Letters to the Editor

Platelet Aspirin Resistance Detection and Validation

In a recent paper in the *Journal,* Tantry et al. (1) concluded that the occurrence of aspirin resistance in published reports is overestimated, implying that this was due to the use of assays that did not measure cyclooxygenase-1 (COX-1) activity. Although these investigators reported an incidence of aspirin resistance of ~0.4%, several reviews estimate, based on a large number of studies, that the incidence of aspirin resistance is between 5% and 45% (2). Moreover, the Tantry et al. (1) study has serious limitations that call into question the generalizability of their findings.

First, their research population consisted primarily of patients with stable angina. A number of studies have demonstrated that aspirin resistance is more prevalent in patients with acute coronary syndromes than in patients with stable angina (2), and thus their study may underestimate the prevalence of aspirin resistance in those at greatest risk. Second, by employing a dose of 325 mg of aspirin, their data may not be applicable to the vast majority of patients who currently are treated with 81 mg per day. Third, because their definition of aspirin resistance has not been validated against clinical outcomes, it is arbitrary and thus must be viewed as speculative. Fourth, the thrombelastograph (TEG) assay they use has not undergone extensive critical evaluation.

Tantry et al. (1) also do not accurately portray the VerifyNow–ASA System (Ultegra System, Accumetrics, San Diego, California), which employs arachidonic acid (AA) as the agonist and thus does assess COX-1 activity. When compared to light transmission aggregometry (LTA) using AA, the VerifyNow assay demonstrated 91.4% sensitivity and 100% specificity (VerifyNow–ASA package insert). Although a previous generation of the VerifyNow device did use propyl gallate (PG) as the agonist, Schwartz et al. (3) demonstrated that PG detects aspirin-induced inhibition of platelets with 100% sensitivity and differentiates the degree of aspirin-induced inhibition of platelet function produced by single doses of 81 mg and 325 mg, and hence is a specific activator of the aspirin-inhibited COX-1 pathway. Most importantly, results of the VerifyNow assay have been correlated to clinical outcome in several studies, including one published in *JACC* (4–6).

Several studies, including a recent one by Lee et al. (7) with VerifyNow, have demonstrated that aspirin resistance decreases with increasing dose of aspirin, from 81 mg to 325 mg. Maree et al. (8) also demonstrated using AA-induced LTA as well as serum thromboxane measurements, the gold standard, that "many patients who are prescribed low-dose aspirin (81 mg) have persistent uninhibited platelet COX activity." Further, Serebruany et al. (9) have shown that major bleeding increases from 1% to 3% as aspirin dose is increased from 81 mg to 325 mg Thus, there is a graded effect in both safety and efficacy of aspirin that should be considered.

Noncompliance and drug interactions with nonsteroidal anti-inflammatory drugs (e.g., ibuprofen) contribute to the reported incidence of "aspirin resistance" in the real world of clinical practice, and many investigators, including Cotter et al. (10), conclude that "nonadherence is a significant mediator of poor outcome . . . and it is important to evaluate whether or not patients are taking their medications in clinical settings." Thus, assays that ensure an antiplatelet effect may have great clinical value even in patient populations in whom, as reported by Tantry et al. (1), biochemical aspirin resistance is uncommon.

As stated by Schneider (11) in an accompanying editorial, initial techniques used to assess the effect of glycoprotein IIb/IIIa inhibitors on platelet function were inadequate. The original VerifyNow IIb/IIIa assay was used in the AU-Assessing Ultegra (GOLD) study (12), which served to definitively establish the correlation between platelet inhibition and clinical outcomes.

***Robert S. Hillman, PhD**

*Accumetrics
3985 Sorrento Valley Boulevard
San Diego, California 92121
E-mail: rhillman@accumetrics.com

doi:10.1016/j.jacc.2006.03.021

REFERENCES

1. Tantry US, Bliden KP, Gurbel PA. Overestimation of platelet aspirin resistance detection by thrombelastograph platelet mapping and validation by conventional aggregometry using arachidonic acid stimulation. J Am Coll Cardiol 2005;46:1705–9.
2. Mason PJ, Jacobs AK, Freedman JE. Aspirin resistance and atherothrombotic disease. J Am Coll Cardiol 2005;46:986–93.
3. Schwartz KA, Schwartz DE, Pittsley RA, et al. A new method for measuring inhibition of platelet function by nonsteroidal antiinflammatory drugs. J Lab Clin Med 2002;139:227–33.
4. Chen WH, Lee PY, Ng W, Tse HF, Lau CP. Aspirin resistance is associated with a high incidence of myonecrosis after non-urgent percutaneous coronary intervention despite clopidogrel pretreatment. J Am Coll Cardiol 2004;43:1122–6.
5. Cheng X, Chen WH, Lee P, Ng W, Kwok Y, Lau CP. Prevalence, profile, predictors, and natural history of aspirin resistance measured by the ultegra rapid platelet function assay–ASA in patients with coronary heart disease. Presented at: AHA 6th Scientific Forum on Quality of Care and Outcomes Research in Cardiovascular Disease and Stroke; Washington, DC: May 7–9, 2006.
6. Lev E, Bray PF, Patel R, Delao T, Granada J, Kleiman NS. Aspirin and clopidogrel drug response in patients undergoing percutaneous coronary intervention: a role for dual drug resistance? Presented at: ACC 2005 Scientific Meeting; Orlando, FL: March 6–9, 2005.
7. Lee PY, Chen WH, Ng W, et al. Low-dose aspirin increases aspirin resistance in patients with coronary artery disease. Am J Med 2005; 118:723–7.
8. Maree AO, Curtin RJ, Chubb A, et al. Cyclooxygenase-1 haplotype modulates platelet response to aspirin. J Thromb Haemost 2005;3: 2340–5.
9. Serebruany VL, Steinhubl SR, Berger PB, et al. Analysis of risk of bleeding complications after different doses of aspirin in 192,036 patients enrolled in 31 randomized controlled trials. Am J Cardiol 2005;95:1218–22.
10. Cotter G, Shemesh E, Zehavi M, et al. Lack of aspirin effect: aspirin resistance or resistance to taking aspirin? Am Heart J 2004;147: 293–300.
11. Schneider DJ. On defining aspirin resistance. J Am Coll Cardiol 2005;46:1710–1.
12. Steinhubl SR, Talley JD, Braden GA, et al. Point-of-care measured platelet inhibition correlates with a reduced risk of an adverse cardiac event after percutaneous coronary intervention: results of the GOLD (AU-Assessing Ultegra) multicenter study. Circulation 2001;103:2572–8.

REPLY

We appreciate Dr. Hillman's interest in our study assessing cyclooxygenase (COX)-1 inhibition by stimulation of platelets with arachidonic acid (AA) in platelet-rich plasma and whole blood. We address his comments: