Letters to the Editor

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Aspirin and clopidogrel resistance: an emerging clinical entity

We read with interest the recent article which reviewed the issue of aspirin and clopidogrel resistance.1 The authors review the aspirin and clopidogrel clinical trial data and conclude that both therapies have emerged as efficacious in both the primary and secondary prevention settings. The referenced data for a beneficial effect of clopidogrel on the primary prevention of cardiovascular (CV) disease events is not quoted. In fact, the recent results from the CHARISMA trial suggest that the long-term addition of clopidogrel to aspirin is inappropriate for broad populations and may indeed be harmful in primary prevention patients.2 Aspirin is the only antiplatelet agent with incontrovertible data proving it valuable in the prevention of first CV events. The discussion of aspirin and clopidogrel resistance that follows admittedly provides no clear definition of the two terms. Although a definition of aspirin or clopidogrel resistance has not been universally accepted, a reasonable approach would be to limit the definitions to the known pharmacological pathways exhibited by the two drugs, respectively. In the case of aspirin, resistance should be confined to the failure of aspirin to block arachidonic acid-induced platelet aggregation, as this is the most precise mechanism to identify its effect on the COX-1 pathway. Similarly, clopidogrel resistance should be limited to its efficacy in inhibiting ADP-induced platelet aggregation through blockade of the P2Y12 purinergic receptor. The authors identify these as the key mechanisms of action by which both agents exert their clinical effects. Despite this admission, the authors continue to suggest that there is an unpredictable response and variability to aspirin therapy. Recent data demonstrate that resistance under its pharmacological definition is extremely rare,3 whereas clopidogrel response to ADP-induced aggregation is broad, as seen in Figure 2 of the authors’ article. This more exact definition would then essentially rule out the results of the non-specific assays (i.e. VerifyNow Rapid Platelet Function Assay, PFA-100) and their associated reports of prevalent aspirin resistance. We agree that non-specific measurements may be important if future studies reveal their relationship to clinical events, but to characterize these as adequate tests for assessing the response to aspirin therapy is invalid.

Finally, the authors ask, how many (of the millions of patients taking low dose aspirin) are taking the wrong drug? We suggest that the answer to this question is likely none, as aspirin is the justifiable cornerstone of any pharmacological strategy for the prevention both primary and secondary CV events.

References


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Aspirin and clopidogrel resistance: an emerging clinical entity: reply

We are glad the authors of this letter to the editor found our article interesting.1 They raise some valid points. However, it was not our intent to claim that both aspirin and clopidogrel had a role in primary prevention. We would not endorse that approach without randomized clinical trial data to support such a position. Indeed, post-CHARISMA, we agree that there is no established role for dual antiplatelet therapy in primary prevention.2 Aspirin appears to have a role in primary prevention, but even then, only after appropriate risk stratification.3

The authors are correct that we did not provide a clear definition of antiplatelet resistance. This is because our article was meant to provoke discussion and hopefully future research into the topic. Several methodologies have been used to determine antiplatelet responsiveness3 and the most useful outcome measure would be to see whether variability in response is associated with clinical events. If the answer is yes, as a number of small studies suggest, then the test is potentially useful for risk stratification.5 Furthermore, if there is a way to modulate therapy to alter that increased risk, then measuring antiplatelet variability is worthwhile. If not, then it is largely an academic exercise devoid of clinical value.

The only way to resolve this issue will be to conduct appropriately sized trials with a variety of different measures of platelet function and determination of which test(s) accurately predict clinical outcomes that in turn are able to be influenced by modification of therapy. Until that happens, the field will continue to be a source of controversy and active discussion. In the meantime, we agree with the authors that patients taking aspirin for appropriate reasons ought not to stop on the basis of any in vitro test.

References