The challenge of monitoring platelet response after clopidogrel

Victor L. Serebruany¹* and Shinya Goto²

¹HeartDrug™ Research Laboratories, Johns Hopkins University, Towson, MD 21204, USA; and ²Department of Medicine (Cardiology), Tokai University, Kanagawa, Japan

This editorial refers to: ‘Comparison of four tests to assess inhibition of platelet function by clopidogrel in stable coronary artery disease patients’⁵ by M. Lordkipanidze et al., on page 2877

Despite the established importance of platelet inhibition for the treatment or prevention of thrombotic vascular events, recent oral antiplatelet drug development cannot be considered as a uniform, complete success. In fact, the MATCH,¹ CHARISMA,² and TRITON³ trials raise concerns with regard to the vascular efficacy (questionable, if any) and the obvious increased bleeding risks that arise from more potent antiplatelet regimens. Therefore, attempts to identify the high-risk cohorts that experience worse clinical outcomes or excessive haemorrhagic complications should be undertaken and represent the top priority for further antiplatelet drug development. The delicate balance between meaningful antithrombotic effects and acceptable bleeding risk is especially sensitive in certain regions of the world, such as in Asia,⁴,⁵ where federal authorities are extremely concerned about the potential overdosing of antithrombotic agents. In some countries such as Japan, lower doses of antiplatelet agents are approved in order to combat bleeding complications. For instance, the allowed ticlopidine dose in Japan is only 200 mg/day, whereas in the rest of the world the standard dose is 500 mg/day. The Japanese goal was to reduce the safety concerns with ticlopidine, and a stand-alone Phase III clinical trial comparing ticlopidine (200 mg/day) with clopidogrel (300 mg loading followed by 75 mg daily maintenance dose) in acute coronary syndrome patients, similar to the CLASSIX trial,⁶ was carried out in Japanese patients, which suggested similar safety profiles for the two thienopyridines.⁷ Moreover, without loading, ticlopidine and clopidogrel exhibited similar efficacy in terms of secondary prevention in the Japanese patients after non-cardioembolic stroke.⁸ A 25 mg clopidogrel pill is now available in Japan, and physicians are able to titrate the maintenance dose. The introduction of a lower dose tablet in the rest of the world would be helpful for the individualization of antiplatelet drugs.

Hypothetically, individual tailoring of antiplatelet regimens is a logical and reasonable strategy for improving outcomes with chronic, preventive, oral antiplatelet therapy. Although presently lacking, a reliable biomarker to measure the antiplatelet effect is needed. The randomized, double-blind study, in 116 patients with documented stable coronary artery disease, by Lordkipanidze et al.,⁹ is timely, elegant, well designed, convincing, and an important contribution to the field. Assessment of platelet response before and after clopidogrel dosing has been performed utilizing conventional light transmission and whole blood impedance aggregometry, PFA-100, and VerifyNow cartridge-based analysers. The major advance in the index study is that platelet assessment was done serially, before and after drug administration, using all four functional tests. The authors conclude that measurement of platelet inhibition by clopidogrel is highly test specific, the assays are not interchangeable, and, most importantly, cannot be currently recommended for routine clinical practice. This pessimistic, but fair and balanced, message deserves further clarification.

Before applying routine platelet function assessment in patients treated with antiplatelet agents, we need to understand better the shortcomings of antiplatelet monitoring and a few major mysteries need to be solved. We have no answer as to whether heightened platelet activity at baseline leads to worse vascular outcomes, or whether inhibiting platelets improves outcomes independently from the pre-treatment platelet activity. While the answers seem simple and obvious, facts and credible data are mostly lacking. Another missing piece of the puzzle is how to balance thrombotic and bleeding risks. For maintenance regimens, we have no clue as to the optimal degree or range (if any) of residual platelet activity necessary to prevent vascular occlusive events while avoiding excessive bleeding.¹⁰ These data are urgently needed before a transition to individual tailoring of antiplatelet regimens based on serial assessment of platelet activity becomes a reality, and can be intelligently advocated.

Even if we fill the knowledge gap with regard to the association between platelet activity inhibition and clinical outcomes, the clopidogrel equation remains difficult. Linking low clopidogrel
Algorithm for the Patient to Become “Resistant”

Coronary stenting for ACS, discharge on dual antiplatelet therapy

Minor bleeding episode leading to clopidogrel and aspirin discontinuation

Viral infection, tooth extraction, stress, or trauma

Rebound platelet activation, secondary thrombotic event, stent thrombosis

Platelet testing in the Cath Lab revealing activated platelet biomarkers caused by aspirin or/and clopidogrel “resistance”

Figure 1 Algorithm for the patient to become ‘resistant’.

response to impaired outcomes\textsuperscript{11,12} is a very attractive hypothesis, but we need to have definite proof that clopidogrel is even on board by measuring drug thiol or carboxyl metabolite(s) to confirm compliance. Obviously, the thrombotic burden in some patients exceeds the ability of even high dose loading with clopidogrel to prevent secondary events. However, it is not reasonable to generalize all clinical scenarios and blame low clopidogrel response for recurrent events, especially acknowledging that no-load, 75 mg clopidogrel saved 119 lives, and provided an absolute mortality benefit after acute myocardial infarction in the COMMIT trial.\textsuperscript{13} Based on the present laboratory definitions of low response or clopidogrel ‘resistance’, at least 70% of all COMMIT patients would be considered poor clopidogrel responders, yet COMMIT is the most successful clopidogrel trial. This obvious disconnection warns us against simplistic and premature conclusions that poor clopidogrel response, as assessed by the platelet tests, causes myocardial infarction or ischaemic stroke. A more reasonable and practical clinical scenario is outlined in Figure 1.

Testing multiple doses of antithrombotics in Phase III clinical trials may become a reality in the near future, when heterogeneous cohorts will be treated differently. Uniformly accepted bedside platelet function testing will be beneficial if the changes in platelet activity actually predict vascular events. Unless we have definitive proof that the patient is indeed adherent to antiplatelet medication, any speculation on potential clopidogrel harm, that is sometimes region specific (e.g. liver dysfunction in Japanese),\textsuperscript{7} should be avoided.

Presently, the body of available evidence suggests that routine assessment of platelet function for monitoring antiplatelet therapy cannot be recommended. We need to know more before we are able to use platelet data to determine risk. A large-scale, multicentre outcomes study, backed up with universal quality platelet function assessments, is needed to prove that serial platelet measures are useful tools for benefit/risk stratification, and tailored antiplatelet strategies.

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\textbf{References}


