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## Responding to the FDA's clopidogrel warning: Real life is complicated

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A *sine qua non* for drug approval by the 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.<sup>1</sup> This increasing understanding of the role of genetics in variable drug responses led the US Food and Drug Administration in 2007 to begin to incorporate pharmacogenetic information in drug labels.<sup>2</sup>

In some cases, available data have allowed drug labeling to include specific and highly directive advice. For example, empirical studies, followed by a large randomized clinical trial, demonstrated that pre-prescription genotyping to avoid the antiretroviral agent abacavir in subjects carrying the HLA variant B\*5701 can strikingly reduce, if not eliminate, the risk of drug-related severe skin reactions.<sup>3,4</sup> The FDA label now carries the unambiguous recommendation warning stating that such testing should be done, and the drug not prescribed in patients with the variant. However, it is likely that single genetic variants with such large effects and predictive value on drug response or adverse effects are more often the exception than the rule; rather, a few or many genetic variants, each with relatively modest effect, contribute to a continuum of drug response in the treated population. Defining the clinical utility of such genetic variants poses important challenges to how pharmacogenetic information may be incorporated into practice. The widespread use of clopidogrel, the well-documented large interindividual variation in response to the drug, and the emerging understanding of the genetics of that variability is the latest example of such a challenge.

### What is known

Remarkably, when clopidogrel was approved in 1997, its mechanism of action was not known. Great inter-individual variability in response was recognized soon after,<sup>5</sup> and since then, we have learned that clopidogrel must first be converted to an active metabolite which then binds and irreversibly inhibits P2Y<sub>12</sub> (ADP) receptors on platelets to exert its anti-platelet effect.<sup>6</sup> Studies indicate that this bioactivation step is largely but not exclusively

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dependent on the activity of a specific hepatic P450 cytochrome enzyme, termed CYP2C19.<sup>7</sup> There are several common variants of the *CYP2C19* gene. The normally functioning allele is termed \*1, but the \*2 allele, that results in loss of function of the encoded protein, is common across many populations. Homozygotes for the loss of function allele (poor metabolizers) represent 2–3% of Caucasians and African Americans, and up to 15–20% of East Asians; heterozygotes represent 30–35% and 40–45% 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 fashion;<sup>7,8</sup> that is, individuals treated with clopidogrel with the \*2/\*2 genotype are less responsive than those with the \*1/\*2 genotype who in turn are less responsive than those with the \*1/\*1 genotype. The surrogate endpoint 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 display increased cardiovascular event rates compared to those with other genotypes.<sup>8–10</sup> 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 subjects on clopidogrel with the \*1/\*2 genotype (intermediate metabolizers) compared to those with \*1/\*1.<sup>10</sup> In addition, the effect of rarer *CYP2C19* variants that reduce enzyme function (e.g., \*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.<sup>11,12</sup> 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.<sup>13</sup> Some proton pump inhibitors (PPIs), notably omeprazole,<sup>14</sup> 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.<sup>15–17</sup>

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, while increasing the dose in \*2/\*2 subjects seems rational, limited available data do not strongly support this strategy.<sup>18</sup> While the FDA's warning does serve to bring the attention of the prescribing community new data that affects variability in response to drug therapy, the advisory has also generated concern since 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 emerging consensus that common gene variants explain a smaller proportion of the heritability of common diseases than had been anticipated and hoped for less than a decade ago.<sup>19</sup> Pharmacogenetics “hype” has promulgated a vision that knowing a few genotypes might allow a clear distinction between responders and non-responders, or 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 → bioactivation (by a single gene product) → 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 ~70%.<sup>20</sup> A genome-wide association study (GWAS) identified the *CYP2C19* locus as the single most important contributor to this variability, but the contribution of variability was “only” ~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 GWAS 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 variants that escaped detection with current GWAS 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 modestly reduced *CYP2C19* activity (e.g. \*1/\*2), while \*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.<sup>21</sup>

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 P2Y<sub>12</sub> 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 *CYP2C19* genotype into their clinical decision making practices.

## What response might a clinician adopt?

The accompanying ACCF/AHA position paper 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 inter-regnum (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 pre-prescription genotyping versus INR measurements. The best test of platelet function and how this should be deployed in practice is not yet standardized;<sup>22,23</sup> One appealing option is to incorporate both genetic testing and platelet function monitoring into management of P2Y<sub>12</sub> inhibitor therapy.<sup>13,23</sup> Initial genetic testing will identify patients at risk for drug failure, while intermittent platelet function testing could be viewed as analogous to INR measurements for warfarin – and allow the clinician to address the large proportion of variance in drug action even after *CYP2C19*\*2 is factored in.
- Use pre-prescription genotyping to guide therapy: Since many cardiovascular events occur within the first few hours to days following PCI, 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” (i.e. prasugrel for now) to all: Prasugrel action does not appear to be affected by *CYP2C19* genotype. In the TRITON-TIMI 38 trial, the drug produced fewer cardiovascular events but more bleeding.<sup>24</sup> Thus, use of prasugrel in all patients would preempt *CYP2C19* genetic testing, but increase exposure to adverse bleeding complications. To increase benefit:risk 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 soon coming off patent and soon to be much less expensive than newer agents. However, as the ACCF/AHA statement 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: which platelet function test is best, how to get timely genetic data on which to act, 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.<sup>25</sup> Thus, we believe 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 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. While the “gold standard” for altering practice is the randomized clinical trial (RCT), a major challenge remains development of methods to deploy what we know about genomic variation and human traits. The conduct of RCTs 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 that clearly define treatment options superior to the current standard of care.

Ignoring the newly-emerging data regarding *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 1–2 years (at most) away from sub-\$1000 whole genome sequencing. This kind of technologic development, which raises a myriad of operational, ethical, educational, interpretative, and regulatory challenges,<sup>26</sup> will enable a much broader view of how a near-future pharmacogenomic discoveries will be translated into clinical practice.

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