The Use of Platelet Function Assays May Help to Determine Appropriate Antiplatelet Treatment Options in a Patient With Recurrent Stroke on Baby Aspirin Against

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Patients with ischemic stroke of arterial origin are commonly prescribed aspirin because it has been shown in placebo-controlled trials to reduce the risk of a recurrent stroke and other major vascular events by approximately 13% (95% CI, 6% to 19%). The mechanism by which aspirin “works” is that, at doses as low as 0.5 mg/kg, it irreversibly inactivates platelet cyclo-oxygenase-1 by at least 95% and thereby blocks the generation of thromboxane, a platelet agonist and potent vasoconstrictor.

If patients experience a recurrent arterial ischemic stroke at the time of taking low-dose (50 to 100 mg per day) “baby” aspirin, it is reasonable to ask whether the recurrence was due to a “failure” of low-dose aspirin to fully inhibit platelet cyclo-oxygenase-1 (and platelet function). In the same way that we measure the international normalized ratio to monitor and adjust warfarin therapy, it is reasonable to question whether platelet function assays could help determine future antiplatelet treatment options in patients with recurrent arterial ischemic stroke at the time of taking baby aspirin.

A variety of laboratory assays of the antiplatelet effects of aspirin are available, including measures of thromboxane production (eg, urinary 11-dehydro-thromboxane B2) and measures of thromboxane-dependent platelet function (eg, light transmission aggregation, Ultegra rapid platelet function assay). However, unlike the international normalized ratio, which has been standardized and correlates with both laboratory and clinical responses to warfarin, most of the currently available platelet function assays have not been standardized or been shown to reliably distinguish individual patients at high risk from those at low risk, and no randomized trials have demonstrated that altering platelet therapy on the basis of laboratory testing optimizes the cardiovascular protective effect of aspirin.

Trials are needed in which patients with recurrent stroke are randomized to usual care or to a management strategy involving routine platelet function testing followed by titration of the dose, or change in the choice, of the antiplatelet drug régime according to the results of the test and then measuring recurrent stroke and other major vascular events (efficacy), brain and other hemorrhagic events (safety), and costs (of tests, drugs, and clinical events saved and caused).

At the time of awaiting the results of such a trial, clinicians caring for patients with recurrent arterial ischemic stroke at the time of taking baby aspirin should exclude poor compliance and drug interactions (eg, ibuprofen) as modifiable causes of recurrent stroke. Other possible causes of aspirin failure include nonplatelet sources of thromboxane production, increased platelet production in response to stress (eg, postsurgery), and genetic polymorphisms for cyclo-oxygenase-1 and other genes involved in thromboxane biosynthesis, but these mechanisms are less well established and might not be treatable.

Higher doses of aspirin are generally not recommended because they have not been proven in randomized controlled trials to be more effective than lower doses of aspirin for preventing recurrent stroke, and they increase the risk of gastrointestinal bleeding by suppressing mucosal production of gastroprotective prostaglandins. However, recent observational studies suggest that: (1) not all patients treated with aspirin have complete inhibition of thromboxane-dependent platelet function; (2) higher doses of aspirin are more effective than lower doses in suppressing platelet function; and (3) incomplete inhibition of platelet function may be an independent predictor of cardiovascular events. One possible explanation for the discordance between the randomized controlled trial and observational data are that patients assigned higher-dose aspirin in randomized controlled trials had higher discontinuation rates (due to adverse
effects), which may have masked any benefit in preventing vascular events compared with low-dose aspirin. A second possible explanation is that higher doses of aspirin might not only affect platelet function, but also affect endothelial production of the vasodilator prostacyclin (by inhibiting cyclo-oxygenase-2), which could negate any additional cardiovascular benefits of a higher dose. A third possible explanation for the lack of evidence of benefit of a higher dose of aspirin is that no randomized controlled trials were designed to examine whether there are subgroups of poor responders to low-dose aspirin who might benefit from a higher dose.

In the absence of evidence from randomized controlled trials of a benefit of higher doses of aspirin (eg, 325 mg per day) compared with low-dose aspirin for stroke protection, patients who experience recurrent stroke despite low-dose aspirin in whom a decision is made to continue on aspirin should maintain the low dose. Alternatively, they could be switched to another antiplatelet treatment such as the combination of 25 mg aspirin and 200 mg extended-release dipyridamole twice per day or 75 mg clopidogrel per day. Platelet function testing might identify aspirin-treated patients with incomplete inhibition of platelet cyclo-oxygenase-1 who may be at increased risk of recurrent stroke, but routine testing cannot be recommended to guide decisions regarding the dose of aspirin or the choice of an alternative antiplatelet agent until there is evidence that modifying antiplatelet therapy according to the results of platelet function testing reduces the risk of subsequent stroke and other cardiovascular events.

**Disclosures**

G.J.H. has received honoraria for serving as a member of the Steering Committee of the TRA-2P TIMI 50 trial (Schering Plough) and for speaking at scientific symposia sponsored by Sanofi-Aventis. J.W.E. has received consulting fees and honoraria for lecturing at sponsored scientific symposia from Bristol Myers Squibb, Sanofi-Aventis, Eli Lilly, Astra, and Novartis. There are no other conflicts to report.

**References**


**Key Words:** antiplatelet drugs
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Stroke. 2010;41:2398-2399; originally published online August 19, 2010;
doi: 10.1161/STROKEAHA.110.593582

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/41/10/2398

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