

Resistance to clopidogrel and aspirin

Vlad VINTILA, MD,
University Hospital of Bucharest, Cardiology and Internal Medicine Department
„Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania
ESC training fellow, WHRI, Cardiff University, United Kingdom

Antiplatelet therapy is an essential medication in the treatment of patients with coronary heart disease. This statement is based on a great number of clinical studies in which aspirin and clopidogrel have been compared to placebo or between themselves

in the treatment of various stages of cardiac disease. The data showed an improvement in the total and cardiovascular surviving rate and the relative risk reduction of myocardial infarction and stroke (ISIS 2, TPT, HOT with aspirin, CAPRIE, CURE, CLARITY-TIMI 28, COMMIT/CCS-2, with clopidogrel). □

However, questions appeared about various rates of patients who did not respond to this antiplatelet therapy and the problem of resistance has been raised, first for aspirin, then for clopidogrel as well.

The objective of this paper was to review the literature via PubMed and Medline and to analyze the relevant works dealing with aspirin or clopidogrel resistance.

The pooled data revealed three major causes of antiplatelet therapy failure, in fact “continued occurrence of ischaemic events despite adequate platelet therapy and compliance”: clinical factors, cellular factors and genetic factors. The clinical factors identified were: failure to prescribe, noncompliance, low absorption, ibuprofen interaction, congestive heart

failure, hyperglycaemia, catecholamine surges. The cellular factors identified were insufficient COX-1 suppression, over-expression of COX-2 mRNA, increased norepinephrine, erythrocyte-induced platelet activation and some others. The third category, the genetic causes would include genetic COX-1 levels, von Willebrand factor receptor polymorphism, collagen receptor polymorphism, P₂Y₂ single nucleotide polymorphism and some others. The first category of causes is not to be considered in terms of true resistance.

Biological resistance should be established by biochemical analysis that implies a threshold value for different markers of platelet function, measured in the whole blood or in the urine. Four methods are considered: Aggregometry, Platelet Function Analyzer (PFA), VerifyNow

Rapid Platelet Function Assay and Urinary determination of 11-dehydro thromboxane B₂ levels (high levels means uninhibited platelet COX-1 activity).

The rate of resistant patients to the antiplatelet therapy is not yet clearly defined for clopidogrel, but for aspirin ranges from 5% to the impressive figure of 45%. Some unanswered questions about clopidogrel resistance are to be handled in a number of specially designed sub studies of the last completed clopidogrel trial, the CHARISMA trial.

After putting the positive diagnosis, which is yet seldom checked in clinical practice, we have to treat this entity. Beyond the use of aspirin in conjunction with clopidogrel, the options of medical treatment are limited. To increase the antiplatelet drug dosage is not an easy option, due to increased risk of hemorrhagic events. These apply for increased dosages of aspirin and increased dosages of clopidogrel beyond 600 mg. There are some alternative thienopyridine agents such as prasugrel or some new non- thienopyridine P₂Y₂ inhibitors (cangrelor) in research, but their way to the clinical practice is long. □



Aspirin and clopidogrel resistance: an emerging clinical entity

TH Wang, DL Bhatt, EJ Topol

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