

Predicting clinical outcomes after clopidogrel use: easier to postulate than to prove and implement

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Platelet activation plays a pivotal role in recurrent thrombosis after an acute coronary syndrome.¹ Dual antiplatelet therapy with aspirin and clopidogrel is an established pharmacologic strategy to significantly reduce the risk of such adverse vascular complications.² The introduction of more potent antiplatelet regimens with prasugrel³ and ticagrelor⁴ has proven to convey some advantages compared with clopidogrel, yet clinical utilization of novel strategies is still scarce.

For nearly a decade, particular focus was given to the concept of clopidogrel “resistance” (CR), as a potential shortcoming. According to several reports, the incidence of CR in high-risk patients is in the range of 4% to 30%.^{5,6} A number of clinical factors have been identified that contribute, at least in part, to CR, such as patient weight, age, diabetes, unauthorized dose reductions, premature withdrawal of the drug, poor gastrointestinal absorption, or drug–drug interactions. Likewise, several cellular mechanisms have been postulated to trigger CR, for example, accelerated platelet pool formation, decreased cellular metabolic activity, upregulation of P2Y₁₂ or P2Y₁ receptors, impaired activation of P2Y₁, and insufficient suppression of catecholamine-induced platelet activation, to mention a few. Finally, even genetic predispositions have been put forward to explain CR.^{7,8} As far as one can tell today, the mechanisms of CR are likely to be multifactorial. On top of this uncertainty, it is still not even clear whether CR, in fact, is clinically relevant.

The elegant paper on the platelet to red cell distribution width ratio as a new marker of CR published in this issue of *Polish Archives of Internal Medicine (Pol Arch Intern Med)*⁹ represents a quality improvement compared with many previously published studies addressing CR. The authors linked residual platelet activity to

clopidogrel-associated outcomes, and further determined genetic polymorphisms in autologous samples. This analysis was embedded within the framework of an international European trial (ONSIDE TEST; NCT01930773), thus strengthening the validity of the presented evidence.

This work may stimulate the search for better biomarkers of CR. Without such careful consideration, recommendations to increase either the loading or the maintenance doses of clopidogrel are not justified. Some clinicians postulate that such recommendations be based on measured low platelet responsiveness or the presence of a hypothetical CR in a given patient. However, as long as dose increase endorsements are not based on hard clinical outcomes, they are untimely. Indeed, proclaiming the principle of “the more, the better” for platelet inhibition in acute coronary syndromes without balancing against increased bleeding risks is simply wrong. This reasoning may be applicable for cholesterol lowering or for the treatment of arterial hypertension, but not for antithrombotic strategies. Again, only reliable clinical outcome data should inform clinical decision making.

The index paper also indirectly supports the postulate that drug noncompliance¹⁰ and premature drug discontinuations¹¹ may be an important and most logical practical reason for CR. With regard to compliance, one can divide patient settings into acute (in-hospital) and chronic maintenance (outpatient). Usually clopidogrel administration is controlled much better in the hospital than in an ambulatory setting. Therefore, platelet data suggesting “resistance” may have merit when properly assessed during the loading regimens because clopidogrel is indeed “on board.” Likewise, one should be reasonably suspicious of drug withdrawal when impaired platelet

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response during clopidogrel maintenance therapy is observed in outpatients. Measuring clopidogrel metabolites may avoid this controversy, serving as a direct proof that medication intake has taken place.

These considerations are also relevant for interpretation of a clinical trial. One example is the COMMIT trial (Clopidogrel and Metoprolol in Myocardial Infarction Trial),¹² in which 45 852 patients with suspected acute myocardial infarction were randomly allocated to clopidogrel, 75 mg/d (n = 22 961), or matching placebo (n = 22 891), in addition to aspirin, 162 mg/d and fibrinolytic therapy. The coprimary endpoint of total mortality showed that 119 lives were saved in the clopidogrel-added arm, which is a significant finding. Unfortunately, clopidogrel metabolites were not measured in the study. For the proper interpretation of this result, it is important to remember that the mentioned mortality benefit was achieved exclusively in patients who received no particular loading-dose of clopidogrel, that is, patients were given the standard maintenance dose of 75 mg/d from study enrollment. Ironically, the majority of such patients would be considered as having CR if assessment by any platelet test had been performed.¹³

Reflecting further on the adherence issue, in fact no large study has ever controlled for compliance to clopidogrel. Pill counts and telephone interviews are not regarded sufficient to document strict compliance. As suggested by the index paper by Tomaniak et al,⁹ measuring clopidogrel metabolites and simultaneously assessing platelet reactivity in autologous samples is mandatory to prove that the patients who experience new vascular events indeed take clopidogrel.

Yet another aspect within adherence relates to the hypothesis that interindividual variability of response after clopidogrel administration could be related to unpredictability in gastrointestinal drug absorption, which may potentially be impaired in patients with myocardial infarction. Very much also for this line of research, strict compliance rules should apply.

Taken together, based on our current knowledge, it seems that the entire issue of “resistance” should trigger new thought paradigms by measuring clopidogrel metabolites as a mandatory additional assessment for proving insufficient drug response. This is especially true now that we have clinical evidence showing that abrupt discontinuation of clopidogrel is associated with worsened vascular outcomes.¹⁴ Again, these data indirectly support the concept that it is not CR per se, but rather lack of adherence that may provoke additional acute vascular events, including late stent thrombosis. In conclusion, the concept of routine measurements of clopidogrel metabolites should be explored further not only as a useful research tool, but also as a potential additional clinical test to save lives. In the ideal world, a large-scale multicenter randomized clinical study with hard clinical endpoints should be

considered. The study design should be supported by comprehensive serial platelet assessments and strict compliance rules, including the measurement of clopidogrel metabolites. Only then the cardiovascular community will be able to determine whether CR is a real jeopardy to patients (as suggested by certain platelet biomarkers) or an artifact (as suggested by emerging randomized clinical evidence).¹⁵

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