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Clopidogrel: A Case for Indication-Specific Pharmacogenetics

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Abstract

The CYP2C19*2 loss-of-function allele is associated with reduced generation of active metabolites of clopidogrel. However, meta-analyses have supported or discounted the impact of genotype on adverse cardiovascular outcomes during clopidogrel therapy, depending on studies included in the analysis. Here we review these data and conclude that evidence supports a differential effect of genotype on protection from major adverse cardiovascular outcomes following percutaneous coronary intervention (PCI), but not for other clopidogrel indications.

Clopidogrel was marketed in 1997, but it was only in 2006 that the first evidence of a potentially important effect of CYP2C19 genotype on the drug's action was reported.[1] Three articles highlighting the potential impact of cytochrome P450 2C19 (CYP2C19) genotype on major adverse cardiovascular events with clopidogrel therapy were then published simultaneously in the *New England Journal of Medicine* (*NEJM*) and *The Lancet* in early 2009. These data increased interest in the clinical utilization of pharmacogenetic data to guide antiplatelet therapy, and in 2010 a boxed warning was added to the clopidogrel label by the US Food and Drug Administration (FDA) to alert clinicians to the impact of CYP2C19 genotype on clopidogrel efficacy.

Clopidogrel is a prodrug requiring two-step enzymatic metabolism to generate the active metabolite—a process in which CYP2C19 plays a critical role. A common loss-of-function polymorphism in CYP2C19, called *2, is seen in up to 30% of individuals of European and African ancestry and 70% of those of Asian ancestry; homozygotes for the *2 allele (poor metabolizers) constitute ~3–4% and 10–15% of these ancestries, respectively. Many studies provide clear evidence that *2 allele carriers (*2 heterozygotes or homozygotes) have lower

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CONFLICT OF INTEREST

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active metabolite plasma concentrations and higher levels of on-treatment platelet reactivity (less antiplatelet effect), although much variability within genotype groups remains.[2-5]

The three early studies in *NEJM* and *The Lancet*, and several others showing a significant effect of CYP2C19*2 on cardiovascular outcomes, involved clopidogrel-treated patients of whom the majority (>70%), or all, underwent PCI. These studies also provided evidence that the greatest risk was for post-PCI stent thrombosis, with odds ratios in excess of 3.0.

Based on the accumulating published data, along with internal data available at the FDA, in March 2010 the FDA added a boxed warning to the product label for clopidogrel, alerting clinicians to the risk of reduced clopidogrel efficacy in CYP2C19 poor metabolizers (Table 1). It is important to note that the boxed warning focuses on poor metabolizers and on patients taking clopidogrel following acute coronary syndrome (ACS) or PCI.

This boxed warning left the cardiovascular care community with great uncertainty regarding the role of CYP2C19 genetic testing in clinical practice. This uncertainty increased later in 2010 with the publication of data from two clinical trials: CURE and ACTIVE-A.[6] These pharmacogenetic analyses arose from randomized, placebo-controlled clinical trials and did not reveal a significant relationship between CYP2C19 genotype and outcomes in clopidogrel-treated patients. However, they differed markedly from the earlier studies in the populations studied. The CURE trial enrolled patients with non–ST-segment elevation myocardial infarction (NSTEMI), only 15.5% of whom underwent PCI. The ACTIVE-A trial enrolled patients with atrial fibrillation in whom warfarin was not being utilized.

The clopidogrel pharmacogenetics data from CURE and ACTIVE-A initially raised questions about the validity of the earlier studies, but evaluation of the body of literature suggested the larger issue might be the magnitude of risk based on genotype, relative to the magnitude of clopidogrel benefit in the treatment group. Specifically, clinical trials evaluating the benefit of thienopyridines (clopidogrel and ticlopidine) in PCI patients documented relative risk (RR) reductions of 30–85% vs. placebo. By contrast, the RR reduction in the CURE trial (NSTEMI patients, most of whom did not undergo PCI) was 20%, and in the ACTIVE-A trial, atrial fibrillation patients it was 11%. Thus, both of these studies enrolled patients at lower risk for adverse cardiovascular events, regardless of genotype. By contrast, PCI patients derive greater benefit from clopidogrel, so it is not surprising that they would also be at greater risk from the loss-of-function CYP2C19 alleles.

Several meta-analyses of clopidogrel pharmacogenetics have been published recently and, depending on the meta-analysis, have added clarity or confusion. One caveat of interpreting meta-analyses is the homogeneity of the studies or patient populations included. The meta-analysis by Mega *et al*. focused on studies that included coronary artery disease patients who were managed predominantly with PCI.[7] It encompassed 9,685 patients from nine studies, and all studies provided data for conduct of the meta-analysis. Risk of cardiovascular death, myocardial infarction, and stroke was significantly increased, with hazard ratios (HRs) and 95% confidence intervals (CIs) of 1.57 (1.13–2.16), 1.55 (1.11–2.17), and 1.76 (1.24–2.50) among *2 carriers (*1/*2 and *2/*2), intermediate (*1/*2), and poor (*2/*2) metabolizers, respectively. Consistent with the primary studies, the authors observed that the risk for stent thrombosis was nearly double that for other adverse cardiovascular events, with HRs of 2.67 to 3.97 for intermediate and poor metabolizers, respectively (see Table 2). These data provided compelling evidence for the influence of CYP2C19 genotype on cardiovascular outcomes among high-risk coronary disease patients, particularly those undergoing PCI.

The most recently published meta-analysis came to different conclusions, and it has created much controversy and confusion about the role of CYP2C19 genotype on clopidogrel efficacy. Holmes *et al*. took a different approach from that of Mega and colleagues by

including all studies in which clopidogrel pharmacogenetics was tested relative to cardiovascular outcomes.[2] These included the studies in high-risk PCI patients that constituted the meta-analysis by Mega, but also studies in lower-risk populations for which the overall benefit of clopidogrel was much lower or absent. Additionally, the analysis focused largely on *2 carrier status, in which intermediate and poor metabolizers were combined into a single group. The analysis, which encompassed 32 studies, concluded that CYP2C19*2 carriers were not at clinically relevant risk for adverse cardiovascular outcomes based on genotype (RR 1.18; 95% CI: 1.09–1.28). The authors argue that small-study bias (presumably arising from publication bias) and inability to directly evaluate modification of treatment-only studies in most/all of the small studies are the reasons underlying the discrepant findings. An alternative conclusion is that the smaller treatment-only studies contained a much larger proportion of PCI patients, a population that benefits markedly from clopidogrel, relative to the large placebo-controlled studies that enrolled patients with indications for which clopidogrel had less or no efficacy.

We contend that the heterogeneity in patient populations, the risk for adverse cardiovascular outcomes, and therefore the attendant benefit from clopidogrel are so different among the various study populations that interpretation of data derived from a pooled population is difficult. We agree that the effect of *2 in lower-risk populations is not evident, but assert that it is misguided to disregard the real, well-documented risk in higher-risk PCI patients who are *2 carriers.

Holmes *et al.* placed particular focus on active comparator trials (CURE, ACTIVE-A, CHARISMA, CLARITY-TIMI 28), and we use these to illustrate our concerns with the diversity of patient populations and indications included in the meta-analysis. As noted above, CURE's population consisted of patients with NSTEMI, of whom a very small percentage received PCI, and the risk reduction of clopidogrel vs. placebo was only 20%. The ACTIVE-A trial studied patients with atrial fibrillation, an indication for which clopidogrel is rarely used; the benefit of clopidogrel was an 11% risk reduction. CHARISMA was a trial of patients with documented cardiovascular disease or risk for cardiovascular disease, and it showed no benefit of clopidogrel over placebo. As such, this does not represent an indication for clopidogrel.

The only relatively high-risk population among these trials of focus was CLARITY-TIMI 28, which included patients receiving fibrinolytic therapy, of whom >50% also had a PCI. Collectively, these trials showed little effect of CYP2C19 genotype on outcomes—not because the placebo arm allowed direct measurement of effect modification, but because the patient populations in three of the four studies were those with lower risk for adverse cardiovascular outcomes and for which clopidogrel had a much smaller effect in the intervention arm as a whole. It is also important to note that most of the studies on this topic do not control for concomitant use of CYP2C19 inhibitors, which can effectively convert an extensive metabolizer to an intermediate or poor metabolizer, and their use would therefore minimize the ability to detect differences by genotype.

Curiously, the exclusion in the recent meta-analysis of trials with a primary end point of stent thrombosis created a potential bias against this end point, yet the meta-analysis still found a significant risk among *2 carriers. In fact, all the meta-analyses have found significant risk for stent thrombosis, an end point that in essence allows for focus on the high-risk PCI population. The odds ratios for stent thrombosis in the four major meta-analyses, shown in Table 2, leave little doubt about the risk for this uncommon but life-threatening outcome among *2 carriers. Over half a million patients undergo PCI each year in the United States alone, all of whom have an indication for dual antiplatelet therapy. This represents a large population at risk for adverse outcomes based on their genotype, and it

argues that those receiving clopidogrel after PCI should have their antiplatelet therapy guided by CYP2C19 genotype.

Finally, an editorial accompanying the 2011 *JAMA* meta-analysis[2] suggested that the FDA exhibited "irrational exuberance" and was premature in issuing a boxed warning on CYP2C19 genotype for clopidogrel.[8] We strongly disagree with this assessment for several reasons. First, the FDA label (Table 1) focuses on poor metabolizers (*2*2 homozygotes). The meta-analysis by Holmes *et al.* focused on *2 carrier status (a combined group in which heterozygotes would be expected to outnumber the number of homozygotes by approximately 5 to 1).[2] Only one sentence in the meta-analysis was devoted to *2/*2 homozygotes, in which, in fact, significant risk was found. Additionally, the FDA label focuses on ACS and PCI patients, whereas the meta-analysis includes a much broader patient population, as discussed above.

Should the FDA have been clearer in the language of their boxed warning by stating that "poor metabolizers" means loss-of-function homozygotes? Possibly. Should the FDA revise the label, based on data published since early 2010, and limit the statements to only those undergoing PCI but broadening the language to include intermediate metabolizers (*2 heterozygotes)? Probably. Nonetheless, we believe the data continue to support the premise that high-risk clopidogrel-treated coronary disease patients—particularly those undergoing PCI—who have the *2*/2 genotype are at high risk for adverse cardiovascular events. In fact, the totality of data now strongly suggest that intermediate metabolizers (*1/*2) should be added to the high-risk group among those treated with clopidogrel after PCI.

In summary, we assert that the accumulating evidence on clopidogrel pharmacogenetics over the past three years points to a case of rational exuberance for "indication-specific pharmacogenetics." Specifically, the data strongly support that the population for whom clopidogrel provides the greatest benefit (post-PCI patients) is also the population for whom CYP2C19 genotype matters most clinically. Although the data do not support genotype-guided therapy of clopidogrel for other indications, for which the drug's overall effect is much more modest, the data are compelling for the impact of genotype on outcomes among post-PCI patients.

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Table 1

US Food and Drug Administration boxed warning on the clopidogrel (Plavix) product label

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

- 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.

Table 2

Risk for stent thrombosis among clopidogrel-treated patients in major meta-analyses

Ref.	Year	Patient population in entire meta-analysis	Sample size (stent thrombosis analysis)	CYP2C19 genotype relative risk for stent thrombosis[a]
Hulot *et al.*[9]	2010	Established CAD	4,905	*1*2: 3.34 (1.84–5.93) *2*2: 4.68 (1.55–14.11) *2 carrier: 3.45 (2.14–5.57)
Mega *et al.*[7]	2010	Aggressively managed CAD patients	6,094	*1*2: 2.67 (1.69–4.22) *2*2: 3.97 (1.75–9.02) *2 carrier: 2.81 (1.81–4.37)
Bauer *et al.*[10]	2011	Established CAD	19,328	*2 carrier: 1.77 (1.31–2.40)
Holmes *et al.*[2]	2011	Unselected[b]	16,008	*2 carrier: 1.75 (1.50–2.03)

CAD, coronary artery disease.

[a]The symbol *2 can refer to any CYP2C19 loss-of-function allele. See text for details.

[b]Meta-analysis excluded studies with stent thrombosis as primary end point.