Platelet function testing in atherothrombotic disease: steps forward in managing resistance to antiplatelet therapy

Erik L. Grove[1], Anne-Mette Hvas[2], Steen D. Kristensen[1]

[1] Department of Cardiology, Aarhus University Hospital Skejby, Denmark
[2] Department of Clinical Biochemistry, Centre for Haemophilia and Thrombosis, Aarhus University Hospital Skejby, Denmark

Platelets are key players in atherothrombosis, and antiplatelet therapy is the mainstay of treatment and secondary prevention of cardiovascular events [1]. Despite this proven benefit, the considerable number of vascular events among high-risk patients despite antiplatelet therapy constitutes a major problem in clinical cardiology. Recently, several studies have reported a highly variable response to aspirin and clopidogrel, and an association between low platelet inhibition and thromboembolic events has been reported in a substantial proportion of patients [2-4]. Given the prevalence of atherothrombotic disease, the potential impact of insufficient platelet inhibition is extensive.

In this issue of *Kardiologia Polska*, a working group (WG) presents a position paper on resistance to antiplatelet therapy. 'Resistance' to aspirin and other antiplatelet drugs is the focus of much attention, but diagnosis, definition, mechanisms and clinical consequences are yet to be determined. An unequivocal interpretation of results obtained in previous studies is difficult due to different study populations, endpoints and methods used to evaluate drug response, but recent meta-analyses seem to concur in confirming an association between low responsiveness and cardiovascular risk [3-5]. Currently, a large number of ongoing laboratory as well as clinical studies are aiming to clarify these issues. Universal cut-off values for in vitro assays remain to be determined, and the recommendations of the WG is a commendable initiative to facilitate appropriate design of future studies.

The mechanisms leading to insufficient inhibition of platelet aggregation are not fully elucidated and are likely multifactorial. Arterial thrombosis is multifactorial, and thus many adverse thrombotic events likely reflect treatment failure or non-adherence rather than actual resistance to antiplatelet therapy. Possible mechanisms of 'resistance' to antiplatelet therapy include the presence of COX-1 and $P2Y_{12}$ variants less responsive to inhibition by aspirin and clopidogrel, drug interference, decreased bioavailability and increased residual platelet activity, e.g. as a result of increased platelet turnover [6]. First and foremost, it is important to stress that when investigating the pharmacological effect of a drug, optimal compliance must be ensured. Preferably, compliance should be optimized by observed drug ingestion or confirmed by measurements of appropriate drug metabolites directly reflecting inhibition of the pharmacological target. Specifically, compliance with aspirin treatment should be tested with measurements of serum thromboxane B_2 and, when testing the response to treatment with clopidogrel, measurement of drug metabolites should be performed if possible.

The choice of platelet function test for evaluation of response to aspirin and clopidogrel is much discussed. Light transmission aggregometry induced by either ADP or arachidonic acid is the most well-studied method. The suggestion of specific agonists and concentrations by the WG is an important step towards establishing a standardized way of measuring platelet response to antiplatelet therapy. In any case, one should bear in mind that optical platelet aggregometry in platelet rich plasma, although often considered the reference method, has several drawbacks: it is not very reproducible, it is time-consuming, and also the test is non-physiological in that selected platelets in suspension are tested in an artificial environment with low concentrations of calcium and magnesium ions. Furthermore, despite using relevant agonists such as arachidonic acid and ADP, optical platelet aggregometry is not entirely specific in testing the effect of aspirin and clopidogrel, and this consideration is also highly relevant when using the large armamentarium of point-of-care tests. We agree with the WG that testing the pharmacological effect of a drug should be performed with tests that specifically reflect the biochemical pathway inhibited by the drug. Furthermore, well-designed studies comparing optical platelet aggregometry with point-of-care tests and metabolite measurements in compliant individuals are warranted.

Address for correspondence:
Steen Dalby Kristensen, MD, DMSc, FESC, Department of Cardiology, Aarhus University Hospital Skejby, Brendstrupgaardsvej 100,
DK-8200 Århus N, Denmark, tel.: +45 89 496 269, fax: +45 89 496 009, e-mail: steendk@dadlnet.dk

When considering laboratory defined drug resistance, the amount of data suggesting any course of action is scarce. A recent meta-analysis comparing cardiovascular events in patients with and without aspirin 'resistance' suggested that nonresponsive patients are facing a nearly fourfold higher risk of non-fatal and fatal cardiovascular, cerebrovascular, or other vascular events than patients who are aspirin-sensitive [4]. Of note, in studies that included the use of concomitant clopidogrel and/or glycoprotein IIb/IIIa inhibitors, aspirin low-responders did not derive any additional benefit from these antiplatelet drugs. Thus, despite clopidogrel and/or glycoprotein inhibitors, the relative risk of cardiovascular events was basically unchanged, suggesting that new thinking and new antiplatelet drugs are warranted. Notwithstanding the important issue of thorough compliance control, these results emphasize what is also stated by the WG: that any use of supplementary (i.e. dose increments) or alternative (e.g. $P2Y_{12}$ or thromboxane A_2 receptor antagonists) antiplatelet therapy should be restricted to protocol-guided and, preferably, randomized settings. However, even though evaluation of platelet response to aspirin and clopidogrel at present has no role in daily practice, this is a rapidly evolving field, and in particular in patients with stent thrombosis data are accumulating that laboratory measurements may be important. Also, appropriate testing of platelet function may become a valuable tool to individualize therapy as treatment with combinations of new, strong antiplatelet drugs is likely associated with a high risk of bleeding.

There is widespread interest in the evaluation of platelet function to better understand and define the effect and failure of antiplatelet drugs. Platelet function testing may be implemented in predicting cardiovascular risk and optimizing individually tailored antiplatelet therapy. The position paper represents a significant step forward in this process.

Acknowledgements

References

1. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002; 324: 71-86.
2. Maree AO, Fitzgerald DJ. Variable platelet response to aspirin and clopidogrel in atherothrombotic disease. *Circulation* 2007; 115: 2196-207.
3. Snoep JD, Hovens MM, Eikenboom JC, et al. Association of laboratory-defined aspirin resistance with a higher risk of recurrent cardiovascular events: a systematic review and meta-analysis. *Arch Intern Med* 2007; 167: 1593-9.
4. Krasopoulos G, Brister SJ, Beattie WS, et al. Aspirin 'resistance' and risk of cardiovascular morbidity: systematic review and meta-analysis. *BMJ* 2008; 336: 195-8.
5. Snoep JD, Hovens MM, Eikenboom JC, et al. Clopidogrel nonresponsiveness in patients undergoing percutaneous coronary intervention with stenting: a systematic review and meta-analysis. *Am Heart J* 2007; 154: 221-31.
6. Guthikonda S, Lev EI, Patel R, et al. Reticulated platelets and uninhibited COX-1 and COX-2 decrease the antiplatelet effects of aspirin. *J Thromb Haemost* 2007; 5: 490-6.