

# Critical Evaluation of: “CYP2C19 Genotype, Clopidogrel Metabolism, Platelet Function, and Cardiovascular Events: A Systematic Review and Meta-Analysis”

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## *Introduction*

Following the recently published meta-analysis that questions the association between CYP2C19 genotypes and cardiovascular outcomes in patients taking clopidogrel<sup>1</sup> it is important to revisit the evidence for genotyping these patients. Although studies have both supported and refuted an association between CYP2C19 genotypes and outcomes in clopidogrel patients, a meta-analysis merging this data to draw a single conclusion is likely to have important limitations. In response to conflicting evidence new hypotheses about the interaction between the CYP2C19 genotypes and clopidogrel are also emerging, such as the hypothesis put forth by M. J. Cohen suggesting that clopidogrel may have thrombogenic metabolites responsible for poor outcomes that are more prevalent when clopidogrel is taken with proton pump inhibitors.<sup>2</sup> We aim to summarize the evidence of pharmacogenomics interactions in clopidogrel patients, discuss the impact on healthcare dollars, evaluate the *Holmes, et al* meta-analysis,<sup>1</sup> gain insight through experts in the field, and discuss additional relevant pharmacogenomic factors.

## *The Clopidogrel and CYP2C19 Genotype Interaction*

Understanding the interaction between CYP2C19 variant alleles and clopidogrel response is crucial because of the current role of clopidogrel in treatment guidelines for acute coronary syndrome,<sup>3,4</sup> peripheral artery disease,<sup>5</sup> coronary artery disease,<sup>6,7</sup> and stroke.<sup>8,9</sup> As a thienopyridine, clopidogrel irreversibly inhibits the adenosine diphosphate P2Y<sub>12</sub> receptor found on platelets that is responsible for their aggregation.<sup>10</sup> Differences in platelet inhibition between patients following administration of clopidogrel and effects on cardiovascular outcomes are well documented,<sup>11</sup> suggesting patient-specific factors play an important role in the benefit of clopidogrel therapy.

Because clopidogrel is a prodrug requiring metabolism by hepatic CYP450 enzymes to an active metabolite for activity and CYP2C19 has been identified as the most important enzyme in the activation of clopidogrel,<sup>12</sup> variations in CYP2C19 gene expression has become of special interest. Individuals classified as poor metabolizers (PMs) are those that express a \*2,3,4,5,6,7, or 8 CYP2C19 allele whereas individuals with a \*17 allele are classified as extensive metabolizers (EMs) (\*1 allele indicates the wild-type).<sup>13</sup> In the case of clopidogrel, extensive metabolizers have increased plasma levels of the active metabolite whereas poor metabolizers are less capable of metabolizing the prodrug to the active form and, consequently, have lower plasma levels. Although the resulting impact on clinical outcomes is still being debated by countless studies and meta-analyses, discovering the true connection between CYP2C19 poor metabolizer genotypes and outcomes is important because of the large prevalence of

these loss-of-function genotypes. Approximately 60% of Asians, 30% of Caucasians, and 35% of Africans are estimated to carry at least one copy of a poor metabolizer allele,<sup>13,14</sup> and are, therefore, at risk for a poor response to clopidogrel therapy.

### *Economic Impact of Non-Responders*

Patients requiring restenting incur considerable costs, as demonstrated in a 2005 study of members of a large PBM. The population study was patients undergoing initial PCI between 1/1/00 and 12/31/00 (N=3,258) and followed to 1 year. Members who underwent repeat revascularization procedures within one year of the original procedure incurred an additional incremental mean cost of \$25,000.<sup>15</sup>

Medco, a leading PBM, finds the genotyping information for the interaction between the CYP2C19 enzyme and clopidogrel important enough to include on their website, and provides genetic testing services to its members. In addition, Medco is funding a study entitled Genotype Guided Comparison of Clopidogrel and Prasugrel Outcomes Study (GeCCO). This study is designed to compare the effectiveness of clopidogrel in CYP2C19 extensive metabolizers (EM) with prasugrel in adults recently hospitalized for acute coronary syndrome (ACS) with primary, delayed, or planned percutaneous coronary intervention (PCI).<sup>16</sup>

### *Holmes, et. al. Meta-Analysis Methodology Considerations*

According to Drug Information: A Guide for Pharmacists, there are several questions that should be answered when assessing a meta-analysis.<sup>17</sup> Although the authors of the aforementioned meta-analysis utilize solid methodology overall, there are some shortcomings which should be pointed out. One that should not be overlooked is that there was wide variety in the patient population in the various trials chosen for inclusion. The authors themselves recognize that the inclusion of patients with both stable CHD and ACS might dilute an association if the magnitude of effect of clopidogrel was greater in ACS patients.<sup>1</sup> In addition, the authors used composite outcomes that differed across studies which may have influenced their conclusions. Other limitations include the use of aggregate data rather than participant data, which lacks the power to detect differences in subgroups, such as those taking aspirin or drugs that may be competitive inhibitors of CYP2C19. The authors were not blinded to selection, names of authors of the original studies, place of publication or study results, another potential limitation of this meta-analysis.

An additional factor to consider is the composite outcomes of the various trials in this meta-analysis. The use of composite endpoints in clinical trials has been a topic of much discussion by statisticians as well as practitioners and is a complicated and controversial methodology. Sometimes researchers will combine clinically meaningful endpoints with more nebulous endpoints that can “blunt” the meaningful endpoints. The combined endpoints often include stroke or MI, need for another procedure, or death. Clearly these are not equal in the viewpoint of the patient or the practitioner, however, they have become the standard in large cardiovascular trials.

### *Clinician Viewpoint*

Experts in the field of cardiology also question the results of the meta-analysis. “This conclusion is directly contradicted by the data presented,” said Eric J Topol, MD, who was actually an investigator in one of the studies analyzed by the *Holmes, et al* meta-analysis.<sup>18</sup> Topol and colleagues also criticize the lack of homogeneity of the data merged in the analysis and the neglect to individually consider data concerning stent thrombosis given the overwhelming evidence in that population of patients. Dr. Samir B. Damani, MD, PharmD., writes that although other genetic and environmental factors have been identified as possible contributors to responsiveness to clopidogrel therapy, most evidence points to CYP2C19 variants as being the main cause of poor outcomes.<sup>19</sup> Drs. Damani and Topol believe that enough evidence exists to support customizing clopidogrel therapy for individual patients based on pharmacogenomics. Some cardiology experts say the argument is not whether to conduct genotype testing in clopidogrel patients but rather which patients to test.<sup>20</sup> Because the strongest evidence for genotyping is in acute coronary syndrome patients undergoing percutaneous intervention, this population may be the most likely to benefit while at the same time being the least reasonable to test given the turnaround time of genotype testing and the urgency of the situation.

### *Other Pharmacogenomic Considerations*

The result of this meta-analysis should be interpreted with caution for many reasons, one of which is the lack of consideration of the number of variant alleles in subjects typed as poor and normal metabolizers in all included studies. Some literature would suggest that poor outcomes as a result of clopidogrel use in CYP2C19 poor metabolizer genotypes occurs statistically significantly more frequently only when two poor metabolizer alleles are present, not just one.<sup>21</sup> Assuming the number of poor metabolizer alleles present to be important in outcomes, studies that lump those subjects with one or two poor metabolizer alleles together into one group may dilute the true potency of the double loss of function allele effect. This dilution is a possible explanation for the mixed results in clopidogrel studies using outcomes as endpoints but failing to distinguish allele groups.

In addition to considering the genetic variance in CYP2C19 alleles clinicians should consider the impact of polymorphisms in the ABCB1 gene. Also shown to be linked to outcomes including death, myocardial infarction, and stroke,<sup>21</sup> genetic variations in the ABCB1 gene, which encodes for the P-glycoprotein multidrug resistant-1 efflux transporter, can result in decreased intestinal absorption of clopidogrel.<sup>22</sup> Although ethnic frequencies of allele variance is not well studied, two studies suggests that the offending T allele may be more prevalent in blacks than other races.<sup>23,24</sup> ABCB1 alleles TT and CT have been shown to have a statistically significant impact on cardiovascular outcomes compared to the wild-type alleles CC.<sup>21</sup> In one study, individuals with two CYP2C19 loss of function alleles in addition to either an ABCB1 TT or CT genotype demonstrated a hazard ratio of 5.31 for the outcomes of death, myocardial infarction and stroke in comparison to wild-type genotypes.<sup>21</sup> If investigators fail to identify the ABCB1 TT and CT genotypes in those subjects who are otherwise deemed the normal CYP2C19 metabolizers and, therefore, the control group for studies included in this meta-analysis, those hidden genotypes may produce more negative outcomes than would otherwise exist in a control group, skewing the results. Although the possibility those variations in the CYP2C19 and ABCB1 alleles are risk

factors for cardiovascular outcomes independently of clopidogrel use, such a relationship has not been demonstrated.<sup>21</sup>

### *Summary*

Without a doubt, there are myriad factors that a practitioner must consider when evaluating a patient for clopidogrel therapy. There are arguments both for and against genotyping and/or platelet function testing. In addition, the role of drug interactions, gastric emptying, concomitant diseases and compliance/adherence must all be considered in the decision-making process.

The authors of this meta-analysis may have benefited from the opinion and expertise of practitioners in the search and retrieval of trials, as well as their analysis and conclusions. For practitioners, it would be wise to examine the totality of the evidence, and not just the information presented in this meta-analysis.

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