

Pharmacogenomics and Clopidogrel Irrational Exuberance?

Steven E. Nissen, MD

ON MARCH 12, 2010, THE US FOOD AND DRUG Administration (FDA) announced that clopidogrel would receive a “boxed warning,” the agency’s highest level of alert (BOX).¹ The background for this warning originated from the observation that clopidogrel is a prodrug that requires metabolic conversion to its active moiety by cytochrome P450 subclass 2C19 (*CYP2C19*). Specifically, the boxed warning cautioned that slow metabolism of clopidogrel was associated with higher cardiovascular event rates and suggested that genetic testing could identify individuals who were slow metabolizers, thereby allowing physicians to implement “alternative treatment strategies.” This FDA announcement was instantly controversial. In a highly unusual move, the American Heart Association (AHA) and American College of Cardiology (ACC) rapidly issued a consensus document stating that “The evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time.”² This scientific controversy has continued unabated for nearly 2 years.

In this issue of *JAMA*, Holmes et al³ provide a critical analysis that is useful for resolving this ongoing debate. The authors meticulously examined 32 original research studies that evaluated *CYP2C19* genotyping as a predictor of response to clopidogrel therapy. Twenty-six studies assessed the relationship between the *CYP2C19* genotype and levels of clopidogrel metabolites, platelet reactivity, and clinical outcome, including risk of bleeding in patients treated with clopidogrel. Six studies were randomized clinical trials that studied the relationship between *CYP2C19* genotype and occurrence of major cardiovascular clinical outcomes, including bleeding. The results of these analyses showed no evidence for a significant association between *CYP2C19* genotype and any important cardiovascular outcome.

It now appears that the FDA warning reflected a case of “irrational exuberance,” a phrase popularized by former chairman of the Federal Reserve Alan Greenspan when describing the exponential increase in stock prices a few years before the “dot-com bubble” burst in March 2000.^{4,5} The enthusiasm for dot-com stocks led to unrealistic expectations for rapid suc-

cess of companies without documented financial performance. Similarly, the success of pharmacogenomics in some fields of medicine has led to unrealistic expectations for many other specialties, including cardiovascular medicine. In oncology, pharmacogenomic approaches have revolutionized treatment, such as the enhanced response of patients with human epidermal growth factor receptor 2 (*HER2*)-positive breast cancer to trastuzumab.⁶ Unfortunately, in the popular press, the concept of personalized medicine has taken on a nearly cult like following with public pronouncements describing how future physicians will use therapies that reflect the specific genetic makeup of individual patients. No matter how promising, pharmacogenetic approaches to treatment must withstand the same scrutiny required of all therapeutic advances—careful evaluation through well-designed randomized clinical trials.

In the case of clopidogrel pharmacogenomics, what went wrong? First, most initial studies that supported genetic testing were primarily based on analysis of surrogate markers, typically examining the association between *CYP2C19* loss-of-function alleles and clopidogrel metabolites, platelet reactivity, or both. Over the last several decades, clinicians and researchers have learned painful lessons about the substitution of surrogate end points, such as relying on cholesterol or glucose levels as alternatives for clinically important cardiovascular events such as death, myocardial infarction, or stroke. Repeatedly, drugs that improve biochemical or physiological measures of disease have failed to favorably affect clinical outcomes. Examples include estrogen, rosiglitazone, torcetrapib, and nesiritide. Accordingly, when examining the pharmacogenetic factors influencing the efficacy of a drug such as clopidogrel, the effects of *CYP2C19* loss-of-function alleles on antiplatelet efficacy cannot be equated to increases in cardiovascular morbidity and mortality.

It also appears that initial enthusiasm for *CYP2C19* genetic testing may have been inappropriately influenced by publication bias, a vexing problem in medical research not limited to commercially sponsored trials.⁷ In the study by Holmes et al,³ there was strong evidence that publication bias affected the smaller studies (<200 patients) that examined outcomes in patients with loss-of-function alleles (Harbord test $P = .001$). In

Author Affiliation: Department of Cardiovascular Medicine, Cleveland Clinic Foundation, Cleveland, Ohio.

Corresponding Author: Steven E. Nissen, MD, Department of Cardiovascular Medicine, Cleveland Clinic Foundation, 9500 Euclid Ave, Desk F25, Cleveland, OH 44195 (nissens@ccf.org).

See also p 2704.

Box. Boxed Warning Appearing at the Top of the Product Label Approved by the US Food and Drug Administration for Clopidogrel

Warning: Diminished Effectiveness in Poor Metabolizers. (See full prescribing information for complete boxed warning.)

- Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally *CYP2C19*.

- Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal *CYP2C19* function.

- Tests are available to identify a patient's *CYP2C19* genotype and can be used as an aid in determining therapeutic strategy.

- Consider alternative treatment or treatment strategies in patients identified as *CYP2C19* poor metabolizers.

the smallest studies (ie, with ≤ 99 CVD events), the point estimate for the hazard ratio for cardiovascular morbidity and mortality was 1.83 (95% CI, 1.50-2.23). When analyses were restricted to larger studies (ie, with ≥ 200 events), the point estimate for the hazard ratio for cardiovascular morbidity and mortality was 0.97 (95% CI, 0.86-1.09), indicating no evidence for a less favorable outcome in slower metabolizers. Their careful attention to the issue of publication bias allowed the authors to more accurately assess the clinical relevance of slow metabolism of clopidogrel. The results are compelling.

Prior recent studies and systematic reviews that have attempted to ascertain the importance of clopidogrel pharmacogenomics on the efficacy of clopidogrel have yielded contradictory findings.⁸⁻¹¹ In the recently published GRAVITAS trial, more than 2000 patients with high residual platelet reactivity after standardized clopidogrel dosing were randomized to continue this dosage vs a doubling of the standard dosage.¹⁰ During 6-month follow-up, the hazard ratio for cardiovascular death, myocardial infarction, and stroke was 1.01 (95% CI, 0.58-1.76). Although these authors used functional testing of platelet reactivity rather than genetic testing, the results provide no evidence that differences in response to clopidogrel influenced clinical outcomes. An analysis of 2 large randomized trials involving 5059 patients also showed no modification of the benefits of clopidogrel in patients with reduced-function alleles.¹¹ However, another meta-analysis concluded that even 1 reduced-function allele was associated with a significantly increased risk of major cardiovascular events.¹⁰ None of the prior systematic reviews were as thorough and rigorous as the report by Holmes et al.^{8,9}

The consequences of the FDA's leap to judgment regarding *CYP2C19* testing cannot be underestimated. Several companies subsequently received FDA approval to market products for testing either *CYP2C19* reduced-function alleles or

platelet reactivity. The societal cost of such testing procedures remains unknown, but according to the FDA, the "per-patient" charge for genetic testing ranges from \$60 to \$500.¹² Because clopidogrel is one of the most widely used drugs in medicine, the potential cost to the health care system of universal genetic testing is substantial. Preventing inappropriate *CYP2C19* testing could yield substantial savings for the health care system. In this respect, the study by Holmes et al,³ which provides no evidence to support *CYP2C19* testing, should influence clinical practice.

Like all meta-analyses, the report by Holmes et al³ has important limitations. Although the authors attempted to compensate for publication bias, it remains possible that other informative but unpublished studies might alter their conclusions. The authors did not have access to patient-level data, which is always preferred when conducting this type of analysis. A large randomized controlled trial is needed to adequately test the clopidogrel pharmacogenomic hypothesis. In the absence of such a study, physicians should use *CYP2C19* or platelet reactivity testing rarely, if ever, and interpret the results with caution. It is still likely that pharmacogenomics has a bright future in cardiovascular medicine, but the pharmacogenomics approach to drug therapy must undergo the same rigorous testing for efficacy and cost-effectiveness that is required for other therapies. Overzealous adoption based on limited biochemical data does not serve the public interest.

Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

REFERENCES

1. Plavix (clopidogrel): reduced effectiveness in patients who are poor metabolizers of the drug. US Food and Drug Administration. <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm204256.htm>. Accessed December 2, 2011.
2. Holmes DR Jr, Dehmer GJ, Kaul S, Leifer D, O'Gara PT, Stein CM. ACCF/AHA clopidogrel clinical alert: approaches to the FDA "boxed warning": a report of the American College of Cardiology Foundation Task Force on clinical expert consensus documents and the American Heart Association endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2010;56(4):321-341.
3. Holmes MV, Perel P, Shah T, Hingorani AD, Casas JP. *CYP2C19* genotype, clopidogrel metabolism, platelet function, and cardiovascular events: a systematic review and meta-analysis. *JAMA*. 2011;306(24):2704-2714.
4. Irrational exuberance. Wikipedia. http://en.wikipedia.org/wiki/Irrational_exuberance. Accessed December 2, 2011.
5. Dot-com bubble. Wikipedia. http://en.wikipedia.org/wiki/Dot-com_bubble. Accessed December 2, 2011.
6. Soh TI, Yong WP, Innocenti F. Recent progress and clinical importance on pharmacogenetics in cancer therapy. *Clin Chem Lab Med*. 2011;49(10):1621-1632.
7. Fanelli D. Do pressures to publish increase scientists' bias? an empirical support from US States Data. *PLoS One*. 2010;5(4):e10271.
8. Mega JL, Simon T, Collet JP, et al. Reduced-function *CYP2C19* genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. *JAMA*. 2010;304(16):1821-1830.
9. Bauer T, Bouman HJ, van Werkum JW, Ford NF, ten Berg JM, Taubert D. Impact of *CYP2C19* variant genotypes on clinical efficacy of antiplatelet treatment with clopidogrel: systematic review and meta-analysis. *BMJ*. 2011;343:d4588.
10. Price MJ, Angiolillo DJ, Teirstein PS, et al. Platelet reactivity and cardiovascular outcomes after percutaneous coronary intervention: a time-dependent analysis of the Gauging Responsiveness with a VerifyNow P2Y12 assay: Impact on Thrombosis and Safety (GRAVITAS) trial. *Circulation*. 2011;124(10):1132-1137.
11. Paré G, Mehta SR, Yusuf S, et al. Effects of *CYP2C19* genotype on outcomes of clopidogrel treatment. *N Engl J Med*. 2010;363(18):1704-1714.
12. Clopidogrel receives boxed warning for reduced benefit in poor metabolizers. Medscape. <http://www.medscape.org/viewarticle/720564>. Accessed December 2, 2011.