e-ISSN: 2807-7970

AKSONA

Volume 3 Number 1, January 2023

The Role of Dual Antiplatelet in Stent-Assisted Coiling in Wide-Neck Aneurysm

Ricky Gusanto Kurniawan[1], Bambang Tri Prasetyo[1], Beny Rilianto[1], Abrar Arham[1]
[1] National Brain Center Hospital Prof. Dr. dr. Mahar Mardjono, Jakarta, Indonesia

Article info

Article History:
Received Jul 1, 2022
Revised Sept 17, 2022
Accepted Oct 12, 2022
Published Jan 31, 2023

Keywords:
Dual antiplatelet
In-stent thrombosis
Stent-assisted coiling
Therapy
Wide-neck aneurysm

ABSTRACT

Stent-assisted coiling (SAC) in wide-neck aneurysm treatment is associated with antiplatelet use. Dual antiplatelet therapy (DAPT) has been the gold standard for protecting against thrombosis events and is widely accepted for endovascular embolization treatment with a stent-assisted or flow diverter. Some patients experience vascular events due to the reduced efficacy of antiplatelet agents despite taking DAPT. The reported thrombosis rates during stent-assisted coiling embolization range from 2% to 20%. Thromboembolic complications, such as in-stent thrombosis, can manifest in 4.6% of cases. The correlation between platelet reactivity during treatment and bleeding events remains unclear. However, the association between High Residual Platelet Reactivity (HRPR) or hyporesponsiveness and ischemic events is well established. Based on various laboratory definitions, hyperresponsiveness in patients with clopidogrel occurs in about 14–30% of patients due to major and minor bleeding. Therefore, the optimization of antiplatelet therapy has developed significantly in the neurointerventional community.

Corresponding Author
Ricky Gusanto Kurniawan
National Brain Center Hospital Prof. Dr. dr. Mahar Mardjono, Jakarta, Indonesia
email: rickygk@gmail.com

INTRODUCTION

Stent-assisted coiling is an endovascular therapy for unruptured wide-necked intracranial aneurysms. This treatment is associated with the use of dual antiplatelet therapy.[1,2] There is no standard definition of DAPT therapeutic failure. We previously discussed the DAPT response's failure in the context of thrombosis events. Then it grew with something we can measure, which is functional platelet aggregations caused by DAPT, but the terminology has been changed. They correlated the cut-off of the functional aggregation tests with the adverse effect of the antiplatelet itself, either hemorrhagic or ischemic, as the endpoint. Based on the cut-off point, we classified it as having no responsiveness, hyporesponsiveness, or hyperresponsiveness to DAPT.[3,4,5]

Several factors influence antiplatelet responsiveness. The intraindividual antiplatelet response to aspirin and clopidogrel has been extensively studied. It is correlated with the antiplatelet's pharmacokinetics (PK) or pharmacodynamics (PD). Platelet responsiveness can be increased by underlying disorders such as atherosclerosis, hyperlipidemia, diabetes, smoking, and inflammation. Drug efficacy is also influenced by differences in intestinal absorption, adherence, and drug effects metabolized by CYP enzymes (omeprazole, statins, and other drugs) because of the same need for cytochrome P450 enzymes. In multivariate analyses, PK and PD clopidogrel responsiveness were associated with age > 55 years, female gender, diabetes mellitus comorbidity, and obesity (> 25 kg/m2).

The incidence of aspirin resistance in patients with cardiovascular disease ranges from 5-60%, depending on the diagnosis, type of testing used, and population studied. Even though clopidogrel has been used to treat acute coronary syndrome (ACS) for over a decade, it was found that about 40% of patients had insufficient antiplatelet efficacy. Biological studies have described a broad interindividual variability of antiplatelet agent responses, especially to P2Y12 receptor inhibitors. Some patients showed suboptimal responses due to the reduced bioavailability of the active drug. This is related to the metabolism of the P2Y12 receptor inhibitor.[4,5,6]

A third new generation of P2Y12 blockers (thienopyridine) has demonstrated its clinical benefit in large randomized controlled trials, such as prasugrel and ticagrelor. These three agents, along with clopidogrel, are different in their metabolism (the most notable difference), drug interactions, onset of action, adverse effects, and reversibility. P2Y12 blockers play an essential role in platelet activation and aggregation compared to the other two thienopyridines.

P2Y12 receptors can be irreversibly inhibited by clopidogrel and prasugrel, whereas ticagrelor causes reversible receptor inhibition. Ticagrelor should be taken twice daily. Compared with other thienopyridines, ticagrelor is usually prescribed, but patient compliance is the biggest challenge compared with the other P2Y12 receptor inhibitors. Clopidogrel and prasugrel are both prodrugs that must be metabolized in the liver first. Still, prasugrel is more efficiently converted to its active ingredient via a single-step metabolism involving cytochrome P450 enzymes (CYPs) than clopidogrel is. Conversion to active substances is more complicated, requiring a two-step active component conversion process. According to recent research, the first metabolic process involves CYP1A2, CYP2C19, and CYP2B6, while the second metabolic step involves CYP3A, CYP2B6, CYP2C19, and CYP2C9.[6–11]

Several studies have shown that people respond well to clopidogrel, though the optimal loading and maintenance doses, switching to another thienopyridine with prasugrel and ticagrelor, and the tests used to assess platelet reactivity are still debated.[12]

REVIEW

Stent-Assisted Coiling and Role of Dual Antiplatelet in Wide-Neck Aneurysm

Stent-assisted coiling is an endovascular therapy commonly used for unruptured wide-necked intracranial aneurysms. SAC has the advantage that it can reach the posterior circulation and is effective for sidewall aneurysms. SAC itself tends to be less expensive than other endovascular therapies.[1,2] Thrombosis and bleeding are two complications that can occur after SAC. However, in contrast to stent placement in acutely ruptured aneurysms, it is generally avoided, and dual antiplatelet therapy is not required because invasive interventions, ventriculostomy, and the potential for secondary infarction could happen in the future.[6,7]

Platelet Function Test

Light Transmission Aggregometry (LTA) is the gold standard for measuring functional aggregation assays in response to ADP. However, it is unsuitable for drug monitoring because it demands long turn-around times and short sample stability. HRPR (high residual on-treatment platelet reactivity), or what we call "hypo response," is the absolute difference between baseline and post-treatment aggregation of 10% in response to both 5 and 20 mol/l AD. LTA has shown a good correlation with peak plasma levels of the active metabolite clopidogrel (AMC), although platelet aggregation is stimulated by high concentrations of ADP (20 mol/l). The disadvantages of LTA are that it is not widely used because of the

cost of the machine, requires several steps for analysis, is only available in specialized laboratories, isn't as standardized, and is heavily affected by pre-analytical variables.[6,13,14]

New maintenance testing methods are currently available, with the advantages of semi-automation, minimal or no sample preparation required, and low sample volumes needed. This study revealed that the flow cytometric VASP and P2Y12 assays are the best platelet function tests to determine peak plasma levels of AMC. Therefore, this platelet function test is likely the most accurate for measuring the true biologic activity of clopidogrel in vivo. Automated tests, the P2Y12 test and VASP, may be useful in assessing the effect of antiplatelet treatment, including thienopyridine therapy, although they may not detect primary hemostasis. Further differences between these tests should be based on their sensitivity and specificity in predicting atherothrombotic events after percutaneous coronary intervention (PCI), as well as their cost and labor intensity.[3,15,16]

The VASP assay is the only specific test for P2Y12 inhibition and is not affected by the effect of ADP on the P2Y1 receptor. It is measured with the platelet reactivity index (PRI). This assay has been standardized, but the disadvantage is that this method needs a few steps for the testing, which is time-consuming and costly.[16]

Several studies have predicted thrombotic events by investigating the cut-off PRI value. Bonello *et al*. were the first to use the VASP assay to determine the correlation of HRPR with clopidogrel and clinical incidence. This prospective, multicenter, randomized study of clopidogrel resistance was defined as a VASP index after a 24-hour loading dose with a frequently reported PRI limit of 48% to 53%. Currently, a VASP PRS >50% means HRPR, and a PRI <16% means lower platelet reactivity (LPR) or hyper response.[8,12,17]

P2Y12 is a simple point-of-care test often used as a platelet function test because of its ease of use and validation with LTA, availability in clinical settings, rapid results, and ability to be performed on whole blood and specifically to measure P2Y12-mediated aggregation. This is one of the most widely used laboratory assays.[18]

Evidence-based antiplatelet therapy is emerging for optimal treatment to prevent bleeding and ischemic events. Th VASP and VerifyNow P2Y12 laboratory assays were the main focus of this article because they are the most widely used and correlate well with LTA. This therapeutic window will inform future studies designed to optimally avoid thrombotic and bleeding events during P2Y12 inhibitor therapy.

Almandoz *et al*. found that patients on aspirin/prasugrel DAPT (16.7%) had a higher risk of major hemorrhagic complications after PED (Pipeline Embolization Device) procedures than those on aspirin/clopidogrel DAPT (2.9%).[19] Due to the increased risk of major perioperative hemorrhagic complications, they changed their DAPT protocol for PED procedures, expanded their target PRU in PED patients, established clopidogrel cut-off 60< PRU > 240 as the strongest independent pre-procedure predictor of hemorrhagic and thromboembolic events, and for elective cases will not undertake until the patient is within the target PRU range in pre-procedure. P2Y12 receptor inhibition testing was done no earlier than the day before the procedure was given. Kim *et al*. brought this cut-off point into their protocol.[3]

Genetic Test

Biological studies have described a broad interindividual variability of antiplatelet agent responses, especially to P2Y12 receptor inhibitors. Some patients showed a lack of optimal response in the presence of decreased bioavailability of the active drug. This is related to the metabolism of the P2Y12 receptor inhibitor. Compared with the other two thienopyridines, ticagrelor is a compound that does not require liver activation to exert its anticoagulant effect. Clopidogrel and prasugrel are both prodrugs that require hepatic metabolism, but prasugrel is more effectively converted to the active ingredient by a one-step metabolism containing the cytochrome P450 enzyme (CYP), whereas the conversion of clopidogrel is more complex and requires a two-step conversion process. According to a recent study, the first metabolic process involves CYP1A2, CYP2C19, and CYP2B6, while the second metabolic step involves CYP3A, CYP2B6, CYP2C19, and CYP2C9. The active metabolite permanently blocks the platelet ADP P2Y12 receptor, which causes impaired platelet function.[5,6,9,10] Thus, patients will experience treatment failure.

P2Y12 blockers (thienopyridine), except ticagrelor, were the allowed gene polymorphisms in about 18% of this trend. This is related to the frequency of homozygotes, which occur in around 2% of the population, compared to heterozygotes, which occur in around 30% of the population, both of which are at higher risk. The CYP2C19 gene polymorphisms contribute to the response to clopidogrel therapy. However, it needs necessary to adequately explain the lack of response from most people. Previous trials have shown that identifying CYP2C19 status only explains 12%–15% of the poor or no response to clopidogrel. Therefore, some patients with "wild-type" CYP2C19 still achieve a sufficient antiplatelet response to clopidogrel within one month of therapy. At this point, genetic testing is not the answer to explain the poor antiplatelet response to clopidogrel therapy.[9,10]

There are recommendations about the role of genetic testing as a routine treatment or approach to safety and pharmacological efficacy. The American Heart Association and the American College of Cardiology Foundation have found that there are clinical problems, such as a lack of information that routine testing improves outcomes for significant subgroups of patients, widespread variability of CYP2C19 gene polymorphisms, high cost, replacement associated with genetic testing, availability of other thienopyridines and P2Y12 ADP receptor antagonists, and using platelet function testing as an alternative to monitoring therapy.[15] However, in the expert clinical consensus document, they suggest genetic testing for patients at high risk of thrombotic complications (stent thrombosis, multivessel PCI procedures, and/or other risk factors associated with high platelet responsiveness) may be beneficial.[15,16,17]

Role of Antiplatelet in Neuro-endovascular Procedure Setting

No comparative studies validate PRU 85–208 slices in neuroendovascular procedures, but many neuroendovascular studies used this cut-off and adapted or extrapolated from the early PCI literature. Many practitioners have noticed that patients who take clopidogrel before the procedure (as opposed to loading immediately before the procedure) may have fewer thromboembolic complications. The clopidogrel response was assessed using the VerifyNow test in all patients no earlier than one day before the procedure. Kim *et al*. recommended, if possible, that patients undergoing neuroendovascular intervention be on DAPT at least 5–7 days before the procedure; some practitioners recommend at least 14 days.[3] Almandoz *et al.* recommended DAPT be administered 10–30 days after any changes in doses or another P2Y12 receptor antagonist before the procedure, and if the function test is not within the range, recommend changing to another thienopyridine or rescheduling the procedure.[19]

Reloading doses of clopidogrel (300 mg) and rechecking platelet function after 1 hour is recommended for a patient with hyporesponsiveness; if it is already within the target range, the procedure can be performed; if not, the procedure can be rescheduled for 2-3 weeks later, and the clopidogrel dose is increased to 150 mg.[3] Higher loading doses (600 mg versus 300 mg), multiple loading doses (600 mg twice over 2 hours), and maintenance doses (150 mg daily) of clopidogrel indicated increased platelet inhibition. According to studies, 30–40% of hyporesponsive patients will become responders by more than half after 30 days, even without increasing the doses.[3,5] Also, a loading dose of clopidogrel (usually 300–600 mg) may be given orally if there is an urgent need for neuroendovascular intervention.

Patients known to have a poor response to clopidogrel or even no response should be switched to another new P2Y12 blocker agent like prasugrel with loading doses of 60 mg followed by 10 mg maintenance doses or ticagrelor with 180 mg loading doses and 90 mg maintenance doses. However, many practitioners still consider using it, even though it has been proven to decrease platelet reactivity and increase bleeding risk. This was one of the reasons for choosing to advance the PRU cutoff point from 80 to 200 become 60 to 240 for the PED procedure because of the higher incidence of stent thrombosis and to try to avoid the risks of bleeding caused by substituting with prasugrel.[19]

Almandoz *et al.* suggested that patients who needed emergency PED procedures should take ticagrelor (180 mg once a day, then 90 mg twice a day) before the procedure, without testing for P2Y12 receptor inhibition and then switch to clopidogrel on day 30 postoperatively.[11,19] This protocol is based on studies that show that 30–40% of hyporesponsive patients improve by more than half after 30 days, even without increasing the doses. Some studies suggested focusing on another risk factor that affects clopidogrel's pharmacokinetics and pharmacodynamics or using another P2Y12 blocker agent, like prasugrel with a 60 mg loading dose and a 10 mg maintenance dose, or ticagrelor with a 180 mg loading dose and a 90 mg maintenance dose.[3] Kim *et al.* suggested reducing the clopidogrel doses for hyperresponsive patients. If the PRU is at the target point the days before the procedure, the dose can be reduced to 75 mg daily or every third day, and the procedure can be repeated.[3] There is no evidence to adjust antiplatelet doses related to monitoring functional platelet testing, but there is evidence that 30 days of functional platelet testing is correlated with the adverse effect. Two articles in the literature suggested examining the functional platelet 2-4 weeks after the procedure.[3,12]

CONCLUSION

One of the challenging points is the therapeutic window of antiplatelets in managing the risks of thrombosis and hemorrhagic complications when using DAPT. Even though there are no particular guidelines for neuroendovascular intervention stand-in based on the cardiology PCI procedure, we can use and adapt some protocols from a few authors based on their research in endovascular intervention procedures that are more established right now. We hope that there will be more evidence about these situations in the future so that we can come up with specific guidelines for the safety and effectiveness of using DAPT for neuroendovascular intervention in coiling embolization of aneurysms with stent-assisted procedures

or using the flow diverter.

Acknowledgement
The authors thank the Indonesia National Brain Center Hospital, Indonesia, for the support that made this study complete.

Author contributions
RGK, BTP, BR, and AA contributed to the conception, design, and acquisition of the study. RGK, BR, and PRW wrote the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version of the manuscript.

Conflict of Interest
The authors have no conflicts of interest to disclose for this report.

Funding
No funding was received for this case report.

REFERENCES

1. Bechan RS, Sprengers ME, Majoie CB, Peluso JP, Sluzewski M, van Rooij WJ. Stent-assisted coil embolization of intracranial aneurysms: Complications in acutely ruptured versus unruptured aneurysms. *Am J Neuroradiol*. 2016;37(3):502–7.
2. Maldonado IL, Bonafé A. Stent-assisted techniques for intracranial aneurysms. In: Murai Y, editor. Aneurysm. InTech; 2012. p. 291–312.
3. Kim KS, Fraser JF, Grupke S, Cook AM. Management of antiplatelet therapy in patients undergoing neuroendovascular procedures. *J Neurosurg*. 2018;129(4):890–905.
4. Dong J, Wang F, Sundararajan S. Use of dual antiplatelet therapy following ischemic stroke. *Stroke*. 2020 ;51(5):e78–80.
5. Alhazzani A, Venkatachalapathy P, Padhilahouse S, Sellappan M, Munisamy M, Sekaran M, et al. Biomarkers for antiplatelet therapies in acute ischemic stroke: A clinical review. *Front Neurol*. 2021;12.
6. Jiang X-L, Samant S, Lesko LJ, Schmidt S. Clinical pharmacokinetics and pharmacodynamics of clopidogrel. *Clin Pharmacokinet*. 2015;54(2):147–66.
7. Cuisset T, Grosdidier C, Loundou AD, Quilici J, Loosveld M, Camoin L, et al. Clinical implications of very low on-treatment platelet reactivity in patients treated with thienopyridine: The POBA study (predictor of bleedings with antiplatelet drugs). *JACC Cardiovasc Interv*. 2013;6(8):854–63.
8. Oliphant CS, Trevarrow BJ, Dobesh PP. Clopidogrel response variability: Review of the literature and practical considerations. *J Pharm Pract*. 2016 ;29(1):26–34.
9. Loer HLH, Türk D, Gómez-Mantilla JD, Selzer D, Lehr T. Physiologically Based Pharmacokinetic (PBPK) modeling of clopidogrel and its four relevant metabolites for CYP2B6, CYP2C8, CYP2C19, and CYP3A4 drug–drug–gene interaction predictions. *Pharmaceutics*. 2022;14(5):915.
10. Ray S. Clopidogrel resistance: The way forward. *Indian Heart J*. 2014;66(5):530–4.
11. Almandoz JED, Crandall BM, Scholz JM, Fease JL, Anderson RE, Kadkhodayan Y, et al. Pre-procedure P2Y12 reaction units value predicts perioperative thromboembolic and hemorrhagic complications in patients with cerebral aneurysms treated with the Pipeline Embolization Device. *J Neurointerv Surg*. 2013;5(Suppl 3):iii3–10.
12. Norgard NB, DiNicolantonio JJ. Clopidogrel, prasugrel, or ticagrelor? A practical guide to use of antiplatelet agents in patients with acute coronary syndromes. *Postgrad Med*. 2013;125(4):91–102.
13. Sharma P, Sachdeva MUS, Kumar N, Bose S, Bose P, Uppal V, et al. A comparative study between light transmission aggregometry and flow cytometric platelet aggregation test for the identification of platelet function defects in patients with bleeding. *BLOOD Res*. 2021;56(2):109–18.
14. Lenk E, Spannagl M. Platelet function testing-guided antiplatelet therapy. EJIFCC. 2014;24(3):90–6.
15. Bhopalwala AM, Hong RA, Khan ZR, Valentin MR, Badawi RA. Routine screening for CYP2C19 plymorphisms for patients being treated with clopidogrel is not recommended. *Hawaii J Med Public Heal*. 2015;74(1):16–20.
16. Ding P, Wei Y, Chen N, Liu H. Validation of a new ELISA-based vasodilator-associated stimulated phosphoprotein phosphorylation assay to assess platelet reactivity index in a chinese population. *SAGE Journals*. 2018;24(3):452–61.
17. Bonello L, Mancini J, Pansieri M, Maillard L, Rossi P, Collet F, et al. Relationship between post-treatment platelet reactivity and ischemic and bleeding events at 1-year follow-up in patients receiving prasugrel. *J Thromb Haemost*. 2012;10(10):1999–2005.
18. Jeong Y-H, Bliden KP, Antonino MJ, Park K-S, Tantry US, Gurbel PA. Usefulness of the VerifyNow P2Y12 assay to evaluate the antiplatelet effects of ticagrelor and clopidogrel therapies. *Am Heart J*. 2012;164(1):35–42.
19. Almandoz JED, Crandall BM, Scholaz JM, Fease JL, Anderson RE, Kadkhodayan Y, et al. Last-recorded P2Y12 reaction units value is strongly associated with thromboembolic and hemorrhagic complications occurring up to 6 months after treatment in patients with cerebral aneurysms treated with the pipeline embolization device. *Am J Neuroradiol*. 2014;35(1):128–35.

TABLES AND FIGURES

Table 1. Comparison functional and biochemical laboratory test methods summaries

Test	Description	Sampling	Methods	Advantages	Disadvantages
Light Transmission Aggregometry (LTA) in platelet rich plasma	Optical detection of platelet aggregation in response to ADP	Plasma	Optical measurement of platelet aggregation	Gold Standard	- High cost - Only available in specialized laboratory - Time consuming - Lack standardization
VerifyNow@P2Y12	Optical detection of platelet-coated beads in response to ADP	Whole blood	Optical measurement of platelet aggregation	Simple and readily available in clinical setting Quick result	Affected by numerous pre-analytical variable
VASP	Flow cytometry method determines VASP phosphorylation status	Whole blood	Flowmetric measurement of platelet aggregation	Only test to specifically measure P2Y12 Standard methodology	- Not readily available - Number of steps involved to perform test - High cost

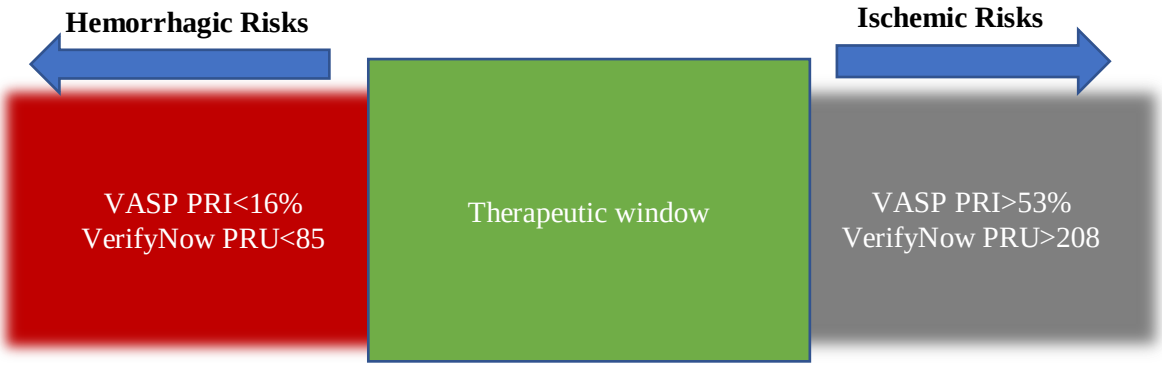

Figure 1. Cut-off point correlated with ischemic and haemorrhagic