When one discusses pharmacogenetics in cardiology practice, it is almost obligatory to discuss clopidogrel. Clopidogrel is an antiplatelet used for acute coronary syndrome (ACS), percutaneous coronary intervention (PCI) with stenting, and as secondary stroke prevention in patients with aspirin allergy, among other indications. Clopidogrel is a prodrug that must be metabolized through the cytochrome P450 system to form the active molecule. Consequently, differences in hepatic metabolism are responsible for considerable variability in clopidogrel response across patients. Indeed, my colleagues and I now have managed dozens of cases where pharmacogenetics has played a central role in the efficacy of clopidogrel.

**Case Study: Clopidogrel failure**

Clopidogrel is commonly prescribed to patients after PCI to prevent clots from forming in and around their new drug-eluting stent (DES). Indeed, this is how we used the antiplatelet in a 56-year-old man after PCI with for coronary artery disease. Three weeks after stent placement, the man returned to our center because he was experiencing cardiac chest pain. He insisted that had been taking clopidogrel exactly as prescribed, along with all of his other medications. Angiography showed that he had developed thrombosis (blood clots) in the stent. Pharmacogenetics testing, however, revealed why he had developed thrombosis: he was a CYP2C19 poor metabolizer.
The clopidogrel molecule, itself, has very little platelet-inhibiting ability. Cytochrome P450 enzymes, mainly CYP2C19 is responsible for “activating” the prodrug, clopidogrel, into one or more active metabolites. Since our patient was a CYP2C19 poor metabolizer, the medicine he was dutifully taking remained in its native state without exerting an anti-platelet effect. Based on the pharmacogenetics testing results, the man was switched to ticagrelor and had no further thrombosis at the stent.

Is it time for routine pharmacogenetics testing before clopidogrel?

In 2010, an expert panel convened by the American College of Cardiology Foundation and the American Heart Association reported on the potential for altered CYP2C19 metabolism to lead to adverse clinical outcomes. The panel’s recommendations led to the FDA’s decision to issue a “black box” warning on clopidogrel regarding CYP2C19 metabolism. Clinicians are supposed to be aware of the ramifications of altered metabolism, yet neither the expert panel nor the FDA recommended routine CYP2C19 polymorphism testing prior to clopidogrel use. Unfortunately, this puts providers in reactive posture. Without pharmacogenetics data on patients, we must assume that all patients can metabolize the drug as most patients will. The obvious weakness in that approach is when a patient, like the one described, fails to benefit from the drug. Polymorphism testing then confirms what we already suspect after the patient experiences an adverse event.

For some clopidogrel indications, pharmacogenetics testing is certainly not needed because the risk of treatment failure is low. However, stent thrombosis is associated with long-term morbidity and possibly fatal outcomes. Moreover, approximately one in five patients undergoing PCI with stenting does not respond to clopidogrel, which may be due to, at least in part, genetic polymorphisms in hepatic metabolism. With these realities in mind, routine (or more common) pharmacogenetics testing becomes a reasonable consideration.

Some institutions have started enacting local screening protocols, despite these recommendations. For example, in June 2012 the University of Florida Health Personalized Medicine Program launched CYP2C19 testing for patients undergoing cardiac catheterization. While testing was initially paid for by grant support, the CYP2C19 testing remains on the post-PCI order set today as the standard of
care for patients undergoing PCI. A pharmacist reviews all genotyping results and contacts the treating physician for patients with the poor or intermediate metabolizer phenotype to recommend alternative antiplatelet therapy in the absence of any contraindications. Moreover, an alert appears in the electronic health record to help guide future decision-making. We anxiously await outcomes data from this program.

**Genotype informs dose selection: Warfarin**

Warfarin has become legend for its drug interactions and its intra- and interpatient variability. Pharmacogenetics testing can be used to predict some of this variability. Specifically, pharmacists involved in cardiology medication therapy management can recommend a safe and effective initial warfarin dosage by knowing a person’s CYP2C9 and VKORC1 genotypes. As a cytochrome P450 enzyme, CYP2C9 affects plasma levels and clearance of warfarin. VKORC1, on the other hand, controls the oxidation state of vitamin K. Genotypic variations in VKORC1 explain differences in warfarin sensitivity. Indeed, the Clinical Pharmacogenetics Implementation Consortium has developed an algorithm to support medication decisions based on CYP2C9/VKORC1 genotyping results. Consequently, genotype-guided warfarin dosing has become the standard of care at several institutions. These efforts have been spearheaded by pharmacy services as part of medication therapy management.

**SLCO1B1 and Statin-induced myopathies**

While statins are an effective means of treating dyslipidemia with few adverse effects, myopathies continue to limit their use in some patients. Statin-induced myopathy ranges from mild muscle ache to serious rhabdomyolysis. To date it has been difficult to predict who might develop myopathy; a standard starting dose is usually prescribed and changed if side effects occur. If the consequence is myalgia, this is a reasonable approach. If the side effect is rhabdomyolysis, however, the result could be fatal. In general, myopathies are more common and more serious when a patient takes a high dosage and/or another medication that interferes with statin metabolism. Researchers and providers have now realized that dose-dependent toxicities and “idiosyncratic” drug reactions can often be traced to an underlying genetic polymorphism related to metabolism or mechanism of action.
Indeed, this appears to be at play in statin-induced myopathy.

Pharmacogenetics is beginning to influence statin therapy decisions. For instance, certain polymorphisms of the \textit{SLCO1B1} gene make patients who carry them more susceptible to statin-induced myopathy, particularly simvastatin (for reasons that are not entirely clear). The association has enough clinical relevance that Vanderbilt University has incorporated \textit{SLCO1B1} genotyping into routine clinical practice. As such, patients with a certain \textit{SLCO1B1} polymorphism are either given a very low dose of a statin drug (likely not simvastatin) or an alternate lipid-lowering regimen. As outcomes data become available, other organizations may follow this model.

**An eye to the future**

Clopidogrel, warfarin, and statins (particularly simvastatin) are examples where pharmacogenetics can influence cardiology practice today. However, several other drugs and drug classes may soon join their ranks. Nascent research is showing that uncommon genetic polymorphisms can have significantly change outcomes with aspirin, beta-blockers, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor blockers, calcium channel blockers, and digoxin. While testing in patients with unusual reactions to these medication classes may not yet be ready for routine use by clinicians and pharmacists, anecdotal reports are increasingly common. Pharmacists are seeing them as frequently as cardiologists are, if not more often.

Consider the experience of pharmacist Olivia Santoso Bentley. Dr. Bentley was discussing pharmacogenetic testing results with a woman during medication therapy management. The pharmacist informed the woman she was a poor metabolizer of metoprolol and at risk for severe beta blockade. The woman had an immediate and profound emotional reaction to this information. The patient explained that just two weeks prior, her mother had had a heart attack and was discharged on metoprolol. Within two days of discharge, she was back in the hospital because “her heart almost stopped,” which no doubt meant severe bradycardia. It was then obvious that her mother shared this polymorphism, but the information came too late to prevent her mother’s adverse event. Fortunately, the patient’s mother survived this ordeal.
While it is too soon to make firm testing and treatment recommendations for most cardiovascular drugs using pharmacogenetics, it is not difficult to track the arc of history in this field. The use of pharmacogenetic testing in cardiology is rapidly expanding and constantly refining. Basic and clinical research should be accelerated by growing and widespread interest and, more specifically, by federal programs such as the Precision Medicine Initiative. It is an exciting time.

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References


