Platelet Function Testing for Aspirin Resistance
Is Reasonable to Do
Yes!

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When discussing the issue of aspirin resistance and platelet function testing, there are a number of data-based conclusions that I believe we can agree on:

(1) Aspirin resistance is a real phenomenon. There are dozens of studies and a number of meta-analyses that show on average 15% to 25% of individuals will be aspirin-resistant (ie, lack of the anticipated antiplatelet response when taking aspirin).1,2 The largest meta-analysis included 42 studies and reported a 27% rate of aspirin resistance.3 Rates may be slightly higher in patients with stroke.4,5 The rate of aspirin resistance appears to increase with lower doses of aspirin and may be higher when using enteric-coated aspirin.3,4 The rate of aspirin resistance appears to increase with age above the mid-60s.1 Perhaps this relates to gastrointestinal issues such as stomach pH, which increases with age due to lower acid production.

(2) Aspirin resistance has clinical consequences. Various studies, most in cardiac patients, have shown that individuals with aspirin resistance have an increased risk of having a cardiovascular event (stroke, myocardial infarction, vascular death) when followed for 2 to 5 years.6 A recent meta-analysis of 20 studies with >2900 patients reported that individuals with aspirin resistance had a significantly increased risk (3.85 OR) of having a cardiovascular event.7 Compliance with aspirin therapy was confirmed in 14 studies, and the dose of aspirin varied from 75 mg/day to 325 mg/day. Given these data and conclusions, there are several controversial points to consider:

(1) What is the optimal method to determine aspirin resistance? This is 1 of the most common limitations mentioned in research on this topic. Different techniques for measuring aspirin resistance can produce somewhat different results. Assays using arachidonic acid as the agonist with just platelets report lower rates of aspirin resistance, typically approximately 5%. Tests using whole blood assays and point-of-care testing paradigms report higher rates ranging from 15% to 40%.2,8

This variance is true of most tests of coagulation functions. However, this variation does not negate the concept of aspirin resistance or its clinical implications. Like with other tests, what is required is some consensus on a testing paradigm and normal ranges.

Another misconception is that aspirin resistance is an all-or-nothing phenomenon. Like with most biological systems, the antiaggregation response to aspirin is almost certainly a continuum with lower responses associated with a higher risk of ischemic events, whereas higher responses may increase the risk of a hemorrhagic event.

(2) Can aspirin resistance be overcome and thereby reduce the rate of ischemic events? In some studies, increasing the dose of aspirin can reduce the overall rate of aspirin resistance, although at least 5% to 10% of patients do not appear to have a significant response to aspirin at any reasonable dose. We have found that adding clopidogrel to aspirin can reduce the overall rate of aspirin resistance, although some patients fail to respond to even combination therapy.4 Genetic and metabolic factors may cause some cases of aspirin resistance.

Increasing the dose of aspirin carries some risks and some unknowns. Higher doses of aspirin can increase the risk of gastrointestinal hemorrhage and other side effects. At higher doses, aspirin may inhibit the activity of the cyclo-oxygenase-2 enzyme, which produces prostacyclin, a potent endogenous antiplatelet compound and vasodilator. Like with any biological system, there must be a balance between too little and too much of any effect.

(3) Can changing the dose of aspirin to achieve and maintain an effective level of antiplatelet activity result in a reduction in ischemic events without excess bleeding? This is the “Holy Grail” of this line of research. It is a very relevant issue for several reasons: (1) approximately 35% to 40% of patients with stroke are taking aspirin at the time of their event; and (2) in much of the world, aspirin is the only antiplatelet agent that is readily available and affordable. Therefore, there are important public health implications for being able to optimize the efficacy and safety of aspirin.

Some have observed that clinical trials of aspirin have failed to demonstrate enhanced efficacy with higher doses; therefore,
checking platelet function is likely to be irrelevant. Such statements are based largely on indirect comparisons of diverse studies; such comparisons are typically erroneous or misleading. In the ATC meta-analysis, the few studies that directly compared high-dose versus low-dose aspirin did show evidence of enhanced efficacy with higher doses, although the small number of outcome events limits firm conclusions.

In summary, aspirin resistance is common and carries significant clinical consequences. Although we cannot prove that altering therapy in affected patients would reduce the risk of ischemic events, it seems reasonable to perform studies to determine the wisdom of such an approach. Would you want to take a medication that is not working as intended?

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References

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