Clopidogrel Pharmacogenetics — Why the Wait?

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More than 3 million people annually in the United States receive prescriptions for the antiplatelet drug clopidogrel after stenting for acute coronary syndrome.[1] Although genetic variants that are present in a minority of patients of European ancestry and that predict variable clopidogrel response were identified more than a decade ago, genotype-guided prescribing is not routine, in part owing to uncertain benefits of this approach as compared with universal use of newer agents. In this issue of the *Journal*, Claassens et al.[2] report the results of the CYP2C19 Genotype-Guided Antiplatelet Therapy in ST-Segment Elevation Myocardial Infarction Patients — Patient Outcome after Primary PCI (POPular Genetics) trial, and these results support genotype-guided therapy for acute coronary syndrome.

Clopidogrel was approved by the Food and Drug Administration (FDA) in 1997 for the reduction of atherosclerotic events. It was known to be a prodrug, but it was not until 2006 that CYP2C19 was identified as the bioactivating enzyme.[3] Common genetic variants in *CYP2C19* affect enzyme function and clopidogrel response. Persons with "normal" CYP2C19 activity who received a typical dose of clopidogrel (75 mg per day) for 7 days had a mean (±SD) 48.9±14.9% reduction in platelet activity (measured as aggregation induced by adenosine diphosphate), whereas heterozygotes for loss-of-function variants (24 to 47% of the population, depending on ancestry) had no change in platelet activity with the same dose.[3] Furthermore, although higher doses of clopidogrel can overcome this enzyme inhibition in heterozygotes, such dose increases are ineffective in "poor metabolizers" — persons who carry two loss-of-function alleles.[4] The frequency of this poor-metabolizer phenotype varies from 2.5% in populations of European ancestry to 14.5% in East Asians and 46.4% in Pacific Islanders.[5]

As clopidogrel use increased, retrospective data consistently showed decreased clopidogrel efficacy in loss-of-function variant carriers with acute coronary syndrome.[6] On the basis of these data, the FDA added a black-box warning in 2010, recommending that practitioners "consider alternative treatment or treatment strategies" in patients with loss-of-function variants, but stopped short of recommending genotype testing. The response from the cardiology community was lukewarm[7] or downright hostile,[8] focusing on the limitations of the data (including variability in effect even within genotyped subgroups, unknown patient adherence, uncertainty around defining high-risk persons, and lack of data from patients with cerebrovascular and peripheral vascular disease) and recommending "careful clinical judgment"[7] rather than pharmacogenetic testing.

The introduction of the newer antiplatelet drugs prasugrel and ticagrelor changed the question. These drugs have no apparent major pharmacogenetic issues, equal or superior efficacy to that of clopidogrel in cohorts that include all *CYP2C19* genotypes, potentially increased bleeding risk, and higher cost than clopidogrel, which became generic in 2012. Can *CYP2C19* genotype testing guide the right treatment choice among these alternatives? In the POPular Genetics trial, patients with acute coronary syndrome were randomly assigned to receive standard treatment (prasugrel or ticagrelor) or genotype-guided treatment (clopidogrel in those without *CYP2C19* loss-of-function variants; standard treatment otherwise). In the genotype-guided group, there was no effect on the incidence of thrombotic events and fewer, albeit minor, bleeding events than in the standard-treatment group. Thus, a genotype-guided strategy led to outcomes that were at least as good as, if not better than, outcomes with the standard approach of prescribing prasugrel or ticagrelor to all patients.

These data reinforce the concept that preprescription genotyping can improve outcomes of antiplatelet therapy. Prescribing prasugrel or ticagrelor to all patients exposes many to increased bleeding risk and, for the time being, increased cost. Prescribing clopidogrel without genotyping exposes variant carriers to blunted responses or lack of response. Genotyping identifies the subgroup without these variants, for

whom clopidogrel is the best and least expensive antiplatelet agent available.

We have known since time immemorial that every drug produces variable effects across populations, and we now understand the genetic basis for some of that variability. So why is *CYP2C19* testing not the standard of care to guide antiplatelet therapy? The logistics of widely implementing pre-prescription genotyping are nontrivial. Whether point-of-care testing with a rapid turnaround time (as in some of the patients in the POPular Genetics trial) or preemptive testing (placing important pharmacogenetic results in electronic records with decision support that is triggered when a target drug is prescribed)[9] is most effective remains to be defined. Costs remain a moving target, and earlier simulations that estimated the cost of incorporating genotype data[10] into prescribing should now be reexamined.

The POPular Genetics trial provides strong support for a genotype-guided approach to clopidogrel prescribing in patients of European ancestry, in whom the contribution of *CYP2C19* variants was first defined; a minority of patients of European ancestry carry loss-of-function variants, and very few are poor metabolizers. The result has even greater implications for parts of the world where these variants are much more common. Professional societies, which increasingly view atherosclerosis as a worldwide epidemic, must now rethink their stance with respect to genotyping to improve the effectiveness of clopidogrel therapy.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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Drug Regulation in the Era of Individualized Therapies

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Kim et al., in a report now published in the *Journal*,[1] describe the discovery, development, and administration of an antisense oligonucleotide (ASO) therapy specifically designed for a single patient with CLN7 neuronal ceroid lipofuscinosis (a form of Batten's disease), a fatal genetic neurodegenerative disorder.[2] In this patient, a known pathogenic point mutation was found to be present in one copy of the gene *MFSD8* (also known as *CLN7*), and a previously undescribed insertion of a retrotransposon was present in the other copy. Retrotransposons are stretches of DNA that are sometimes described as mobile elements; thousands are present in the human genome, and some are capable of moving to a new location — such as the middle of a gene — through a "copy and paste" mechanism. The authors showed that the retrotransposon inser-