Antiplatelet Effect of Aspirin in Patients With Cerebrovascular Disease

To the Editor:

The intriguing study by Alberts et al¹ regarding aspirin resistance in 129 patients with cerebrovascular disease highlights the potentially important implications of interpatient variability in response to set doses of antiplatelet agents, but also raises several important issues regarding the extrapolation of ex vivo results to clinical care. Their study focused on the level of antiplatelet activity of aspirin as measured by the platelet function analyzer (PFA)-100 point of care test. Using this device and a unique but unvalidated cut-off for dichotomizing patients into aspirin responders and nonresponders, they found that significantly more patients had inadequate platelet inhibition when receiving ≤162 mg of aspirin/d, compared with those taking ≥325 mg aspirin/d (56% versus 28%, P<0.01). They also found that patients taking entericoated aspirin were less likely to achieve adequate platelet inhibition compared with those taking an uncoated preparation. Although the study was too small, and follow-up too short to allow for clinical correlations, the authors do discuss that, based on the results of their study, they have started using the results of the PFA-100 to alter patients’ aspirin regimen, with 15% of their patients now receiving 650 mg to 1300 mg of aspirin daily. We feel that it is important to highlight the limitations and potential hazards of translating these ex vivo results to clinical practice.

First, as the authors highlight in their discussion, correlation between aspirin responsiveness measured ex vivo and clinical outcomes is needed before the results of the PFA-100 should be used to adjust aspirin therapy. In fact, that has already been done in the largest study to date of aspirin responsiveness in atherosclerosis patients. Gum et al prospectively evaluated 326 patients with stable cardiovascular disease using standard light transmittance aggregometry as well as the PFA-100.² They followed these patients for a mean of 679 days and found that aspirin resistance, only as determined by light transmittance aggregometry, was associated with a significant increase in risk of myocardial infarction, stroke, and death (24% versus 10%, P=0.03).³ Although not reported in the primary manuscript, no correlation between PFA-100–determined aspirin resistance and clinical outcomes was found (12.9% versus 15.1%, P=0.4).³ One possible explanation for this lack of correlation between PFA-100 results and clinical outcomes is the test’s strong association with von Willebrand factor levels, which were not measured in either the study by Gum or Alberts.⁵,⁶

Second, the use of higher doses of aspirin has never been shown to confer even a trend toward greater benefit in large-scale clinical trials.⁷,⁸ Although it certainly is possible that a subgroup of patients may benefit from higher doses of aspirin, in order to reconcile this hypothesis with the clinical data one would have to assume there is an equal-sized subgroup that is put at greater risk of thrombotic events by receiving a higher dose of aspirin—a hypothetical subgroup that we are unable to identify. The conflicting findings between the large-scale clinical trials and the study by Alberts regarding aspirin dose-dependency may be explained by the inherent lack of sensitivity of the PFA-100 in measuring responsiveness to lower doses of aspirin.⁹

Finally, increasing the aspirin dose is not a benign therapeutic maneuver. It has been estimated that prophylactic aspirin therapy is responsible for as much upper gastrointestinal (GI) bleeding as all other nonsteroidal antiinflammatory drugs combined.¹⁰ Although there is no dose of aspirin that appears to be free of GI side effects,¹¹ the risk clearly increases with increasing doses of aspirin.¹² In the UK-TIA trial the odds ratio for a gastrointestinal hemorrhage was 2.57 (95% CI, 1.20 to 5.53) in those subjects randomized to 300 mg of aspirin daily compared with placebo, whereas the odds ratio for those randomized to 1200 mg daily compared with 300 mg daily was 1.62 (95% CI, 0.94 to 2.79).⁷

In light of the clinical data supporting no relationship between PFA-100 results in aspirin-treated patients and their subsequent risk of a thrombotic event, along with the uniform findings across a number of clinical trials that increased aspirin dose leads to nothing other than an increase in the risk of GI bleeding, we feel it is imprudent to increase aspirin dose based on results obtained with the PFA-100.

Jay S. Varanasi, MD
Steven R. Steinhuibl, MD
Division of Cardiology
University of North Carolina
Chapel Hill, NC


Conflict of Interest: Steven R. Steinhubl, MD has received research support in the past and has served as a consultant for Accumetrics Inc, manufacturers of the Ultegra-Rapid Platelet Function Assay. He has also served as a consultant for and has received research support from Sanofi-Synthelabo and Bristol-Myers Squibb, manufacturers and marketers of clopidogrel.
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Stroke. 2004;35:e144-e145; originally published online April 8, 2004;
doi: 10.1161/01.STR.0000126473.18096.ab
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/35/6/e144

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