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Responding to the Clopidogrel Warning by the US Food and Drug Administration
Real Life Is Complicated
Dan M. Roden, MD; Alan R. Shuldiner, MD

A sine qua non for drug approval by the US Food and Drug Administration (FDA) is demonstrated efficacy in populations of patients. However, it is virtually axiomatic that individuals vary in their responses to drugs. Work over decades has built a knowledge base that describes the role of genetic variation as a modulator of both drug efficacy and rare adverse drug effects.1 This increasing understanding of the role of genetics in variable drug responses led the FDA in 2007 to begin to incorporate pharmacogenetic information in drug labels.2

What Is Known
Remarkably, when clopidogrel was approved in 1997, its mechanism of action was not known. Great interindividual variability in response was recognized soon after,3 and since then, we have learned that clopidogrel must first be converted to an active metabolite, which then binds and irreversibly inhibits P2Y12 (ADP) receptors on platelets to exert its antiplatelet effect.6 Studies indicate that this bioactivation step is largely but not exclusively dependent on the activity of a specific hepatic cytochrome P450 enzyme, termed CYP2C19.7 There are several common variants of the CYP2C19 gene. The normally functioning allele is termed *1, but the *2 allele, which results in loss of function of the encoded protein, is common across many populations. Homozygotes for the loss of function allele (poor metabolizers) represent 2% to 3% of whites and blacks, and up to 15% to 20% of East Asians; heterozygotes represent 30% to 35% and 40% to 45% of these populations, respectively. When ex vivo measures of platelet aggregation are used to define drug effect, loss of function alleles can be shown to decrease drug action in a gene-dose dependent fashion7,8; that is, individuals treated with clopidogrel with the *2/*2 genotype are less responsive than those with the *1/*2 genotype (intermediate metabolizers) who in turn are less responsive than those with the *1/*1 genotype. The surrogate end point of inhibition of platelet aggregation has been partially validated by retrospective examinations of outcomes in patients receiving the drug for clinical indications, in which *2/*2 homozygotes (and possibly also *1/*2 heterozygotes) display increased cardiovascular event rates compared to those with the *1/*1 genotype.8–10 These recent findings have led to the FDA-mandated black box label for clopidogrel that now alerts physicians and patients of the role of common CYP2C19 gene variants in mediating the drug’s actions.

What Is Uncertain
Despite the dependency of clopidogrel bioactivation on CYP2C19 activity, not all studies show increased cardiovascular events in patients on clopidogrel with the *1/*2 genotype compared to those with *1/*1.10 In addition, the effect of rarer CYP2C19 variants that reduce enzyme function (eg, *3 or *5) has not been studied. Emerging data suggest that CYP2C19*17, a relatively common allele that results in increased enzyme expression and activity, may be associated with a modest increase in clopidogrel responsiveness.11,12 However, the *2 and *17 variants are in linkage disequilibrium, so it is not certain that the effects of this variant are independent of that of the *2 variant.13 Some proton pump
inhibitors (PPIs), notably omeprazole, are potent CYP2C19 inhibitors, and omeprazole’s reversal of clopidogrel’s effect on ex vivo measured platelet function is readily demonstrated. However, there are highly contradictory data on whether coadministration of PPIs and clopidogrel alters cardiovascular event rates.15–17

Most importantly, no studies have been published to define a clinical strategy that would exploit this pharmacogenetic information to optimize outcomes with clopidogrel. Thus, for example, although increasing the dose in *2/*2 subjects seems rational, limited available data do not strongly support this strategy.18 Whereas the FDA’s warning does serve to bring the attention of the prescribing community to new data that affects variability in response to drug therapy, the advisory has also generated concern because the practitioner is only offered a series of possible responses, none of which has been tested in any reasonable fashion.

**Why Is This So Confusing?**

We suggest that one explanation for this confusion arises from differing expectations—in the genetics community, among clinicians, and perhaps among regulators—over the contribution of single genetic variants to common human traits. In the genomics community, there is now an emerging consensus that common gene variants explain a smaller proportion of the heritability of common diseases than had been anticipated.19 Pharmacogenetics “hype” has promulgated a vision that knowing one or a few genotypes might allow a clear distinction between responders and nonresponders or help identify those likely to suffer catastrophic side effects. This can happen—abacavir is one example—but the reality is that biology is often much more complicated than a few arrows on a simple linear drug response pathway: clopidogrel \( \rightarrow \) bioactivation (by a single gene product) \( \rightarrow \) effect. In the case of clopidogrel, we do have data: For example, a large study in the Amish, a group with extensive family relationships, showed that the genetic component of variability in the extent to which clopidogrel inhibits ADP-triggered platelet aggregation was \( \approx 70\% \).20 A genome-wide association study identified the CYP2C19 locus as the single most important contributor to this variability, but the contribution of variability was “only” \( \approx 12\% \). To a clinician, that may sound like a small number, but to a geneticist this is an enormous contribution. Importantly, there were no other strong association signals apparent in the genome-wide association study suggesting that the majority of the genetic variability in clopidogrel response may be due to more modest effects of many other common variants or perhaps rare or other kinds of genetic variants that escaped detection with current genome-wide association study methodology.

This moderate influence of genetic variation in CYP2C19 may also explain some of the uncertainties over the PPI effect: it is conceivable that an interaction between PPIs and clopidogrel would only be clinically meaningful in individuals with reduced CYP2C19 activity (eg, *1/*2), whereas *1/*1 homozygotes would display sufficient enzyme activity that PPI coadministration would not alter platelet inhibition. This is a hypothesis to be tested, and in any case, as with all drug therapy, it is important to weigh risks and benefits, and a major benefit of PPIs in this setting is prevention of gastrointestinal hemorrhage.21

A recurring theme in complex traits, like pharmacogenomics, is that genetic variation does not confer absolutes, but rather alters probabilities of particular outcomes. This necessarily means that while drug responses may be stochastic (“good” or “bad”) in an individual, this is rarely the case in a population: event rates in patients receiving effective P2Y12 inhibition are not zero, nor are they 100% in patients not receiving drug, or in those genetically unable to generate active drug. Physicians can be quite adept at considering multiple lines of probabilistic evidence-based data in formulating a treatment plan for a given patient. However, they are now presented with an FDA warning on CYP2C19 and clopidogrel in the face of a gap in knowledge as to how to incorporate the CYP2C19 genotype into their clinical decision-making practices.

**What Response Might a Clinician Adopt?**

The accompanying American College of Cardiology Foundation/American Heart Association Clopidogrel Clinical Alert22 nicely outlines possible actions by clinicians:

- **Do nothing:** follow guidelines: This is a default position, and is tenable in the absence of availability of any other data or testing. This may especially be the case in an interregnum (now) between identification of an important predictor of drug response like CYP2C19 genotype and solid data on how reasonably to respond to it.

- **Use platelet function testing as an alternative to genetic testing:** Variability in response to clopidogrel is reminiscent of variable warfarin response; here too, there continues to be argument over the utility of preprescription genotyping as an adjunct to international normalized ratio measurements. The best test of platelet function and how this should be deployed in practice is not yet standardized2324(662,164),(696,248). One appealing option is to incorporate both genetic testing and platelet function monitoring into management of P2Y12 inhibitor therapy.13,24 Initial genetic testing will identify patients at risk for drug failure, whereas intermittent platelet function testing could be viewed as analogous to international normalized ratio measurements for warfarin and allow the clinician to address the variance in drug action even after CYP2C19*2 is factored in.

- **Use preprescription genotyping to guide therapy:** Because many cardiovascular events occur within the first few hours to days after percutaneous coronary intervention, a rapid turnaround time is essential. The questions here are how and whether to adjust clopidogrel dose or to choose an alternative drug; and in whom: just poor metabolizers (*2/*2 homozygotes) or also in intermediate metabolizers (*1/*2 heterozygotes)? In addition, third-party payers may or may not reimburse for genetic testing without the evidence base to support its efficacy.

- **Ignore clopidogrel and prescribe “alternate P2Y12 inhibitors”** (ie, prasugrel for now) to all: Prasugrel action does not appear to be affected by CYP2C19 genotype. In the Trial to Assess Improvement in Therapeutic Outcomes by
Optimizing Platelet Inhibition With Prasugrel—Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) trial, the drug resulted in fewer cardiovascular events but more bleeding. Thus, use of prasugrel in all patients would preempt CYP2C19 genetic testing but increase exposure to adverse bleeding complications. To increase the benefit: risk ratio and manage costs, a more individualized approach might be to prescribe clopidogrel in patients without at-risk genotypes and other drugs such as prasugrel in subjects with CYP2C19 variant genotypes. This option might also be cost effective, with clopidogrel coming off patent and soon to be much less expensive than newer agents. However, as the American College of Cardiology Foundation/American Heart Association Clopidogrel Clinical Alert correctly points out, the evidence base for this option currently does not exist.

It is clear that none of these options are well supported by data and that major issues are unsettled: eg, which platelet function test is best, how to get timely genetic data on which to act, how to act, and the economics of genetic testing versus complications avoided.

**Practice Versus Regulation**

The drug label is meant to convey important information for drug use and for marketing. Thus, we believe that the FDA has little choice but to inform prescribers of new information that may affect the way in which their patients respond to drugs. To ignore the CYP2C19 data would be to place the regulatory agency in the unconscionable position of having a label that does not accurately describe the risks and benefits of drug treatment.

The uncertainties over the use of genetic testing in the management of clopidogrel and other drugs, such as warfarin or tamoxifen, reflect impressive progress in pharmacogenetics coupled to uncertainties over how to incorporate that progress into practice. This is the paradox of evidence-based medicine in populations versus individualized medicine. Whereas the “gold standard” for altering practice is the randomized clinical trial, a major challenge remains development of methods to deploy what we know about genomic variation and human traits. The conduct of randomized clinical trials in large unselected populations, most of whom will not carry risk alleles, is inefficient and cost prohibitive. Thus, it will be important to consider novel study designs such as genotype enrichment in populations at high risk for events, and comparative effectiveness study designs incorporating genetics that clearly define treatment options superior to the current standard of care.

Ignoring the newly emerging data on CYP2C19 genotype and clopidogrel response does not seem to be the best approach. Another way of looking at the tension in this area is to pose the question: “If the genotyping data were readily and simply available at the time of prescribing, should it be used?” Stated this way, the answer would almost certainly be “yes”: there seems little downside to at least knowing which patients can take the standard dose of the about-to-be cheaper drug and which need extra thought. This idea, which might easily apply to many drugs, can be posed because of an extraordinarily rapidly evolving genotyping environment: We are 1 to 2 years (at most) away from sub-$1000 whole genome sequencing. This kind of technological development, which raises a myriad of operational, ethical, educational, interpretative, and regulatory challenges, will enable a much broader view of how near-future pharmacogenomic discoveries will be translated into clinical practice.

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**References**


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