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Clopidogrel Resistance by P2Y12 Platelet Function Testing in Patients Undergoing Neuroendovascular Procedures:

Incidence of Ischemic and Hemorrhagic Complications

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Abstract

Purpose: The purpose of the study was to assess clopidogrel resistance and whether "intensified" antiplatelet therapy guided by platelet inhibition tests during neuroendovascular procedures would reduce ischemic complications.

Methods: We conducted a retrospective review of patients at Mayo Clinic in Jacksonville, Florida, who underwent neuroendovascular (NV) procedures and had P2Y12 platelet function testing from October 1, 2009, to September 30, 2010. The primary end-point was to determine P2Y12 resistance to antiplatelet therapy in patients who underwent NV procedures. Secondary objectives included incidence of hemorrhagic and ischemic events and a correlation between resistance and genetic CYP2C19 testing.

Results: 160 patients underwent P2Y12 platelet function tests. Eighty-one patients (81/160, 50.6%) met inclusion criteria. Platelet function tests identified 64 patients (79%) as non-resistant (≥20% P2Y12 inhibition) and 17 (21%) as resistant (<20% inhibition) after initial clopidogrel loading. There was an increased rate of death when a complication occurred in the resistant group by 30 day (17% versus 3%; p=0.059) and 90 day follow-up (23% versus 4%; p=0.032). There was no significant association found between complication and loading dose (p=0.0721).

Conclusions: 21% of patients undergoing NV procedures were resistant to clopidogrel. Intensifying antiplatelet therapy to achieve ≥20% inhibition on platelet function testing did not result in higher numbers of ischemic or hemorrhagic events, but there was a trend toward more death in the resistant group by 30 and 90 days of those experiencing complication(s).

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(NV) neuroendovascular

(CYP) cytochrome P-450

(PPI) proton pump inhibitors

(PCI) percutaneous coronary intervention

List of Commercial Products: Aspirin (Acetylsalicylic Acid) (Bayer Corp, Morristown, NJ, USA)

Clopidogrel (Plavix®) (Bristol Myers Squibb/Sanofi Pharmaceuticals, Princeton, NJ, USA)

VerifyNow® (Accumetrics Inc., San Diego, CA, USA)

Ticlopidine (Ticlid®) (Roche Laboratories, Basel, Switzerland)

Prasugrel (Effient®) (Eli Lilly & Co., Indianapolis, IN, USA)

Eptifibatide (Integrilin®) (Merck & Co., Inc., Whitehouse Station, NJ, USA)

Abciximab (Reopro®) (Janssen Pharmaceuticals, Inc., Titusville, NJ, USA)

Tirofiban (Aggrastat®) (MGI Pharma, Inc., Bloomington, MN, USA)

Pantoprazole (Protonix®) (Pfizer Inc., New York, NY, USA)

Omeprazole (Prilosec®) (Procter and Gamble Pharmaceuticals, Mason, OH, USA)

Famotidine (Pepcid®) (McNeil Consumer & Specialty Pharmaceuticals, Fort Washington, PA, USA)

Ticagrelor (Brilinta®) (AstraZeneca Pharmaceuticals, Wilmington, NC, USA)

Keywords

platelets; stent; stroke; hemorrhage; subarachnoid

Introduction

Thromboembolic events present a significant risk during the intraoperative and postoperative period following neuroendovascular (NV) therapy due to risk of antiplatelet resistance. Antiplatelet medications such as aspirin and clopidogrel remain the principal agents for prevention of thromboembolic complications. Currently, there is minimal published data regarding outcomes associated with antiplatelet resistance in NV procedures.[1] Therefore, identification and review of outcomes regarding antiplatelet therapy may be beneficial in developing standards of management.

Therapy with aspirin has been shown to reduce the relative risk of thromboembolic stroke by 20%-25%.[2] Aspirin irreversibly inactivates platelet cyclo-oxygenase-1, thereby blocking the generation of thromboxane, a platelet agonist and potent vasoconstrictor.[3] However, not all patients treated with aspirin have complete inhibition of thromboxane-dependent platelet function.[4] Clopidogrel, a thienopyridine P2Y12 ADP-receptor antagonist, requires conversion to its active metabolite to inhibit platelet aggregation. In patients undergoing NV procedures, clopidogrel resistance rates have been reported in up to 50%.[1] Ischemic complications can occur due to decreased response to clopidogrel or aspirin; therefore, aspirin and clopidogrel resistance testing should be a consideration.

There is evidence of substantial individual variability in response to clopidogrel. Resistance to P2Y12 platelet reactivity in patients receiving clopidogrel is associated with increased risk of cardiac, cerebrovascular, and peripheral arterial events. Patients undergoing carotid endarterectomy may significantly reduce their thromboembolic potential through targeted preoperative antiplatelet therapy, without increasing the risk of bleeding

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complications.[2] We hypothesized that patients resistant to antiplatelet therapy could be adequately loaded to attain efficacy without increased adverse events.

Methods

Trial Design

This study was conducted as an observational, retrospective review at Mayo Clinic in Jacksonville, Florida, from October 1, 2009 to September 30, 2010. A successful NV procedure was defined as the lack of hemorrhagic or ischemic complication. Complications were assessed prior to, during, and three months following each NV procedure. Efficacy was defined as the ability to obtain adequate P2Y12 platelet inhibition (≥20%) and prevent thrombotic complications. The study protocol was approved by the Mayo Clinic Institutional Review Board.

Study Population

Patients were eligible for inclusion if they were 18 years of age or older, had documented antiplatelet therapy, a VerifyNow P2Y12 platelet function test, and underwent a recent NV procedure. Patients were excluded if they were pregnant.

Study Protocol

All "elective" NV procedure patients received standard doses of aspirin 325mg and clopidogrel 75mg daily for five to seven days prior to their procedure. "Emergent" NV procedure patients were loaded with 650mg of aspirin and either 300mg or 600mg of clopidogrel. They also may have received heparin or a glycoprotein IIb/IIIa antagonist for a short duration until a rapid enteral load of aspirin and clopidogrel could take effect. All patients received a baseline P2Y12 platelet function test to identify clopidogrel resistance and determine whether they would need another loading dose to achieve P2Y12 response around 20% before the NV procedure. All patients followed the intensified antiplatelet protocol with the goal of achieving adequate P2Y12 platelet inhibition prior to procedure (Figure 1).

Platelet function was assessed using the VerifyNow assay (Accumetrics Inc., San Diego, California) to monitor responsiveness to the three main classes of antiplatelet therapies: aspirin, thienopyridines (clopidogrel, ticlopidine, or prasugrel), and glycoprotein IIb/IIIa inhibitors (eptifibatide, abciximab or tirofiban).[5] VerifyNow is a simple, rapid, point-of-care method that has several advantages: small sample volumes, use of whole blood, and no pipetting. The test was used to assess the effect of clopidogrel resistance on P2Y12 inhibition of platelet function.[5,6]

The VerifyNow P2Y12 Assay reports two results: the P2Y12 Reactive Units (PRU) and the percent inhibition. Results should be interpreted in conjunction with other laboratory and clinical data. The ideal percent of platelet inhibition is ≥30% for clopidogrel, based on literature for the VerifyNow assay.[5,6] However, 20-30% inhibition is considered an intermediate response. For the purpose of this study, we defined resistance to clopidogrel as <20% inhibition after two platelet function tests and non-resistance as ≥20% inhibition. Inhibition of platelet aggregation may range from <10% to almost complete inhibition, and adding clopidogrel to aspirin enhances overall antiplatelet effects.[5,7,8] Duel antiplatelet therapy, such as aspirin and clopidogrel, prior to stenting procedures is considered standard of care.[9] Therefore, platelet function testing in patients undergoing cerebrovascular stent placement may provide a valuable identification tool in the prevention of stent-related complications.[10]

If clopidogrel resistance was identified, an alternative antiplatelet agent (ticlopidine, prasugrel or ticagrelor) was employed. [6,9,11] Once adequate inhibition was reached (≥20%), NV procedures were performed. Following each procedure, patients were placed on a maintenance dose for one month. Patients were given aspirin 325mg and clopidogrel 75mg if non-resistant. If clopidogrel resistance was noted on the initial platelet tests, the maintenance dose was increased to 150mg daily (divided 75mg BID). If a patient was completely resistant to clopidogrel after several loading doses, the patient was then loaded with ticlopidine, or if resistant to that medication, switched to prasugrel, which has little-to-no P2Y12 resistance.

End Points

The primary endpoint was to determine antiplatelet resistance in patients who underwent NV procedures. To understand the primary resistance endpoint, a comparison was performed to assess whether patients received the appropriate loading and maintenance dose based on resistance pattern. Secondary endpoints included comparing incidence of hemorrhagic and ischemic complications and determining the correlation between antiplatelet resistance and genetic testing.

Statistical Analysis

Comparisons were performed between groups based on incidence of complications at procedure and by 30 and 90 days. Complications in resistant and non-resistant patients and relationships between high versus standard

Figure1. NeuroEndovascular Antiplatelet Protocol for Management of Clopidogrel Resistance

Patient took aspirin 325 mg and clopidogrel 75 mg daily prior to the procedure or patient received a loading dose prior to emergent procedure.
Clopidogrel resistance testing performed and has less than 20% inhibition immediately before stent procedure.

↓

Give a loading dose of 300 mg or 600 mg of clopidogrel.
Perform a second clopidogrel resistance test at least 6 hours after a loading dose of 300 mg and a minimum of 2 hours after a loading dose of 600 mg.

↓

If the second clopidogrel resistance test has less than 20% inhibition after the loading dose, the options include:

Option 1 - Reload with clopidogrel and check a third clopidogrel resistance test (e.g., borderline resistance of 18% inhibition)
Option 2 - Switch to ticlopidine. ticagrelor, or prasugrel
Option 3 –Start IV glycoprotein IIb/IIIa antagonist eptifibatide (Integrilin) or abciximab (Reopro)

↓

If Option 1 is chosen and the patient is reloaded with clopidogrel, a third clopidogrel resistance test should be ordered and interpreted as follows:

- If the clopidogrel resistance test has a 20% or greater inhibition, the patient will receive aspirin and clopidogrel will be increased to 75mg twice daily following procedure.
- If the clopidogrel resistance test has less than 20% inhibition, the patient will be loaded with ticlopidine 500 mg followed by 250 mg twice daily *OR* ticagrelor 180 mg x1 then 90 mg twice daily *OR* prasugrel 60 mg x 1 then l0 mg daily.

*Of note, there may be a 24-hour period of overlap of aspirin and BOTH clopidogrel and ticlopidine before the clopidogrel is discontinued.

**A lower dose of aspirin (75-100 mg/day) is recommended if taken concurrently with ticagrelor

Definitions:
Non-resistant: ≥ 20% after 1 platelet function test
Resistant: < 20% after 2 platelet function tests

Figure 1. NeuroEndovascular Antiplatelet Protocol for Management of Clopidogrel Resistance

Table 1.Baseline Characteristics of the Study Patients by Resistance Group

Characteristic	Resistant (n= 17)	Non-Resistant (n= 64)
Age, mean (SD), yr	61 ± 14.3	66 ± 13.1
Sex, No (%)		
Women	11 (65)	37 (58)
Men	6 (35)	27 (42)
Ethnicity, No (%)		
White	15 (88)	53 (83)
African American	1 (6)	8 (12)
Hispanic	0 (0)	1 (2)
Asian	1 (6)	0 (0)
Other	0 (0)	2 (3)
Medical History, No (%)		
Diabetes Mellitus	7 (41)	14 (23)
Hypertension	11 (65)	47 (73)
Hyperlipidemia	8 (47)	29 (45)
Prior Stroke	4 (24)	22 (34)
Pharmacotherapy, No (%)		
Pantoprazole	6 (35)	21 (33)
Omeprazole	5 (29)	19 (30)
Famotidine	5 (29)	10 (16)
Statin	8 (47)	43 (67)
Heparin	5 (29)	23 (36)
Coumadin	0 (0)	7 (11)
Enoxaparin	0 (0)	1 (2)
Aspirin/Dipyridamole	0 (0)	1 (2)
Ginkgo Biloba	0 (0)	1 (2)
Indication for Procedure, No (%)		
Stenosis	10 (59)	29 (45)
Aneurysm	5 (29)	31 (48)
Stroke	2 (12)	2 (3)
TIA	0 (0)	2 (3)
Procedure, No (%)		
Angioplasty and stent	8 (47)	23 (36)
Stent assisted coiling	2 (12)	27 (42)
Stent	4 (24)	8 (13)
Angioplasty	0 (0)	1 (2)
Coiling	1 (6)	1 (2)
Craniectomy/Craniotomy	1 (6)	4 (6)
Endarterectomy	1 (6)	0 (0)

doses were categorized using the Fisher's exact test. Complications were divided into type and frequency at both endpoints (procedure and post-procedure) and compared. Patients who had genetic testing performed were categorized by their resistance pattern and correlation to their genetic test result. For the purposes of this study, resistance or non-resistance is defined by the effect of clopidogrel, not aspirin.

Results

Primary Outcome

One hundred and sixty charts were reviewed; 81 patients met study criteria. The major reasons for exclusion were lack of a P2Y12 platelet function test, a procedure was not performed, or the procedure performed was not NV related. Patients were placed into resistant or non-resistant groups based on their platelet function test results. The primary endpoint showed that 17 patients were resistant (21%) and 64 were non-resistant (79%). Patient demographics were similar between groups (Table 1).

Resistance Pattern and Loading Dose

Fourteen resistant patients received high loading doses (300mg to 600mg of clopidogrel) and three received standard (75mg) doses (82% versus 17%). 19 non-resistant patients received high loading doses compared to 45 who received standard (30% versus 70%). The majority of patients received the appropriate dose whether they were deemed resistant or not. In total, there were 33 patients who received high loading doses and 48 who received standard. A statistically significant difference was found between the loading dose received and type of resistance pattern identified (p=0.0002).

Secondary Outcomes

Secondary outcomes were assessed by categorizing hemorrhagic and ischemic complications at defined endpoints on the day of the procedure, by 30 and 90 days. Fourteen patients developed complications and four of these patients experienced more than one complication. A total of 18 complications occurred by the 90-day follow-up. Overall, four resistant patients suffered complications (all of which received high loading doses of clopidogrel and aspirin) and ten non-resistant patients had complications.

Table 3.

Complications in Patient Groups at Designated follow-up periods

Complications, No. (%) (n=81)	Resistant (n=17)	Non-Resistant (n=64)	p-value
Within 24hrs of Procedure			
Total complications (n=8)	2 (12)	6 (9)	0.6717
Hemorrhagic	1 (6)	5 (8)	>0.999
Ischemic	0 (0)	1 (1)	>0.999
Death	1 (6)	0 (0)	0.2099
By 30-day follow up			
Total complications (n=13)	4 (24)	9 (14)	0.4562
Hemorrhagic	1 (9)	5 (8)	>0.999
Ischemic	0 (0)	2 (3)	>0.999
Death	3 (17)	2 (3)	0.0597
By 90-day follow up			
Total complications (n=18)	5 (29)	13 (20)	0.7514
Hemorrhagic	1 (9)	5 (8)	>0.999
Ischemic	0 (0)	5 (8)	0.5784
Death	4 (23)	3 (4)	0.0323

No significant association was found between type of complication and resistance pattern at procedure (p=0.67), by 30 days (p=0.46), or by 90 days (p=0.75) (Table 3). Nine of 33 patients (27%) who received high loading doses and 5 of 48 (10%) who received standard doses had complications. When these patients were compared, no significant association was found between doses received and occurrence of complications (p=0.0721). Overall, the comparison between resistance pattern and occurrence of complication showed non-significant association (p=0.4777)

Procedure

Of the 18 total complications, eight occurred on the day of procedure. The non-resistant group had six total complications: five (8%) hemorrhagic, one (1%) ischemic, and no deaths at procedure..

30-day Follow-up

By 30 days, 73 patients were seen for follow-up, and 13 had complications (four resistant and nine non-resistant) with no difference in resistance pattern versus rate of complication (p=0.4562). There were five deaths by day 30 (two in the non-resistant and three in the resistant group).

90-day Follow-up

By the 90-day follow-up period, 52 patients had documented follow-up appointments of which five patients (one resistant and four non-resistant) had additional complications between the 30 and 90-day period. There was no significant difference in occurrence of complications between resistance groups by the 90-day follow up period (p=0.2105). Total number of patient deaths were similar between both groups (four in the resistant versus three in the non-resistant); however, the proportion of deaths by 90 days (resistant versus non-resistant) suggested a significant difference (23% versus 4%; p=0.03) (Table 2).

Maintenance Dosing

Maintenance doses following procedures were adjusted based on whether the patient was found to be a responder or non-responder. Those considered non-responders received a higher maintenance dose of Clopidogrel 75 mg BID. 19 (23%) patients were prescribed a lower dose of clopidogrel than their resistance pattern would have suggested, and 62 (77%) patients were prescribed a dose that matched their resistance test results.

Genetic Testing

Eight patients had genetic testing performed to assess CYP2C19 function. Six of the eight patients were heterozygous with one normal and one non-expressing allele and were therefore considered “intermediate” genotype. Two patients were homozygous with both normal alleles and were considered “normal” genotype. Both CYP2C19 “normal” genotype patients were seen to have a non-resistant phenotypic response on P2Y12 assay. Of the CYP2C19 “intermediate” genotypes, four were non-resistant and two were resistant. These findings are consistent with what would be expected in “normal” and “intermediate” genotypes.

Drug Interactions

Due to the fact that proton-pump inhibitors (PPI) may affect the clopidogrel platelet inhibition relationship, we noted that 27 patients received pantoprazole, 24 received omeprazole, 15 received famotidine, and 15 patients did not receive any stress ulcer prophylaxis. There were ten (37%) complications in the pantoprazole group and two (8%) in the omeprazole. Three (20%) complications occurred in the famotidine group and three (20%) in the patients not receiving any prophylaxis. Overall, there

Table 2.Patient Complications* in the Study, Complication Type, and Platelet Resistance

Patients	Resist-ance	Complication (Date)	Type of Complication	Related
1	Yes	Hemorrhage and Death (day 1)	Micro aneurysms and L intraparenchymal hemorrhage	Possible
2	Yes	Death (day 90)	Pneumonia	No
3	No	Ischemia (day 1)	Post-procedure L ACA ischemic infarct	Possible
4	No	Hemorrhage (day 1)	Rupture of daughter sac with small SAH during coiling	No
5	No	Ischemia (day 75)	Two episodes of speech deficit and Rarm weakness/discoordination	Possible
6	No	Ischemia (day 42)	Minor stroke- 3 transient ischemicattacks related to hypotension	Possible
7	No	Hemorrhage (day 1) and Death (day 5)	Procedure complicated by L PCA wire perforation requiring parent vessel sacrifice via coil occlusion. Successful angioplasty of basilar artery with spontaneous hemorrhage of L PCA. Extubated but then had respiratory difficulty and symptoms of L PCA infarct. Patient passed away after decision not to re-intubate.	No
8	Yes	Death (day 19)	Dense thrombus of L MCA presented to ED- patient did not recover after procedure. Paralysis and sedation stopped and patient was extubated prior to expiration.	Possible
9	No	Hemorrhage (day 1)	R groin hematoma s/p evacuation	Possible
10	No	Ischemia (day 11) and Death (day 54)	Recurrent TIAs after angioplasty for L vertebral artery stenosis-with dizziness, nausea, slurred speech, R facial droop. Later admitted to Eustis Hospital with coma, fixed gaze and flaccid quadriplegia. Daughter reports father passed away due to stroke.	Possible
11	No	Ischemia (day 70)	Fatigue, slurred speech, TIA s/p coiling for aneurysm- speech improved. Cerebral angiogram done to rule out any major aneurysm recurrence.	Possible
12	No	Hemorrhage (day 1)	Small hematoma palpable underneath incision site. Witnessed having syncopal and hypotensive episode. CT of abdomen/pelvis showed large amount of retroperitoneal blood and clot with evidence of extravasation near R femoral artery. Large RLQ hematoma.	Possible
13	Yes	Death (day 10)	Patient diagnosed with metastatic cholangiocarcinoma. Received chemotherapy but was unable to continue due to low platelet count. Prognosis was poor from oncologic perspective. Patient expired.	No
14	No	Hemorrhage (day 1) and Death (day 6)	R intraparenchymal/intraventricular hemorrhage s/p R MCA stenting. Code status changed to DNR. Patient expired.	Possible

*18 complications total in 14 patients.

was no significant difference between type of medication and incidence of complication (p=0.112) but this may have been due to small sample size.

Discussion

The purpose of this study was to assess the P2Y12 resistance to antiplatelet therapy in patients undergoing neuroendovascular procedures. Additionally, we sought to determine whether “intensified” antiplatelet therapy, based on P2Y12 platelet function testing, would have differences in ischemic and hemorrhagic complications. The theoretical rationale for an intensified P2Y12 antiplatelet therapy is that if the platelets are adequately inhibited, this may prevent stent thrombosis and secondary ischemic complications. However, giving additional antiplatelet agents may lead to more hemorrhagic complications and cost.

Our study found a 21% resistance to thienopyridines (clopidogrel and ticlopidine) used as antiplatelet agents prior to NV procedures similar to Reavey-Cantwell JF, et al.[1] This has important implications since resistance to antiplatelet agents has been shown to increase the rates of stent thrombosis in coronary studies and worsen outcomes.[5,7,12] Further, our patient population had a higher degree of endovascular balloon angioplasty and stent placement (38%) compared to aneurysm coiling as their predominant procedure (43%). Our study analyzed the complication rates in relation to P2Y12 platelet inhibition similar to the GRAVITAS trial, which examined coronary patients with high versus standard antiplatelet regimens.[13]

The GRAVITAS trial compared high versus standard clopidogrel doses in cardiology patients undergoing percutaneous coronary intervention (PCI).[13] The investigators found only a modest reduction in the level of platelet reactivity in patients treated with clopidogrel 150mg versus 75mg daily following procedures. The authors concluded that although the high-dose clopidogrel group did not have a different outcome than the standard group, the study may have been underpowered to detect a difference. The GRAVITAS investigators also suggested that perhaps repeated P2Y12 testing may have merit in the perioperative period as opposed to their study which used a single test. The investigators also found that high-dose clopidogrel therapy in patients did not reduce the rate of death from cardiovascular causes, nonfatal myocardial infarction, or stent thrombosis.[13] Our study found that there was no significant difference between occurrence of complication and resistance patterns by 30 days. By 90 days, the resistant patients who had a complication (n=5) had a higher rate of death in proportion to those non-resistant patients who had complication (n=13) and death (four versus three deaths) (p=0.03). We suggest not overanalyzing this p-value due to our small sample size. Further, when the cause of death was determined by 90 days we found that two of the resistant patients died from unrelated causes (e.g.,

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pneumonia in patient #2 and cancer in patient #13), and one in the non-resistant group appeared unrelated (wire perforation complication in patient #7) (Table 2). We did not find a significant difference in hemorrhagic or ischemic complications between groups with regards to patterns of resistance or loading dose.

Clopidogrel prescribing has fallen under recent scrutiny due to the recent U.S. Food and Drug Administration (FDA) "boxed warning," which raises important questions for practitioners and patients. The warning addresses the need for pharmacogenomic CYP2C19 testing to identify patients with altered clopidogrel metabolism and possible risk for a suboptimal clinical response. The warning is based on the concern that the antiplatelet effect of clopidogrel depends primarily on its activation by the cytochrome P450 (CYP) system, specifically CYP2C19, and that patients with decreased CYP2C19 function metabolize clopidogrel poorly and are at greater risk for variable platelet reactivity.[10,11,12] At this time, genetic testing is not routinely recommended unless there is clinical suspicion of clopidogrel hyporesponsiveness evidenced by breakthrough clinical events on dual antiplatelet therapy. The CYP2C19 test is also not available at all clinics and hospitals. At our facility, it is a send-out test, which takes about five days to return. This can cause a delay in obtaining the results and make it more problematic for practicing physicians.

Cost of the CYP2C19 test must also be considered when choosing whether to utilize the genotype testing versus platelet function testing. The cost for the CYP2C19 genotype test is approximately $453 compared to the $264 of the VerifyNow platelet function assay. Although clopidogrel is primarily utilized, aspects of alternative agents must also be considered in resistant patients. Prasugrel may have a more consistent effect in clopidogrel non-responders and is affected less by genetic variation of the CYP2C19 enzyme; however, it is not currently approved for use in NV patients or procedures, and is contraindicated in patients with stroke.[14] A newer agent, ticagrelor, which has no known resistance was not available at the time of our study.

The issue concerning the interaction between clopidogrel and omeprazole (Prilosec®), a PPI used to reduce stomach acid, is also an important consideration raised by the FDA report in 2009.[15] Omeprazole is a CYP2C19 inhibitor and clopidogrel undergoes oxidation via CYP2C19. When clopidogrel and omeprazole are taken concurrently, the level of active metabolite is reduced thereby possibly decreasing the clinical efficacy of clopidogrel. Therefore, patients on both clopidogrel and omeprazole may be at greater risk for ischemic events. Despite the FDA published report, there is still controversy over the recommended course of therapy in patients concurrently taking these two medications.[16,17,18]

Limitations to this study are its single-center, retrospective design, sample size, and lack of blinded P2Y12 response groups. Ideally, to test the hypothesis that greater P2Y12 platelet inhibition leads to less ischemic complications, the trial design should have blinded P2Y12 test results for either resistant or non-resistant patterns with adequate power to detect unfavorable outcomes. However, we felt given the literature about risks of coronary stent thrombosis and P2Y12 platelet resistance, it was potentially unethical to blind P2Y12 response in NV procedure patients. The SAMMPRIS trial studied 451 patients with intracranial artery stenosis who were randomized and assigned intracranial stenting versus maximal medical therapy with an antiplatelet regimen of aspirin and clopidogrel, lipid management, and blood pressure control.[19] This study was prematurely terminated due to more strokes (composite end point, either ischemic or hemorrhagic) occurring in the stenting arm compared to the medical therapy arm (20.6% versus 11.5%; p=0.009). In addition, the SAMMPRIS trial did not assess for P2Y12 resistance in either arm, and one wonders if some patients who received intracranial stenting had in-stent thrombosis.[19] The strength of our study is that it is the first to analyze the patterns of resistance in relation to ischemic and hemorrhagic complications, P2Y12 platelet resistance, CYP2C19 genotype, and P2Y12 platelet resistance phenotype in patients undergoing NV procedures.

Summary

Twenty-one percent of our study patients undergoing NV procedures were resistant (<20% P2Y12 platelet inhibition) after initial clopidogrel loading. The findings have significant implications, given recent coronary studies showing higher risks of in-stent thrombosis in P2Y12 resistant patients and the failed intracranial stenting trial SAMMPRIS for intracranial stenosis. Our study showed an increased proportion or trend towards death when a complication occurred in the resistant compared to non-resistant group by 30-days (17% versus 3%; p=0.059), and by 90 days (23% versus 4%; p=0.032). There was no significant association found between complication and loading dose (p=0.0721). Future trials should investigate the long-term risks and benefits associated with a customized dosing approach in NV patients.

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