Association and the American College of Cardiology Foundation do not recommend routine CYP2C19 genetic testing in all patients due to many clinical concerns.²⁷ These concerns include lack of prospective, randomized clinical trials to support the effect of CYP2C19 on clinical outcomes, wide variation in CYP2C19 genetic polymorphisms in the general population, the cost and reimbursement issues associated with genetic testing, interpreting the pharmacogenetics test result, availability of other thienopyridine P2Y₁₂ ADP receptor antagonists, and utilizing the platelet function test as an alternative method of monitoring therapy. However, their clinical expert consensus document suggests genetic testing may benefit patients at high risk for thrombotic complications (e.g., patients with prior stent thrombosis, multivessel PCI procedures, and/or other risk factors associated with high platelet reactivity). With the current body of evidence, the Clinical Pharmacogenetics Implementation Consortium Guideline suggests using standard dosing of clopidogrel if a high-risk patient with ACS is undergoing a PCI procedure and is identified as an ultrarapid or extensive metabolizer, or changing to another thienopyridine P2Y₁₂ ADP receptor antagonist if the patient is identified as an intermediate or poor metabolizer.⁶¹ Although point-of-care testing for genetic variation is currently unavailable, there are 4 commercially available tests approved by the Center for Devices and Radiological Health (Spartan RX CYP2C19 Test System by Spartan Bioscience, Inc.; Verigene CYP2C19 Nucleic Acid Test by Nanosphere, Inc.; INFINITI CYP2C19 Assay by AutoGenomics, Inc.; and Roche AmpliChip CYP450 microarray by Roche Molecular Systems, Inc.). Similar concepts may be applied to patients undergoing complex neurovascu-

lar intervention in which CYP2C19 genotyping may be clinically important in a subset of patients. Alternatively, a platelet function test may be used to monitor clopidogrel therapy, although there is no strong evidence to support modifying clopidogrel dose accordingly.

Clinically, variances in platelet reactivity outside acceptable parameters are determined by performing a platelet function test. Based on the predetermined cutoff values, a patient can be categorized as a hypo- or hyper-responder or a nonresponder or as resistant to antiplatelet therapy. Nonresponsiveness or resistance refers to the inability of a medication to inhibit platelet function, so that the medication has a null laboratory and clinical effect.⁷ This can be measured by comparing the results of the platelet function test before and after the drug exposure; however, this may not be a good prognostic indicator due to variable baseline platelet function among patients. Thus, the term “hyporesponsiveness” is used more commonly in clinical practice as the quality indicator of HTPR during antiplatelet therapy. Correspondingly, the term “hyperresponsiveness” is used to identify patients with LTPR during antiplatelet therapy.

Platelet Function Tests

Platelet reactivity during antiplatelet therapy (also known as residual platelet reactivity) may be quantified with the use of a platelet function test. The gold standard method is light/optical transmission aggregometry (LTA) because it can provide comprehensive platelet function evaluation, where it can be used to diagnose various platelet function disorders and bleeding disorders.⁴⁸ When LTA was performed to predict clinical outcomes at 1-year follow-up in patients undergoing elective coronary stent implantation—which included all-cause death, nonfatal acute myocardial infarction, stent thrombosis, and ischemic stroke—the negative and positive predictive values were 94% and 11.7%, respectively, with sensitivity and specificity of 60.2% and 59.1%, respectively (using 5 μ mol/L ADP as the agonist).⁸ However, its clinical use has been limited mainly due to lack of standardization and the time-consuming preparation process. The main issues include choosing an agonist or activator and its specific concentration, as well as the preparation of either platelet-rich or platelet-poor plasma. Ideally, point-of-care testing should be rapid, require low sample volume, minimize sample manipulation or preparation, and correlate well with LTA. Newer methods for point-of-care testing are now available, with advantages that include semiautomation, low required sample volume, and minimal to no required sample preparation.^{48,54,70} In addition to many technical variations in each of the platelet function tests, there also appears to be variation in clinical utility as some are used to monitor antiplatelet treatment effects, screen primary hemostasis, diagnose platelet dysfunction, predict bleeding risk, and guide transfusion therapy.⁴¹ Semiautomated tests include multiple electrode aggregometry, Multiplate (Roche Diagnostics), Platelet Works (Helena Laboratories), vasodilator-stimulated phosphoprotein phosphorylation, Cone and Plate(let) assay, and IMPACT-R (Daned SA). The clinical utility of these tests is limited by additional sample preparation, the requirement of an experienced technician,

and the limited clinical data available in monitoring antiplatelet therapy. Automated tests include Platelet Function Analyzer (PFA-100; Siemens Healthcare Diagnostics) and VerifyNow (Accriva Diagnostics). PFA-100 may be useful in detecting platelet dysfunction in patients without antiplatelet therapy, as in von Willebrand disease, and assessing the effects of aspirin therapy. However, this test does not correlate well with thienopyridine therapy and may be of limited value in some clinical settings. In comparison, VerifyNow may not be useful in detecting primary hemostasis but may be useful in assessing antiplatelet treatment effects, including thienopyridine therapy.

The most commonly used point-of-care platelet function testing is VerifyNow, and it correlates well with LTA ($r = 0.67$ – 0.77).²¹ VerifyNow, previously known as Ultegra Rapid Platelet Function Assay, uses a similar concept as LTA to quantify the degree of platelet aggregation as measured by light transmittance. A whole blood sample is required using a 2-ml Greiner partial fill Vacuette tube, and with its placement in the VerifyNow System (an analyzer instrument) containing a disposable, reagent-specific assay device, the result is available within 5–10 minutes (<http://www.accriva.com/products/verifynow-system-platelet-reactivity-test>). Platelets in the blood sample are activated with a reagent of choice and aggregate around fibrinogen-coated beads. The degree of platelet aggregation in this final chamber changes light transmittance, where a decrease in light transmittance (expressed as low unit of measurement) indicates increased platelet function inhibition (or good response to antiplatelet therapy). Different reagent-specific assay devices can be used to assess the effects of aspirin, P2Y₁₂ inhibitor, or glycoprotein IIb/IIIa inhibitor on platelet function and are expressed as aspirin reaction units (ARUs), P2Y₁₂ reaction units (PRUs), or platelet aggregation units, respectively.

The association between clinical outcomes and residual platelet reactivity in patients undergoing neuroendovascular procedures requiring DAT has been explored in small, retrospective, single-center studies (Table 1). VerifyNow was most commonly used as the platelet function test due to the ease of its use and validation with the LTA. Most of these studies were published in the last 5 years. The collective interpretation of these study results is challenging due to many confounding variables. The variables include the neurointerventionalists' surgical experience, nonstandardized antiplatelet regimens, variable definitions for HTPR and LTPR, and different definitions for adverse clinical events.

There are 4 studies utilizing receiver operating characteristic analyses to identify optimal cutoffs for best predicting thromboembolic and bleeding events based on platelet function analysis (Table 1).^{22,33,34,44} Each of these studies used VerifyNow with the cutoff values established using either PRUs or P2Y₁₂ percentage inhibition. Kang et al. and Nishi et al. found cutoff values for ischemic and bleeding events, respectively, but the specificity and sensitivity were low.^{33,44} Goh et al. and Kashiwazaki et al. found similar cutoff values for major bleeding events with high sensitivity and specificity,^{22,34} but the clinical application of P2Y₁₂ percentage inhibition in assessing antiplatelet therapy remains controversial. This is primarily due to the

TABLE 1. Receiver operating characteristic analysis in endovascular neurosurgery

Authors & Year	Cutoff Value	End Point	AUC (95% CI)	% Sensitivity	% Specificity
Kang et al., 2010	PRU >295	TE	0.675 (0.526–0.825)	75	57
Goh et al., 2013	≥72% inhibition	Major bleed	0.96 (0.89–1)	100	90.9
	≥53% inhibition	Major/minor bleed	0.75 (0.58–0.93)	70	75.7
Kashiwazaki et al., 2014	≤26% inhibition	TE; major bleed	0.79 (0.65–0.93)	81.1	69.2
	≥74% inhibition		0.82 (0.71–0.98)	86.2	87.5
Nishi et al., 2016	PRU ≤175	Bleed	0.63	54	72

AUC = area under the curve; TE = thromboembolism.

VerifyNow was the platelet function test used in each of the 4 studies.

lack of association between P2Y12 percentage inhibition and clinical outcomes,³³ the inability to make the P2Y12 percentage inhibition correspond with PRU, and the dependence of P2Y12 percentage inhibition on a patient's baseline platelet function value. These varied results led Accriva Diagnostics in August 2012 to voluntarily withdraw in North America the reporting of P2Y12 percentage inhibition to accurately assess and reflect platelet function during antiplatelet therapy.

Summary of Experience With Antiplatelet Agents Used in Neuroendovascular Procedures

Antiplatelet agents are necessary for patients undergoing neuroendovascular procedures, particularly intracranial stenting and aneurysm coiling. Evaluation of the classic dual antiplatelet combination of aspirin and clopidogrel constitutes the majority of the published literature in this area (Table 2).⁹ Currently, the combination of aspirin and clopidogrel is recommended prior to neuroendovascular stent deployment, although there is considerable heterogeneity in treatment.¹⁹ The duration of therapy tends to be longer than that for bare metal stent deployment in PCI, with most practitioners prescribing DAT for at least 3 months. Numerous other agents have been investigated to a limited degree in this clinical context, including prasugrel, ticagrelor, cilostazol, and glycoprotein IIb/IIIa inhibitors, such as abciximab and eptifibatide. These agents are primarily used in the case of clopidogrel resistance or, in the case of glycoprotein IIb/IIIa inhibitors, acute procedural thrombosis. The use of more than 1 antiplatelet agent in neuroendovascular procedures permits the prescriber to take advantage of the additive effects of these agents. Several mechanisms of action come into play when combining antiplatelet agents, including inhibition of thromboxane, the P2Y12 ADP receptor, cyclic AMP, and the glycoprotein IIb/IIIa receptor (Table 3).

Aspirin

Aspirin is the most common component of DAT in patients undergoing neuroendovascular procedures. Aspirin is widely available, well tolerated, and has extensive clinical evidence supporting its use in the cardiovascular arena. Aspirin is typically initiated at least 3–5 days prior to carotid or intracranial stenting, although many practitioners

may start therapy as long as 14–21 days prior to a procedure. In emergency neuroendovascular interventions in which preprocedure aspirin therapy is not possible, loading doses have varied from 200 to 650 mg. Based on various laboratory definitions for HTPR, the incidence of aspirin hyporesponsiveness varied from 2.1% to 13.5%.^{5,17,20,36,47,53} Prabhakaran et al. found a strong, inverse relationship between preprocedural weekly aspirin dose and ARUs, in which lower aspirin doses were associated with higher ARUs.⁵³ Their findings suggest that aspirin should be given at a dose of at least 100 mg daily to maintain ARUs ≤ 550. While the antiplatelet effect of aspirin in some individuals may be attenuated, there is no evidence to suggest that this affects outcomes. Likewise, no evidence exists suggesting higher doses of aspirin (> 325 mg/day) or alternative antiplatelet agents are necessary in these cases. Nearly all studies investigating antiplatelet therapy in patients undergoing neuroendovascular procedures include aspirin as part of the antiplatelet therapy regimen, with doses ranging from 81 to 325 mg daily.^{2,16,17,20,22,25,28,34–36,43–47,66,70}

P2Y12 Inhibitors

Clopidogrel

Clopidogrel is the other most common component of DAT in patients undergoing neuroendovascular procedures. Variation in individual response to clopidogrel has sparked a great deal of research and controversy in the cardiovascular and neuroendovascular areas. The incidence of clopidogrel hyporesponsiveness has varied from 21% to 53.1% in patients undergoing neuroendovascular procedures.^{5,15–17,20,34–36,43,45,47,53,70} The use of clopidogrel after coronary interventions is well described, although currently the role of clopidogrel resistance and platelet function testing after PCI is not definitive. The Gauging Responsiveness with a VerifyNow P2Y12 assay: Impact on Thrombosis and Safety (GRAVITAS) study, which evaluated clopidogrel response in 2214 patients with HTPR undergoing PCI with drug-eluting stents, suggested that high-dose clopidogrel was no more effective than standard dose clopidogrel. However, subgroup analyses indicated that achievement of a target PRU (< 208) was associated with a lower risk for cardiovascular events.^{55,56} Asymptomatic and symptomatic thromboembolic events after neuroendovascular intervention have been primarily associated with clopidogrel hyporesponsiveness; this issue can result in events as high as 7.1% within 24 hours of the procedure, 41% within 30 days of the procedure, and

TABLE 2. Outcomes in clopidogrel hyporesponders

Authors & Year	No. of Patients (study dates)*	Treatment		Method & Definition of Hyporesponder	Outcome	
		Neuroendovascular	Antiplatelet		Laboratory	Clinical
Lee et al., 2008	98 (6/2006–4/2007)	Stent (intracranial aneurysms, intra- & extra-cranial artery stenosis)	CLP 300 mg LD (600 mg LD if same day or 300 mg LD if P2Y12 % inhibition <40%)/75 mg daily + ASA 325 mg daily, 5–10 days prior	VerifyNow prior to procedure; ARU <550, P2Y12 % inhibition ≥40%	Aspirin poor responders 2.1% (2/95), CLP poor responders 42.9% (42/98)	Clinical outcome defined in this study as intraprocedural thrombosis & thromboembolic events: overall asymptomatic TE events 3.1% (3/98); CLP poor responders, asymptomatic TE events 7.1% (3/42); no bleeding event data available
Müller-Schunk et al., 2008	50	Stent (extracranial stenosis, intracranial stenosis)	ASA 100 mg + CLP 300 mg LD ≥12 hrs prior, 75 mg daily (or >48 hrs prior); intraprocedure: heparin IV (ACT 200–300 sec); IV tirofiban to dissolve clot	Multiplate analyzer prior to procedure; ≤52 ARU	ASA nonresponders 0, CLP nonresponders 28% (14/50)	Overall transient intrainterventional thrombosis 2; overall TIA or infarction 3; adverse events in nonresponders vs responders 42% (5/12) vs 0% (0/36), p = 0.001
Prabhakaran et al., 2008	76 (5/2005–8/2006)	Stents (intracranial aneurysms, intra- & extra-cranial artery stenosis)	ASA alone 16/76 (21.0%), CLP alone 4/76 (5.3%), or ASA + CLP 56/76 (73.7%), loaded w/in 1 wk prior; intraprocedure: IV heparin (ACT 250–300 sec)	VerifyNow prior to procedure; ARU <550, P2Y12 % inhibition >40%	ASA low responders 4.2% (3/71), CLP low responders 50.9% (28/55)	Intraprocedure acute stent thrombosis or stenosis 0; intraprocedure aneurysmal rupture 1; w/ in 6 mos, TIA 3.9% (3/76); no bleeding event data available
Kang et al., 2010	186: 209 aneurysms (10/2008)	Coil embolization (ICA, ACA, MCA, PCA) ± stent	Intraprocedure: IV heparin 3000 units bolus, then 1000 units/hr	VerifyNow prior to procedure		Overall procedure-related TE events 9.1% (17/186); intraprocedure TE events 4.8% (9/186); postprocedure ischemic events 2.7% (5/186); procedural aneurysmal perforations 1.6% (3/186); procedure-related permanent morbidity or mortality 0
Pandya et al., 2010	238: data analysis based on 216 (2/2006–11/2007)	Embolization, stents (intracranial aneurysm, carotid stenosis, other)	ASA 81 mg daily, CLP 75 mg daily, ≥7 days prior; CLP 300–600 mg, ASA 325 mg LD if emergency	VerifyNow prior to procedure; ARU <550, P2Y12 % inhibition >50%	12% (26/216) ASA inadequate responder, 34% (74/216) CLP inadequate responder	
Drazin et al., 2011	52 (2007–2009)	Stent (intracranial stenosis, cervical carotid artery stenosis, intracranial aneurysms)	CLP 600 mg LD (suboptimal responders 300 mg LD if 10%–19%, 600 mg LD if <10%) + 75 mg daily, ≥12 hrs prior; ASA 81 mg daily day prior	VerifyNow prior to procedure; ARU ≤550, P2Y12 % inhibition ≥20%	ASA suboptimal responders 7/52 (13.5%), CLP suboptimal responders 19/52 (36.5%)	TE events in CLP suboptimal responders vs optimal responders 1 vs 0
Koerner et al., 2012	44 (8/2008–6/2009)	Stent (extracranial, intracranial), percutaneous transluminal angioplasty	ASA 100 mg daily, CLP 75 mg daily, ≥3 days prior; ASA 500 mg LD, CLP 300 mg LD if urgent	Multiplate analyzer prior to procedure; ≤468 ARU min	Hyporesponders 25% (11/44)	Overall new DWI lesions 36% (16/44), new DWI lesions in hyporesponders vs responders 36% (4/11) vs 33% (11/33)

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Authors & Year	No. of Patients (study dates)*	Treatment		Method & Definition of Hyporesponder	Outcome	
		Neuroendovascular	Antiplatelet		Laboratory	Clinical
Delgado Almandoz et al., 2013	44: 48 PED procedures, 54 aneurysms (11/17/2011–7/23/2012)	PED (intracranial aneurysm)	ASA 325 mg daily + CLP 75 mg daily (prasugrel 60 mg LD, then 10 mg daily if CLP hyporesponder; CLP dose reduced if hyperresponder; if prasugrel hyporesponder, then received ticagrelor 180 mg, then 90 mg 2x/day; if prasugrel hyperresponder, then prasugrel dose reduced; prasugrel 60 mg LD, then 10 mg daily, if urgent/emergency) 10 days prior; intraprocedure: heparin (ACT 2–2.5 times baseline)	VerifyNow prior to procedure; PRU 80–200	CLP hyporesponders (PRU >200) 26.2% (11/42); CLP hyporesponders (PRU >240) 21%; CLP hyperresponders (PRU <80) 21.4% (9/42); CLP hyperresponders (PRU <60) 14%	Normal response = PRU 60–240; TE events 8.3% (4/48), bleeding events 8.3% (4/48), major hemorrhagic complications in ASA/prasugrel 16.7% vs ASA/CLP 2.9%, p = 0.16
Goh et al., 2013	47 (5/2010–5/2011)	Coil embolization, balloon remodeling, stent assistance, stent (intracranial aneurysm, stenosis)	ASA 100 mg daily, CLP 75 mg daily, 3 days prior; intraprocedure: IV heparin (ACT 2 times normal); postprocedure: IV heparin (aPTT titration)	VerifyNow prior to procedure; major bleed $\geq 72\%$ inhibition, major & minor bleed $\geq 53\%$ inhibition	Hyperresponders ($\geq 72\%$ inhibition) 14.9% (7/47)	Overall bleeding event during procedure 23.4% (11/47); w/in 24 hrs postprocedure 6.4% (3/47); TIMI major bleeding events† 14.9 (7/47); TIMI minor bleeding events, small groin hematomas of little clinical significance; major bleeding events in hyperresponders 6.4% (3/47)
Fifi et al., 2013	Group A: 49 (9/2006–9/2008); Group B: 47 (10/2008–1/2011; additional 150–600 mg CLP prior to procedure if resistant)	Stent (extra-/intracranial stenosis, intracranial aneurysm)	ASA 81 mg daily + CLP 75 mg daily (600 mg LD if emergency), 5 days prior; intraprocedure: IV heparin (ACT 2 times baseline)	VerifyNow prior to procedure; ARU <550, P2Y12 % inhibition >20%	ASA resistant 5.3% (5/95), CLP resistant 37.5% (36/96)	Overall TE events 7.3% (7/96); TE events in CLP resistant vs nonresistant 16.7% (6/36) vs 1.6% (1/60), p < 0.01
Heller et al., 2013	24: 27 aneurysms, 25 procedures (10/2011–6/2012)	PED (ICA)	ASA & CLP 75 mg daily, ≥ 7 days prior; intraprocedure: IV heparin (aPTT 240 sec); postprocedure: IV heparin (aPTT 50–70 sec) for 12–18 hrs	Light transmission aggregometry prior to procedure; ASA max platelet aggregation $\leq 20\%$, CLP MPA $\leq 60\%$	ASA nonresponders 16% (4/25), CLP nonresponders 4% (1/25)	By Day 1 asymptomatic (MR-DWI) ischemia in all patients 52% (13/25)

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Authors & Year	No. of Patients (study dates)*	Treatment		Method & Definition of Hyporesponder	Outcome	
		Neuroendovascular	Antiplatelet		Laboratory	Clinical
Nordeen et al., 2013	81 (10/2009–9/2010)	Angioplasty & stent, stent-assisted coil, stent, other (procedure performed only at P2Y12 % inhibition $\geq 20\%$)	ASA 325 mg daily (650 mg LD if emergency) + CLP 75 mg daily (300–600 mg LD if emergency or resistant or change to ticlopidine, prasugrel, or ticagrelor), 5–7 days prior, then for 1 mo after procedure; intraprocedure: heparin or glycoprotein IIb/IIIa antagonist IV	VerifyNow prior to procedure; P2Y12 % inhibition $\geq 20\%$ (CLP resistant if P2Y12 % inhibition $< 20\%$ after 2 tests)	CLP resistant 21% (17/81)	W/in 24 hrs of procedure: ischemia 0% vs 1%, hemorrhage 6% vs 8%, $p = \text{NS}$; by 30 days, ischemia 0 vs 3%, hemorrhage 9% vs 8%, $p = \text{NS}$; by 90 days, ischemia 0 vs 8%, hemorrhage 9% vs 8%, $p = \text{NS}$
Delgado Alman- doz et al., 2014	44: 48 PED procedures, 54 aneurysms (11/17/2011–7/23/2012)	PED (intracranial aneurysm)	Same as above	VerifyNow prior to procedure; 10 & 30 days after change in P2Y12 receptor antagonist therapy, after change to medications that may affect CLP metabolism, or any time if TE/hemorrhage; PRU 80–200	CLP hyperresponders (PRU < 80) 62%, CLP hyperresponders (PRU < 60) 50%	Normal response = PRU 60–240; overall TE events 12.5% (6/48); TE events in CLP hyporesponse vs nonhyporesponse 100% (2/2) vs 8.7% (4/46); bleeding events in CLP hyperresponse vs nonhyperresponse 44.4% (4/9) vs 2.6% (1/39); clinical outcome w/ PRU 60–240 up to 6 mos after Tx: overall 12.5% (6/48) TE, 10.4% (5/48) hemorrhagic, major bleed 6.2% (3/48), parenchymal ICH/death 4.2% (2/48); if PRU < 60 , 60% conversion to hyperresponder
Kashiwazaki et al., 2014	66: 66 interventions (10/2011–10/2013)	Stent, coil $\pm$ stent (carotid stenosis, intracranial aneurysm)	ASA 100 mg + CLP 75 mg daily, ≥ 14 days prior; intraprocedure: IV heparin (ACT 2 times baseline); antiplatelet therapy for ≥ 30 days after procedure	VerifyNow w/in 48 hrs of procedure; 26%–74% inhibition	Hyporesponders 28.8% (19/66), hyperresponders 22.7% (15/66)	Overall bleeding events 12.1% (8/66); overall asymptomatic ischemic events 19.7% (13/66); bleeding event in hyperresponders vs nonhyperresponders: 6 (44.4%) in hyperresponse group, 2 (6.9%) in appropriate-response group, $p = 0.001$; ischemic events in hyporesponders vs nonhyporesponders 9 vs 4, $p = 0.001$
Oran et al., 2015	100: 104 aneurysms, flow-diverting stents 33 standard group (no test) vs 71 aggregometry group (test); (1/2010–6/2013)	Flow-diverting stents (intracranial aneurysm)	ASA 300 mg LD + CLP 600 mg LD (if resistant, ticlopidine 1 g &/or IV tirofiban or IV heparin higher dose), 8–12 hrs prior; intraprocedure: IV heparin 5000–10,000 units bolus (ACT 2–3 times baseline)	Multiplate analyzer prior to procedure; ASA AUC ≤ 500 , CLP AUC ≤ 468	CLP hyporesponders 25% (17/68)	Symptomatic thrombotic events in no-test group 9.1% (3/33), death in no-test group 3.1% (1/32), major bleeding event in aggregometry group 2.8% (2/71)

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TABLE 2. Outcomes in clopidogrel hyporesponders

Authors & Year	No. of Patients (study dates)*	Treatment		Method & Definition of Hyporesponder	Outcome	
		Neuroendovascular	Antiplatelet		Laboratory	Clinical
Asai et al., 2016	181: 189 procedures (8/2010–7/2013)	Coil, stent/coil	ASA + CLP usually (up to 3 antiplatelet drugs w/ cilostazol), ≥5–7 days prior; intraprocedure: heparin (ACT 250–350 sec); post-stent: IV argatroban 60 mg daily for 24 hrs	VerifyNow prior to procedure; <230 (based on GRAVITAS study)	34.9% (66/189) CLP low responders, 5.8% (11/189) ASA low responders	Overall symptomatic ischemic events 4.2% (8/189); symptomatic ischemic events in low responders vs responders 3.0% (2/66) vs 4.9% (6/123), $p = 0.72$; new ischemic lesions on MR-DWI in low responders vs responders 66.7% (44/66) vs 56.1% (69/123), $p = 0.26$; new ischemic lesions >5 mm on MR-DWI in low responders vs responders 39.4% (26/66) vs 21.1% (26/123), $p = 0.01$
Brinjikji et al., 2015	698: 805 unruptured aneurysms; retrospective review using International Retrospective study of PED (IntrePED) registry (7/2008–2/2013)	PED (ICA, MCA, PCA, basilar artery, or other)	Not available	Platelet testing prior to procedure (73.2% w/ testing)		Platelet testing group 5.5% (28/511) ischemic stroke vs no-platelet testing group 0.8% (4/511) ischemic stroke ($p = 0.06$); platelet testing group 2.3% (12/511) intracranial hemorrhage vs no-platelet testing group 0 intracranial hemorrhage ($p = 0.04$)
Hwang et al., 2015	228 (5/27/2013–4/7/2014; prospective randomized open-label active-control trial w/ blinded outcome assessment)	Coil embolization (unruptured aneurysm)	ASA 100 mg daily (if HTPR to aspirin, 300 mg LD), CLP 75 mg daily (if HTPR to CLP, cilostazol 200 mg LD w/ 200 mg daily as MD if stent-assisted coiling), 5 days prior; antiplatelet therapy discontinued in coiling w/o stent; patients monitored 24 hrs & discharged next day, follow-up in 7 & 30 days after coiling	VerifyNow prior to procedure; ARU <550, PRU <213	Hyporesponders randomly assigned to standard or modified treatment groups: 55.3% (126/228), nonhyporesponders 44.7% (102/228)	Overall TE events 3.9% (9/228); TE events in HTPR-standard vs HTPR-modified treatment vs non-HTPR group 11.1% (7/63) vs 1.6% (1/63) vs 1% (1/102), $p = 0.02$; TE w/in 7 days 11.1% (7/63) standard group vs 1.0% (1/102) non-HTPR group ($p = 0.03$ when adjusted for sex, age, history of CHD, aneurysm diameter, aneurysm neck size); TIMI bleeding criteria w/in 30 days 9.6% (22/228), 0 more than minimal TIMI bleeding criteria during 30 days after coil embolization; 9.5% (6/63) modified group vs 6.3% (4/63) standard group, $p = 0.26$; TE events w/in 30 days in HTPR-standard vs HTPR-modified group 11.1% (7/63) vs 1.6% (1/63), $p = 0.02$

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50% within 60 days of the procedure.^{5,15,20,36,45} This is in contrast to much lower complication rates in patients with appropriate clopidogrel response (1% within 24 hours of the procedure and up to 21.2% within 30 days of the procedure).^{5,15,16,20,43,45}

Several factors influence clopidogrel responsiveness. In multivariate analyses, clopidogrel hyporesponsiveness was associated with age > 55 years, history of diabetes mellitus, female sex, higher body weight, and body mass index (> 25 kg/m²).^{17,33,36,53} Some of these risk factors are known

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TABLE 2. Outcomes in clopidogrel hyporesponders

Authors & Year	No. of Patients (study dates)*	Treatment		Method & Definition of Hyporesponder	Outcome	
		Neuroendovascular	Antiplatelet		Laboratory	Clinical
Nishi et al., 2016	279 (5/2010–4/2013)	Stent (carotid, vertebral), coil embolization (unruptured aneurysm)	ASA 100 mg + CLP 75 mg daily, ≥5 days prior, or ASA 200 mg + CLP 300 mg LD; intraprocedure: IV heparin (ACT 250–300 sec)	VerifyNow prior to procedure	Hyperresponders 30%	Overall major bleeding events 11.1% (31/279); intracranial hemorrhage 3.6% (10/279), subarachnoid hemorrhage 3.2% (9/279), cerebral hemorrhage 0.3% (1/279); bleeding events in hyperresponders vs nonhyperresponders 19% vs 7.69%
Tan et al., 2015	74 (4/2011–8/2013)	PED (ACA, PCA)	ASA 325 mg daily, CLP 75 mg daily, 5 days prior; if emergency, ASA 325 mg + 600 mg CLP LD 2 hrs prior to procedure; nonresponder: CLP 600 mg &/or ASA 325 mg immediately postprocedure before ACT normalization; intraprocedure: IV heparin (ACT 250 sec); abciximab (0.25 mg/kg LD + 0.125 µg/kg/min or 10 µg/min for 12 hrs) if ASA/CLP hyporesponder	VerifyNow prior to procedure; ARU <550, PRU <230	CLP hyporesponders (PRU >208) 52.7% (39/74)	1 day postprocedure: MR-DWI changes 39.2% (29/74); 1 wk postprocedure: TE 6.8% (5/74), intracranial hemorrhage 1.4% (1/74); 4 wks postprocedure: symptomatic TE in CLP hyporesponders vs responders 12.8% (5/39) vs 0%; MR-DWI changes in CLP hyporesponders vs responders 48.4% (15/31) vs 53.9% (14/26); intracranial hemorrhage in hyporesponders vs responders 0% vs 2.9% (1/35)
Wong et al., 2015	90 (5/2002–12/2012; standard therapy [no testing] vs 40 tailored therapy [testing])	Stent (intracranial artery stenosis, aneurysms)	ASA 325 mg daily, CLP 75 mg daily (300–600 mg LD per MD if resistant), 7 days prior	VerifyNow prior & postprocedure; PRU 120–180	CLP hyporesponders 53.1% (17/32), hyperresponders 25% (8/32)	Overall TE complications 1.5%; TE events in CLP hyporesponders 0; overall hemorrhagic complications 16.9%; bleeding events in CLP hyperresponders 25%; TE events during the procedure in standard vs tailored group 5.6% (5/90) vs 2.5% (1/40), $p = 0.648$; TE events after procedure in standard vs tailored group 1.1% (1/90) vs 2.5% (1/40), $p = 0.522$; TIMI bleeding events in standard vs tailored group 17.8% (16/90) vs 15.0% (6/40), $p = 0.455$

ACA = anterior cerebral artery; ACT = activated clotting time; aPTT = activated partial thromboplastin time; ASA = acetylsalicylic acid (aspirin); CHD = coronary heart disease; CLP = clopidogrel; ICA = internal carotid artery; ICH = intracerebral hemorrhage; IV = intravenous; LD = loading dose; MCA = middle cerebral artery; MD = maintenance dose; MPA = maximum platelet aggregation; NS = not significant; PCA = posterior cerebral artery; TIA = transient ischemic attack; TIMI = Thrombolysis in Myocardial Infarction; Tx = treatment.

* Dates given as month/year or month/day/year.

† TIMI bleeding criteria: major = any intracranial bleeding, clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥ 5 g/dl, fatal bleeding; minor = clinically overt bleeding, resulting in hemoglobin drop of 3 to < 5 g/dl.

to increase platelet reactivity independent of antiplatelet therapy and are of clinical importance when predicting thromboembolic events. However, clopidogrel hyporesponsiveness did not consistently translate to thromboembolic events (stent thrombosis, restenosis, or any clinical outcome) in past studies.^{5,33,53} Interestingly, Prabhakaran

et al. found no linear association between preprocedural weekly clopidogrel dose and P2Y₁₂ percentage inhibition.⁵³ Other factors associated with thromboembolic events include history of hypertension, posterior location of treatment, longer operation time, being a current smoker, larger aneurysm size, aneurysm neck diameter, multiple

TABLE 3. Summary of antiplatelet agents used for neuroendovascular indications

Variable	Antiplatelet Agent								
	Aspirin	Clopidogrel	Ticagrelor	Prasugrel	Cilostazol	Cangrelor	Abciximab	Eptifibatide	Tirofiban
Mechanism of action	Irreversible inhibitor cyclooxygenases 1 & 2	Irreversible inhibitor P2Y12 ADP receptor	Reversible inhibitor P2Y12 ADP receptor	Irreversible inhibitor P2Y12 ADP receptor	Reversible phosphodiesterase inhibitor, ADP inhibitor	Reversible inhibitor P2Y12 ADP receptor	Irreversible inhibitor glycoprotein IIb/IIIa receptor	Reversible inhibitor glycoprotein IIb/IIIa receptor	Reversible inhibitor glycoprotein IIb/IIIa receptor
Onset	7–60 mins	2 hrs	30 mins	15–30 mins	3–6 hrs	2 mins	2 hrs	Immediate	5 mins
Duration of action	3–5 days	3–7 days	12–24 hrs	5–9 days	48 hrs	1 hr	48 hrs	2–4 hrs	3–8 hrs
Metabolism	Minimal	CYP450 2C9	CYP450 3A4	CYP450 3A/2B6	Minimal	Dephosphorylation in serum	None	Minimal	Minimal

PED placements, and lack of statin use.^{5,16,20,26,67} Both clinical and procedure-related factors must be considered before determining a patient's risk status for HTPR.

Numerous reports of platelet function testing for clopidogrel have been published in an effort to define the role of HTPR on thromboembolic and bleeding events after neuroendovascular stenting and coiling (Table 1). Assimilation of all these reports is not particularly straightforward because of the variety of procedures, doses, methods of platelet function testing, and time to follow-up in each publication. For instance, procedures such as deployment of the PED may be associated with a higher thrombosis rate due to the technical aspects and the risk factors of the patients who receive this device, particularly when compared with carotid stenting, where flow in the target vessel is higher and less tortuous. Cases of stent-assisted aneurysm coiling typically have a higher risk of thrombosis than aneurysm coiling alone.

Several studies have reviewed the impact of clopidogrel hyporesponsiveness in patients undergoing PED deployment. Delgado Almandoz et al. used 75 mg of clopidogrel and 325 mg of aspirin daily in 44 patients with PEDs.¹⁶ They demonstrated a significant association with clopidogrel hyporesponsiveness (PRU > 240) and thromboembolic events. On the opposite end of the spectrum, they also demonstrated a significant association with PRU < 60 and bleeding events. Daou et al. used 75 mg of clopidogrel and 325 mg of aspirin daily (started 10 days prior to the procedure) in 231 patients with PEDs.¹⁴ Higher odds of complications were associated with clopidogrel PRU values < 70 (hemorrhagic) and > 150 (thromboembolic) after controlling for aneurysm size and aspirin treatment (OR 3, 95% CI 1.2–7.5). As a result, many current clinical trials of flow-diverting treatments for aneurysms have specific parameters for platelet responsiveness in their inclusion criteria (clinical trial no. NCT02186561; clinicaltrials.gov).

Other studies using platelet function testing in patients receiving PEDs were not as definitive. Some investigators found no difference in complications in patients with HTPR.²⁶ Oran et al. used the Multiplate analyzer in 1 cohort of patients and after comparing them with a cohort that did not receive testing, they suggested that thromboembolic complications and morbidity (but not bleeding) were higher in the nontested group.⁴⁶ Another study inves-

tigated patients receiving clopidogrel prior to PEDs and divided the population into 2 cohorts: patients with PRU < 208 and those with PRU > 208.⁶⁷ No difference in bleeding rates or ischemic lesions based on MR diffusion-weighted imaging (DWI) were evident, although there were higher overall thromboembolic events noted in patients with PRU > 208 (12.9% vs 0% in PRU < 208 group, $p = 0.06$). One confounding factor in this study was the concomitant use of abciximab throughout and after the stent deployment procedures (and for 12 hours total).

Clopidogrel hyporesponsiveness has also been investigated in other neuroendovascular procedures and has yielded similar results. Patients undergoing elective unruptured aneurysm coiling were initiated on clopidogrel and other antiplatelet agents at least 5 days prior to their procedure or with a loading dose the day prior to the procedure in 4 separate studies. The results of these reports are relatively consistent. Three of the studies demonstrated that an increased PRU was associated with thromboembolic events.^{15,28,33} Asai et al. did not see a difference in symptomatic thromboembolic events, though MR-DWI lesions were increased in patients with HTPR.⁵ Several other studies reported the results of a mix of patients undergoing aneurysm coiling plus stent-assisted coiling, carotid stenting, or cerebral angioplasty. One study demonstrated a significant difference in mortality in patients with clopidogrel HTPR compared with those with target PRU (23% vs 4% target PRU, $p = 0.03$), but no association with thromboembolic complications between cohorts.⁴⁵ Fifi and colleagues evaluated clopidogrel response in patients undergoing aneurysm coiling or carotid stenting and suggested that occurrence of stent thrombosis was frequently associated with HTPR.²⁰ Conversely, Koerner et al. described patients undergoing stent procedures to various arteries (carotid, vertebral, or basilar) and demonstrated no increase in thromboembolic events in patients with HTPR.³⁵ Two other studies including patients receiving aneurysm coiling (with or without stent assist) suggested that a low PRU in patients receiving clopidogrel was associated with an increased rate of bleeding events (incidence of thromboembolic events was not reported).^{22,44}

The most commonly used method to overcome clopidogrel hyporesponsiveness was to administer additional loading doses of clopidogrel prior to the procedure. Lee

et al. reported a nonstatistical reduction in PRU before and after an additional 300-mg clopidogrel loading dose, but this was based on a small number of patients.³⁶ On the other hand, Fifi et al. reported a significant increase in P2Y₁₂ percentage inhibition in clopidogrel nonresponders after an additional 150–600 mg clopidogrel loading dose and observed a significant percentage of patients converting to responders.²⁰ Alternative P2Y₁₂ inhibitors may be considered in this situation as well.

On the opposite end of the spectrum, there are few studies describing the incidence of bleeding events in clopidogrel hyperresponders. Clopidogrel hyperresponsiveness occurs in 14%–30% of patients and has been associated with major and minor bleeding events based on various laboratory definitions.^{15,16,22,34,44} Nishi et al. identified PRU ≤ 175 as the optimal cutoff. Clopidogrel hyperresponders were at a 2.8 times higher risk for major and minor bleeding events than nonhyperresponders.⁴⁴ The main difference between the 2 groups was a higher incidence in puncture site hemorrhage and not intracranial hemorrhage or retroperitoneal hemorrhage. Goh et al. and Kashiwazaki et al. found ≥ 72 –74 P2Y₁₂ percentage inhibition as the optimal cutoff for predicting major bleeding events.^{22,34} Lower ARU values were not associated with bleeding events.^{34,44}

Not all patients who exhibit hyperresponsiveness consistently express this phenotype after neuroendovascular intervention. Within 6 months of the endovascular procedure, 77.3% of patients who were clopidogrel responders became hyperresponsive and 41.2% of these patients experienced major and minor bleeding events.¹⁵ In clopidogrel hyperresponders, the associated major and minor bleeding events were 19% within 1 week of the procedure, 15.4%–44.4% within 30 days of the procedure, and 33.3% within 6 months of the procedure.^{15,16,34,44} Comparatively, major and minor bleeding events in clopidogrel nonhyperresponders were significantly lower at 7.69% within 1 week of the procedure, 5.7%–6.9% within 30 days of the procedure, and 2.6% within 6 months of the procedure.^{15,16,34,44} Intracranial hemorrhage occurred in both clopidogrel hyperresponders and nonhyperresponders.^{15,16,44}

Definitive conclusions are difficult to make regarding clopidogrel response and treatment success in neuroendovascular procedures due to the heterogeneity of the procedures, cutoff values used with platelet function testing, clopidogrel dosing, and the use of alternative antiplatelet agents. The majority of the literature evaluating concomitant clopidogrel and aspirin use seems to suggest that HTPR is at least modestly associated with thromboembolic events. Platelet function testing seems advisable for detection of risk of thrombosis based on patient characteristics, difficulty of the procedure, and number of stents deployed.^{26,67} An increase in bleeding rates in patients with LTPR has also been reported in some studies, although this is less well defined.¹⁵

P2Y₁₂ Inhibitors

Prasugrel and Ticagrelor

Agents that act at the P2Y₁₂ receptor, but exhibit considerably less variability in response, include prasugrel and ticagrelor. Both agents have been used as alternatives to clopidogrel in patients with HTPR with some success

(Table 4). Patients receiving a PED who exhibited HTPR to clopidogrel were switched to prasugrel in one study. No thromboembolic or bleeding complications occurred.¹³ Similarly, 3 separate cohorts of clopidogrel hyporesponsive patients undergoing a mix of neuroendovascular procedures were switched from clopidogrel to prasugrel or ticagrelor. Significantly higher hemorrhagic events were noted with prasugrel therapy in 1 study ($p = 0.02$), but this was not significant when a patient with basilar artery perforation was excluded from the data analysis ($p = 0.09$).² Only 1 bleeding complication (prasugrel) occurred in the other 2 cohorts.^{25,66} No thromboembolic complications were noted in any one of these 3 studies. These preliminary data suggest that using alternatives to clopidogrel in patients with HTPR may be reasonable, as more patients will become responsive to clopidogrel alternative therapies. However, these alternatives must be used with caution as prasugrel and ticagrelor may convert hyporesponders to hyperresponders, and this has been associated with higher major and minor bleeding rates in both PCI and neuroendovascular settings.^{6,15,51} Similar findings of high bleeding rates in clopidogrel hyperresponders have also been observed, and thus further platelet function testing may be necessary in patients whose antiplatelet therapy is modified. There are limited clinical outcomes data with ticagrelor therapy, and it should be used with caution as the currently approved FDA dosing regimen (180 mg loading/90 mg twice daily) may produce PRUs < 40 .^{3,4,24}

Cilostazol

Hwang et al. published a prospective study of 228 patients undergoing elective aneurysm coil embolization (with the majority having a stent assist).²⁸ Three cohorts of patients were compared: those with non-HTPR on clopidogrel (standard regimen: clopidogrel 75 mg daily, aspirin 100 mg daily), those with HTPR who received the standard treatment regimen, and those with HTPR who received a modified regimen (clopidogrel 75 mg daily, aspirin 300 mg daily, and cilostazol 200 mg loading dose, then 200 mg daily as maintenance dose if stent-assisted coiling). Thromboembolic events were lower in patients with the modified regimen than in patients with HTPR who received the standard regimen (11.1% standard vs 1.6% modified, $p = 0.02$). No differences in bleeding complications were observed among the 3 cohorts. Thus, it appears that the addition of cilostazol to the combination of aspirin and clopidogrel in patients with HTPR may be an acceptable strategy to overcome clopidogrel hyporesponsiveness.

Glycoprotein IIb/IIIa Inhibitors

Glycoprotein IIb/IIIa inhibitors may be used during neuroendovascular procedures, usually either as an adjunct to DAT or as rescue therapy for acute thrombosis. Intravenous administration of glycoprotein IIb/IIIa inhibitors may be used in patients undergoing aneurysm coil embolization or stent placement as an additive protective measure for procedural thrombosis (analogous to their typical use in PCI).⁶² One prospective study compared patients who received preprocedure antiplatelet therapy (aspirin and clopidogrel) versus those who only received

TABLE 4. Alternatives to clopidogrel in patients with HTPR

Authors & Year	No. of Patients (study dates)	Treatment		Method & Definition	Outcome	
		Neuroendovascular	Antiplatelet		Laboratory	Clinical
Akbari et al., 2013	55 ASA/CLP vs 31 ASA/prasugrel (2/15/2010–10/31/2011)	Coil, PED, stent (intracranial aneurysms, AVM, dural arteriovenous fistula, intra-/extracranial stenosis)	ASA 325 mg daily + CLP 75 mg daily (CLP change to prasugrel 60 mg LD/10 mg daily), ≥7 days prior; intraprocedure: IV heparin (ACT 2 times baseline)	VerifyNow prior to procedure & as needed, P2Y12 % inhibition >40%		Overall hemorrhagic events 9.3% (8/86); hemorrhagic events ASA/CLP vs ASA/prasugrel 3.6% vs 19.4%, $p = 0.02$; intracranial hemorrhagic events ASA/CLP vs ASA/prasugrel 1.8% vs 12.9%
Chalouhi et al., 2013	7 (11/2011–7/2012)	Posterior circulation aneurysm	ASA 81 mg daily, CLP 75 mg daily (CLP poor responder: prasugrel 40 mg LD, 5 mg MD), 10 days prior; intraprocedure: heparin 100 units/kg bolus, then dosed per ACT 2 times baseline	VerifyNow prior to procedure, P2Y12 % inhibition ≥30%		Mean 5.5 mos (range 3–7 mos); no ischemic or bleeding complications
Stetler et al., 2013	16: prasugrel (1/2009–7/2011)	Stent (intracranial aneurysm, intracranial stenosis, extracranial artery pathology)	CLP 75 mg daily (CLP 300 mg LD, if urgent; CLP nonresponders changed to prasugrel 40 mg LD, then 5–10 mg daily), ASA ≥81 mg daily, ≥7 days prior; intraprocedure: IV heparin (ACT 250–300 sec); postprocedure: heparin 500 units/hr + dextran 40 20 ml/hr when PTT <100, for 12–18 hrs	VerifyNow prior to procedure; ARU 350–550, P2Y12 % inhibition >20%	P2Y12 % inhibition median 2% & increased to >50% in 77% of patients w/ prasugrel	Mean 3 mos (range 1 to >6 mos); intracranial bleeding or ischemic complications 0, retroperitoneal hematoma 1
Hanel et al., 2014	18 (10/2011–8/2012)	Stent, coil, PED (intra-/extracranial artery; 16 elective, 2 emergency)	ASA 650 mg LD (CLP 600 mg LD + ASA 650 mg LD, if semiurgent), then 325 mg daily + CLP 300 mg LD (if CLP nonresponder, changed to ticagrelor 180 mg LD, then 75 mg daily), 7 days prior	VerifyNow prior to procedure; P2Y12 % inhibition >30%	P2Y12 % inhibition <20% increased to P2Y12 % inhibition >60% in 94.4% of patients w/ ticagrelor	No adverse effects during or following surgery

AVM = arteriovenous malformation.

intraprocedural intraarterial abciximab prior to elective aneurysm coiling.³⁷ Patients who received only intraarterial abciximab had no difference in thromboembolic or bleeding complications compared with those who took DAT in the days prior to the procedure, suggesting intraarterial glycoprotein IIb/IIIa inhibitor infusion may be a suitable replacement for DAT during the procedure. Similarly, glycoprotein IIb/IIIa inhibitors have been used in patients who demonstrate HTPR during neuroendovascular procedures as a means of preventing acute thrombosis in high-risk patients. Data supporting the use of glycoprotein IIb/IIIa inhibitors as the sole agent during neuroendovascular interventions are not sufficient to merit doing this as a standard practice, but the available data do suggest that it may be a reasonable adjunct if it is not possible to load antiplatelet agents prior to the procedure or if patients are known to have HTPR during the procedure.

Glycoprotein IIb/IIIa inhibitors are also used as rescue therapy when thrombosis occurs during the procedure. Typically, procedural thromboses are detected quickly and can be addressed before substantial propagation. Therefore, the thrombosis is not mature and fibrin-rich; rather,

the thrombosis is usually the initial strands of platelets aggregating after initial activation that is amenable to dispersion with glycoprotein IIb/IIIa inhibitors. Numerous reports of using intraarterial bolus infusions of glycoprotein IIb/IIIa inhibitors for successful stent or coil thrombosis treatment are available in the literature.^{23,29,31,50,57,58} Clinicians may also follow the intraarterial bolus with an infusion (again, based on PCI dosing) to run for at least 12 hours after the procedure to further protect against acute thrombosis.^{1,18} Glycoprotein IIb/IIIa inhibitors also appear to be as effective as and safer than intraarterial thrombolysis, further cementing their role in rescue therapy.

The optimal choice of glycoprotein IIb/IIIa inhibitor is not clear and may depend on the formulary preference within each individual institution. No prospective studies in the neuroendovascular realm have been conducted to identify the best agent, and all of the readily available options (abciximab, eptifibatide, tirofiban) have data to support their use in this clinical setting. Glycoprotein IIb/IIIa inhibitors differ in pharmacokinetics, and these differences may be important as they pertain to antiplatelet action during and after the procedure. Briefly, abciximab tends

FIG. 1. Protocol for clopidogrel responsiveness using the VerifyNow test in patients undergoing neuroendovascular procedures. When possible, patients undergoing neuroendovascular stenting should be initiated on DAT 5–7 days prior to the procedure. For select patients and procedures, VerifyNow platelet function analysis should be evaluated prior to the procedure. For patients with PRUs > 240 (HTPR), several potential options exist for rapidly gaining platelet inhibition (options 1–3), each with a corresponding postprocedure treatment plan. For patients with PRUs < 60 (LTPR), clinicians may consider reducing the clopidogrel dose prior to the procedure. Individuals who are hyperresponders to clopidogrel may require a reduced dose or an alternative agent. Patients with a PRU within the goal of 60–240 should continue DAT as initially prescribed. The optimal range of platelet reactivity is not well defined; some clinicians may elect to use a lower threshold of platelet reactivity, such as 60–150.¹⁴ *Clopidogrel dose reduction may be to 75 mg every other day or every third day. The prescriber can maintain the patient on this dose for 7–14 days, then recheck VerifyNow. If PRU remains < 60, consider reducing the dose to 75 mg weekly or 5 mg (oral solution) per day. Reevaluate VerifyNow 5–7 days after each dose change. May also consider using ticagrelor in patients in whom PRU remains < 60 despite significant clopidogrel dose reduction. **The FDA recommends decreasing the aspirin dose to 81 mg daily in patients on ticagrelor therapy based on post hoc analysis completed in the Platelet Inhibition and Patient Outcomes (PLATO) trial, where it showed paradoxical worsening of primary efficacy outcomes (composite of death from vascular causes, myocardial infarction, or stroke at 12 months) with an aspirin dose $\geq$ 300 mg daily. This may be due to an aspirin and ticagrelor interaction and their effect on reduced platelet reactivity.³⁹ The effects of an aspirin dose $\geq$ 300 mg daily with ticagrelor therapy is currently unknown in patients undergoing neuroendovascular procedures, and therefore close monitoring is advised. Figure is available in color online only.

to have a longer action on platelets due to the irreversible binding on the glycoprotein IIb/IIIa receptor. As a result, an intraarterial bolus of abciximab is likely to have a more prolonged pharmacological effect than other glycoprotein IIb/IIIa inhibitors. In addition, in the instance in which bleeding complications ensue, platelet transfusion is likely to be more effective in restoring hemostatic balance in patients receiving abciximab due to the irreversible binding. Other glycoprotein IIb/IIIa inhibitors, such as eptifibatide, exhibit reversible binding and may inhibit recently transfused platelets in the bleeding patient.^{40,65}

Management of DAT for Neuroendovascular Procedures

Platelet function testing appears advisable prior to neuroendovascular procedures, particularly in patients with risk factors for variable clopidogrel response and cases associated with complex aneurysm coil embolization, flow diversion devices, or intracranial stenting. Within each institution, consistent use of a well-validated platelet function test may aid prescribers in predicting clopidogrel responsiveness. The utility of these tests for aspirin resistance is of questionable significance in the majority of these patients. Protocols for adjusting clopidogrel therapy based on plate-

let responsiveness have been proposed, but not validated at this point (Fig. 1).¹⁶ Of note, the VerifyNow PRU cutoff value of 60–240 was based on a study by Delgado Almandoz; however, based on PCI literature, the VerifyNow PRU cutoff value is 85–208. There has been no comparison study to validate a PRU cutoff of 85–208 in the neuroendovascular setting, but many of the cutoff values used in neuroendovascular studies were adapted or extrapolated from initial PCI literature.

When possible, patients should be initiated on clopidogrel and aspirin at least 5 days prior to the procedure to permit these agents to reach maximum pharmacological effect. However, many practitioners start patients on the regimen 14 days prior to the procedure. Patients taking clopidogrel prior to the procedure (compared with loading immediately prior to the procedure) may have lower thromboembolic complications.³³ Patient noncompliance is a major reason for measured HTPR, so specific emphasis to the patient on the importance of these therapies is prudent. If patients present with an urgent need for neuroendovascular intervention, a loading dose of clopidogrel (typically 300–600 mg) is necessary and can be administered orally or via a nasogastric tube.^{20,45,46,67} Likewise, a loading dose may be reasonable if patients present prior to the procedure with PRU > 240 despite preprocedural DAT. This accounts for patients who failed to be adherent to the preprocedure clopidogrel regimen, as well as any patients that merely require a larger loading dose to obtain a therapeutic effect.

For patients who exhibit HTPR with clopidogrel, there are 3 primary ways to overcome clopidogrel hyporesponsiveness: 1) administer an additional clopidogrel loading dose (300 or 600 mg), 2) change clopidogrel to prasugrel, or 3) change clopidogrel to ticagrelor. The safety profile of prasugrel or ticagrelor is uncertain for neurosurgical patients due to the limited availability of data, although it is known that these agents will more predictably provide a high percentage of P2Y₁₂ inhibition and further decrease PRU.^{2–4,16,24,25,37}

In patients who have exquisite response to clopidogrel and have PRU < 60, lower doses of clopidogrel may be necessary. A specific dose-response model has not been developed for hypermetabolizers of clopidogrel, so clinicians are often left to empirical dose reduction and subsequent evaluation of the dose (ideally after 7–14 days on a reduced dose). This usually takes longer than the 5–7 days for hypometabolizers because the extensive activation of clopidogrel prolongs the extent of pharmacological effect. Continuing to give a clopidogrel dose of 75 mg is convenient for the patient because of the available dosage forms, i.e., the patient need only to take the dose less frequently (e.g., every other day or every 3 days). Doses as low as 5 mg daily may be advisable for some hypermetabolizers to avoid giving essentially a week's worth of clopidogrel all at the same time. A recipe for a stable oral suspension is available and easy to make.⁶⁴

Summary

Combination antiplatelet therapy during neuroendovascular procedures, particularly intracranial artery stenting, is a mainstay in therapy. Current evidence suggests that

clopidogrel and aspirin are the preferred combination for this therapy. The pharmacogenetic variability associated with clopidogrel response may need to be considered in cases in which the risk of thrombosis is more substantial (e.g., PEDs). Routine platelet function testing may be helpful in identifying patients at risk for HTPR, and the use of alternative antiplatelet agents such as prasugrel, ticagrelor, or cilostazol may be necessary. In addition, with alteration in platelet therapy, combined planned, long-term platelet function testing is advised in order to identify patients with LTPR.

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Disclosures

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Author Contributions

Conception and design: Cook, Kim, Fraser. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Cook.

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