Precision of VerifyNow P2Y12 Assessment of Clopidogrel Response in Patients Undergoing Cerebral Aneurysm Flow Diversion

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BACKGROUND: Dual antiplatelet therapy (DAT), most commonly with aspirin and Clopidogrel, is the standard of care for intracranial stenting, including flow diversion. Clopidogrel response varies by individual.

OBJECTIVE: To investigate the real-world precision of VerifyNow P2Y12 assessment (Accumetrics, San Diego, California) of Clopidogrel response.

METHODS: Using a prospectively-collected, IRB-approved cerebral aneurysm database 643 patients were identified who were treated with the Pipeline embolization device from 2011 to 2017. Patients with multiple P2Y12 assays drawn within a 24-h window were identified. A single patient could contribute multiple, independent sets. Levels drawn before a 5-d course of DAT and patients who received alternative antiplatelet agents were excluded. Therapeutic range was defined as platelet reaction units (PRU) 60–200.

RESULTS: A total of 1586 P2Y12 measurements were recorded; 293 (46%) patients had more than one assay. One hundred forty (22%) patients had multiple P2Y12 measurements within 24 h. These patients accounted for 230 independent 24-h sets. The average P2Y12 fluctuation across all sets was 35 points; the 25th, 50th, and 75th percentiles were 12, 26, and 48 points, respectively. Of the 230 24-h sets of P2Y12 assays, 76% remained within their original therapeutic category: 100 (43%) all therapeutic, 54 (23%) all hypo-responsive, and 21 (9%) all hyper-responsive. Twenty-four percent of patients fluctuated between therapeutic categories when multiple P2Y12 assessments were drawn within a 24-h period: 29 (13%) between hypo-response and therapeutic, 23 (10%) between hyper-response and therapeutic, and 3 (1%) between hypo-response and hyper-response.

CONCLUSION: Our experience suggests P2Y12 is an often-imprecise measure, and this should be considered when utilizing P2Y12 levels for clinical decisions.

KEY WORDS: Clopidogrel, Antiplatelet, Flow diversion, VerifyNow, P2Y12

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The neurointerventional field inherited the standard practice of dual antiplatelet therapy (DAT) with aspirin and Clopidogrel for stenting procedures from cardiology, where prospective trials demonstrated reduced rates of thromboembolic complications in percutaneous coronary intervention on this regimen. As a prodrug metabolized by the liver to irreversibly inhibit the P2Y12 receptor for ADP on platelets, Clopidogrel has significant therapeutic variability arising from drug interactions, comorbidities, and genetics.[1]

Consensus has subsequently developed based largely on retrospective studies that Clopidogrel hypo-response is associated with ischemic events and hyper-response with hemorrhagic events during and following cerebral embolization procedures. These observations originated in studies of carotid stenting and aneurysm coiling,[2-7] but have come to the fore in the flow diversion era given the increased metal wall coverage of flow diverters and their predominantly elective use.[8-12] Evidence for this consensus was the adoption of therapeutic platelet reaction units (PRU) 60–200

ABBREVIATIONS: CV, coefficient of variance; **DAT,** dual antiplatelet therapy; **LTA,** light transmission aggregometry; **PED,** Pipeline embolization device; **PRU,** platelet reaction units; **TEG,** thromboelastography; **VNP,** VerifyNow P2Y12 assay

as inclusion criteria in prospective studies designed to broaden the indication for the Pipeline embolization device (PED; Medtronic Neurovascular, Medtronic Inc, Dublin, Ireland; PREMIER, NCT02186561). However, controversy persists because there are other retrospective studies reporting no difference in outcomes for Clopidogrel hypo-responders,[13-16] prospective PED trials with low stroke rates despite not testing,[17] and meta-analyses showing higher complication rates in series with antiplatelet therapy monitoring than those without.[18,19]

There are multiple technologies for assessing Clopidogrel response of which the fully-automated, point-of-care VerifyNow P2Y12 assay (VNP; Accumetrics, San Diego, California) is the most commonly used.[8-11] Recent evidence has shown high intraindividual variability in Clopidogrel response, independent of the type of platelet reactivity test used. This is well-documented over periods of weeks to months[20,21] and generally attributed to biology but has not been shown over short time periods that might question the reliability of testing. Assay imprecision could explain the ongoing difficulties using therapy monitoring to guide personalized antiplatelet regimens in cardiac and neuro-intervention.[22,23]

This study arose from the routine clinical observation of discordance between serially drawn PRU levels. Our hypothesis was that many patients on a stable antiplatelet regimen would show substantial variation in PRU, which would influence their "responder status", and at other institutions might lead to changes in antiplatelet therapy. We therefore undertook a retrospective, single-institution study, collecting all P2Y12 levels drawn on patients undergoing PED embolization, excluding those that were not on a stable antiplatelet regimen, and comparing those drawn within 24 h to describe the real-world reliability of VNP.

METHODS

A prospectively-collected, IRB-approved cerebral aneurysm database of patients who underwent PED placement between 2011 and 2017 was retrospectively reviewed for the P2Y12 measurement history of all patients. Individual patient consent was neither sought nor required as this was a retrospective study of P2Y12 values obtained in the course of routine clinical practice with no associated patient risks. The medication history during the times surrounding any VNP assessments was collected. Our routine for all patients has been to initiate DAT consisting of aspirin 325mg daily and Clopidogrel 75mg daily 7 d prior to an elective embolization procedure. Patients taking proton pump inhibitors, which are known to attenuate Clopidogrel's effects, were switched to Famotidine at the time of starting DAT. VNP assessments were conducted once patients were therapeutic in a random selection of patients with increasing frequency after January 1, 2014 as more reports about VNP were published in the neuro-interventional literature. VerifyNow P2Y12 (Accumetrics) is the only antiplatelet therapy test that is routinely used at our institution. In selected cases where patients had clinical signs of hyper-response (e.g. significant bruising, epistaxis, gum bleeding) and a very low PRU, procedures were rescheduled and medications adjusted. None of these patients were included in this study. No action was taken for patients with elevated PRU values as measured by VNP.

Of the patients with multiple P2Y12 measurements, those with assays within 24 h of each other were identified. A single patient with multiple sets of assays within a 24-h window could contribute multiple, independent 24-h sets. Patients were considered therapeutic for Clopidogrel after a 5-d course and measurements drawn earlier were excluded. Measurements taken in the setting of changing dose or frequency of antiplatelet therapy were excluded. Patients who were administered alternative antiplatelet agents such as Abciximab, Prasugrel, or Ticagrelor in the same time frame as the P2Y12 assessments were also excluded. Finally, patients under 18 yr of age were excluded. Demographic information of patients who had at least one 24-hr window containing more than one P2Y12 measurement and qualified based on medication history and age was extracted from medical records.

The therapeutic range was defined as PRU from 60–200, with hypo-response PRU $>$ 200, and hyper-response PRU $<$ 60. The response cutoffs were used to stratify 24-h windows into responder categories based on PRU levels. The mean, standard deviation, and ranges for each 24-h window were computed to assess variability.

RESULTS

A total of 643 patients who underwent PED placement accounted for 1586 VNP measurements. Two hundred ninety-three (46%) patients had more than one assay drawn, 162 of which had multiple P2Y12 measurements recorded within 24 h. Twenty-one patients on alternate antiplatelet medications and 1 patient under 18 yr of age were excluded, resulting in a final group of 140 patients. Two hundred thirty independent 24-h sets (size 2-3) were identified from the final group of 140 patients (Figure 1). Patient age ranged from 18 to 84 yr with an average of 57 ($\pm$ 13 yr) and 79% were female. Patient race was distributed as follows: 54% White, 35% Black, 5% Hispanic, 4% Asian, and 1% other.

These 230 24-hr sets comprised 473 total VNP measurements with an average value of 152 PRU. The average first PRU in the set was 150 ($\pm$ 84) and the average last PRU in the set was 155 ($\pm$ 82). The average time between the first and last PRU in a set was 16.2 hr ($\pm$ 5.8). The average PRU range of all sets was 35 PRU ($\pm$ 36) with a minimum and maximum range of 0 and 225 PRU. The 25th, 50th, and 75th percentiles of ranges were 12, 26, and 48 PRU, respectively (Figure 2).

The 230 sets and 473 VNP measurements can also be visualized based on responder group. Overall, the measurements were 15% hyper-therapeutic (PRU $<$ 60), 55% therapeutic (PRU 60–200), and 31% hypo-therapeutic (PRU $>$ 200). Each 24-hr set fell into one of 6 possible groups, of which 3 were "stable": 100 (43%) of the sets were all therapeutic, 54 (23%) were all hypo-responsive, 21 (9%) were all hyper-responsive. Patients also fell into 3 "unstable" groups: 29 (13%) fluctuated between hypo-response and therapeutic, 23 (10%) fluctuated between hyper-response and therapeutic, and 3 (1%) fluctuated between hypo-response and hyper-response. There were no instances of fluctuation across all three responder categories over a 24-h period. A total of 76% of the 230 sets stayed within one responder

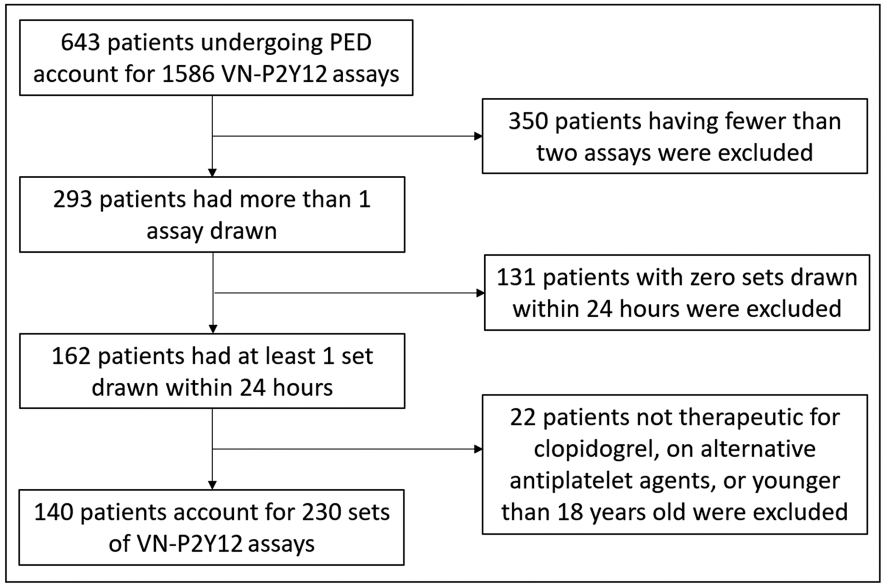

FIGURE 1. *Flow chart of exclusion criteria to reach study sample.*

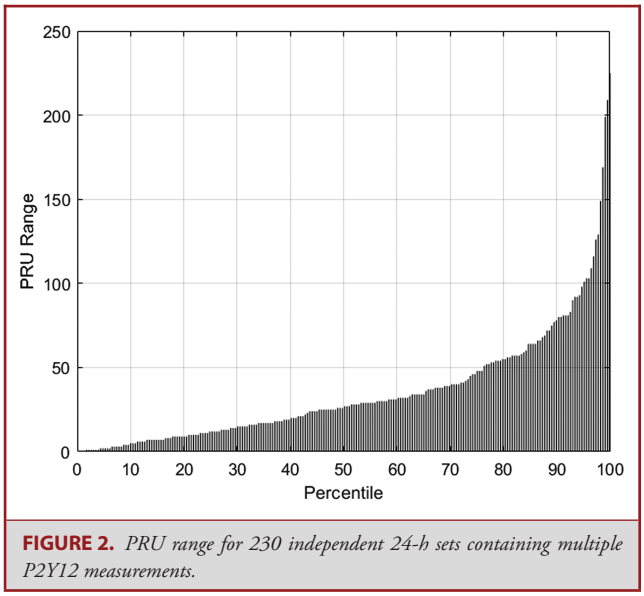

FIGURE 2. *PRU range for 230 independent 24-h sets containing multiple P2Y12 measurements.*

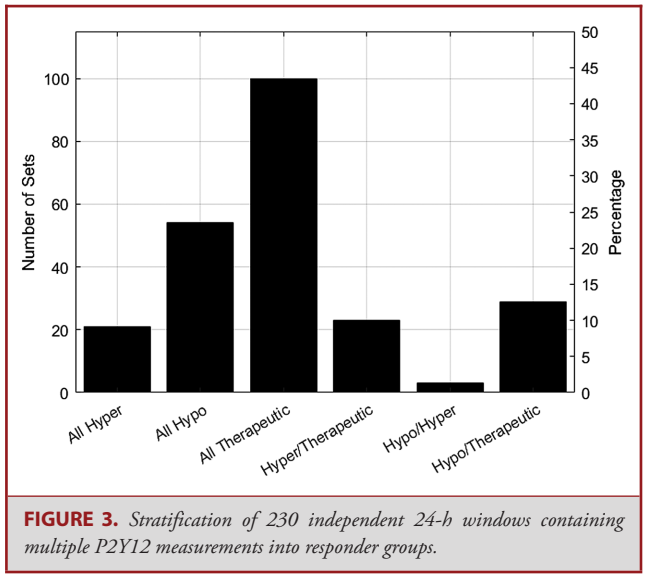

FIGURE 3. *Stratification of 230 independent 24-h windows containing multiple P2Y12 measurements into responder groups.*

category, either all therapeutic response, all hypo-response, or all hyper-response. The remaining 24% of sets fluctuated between responder categories over the course of a 24-h period (Figure 3).

DISCUSSION

This is a retrospective study of the precision of P2Y12 measurement in the therapeutic monitoring of daily Clopidogrel for patients undergoing cerebrovascular embolization. We identified 140 patients who accounted for 230 sets of VNP measurements that were taken within a 24-h period on a stable antiplatelet regimen. The mean and median range for these sets were 35 and 26 PRU units. Using a therapeutic window of PRU 60–200, 76% of these sets were "stable" with all measurements occurring within a single category of response, while 24% of patients fluctuated between therapeutic and hypo- or hyper-response within a 24-h period.

As its role is debated and defined, it is important to understand the challenge of antiplatelet therapy monitoring. Multiple testing modalities have been reported in the neurointerventional literature, including light transmission aggregometry (LTA),[12] impedance aggregometry,[7,12,24] and thromboelastography (TEG)[25,26] each attempting to isolate the action of Clopidogrel in blocking the P2Y12 receptor and measure its effect on overall platelet aggregation amidst confounding pathways. LTA is the historical gold standard but requires centrifugation of platelet rich plasma, while impedance aggregometry and TEG are semiautomated and require agonist preparation and titration or protracted processing.[27]

Because of its ease of use and standardization, the VerifyNow system (Accumetrics) has emerged as the most common methodology for testing Clopidogrel response in the neurointerventional literature.[8-11] The VerifyNow system uses the principle of light transmission which improves as fibrinogen coated beads agglutinate and fall out of solution after exposure to platelets in whole blood. Parallel chambers, one with ADP and P2Y1 agonists and one with thrombin receptor agonists that overcome the effects of P2Y12 inhibition, allow simultaneous determination of the patient response and a reference value.[28] VerifyNow has reasonable concordance with LTA in the assessment of Clopidogrel response, although this is not as high as with VerifyNow assays for aspirin or gpIIb/IIIa inhibitors.[28]

Just as prospective studies on antiplatelet tailoring in the cardiac literature have failed to show a benefit,[22,23] studies of cerebrovascular embolization using VerifyNow and other testing modalities to individualize antiplatelet therapy have shown mixed results. The only prospective study involved elective coiling (70% with stent assistance) in the Korean population. Hwang et al[29] identified 126 patients with PRU > 213, gave half an additional 200mg daily cilostazol (a phosphodiesterase inhibitor which increases cyclic adenosine monophosphate and augments platelet inhibition in patients on aspirin and Clopidogrel), and observed a stroke rate of 11% (7/63) on the standard regimen and 1.6% (1/63) on the modified regimen. In the flow diversion literature, a Turkish group reported 104 consecutive PED cases, the first 34 of which were performed on standard DAT and among the last 71 of which 17 hypo-responders were switched to alternative P2Y12 inhibitors to achieve therapeutic response based on impedance aggregometry. Thrombotic events were observed in 9% of patients on the standard protocol and 3% of the aggregometry group ($P = 0.03$), although multivariate analysis was not performed and, given the lack of randomization, the results may reflect interventionist experience.[24] An American study of 103 patients showed that by measuring PRU after 10 d of DAT, modifying the dose based on a predetermined algorithm, and measuring again after 17 days of DAT, it was possible to bring 89% of patients within therapeutic range PRU (60-240), but still reported a relatively high major stroke rate of 4.9%.[23] Adeeb et al[12] combined data from three American institutions to report a large retrospective study of 399 patients undergoing PED, including 115 Clopidogrel nonresponders. Nonresponders were either switched to ticagrelor (n = 37), bolused with Clopidogrel (n = 51), or continued on standard DAT (n = 27). Rates of ischemic complications (symptomatic or otherwise) were 5.6% for responders, 2.7% for ticagrelor, 9.8% for patients bolused with Clopidogrel, and 51.9% for nonresponders treated with standard DAT.[12]

Heterogeneity is one reason for disagreement about the association between Clopidogrel response and complications after cerebrovascular embolization as well as the mixed results of studies of antiplatelet tailoring. In the study by Adeeb et al,[12] each institution used a different testing method (aggregometry, LTA, and VerifyNow) and thresholds for defining hypo-response were not reported. In other studies, the duration of antiplatelet therapy varies from as little as 3[4] to > 14 d[6,23] and thresholds for therapeutic response vary from PRU < 150[9] to PRU < 240.[10,23] As a result, the proportion of nonresponders varies significantly from 21[16] to 53%.[11]

Intraindividual variation is another reason for dissonance among retrospective studies using VerifyNow to assess Clopidogrel response. Disparate P2Y12 results for the same individual at different points in time can reflect changes in individual biology. Many people become more responsive over time: In the Cardiology literature, Campo et al. reported 300 patients undergoing percutaneous coronary intervention who received 600mg Clopidogrel load and were then maintained on DAT; average PRU and the share of patients with PRU > 235 at 1 d, 1 mo, and 6 mo postprocedure were 190 and 36%, 147 and 13%, and 146 and 13%. By eliminating "false poor responders," PRU at 1 mo was a better predictor of ischemic or hemorrhagic complications than initial PRU.[20] In the cerebrovascular flow diversion literature, Delgado et al. noted a similar phenomenon in their retrospective series of 100 patients, of which 21% showed hyper-response (PRU < 60) after 7 to 10 d of Clopidogrel. After 30 d of treatment, 59% of patients initially within therapeutic range became hyper-responders.[30] The predictability of this response would allow controlled antiplatelet therapy modification.

An individual's PRU is not stereotyped, however, even with identical dose and duration of therapy. As part of another study from the Cardiology literature designed to assess whether higher doses of Clopidogrel can overcome reduced-function CYP 2C19 alleles, Hochholzer et al[31] prospectively followed 247 patients who each received two 14-d courses of Clopidogrel at a 75mg and 150mg dose. The percentage of patients who shifted between an appropriate and insufficient response (PRU > 208) between cycles on the same regimen was 22% for the 75mg dose and 15% for the 150mg dose. Forty-one percent of patients showed a difference of > 40 PRU points between cycles.[31] The authors suggested this may reflect biological variability due to fluctuations over time in platelet production, P2Y12 receptor expression, or changes in hepatic metabolism.

But the variability observed by Hochholzer et al[31] also reflects a degree of assay imprecision. By comparing repeat P2Y12 values drawn from the same person at effectively the same time, the

present study gives a picture of VNP assay precision in a real-world setting. For patients on a stable regimen of aspirin 325mg and Clopidogrel 75mg daily for at least 5 d, the average range in a set of P2Y12 values drawn within 24 h was 35 PRU points. Given a therapeutic range of PRU 60–200, 24% of patients fell into multiple categories of response. Both ranges and therapeutic categories are reported because each can be misleading in certain scenarios. At an initial PRU of 120, a 35-point swing in either direction would not result in a reclassification of therapeutic category; at an initial PRU of 195, a small difference of 10 PRU points could result in reclassification leading some physicians to cancel a procedure or modify antiplatelet dosing.

There is a limited literature on VerifyNow assay precision for Clopidogrel therapy. Karon et al[32] measured P2Y12 in duplicate at an interval of 24 to 28 hours from 10 Clopidogrel-treated volunteers and reported intraassay (eg, from duplicate labs) coefficient of variance (CV) of 7.3% and interassay (eg, at different time points) CV of 12.9%. This variance was higher than reported for healthy volunteers and for the VerifyNow aspirin assay (which differs primarily in using an arachidonic acid as opposed to ADP agonist). Using CV to characterize PRU fluctuation among sets of only four measurements may introduce inaccuracies due to the large uncertainty associated with computed sample variances. For Clopidogrel-treated patients, the correlation between paired measurements drawn on different days was 0.92, suggesting that interindividual variance contributes more to total PRU variance than intraindividual variance, although the assumption of random effects may not be valid in such small populations.[32]

This retrospective, observational study required difficult decisions about time cutoffs for inclusion, specifically the duration of therapy and the interval for repeat measurements. First, Clopidogrel pharmacodynamics is variable but elective treatment after 5 d of therapy is common practice.[2,5,11,14,16,29] Second, there was no standardized interval between dosing and laboratory assessment. A repeat measurement within 24 h would necessarily have a different temporal relationship to the dosing of a daily medication. Reported "assay imprecision" incorporates these irregularities but reflects the clinical setting in which VNP is used and decisions are taken based on its results. Time between lab draw and PRU processing varied but was always between 10 min and 4 h, as recommended by VNP labeling.

Due to the retrospective nature of our study and the fact that VNP was the only modality of antiplatelet therapy monitoring used at our institution, there was no comparison test available. It is typical in this literature for an institution to rely on one type of antiplatelet therapy monitoring.[12]

The lack of a specific rationale for each repeat test is a limitation that arises out of the retrospective nature of this study. The most common scenarios included: rechecking values that do not correlate with symptoms and signs, routine overnight laboratory tests in our closed Neurocritical care unit, and daily values for inpatients awaiting embolization (eg, definitive flow diversion after subtotal coiling of a ruptured aneurysm). We can infer based on the time between repeat tests which of these categories most values fell into. Rechecks would be most likely to occur within 6 h of the original test (8% of sets). Depending on what time of day an embolization occurred, an overnight lab recheck would most likely occur 6 to 20 h after the initial test (61% of sets). Daily values during an inpatient stay are likely to have been drawn within 4 h of each other on consecutive days, or at an interval of 20 to 24 h (31% of sets).

Given the scenarios in which repeat tests were drawn, inpatients accounted for a greater share of this study than studies of elective flow diversion of unruptured cerebral aneurysms.[33] Inpatients are sicker and had more laboratory irregularities, which are known to influence VNP. We repeated the central analyses after excluding patients who met any one of the following criteria: hematocrit < 30%, creatinine > 2.0 mg/dL, platelets < 100,000/mL, and AST or ALT > 100 IU/L. This reduced the number of patients to 121 and sets to 176, but the results were nearly identical: 25% of sets included P2Y12 values that fell into more than one category of therapeutic response and the 25th, 50th, and 75th percentile values for PRU range were 11, 26, and 48. This was not surprising since most common exclusion criteria was hematocrit < 30%, which is known to predictably increase P2Y12 results[34] and for this reason would not be expected to affect assay precision.

This study arose out of our clinical observation of discordance between serially drawn P2Y12 levels. The goal was to describe the precision of VNP in a real-world clinical setting. Studies of cerebrovascular embolization that draw strict inclusion thresholds based on PRU or demand antiplatelet therapy modification based on a number[23] overlook the reality that PRU is not a stable phenomenon. Aggressive therapy modification to achieve a therapeutic response prior to scheduled embolization can lead to hemorrhagic complications.[26] We are not denying the association between antiplatelet therapy and the complications of cerebrovascular embolization. In fact, the imprecision of existing diagnostics—by misclassifying some fraction of patients based on the results of VNP, LTA, TEG, impedance aggregometry, or others—may account for the conflicting reports on this topic and the failure of antiplatelet tailoring programs.

The implications of this study for neurointerventional practice is that continued optimization of diagnostics for assessing Clopidogrel response is needed, including the incorporation of genetic testing. The laboratory result must be interpreted in the context of the patient; clinical signs including excessive bruising or spontaneous epistaxis may still be the best indicator of hyperresponse. The risk of ischemic complications and the importance of achieving therapeutic P2Y12 blockade is increased with distal anterior circulation flow diversion as compared with PED in the internal carotid artery.[33,35] More liberal use of alternative P2Y12 inhibitors with improved pharmacodynamics and more predictable response[1] profiles may be warranted. Although Clopidogrel hypo-response can be overcome with increased dose and duration of therapy,[23] we hesitate to recommend

a re-dosing strategy because it relies on correctly identifying hypo-responders through antiplatelet therapy testing, which is imprecise.

CONCLUSION

Inter-individual variation in Clopidogrel response necessitates monitoring, most commonly with the VNP. In the clinical setting, a person's PRU is not a stable phenomenon, which may reflect biology or assay imprecision. The latter factor is underappreciated in the neurointerventional space and may explain conflicting evidence about ischemic risks in Clopidogrel hypo-responders and the mixed results of individualized antiplatelet regimens.

Disclosures

Dr Coon is a consultant and proctor for Medtronic, Stryker, and Microvention. Dr Colby is a consultant for Microvention. Dr Lin receives research support from Microvention and Stryker, and is a consultant for Medtronic. The other authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENT

We are pleased to comment on this recent article that provides a single-center retrospective evaluation of "Precision of VerifyNow P2Y12 Assessment of Clopidogrel Response in Patients Undergoing Cerebral Aneurysm Flow Diversion". The authors conclude that inter-individual variation in Clopidogrel response necessitates monitoring. The group also reiterates a point that is becoming commonplace, "a person's PRU is not a stable phenomenon, which may reflect biology or assay imprecision". Our own group has also observed this instability with some frequency with our routine use of a light transmission aggregation (LTA) variant of the gold standard, whole blood platelet aggregometry. When "suboptimal responses" result, our treatment algorithm initially included modification of proton pump inhibitor dosing or an increase in Clopidogrel or ASA dosing. We have now abandoned the increase in Clopidogrel dosing and will convert patients to the newer generation P2Y12 inhibitors. While it is logical to consider the utility of monitoring the platelet response when responses are variable, our own group found that instituting a monitoring protocol resulted in a statistically significant decrease in thrombogenic complication rate during stent assisted procedures when compared with our own historical control.[1] This would suggest that despite variability during the course of drug administration, optimization of antiplatelet therapy prior to treatment should be encouraged.

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