EDITORIAL

The moving target of clopidogrel response variability: new tricks of the old dog?

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Multiple randomized trials suggest definite benefits of clopidogrel, either as an alternative[1] or an adjunct[2] to aspirin, for secondary prevention of acute vascular events, including absolute mortality reduction in the largest ever study on acute myocardial infarction.[3] Despite proven efficacy and the broadest possible utilization, antiplatelet protection with clopidogrel has several potential limitations such as delayed onset of platelet inhibition,[4,5] substantial response variability in the acute setting,[6,7] remaining risk for the development of vascular thrombosis,[8,9] and higher rates of perioperative bleeding complications during cardiac surgery[10,11] due to an irreversible nature of platelet $P2Y_{12}$ receptor blockade. It is unclear to what extent clopidogrel per se is responsible for all these shortcomings, how damaging they are in the real-life clinical scenarios, and, most importantly, what can be done to prevent, minimize, or compensate for such limitations.

This issue of the *Polish Archives of Internal Medicine* (*Pol Arch Med Wewn*) contains a small, elegant study[12] suggesting that there are changes in clopidogrel responder status over time, but broad differences between the platelet function tests do not allow for the exact estimation of the frequency of such variable response. Most importantly, the clinical utility of this interesting laboratory phenomenon is unclear and definitely requires a much larger, better randomized study, with uniformed platelet biomarker assessment, long follow-up, and careful collection of clinical events. The authors are absolutely right in not recommending repeated response variability estimates in the current routine clinical practice unless more evidence becomes available.[12]

In fact, all real or perceived limitations associated with response to clopidogrel can be divided into 2 categories: those driven by measuring the levels of multiple biomarkers in platelet studies (variability and durability of response, excess timing needed to exhibit full-scale antiplatelet potency, inefficient inhibition due to increased baseline pre-existent platelet activity), and those scenarios really observed in clinical practice (recurrent vascular events including stent thrombosis, increased bleeding risks). The insufficient platelet inhibition with clopidogrel was termed "clopidogrel resistance". However, such "resistance" still remains the laboratory research finding rather than a proven and clinically relevant fact, despite numerous attempts to link low response to clopidogrel with worsened vascular outcomes[13] in general, and with development of stent thrombosis[14,15] in particular. All these small studies fall way too short to prove that changes in the levels of certain platelet biomarkers may predict outcomes after clopidogrel because they are overpowered by the discrepancy with the available randomized clinical data and contradicting epidemiological evidence so evident in the discussed study as well.

Another critical issue is noncompliance. It seems that noncompliance is a major and the most logical practical reason for no response to clopidogrel. With regard to compliance, it is critical to divide the evidence into acute (in-hospital) and maintenance (outpatient) chronic settings. In fact, clopidogrel administration is controlled much better in the hospital rather than in the outpatient clinic. Therefore, platelet data suggesting "resistance" may have merit when properly assessed during the loading regimens because clopidogrel is indeed on board. However, these studies cannot overcome the power and validity of the COMMIT trial,[3] in which the combination of moderate-dose aspirin, clopidogrel, and streptokinase saved 119 lives in patients with acute myocardial infarction in comparison with patients treated with aspirin and a fibrinolytic agent only. Critical to remember is that absolute mortality benefit has been achieved exclusively in patients who received no-load (75 mg) clopidogrel, and that the majority of such patients will be considered "clopidogrel resistant" if assessed by any modern platelet tests.[16] Should "resistance"

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be real, COMMIT will not yield the best outcome result among all clopidogrel trials. In the outpatient setting, many noncompliant patients will be considered "clopidogrel resistant".

In fact, no platelet study ever has controlled for compliance to clopidogrel. Obviously, pill counts and telephone interviews will not be sufficient to document strict compliance. Determination of active (thiol) and/or intact (carboxyl) clopidogrel metabolites with the simultaneous assessment of platelet activity in the autologuos samples is mandatory to prove that the patient experiencing the second vascular event indeed takes clopidogrel. One established team is working in this right direction linking changes in the levels of platelet biomarkers with the plasma levels of clopidogrel metabolites,[17,18] although the data are not yet sufficient to draw any definite conclusions.

There are few available reports of noncompliance with clopidogrel. Unjustified cessation of clopidogrel therapy has been observed in over 15% of patients with coronary artery disease,[19] and in 18.4% of patients at 3 months and in up to 38.4% of patients at 1 year in a poststroke cohort.[20] These high rates of noncompliance are far greater than any reasonably determined rates of "clopidogrel resistance." Therefore, the postulate that no response, or low response, after clopidogrel may cause worsened vascular outcomes is not valid. Quite opposite, the logical explanation of such an adverse association is that excess vascular events occur more frequently not in "resistant", but in patients not treated, discontinued from antiplatelet agents. Moreover, if minor bleeding events are responsible for drug withdrawal, such patients will most likely stop taking not only clopidogrel, but aspirin as well. This chain of events may lead to rebound platelet activation and second acute vascular events, as documented for cyclooxygenase-2 inhibitors and nonsteroidal anti-inflammatory drugs,[21] aspirin,[22] and clopidogrel.[23] Taken together, it is reasonable to suspect that even minor bleeding complications are enough of a deterrent to stop therapy for some patients, especially when the benefits of the drug are not readily apparent. This limitation of clopidogrel stands in contrast to drugs that alleviate actual symptoms rather than merely preventing acute events. Obviously, we cannot expect platelets to be inhibited when the antiplatelet agent is not on board. Moreover, the reported rates of noncompliance are higher than those of "clopidogrel resistance".

The cost of an error to misjudge why the patient with activated platelets developed vascular event is enormous, and is happening in the everyday clinical practice much more often than one can imagine. Indeed, if "clopidogrel resistance" is a real meaningful finding, then higher loading and maintenance doses of clopidogrel, as well as introduction of much more potent antiplatelet strategies with prasugrel and ticagrelor, are well justified and will result in better outcomes.. In contrast, the clinical utilization of newer antiplatelet agents is quite low, partly due to unclear long-term benefit.[24] Indeed, should "resistance" be a laboratory artifact frequently observed in noncompliant patients, then higher doses and/or more aggressive antiplatelet regimens are harmful and will not only cause more bleeding but result in higher drug discontinuation rates, rebound platelet activation, followed by worsened vascular outcomes. Considering modern trends to use aggressive, although unjustified by randomized outcome evidence, doubled, or even tripled clopidogrel loading doses, mixed with the controversy regarding the higher thrombotic risks observed with drug-eluting stents, promoting "clopidogrel resistance" is harming rather than helping patients, dragging them into increased bleeding and thrombotic risks.

In conclusion, there is no need to add more confusion, and, moreover, no platelet data will help solve or even further advance this controversy. Only a randomized study with the hard outcome or, ideally, survival endpoint, supported by the comprehensive serial platelet assessment, strict compliance rules including the measurement of clopidogrel metabolite(s) will determine whether "clopidogrel resistance" is a real danger (as suggested by platelet biomarkers), or an artificial tool (as suggested by randomized clinical evidence) introduced to help novel antiplatelet agents gain the vascular market share.

REFERENCES

1 CAPRIE Steering Committee. A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events. Lancet. 1996; 348: 1329-1339.

2 CURE Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001; 345: 494-502.

3 Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet. 2005; 366: 1607-1621.

4 Nguyen TA, Diodati JG, Pharand C. Resistance to clopidogrel: a review of the evidence. J Am Coll Cardiol. 2005; 45: 1157-1164.

5 Lev EI, Patel RT, Maresh KJ, et al. Aspirin and clopidogrel drug response in patients undergoing percutaneous coronary intervention: the role of dual drug resistance. J Am Coll Cardiol. 2006; 47: 27-33.

6 Gachet C, Aleil B. The inter-individual variability of the response to clopidogrel. Arch Mal Coeur Vaiss. 2005; 98: 216-225.

7 Serebruany VL, Steinhubl SR, Berger PB, et al. Variability in platelet responsiveness to clopidogrel among 544 individuals. J Am Coll Cardiol. 2005; 45: 246-251.

8 Vats HS, Hocking WG, Rezkalla SH. Suspected clopidogrel resistance in a patient with acute stent thrombosis. Nat Clin Pract Cardiovasc Med. 2006; 4: 226-230.

9 Duffy B, Bhatt DL. Antiplatelet agents in patients undergoing percutaneous coronary intervention: how many and how much? Am J Cardiovasc Drugs. 2005; 5: 307-318.

10 Kapetanakis EI, Medlam DA, Petro KR, et al. Effect of clopidogrel premedication in off-pump cardiac surgery: are we forfeiting the benefits of reduced hemorrhagic sequelae? Circulation. 2006; 113: 1667-1674.

11 von Heymann C, Redlich U, Moritz M, et al. Aspirin and clopidogrel taken until 2 days prior to coronary artery bypass graft surgery is associated with increased postoperative drainage loss. Thorac Cardiovasc Surg. 2005; 53: 341-345.

12 Golański J, Syska K, Chiżyński K, et al. Changes in response to clopidogrel therapy in patients after percutaneous coronary interventions as assessed by different platelet function tests. Pol Arch Med Wewn. 2016; 126: 653-661.

13 Geisler T, Langer H, Wydymus M, et al. Low response to clopidogrel is associated with cardiovascular outcome after coronary stent implantation. Eur Heart J. 2006; 27: 2420-2425.

14 Wenaweser P, Dorffler-Melly J, Imboden K, et al. Stent thrombosis is associated with an impaired response to antiplatelet therapy. J Am Coll Cardiol. 2005; 45: 1748-1752.

15 Barragan P, Bouvier JL, Roquebert PO, et al. Resistance to thienopyridines: clinical detection of coronary stent thrombosis by monitoring of vasodilator-stimulated phosphoprotein phosphorylation. Catheter Cardiovasc Interv. 2003; 59: 295-302.

16 Serebruany VL. Mortality benefit of no-load clopidogrel in COMMIT: not a surprise. J Cardiovasc Pharm Therap. 2006; 11: 99-100.

17 von Beckerath N, Taubert D, Pogatsa-Murray G, et al. A patient with stent thrombosis, clopidogrel-resistance and failure to metabolize clopidogrel to its active metabolite. Thromb Haemost. 2005; 93: 789-791.

18 von Beckerath N, Taubert D, Pogatsa-Murray G, et al. Absorption, metabolization, and antiplatelet effects of 300-, 600-, and 900-mg loading doses of clopidogrel: results of the ISAR-CHOICE (Intracoronary Stenting and Antithrombotic Regimen: Choose Between 3 High Oral Doses for Immediate Clopidogrel Effect) Trial. Circulation. 2005; 112: 2946-2950.

19 Kuchulakanti PK, Chu WW, Torguson R, et al. Correlates and long-term outcomes of angiographically proven stent thrombosis with sirolimus- and paclitaxel-eluting stents. Circulation. 2006; 113: 1108-1113.

20 Hamann GF, Weimar C, Glahn J, et al. Adherence to secondary stroke prevention strategies-results from the German Stroke Data Bank. Cerebrovasc Dis. 2003; 15: 282-288.

21 Serebruany VL, Malinin AE, Bhatt D. Paradoxical Rebound Platelet Activation After Painkillers Cessation: Missing Risk for Vascular Events? Am J Med. 2006; 119: 11-16.

22 Biondi-Zoccai GG, Lotrionte M, Agostoni P, et al. A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50,279 patients at risk for coronary artery disease. Eur Heart J. 2006; 27: 2667-2674.

23 Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, et al. Clopidogrel withdrawal is associated with proinflammatory and prothrombotic effects in patients with diabetes and coronary artery disease. Diabetes. 2006; 55: 780-784.

24 Serebruany VL, Fortmann SD. Underutilisation of novel antiplatelet agents – myths, generics, and economics. Thromb Haemost. 2014; 112: 4-9.