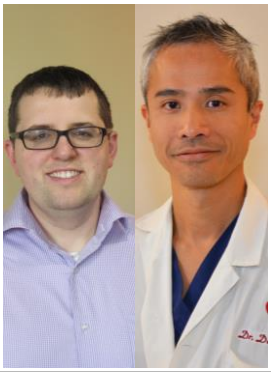
Clinical Chemistry

Clopidogrel and CYP2C19: Pharmacogenetic Testing Ready for Clinical Prime Time?



Article:
M.J. Knauer, E.P. Diamandis, J.-S. Hulot, R.B. Kim, and D.Y.F. So.
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Guests:
Dr. Michael Knauer is a Clinical Chemistry fellow in the Department of Pathology and Laboratory Medicine at the University of Toronto.
Dr. Derek So is a staff cardiologist at the University of Ottawa Heart Institute.

Bob Barrett: This is a podcast from *Clinical Chemistry*, sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I am Bob Barrett.

For patients with acute coronary syndrome who have undergone interventions such as placement of a stent, it has become standard practice to treat them with a combination of aspirin and clopidogrel to prevent subsequent thrombotic events; however, clopidogrel is a drug that requires activation by a liver enzyme, CYP2C19. The *CYP2C19* gene is known to be polymorphic, meaning that there are several variant gene forms. As a result, approximately 3 to 5% of Caucasian and 15 to 20% of Asian populations are poor metabolizers with no CYP2C19 function. This may reduce the efficacy of drugs such as clopidogrel.

CYP2C19 pharmacogenetic testing is available to help guide antiplatelet therapy but there are challenges with implementing this type of guided therapy in clinical practice. The October 2015 issue of *Clinical Chemistry* published a question-and-answer article entitled "Clopidogrel and CYP2C19: Pharmacogenetic Testing Ready for Clinical Prime Time?" That article presented the opinions of three experts who discussed the current state, challenges, and future directions of *CYP2C19* pharmacogenetic testing for clopidogrel therapy.

Today, we have one of the moderators of that article, Dr. Michael Knauer, who is currently a Clinical Chemistry fellow in the Department of Pathology and Laboratory Medicine at the University of Toronto. We also have one of the panelists, Dr. Derek So, a staff cardiologist at the University of Ottawa Heart Institute, an Associate Professor in the Department of Medicine at the University of Ottawa. Dr. So is a leading expert in the field of antiplatelet therapy. Dr. Knauer, let's start with you. What is pharmacogenetics and how does it impact a patient's response to clopidogrel therapy?

Dr. Michael Knauer: Pharmacogenetics is the study of how inherited genetic differences and drug metabolic pathways or targets affect how an individual will respond to a drug in terms of both the therapeutic and adverse affects. Clopidogrel is a prodrug that undergoes a two-step hepatic biotransformation process to an active metabolite by CYP2C19. Clopidogrel active metabolite irreversibly binds with the P2Y12 receptor on platelets and inhibits their activation and aggregation. Many studies have demonstrated that there is substantial inter-individual variation in the antiplatelet response with clopidogrel of which a significant proportion is explained by variation in the plasma concentrations of active metabolite.

The most robust association has been seen with the highly polymorphic enzyme CYP2C19 and the loss of function *2 variant. The growing body of literature has included a genome-wide association study, it has confirmed that CYP2C19 is the major determinant of clopidogrel active metabolite levels and platelet response as well as risk for adverse events.

Bob Barrett: Doctor, are there guidelines for pharmacogenetic testing for clopidogrel and if so, what do they recommend?

Dr. Michael Knauer: Well, in 2010, the U.S. Food and Drug Administration added a boxed warning to clopidogrel labels highlighting the importance of CYP2C19 and their response to clopidogrel, but it made no recommendations on pharmacogenetic testing. Since then, the American College of Cardiology Foundation and the American Heart Association have issued a clinical alert in response to the FDA warning. This expert committee has urged clinicians to be aware of CYP2C19 and that impaired clopidogrel metabolism results in produce platelet inhibition and an increased risk of adverse events; however, the committee did not recommend routine genetic testing prior to clopidogrel initiation but they suggest considering genetic testing in patients at risk for moderate or high risk of poor outcomes.

They also recommend that CYP2C19 poor metabolizers be prescribed alternate antiplatelet therapy instead of clopidogrel. Additional practice guidelines for the Royal Dutch Association for the Advancement of Pharmacy and Pharmacogenetics Working Group, and the Clinical Pharmacogenetics Implementation Consortium (CPIC) have recommended consideration of alternative antiplatelet agents, such as prasugrel or ticagrelor, in patients who are either CYP2C19 intermediate or poor metabolizers.

The CPIC guidelines recommend pharmacogenetic testing in patients with acute coronary syndromes undergoing percutaneous coronary intervention since current evidence does not support routine testing in all patients.

Bob Barrett: Thanks, Dr. Knauer. Now, let's move on to Dr. So. Doctor, in your opinion, who should have pharmacogenetic testing done and what are some of the controversies surrounding pharmacogenetic testing for gunning clopidogrel therapy?

Dr. Derek So: Now, it's actually a very loaded question in that the original recommendation that the FDA put forward in terms of its box warning really did not state which of these groups or patients we would apply this to, but I think when we look at the literature and look at multiple studies that were done, and looking at the true med analysis that were actually completed in this population, those that are actually at highest risk are those patients that have acute coronary syndromes and especially those that have undergone coronary stenting. And so, if we go with the highest risk group, that would be the ones we would definitely put consideration into.

As Dr. Knauer had also stated, one of the things that the ACCHA quite clearly stated in their guidelines is that presently, they don't suggest routine screening in all patients. So I think putting all that together, the groups that we should really consider screening for would be patients that, number one, are on clopidogrel and actually end up with a recurring acute coronary syndrome because certainly, by doing the testing, it would give us more understanding in terms of potential mechanisms of why patients got into trouble.

The other group of course that we should put consideration would be patients that might have trouble initially paying for the more expensive novel drugs that are more potent inhibitors of the P2Y12 receptor but if we give these patients upfront genetic testing and find out they're poor metabolizers, we can potentially select the right drug for the right patients so that upfront, there might be the cost of the genetic testing but later on, what it would provide is that it would provide cost saving because clopidogrel is now generic and it would actually end up that patients would pay less money on a long-term basis.

Bob Barrett: Well, once testing is performed, what should be done with the results?

Dr. Derek So: Yes. So, once testing is done, right now the most common variants that we'll be looking at are the *CYP2C19*3* and **2* variants so that if patients are homozygous carriers of two loss-of-function alleles, for sure those patients should be placed on a more potent P2Y12 agent and the two that are currently available in the market would be ticagrelor and prasugrel.

There is some controversy in terms of patients that are heterozygous carriers because for those patients, there is quite a bit of variability in terms of how well they're actually inhibited by clopidogrel but certainly, if we go by the Pharmacogenetics Implementation Consortium suggestion, even heterozygous patients should be put on a more potent drug and certainly, with a number of studies, that's actually been shown to be the better protective effect by having even heterozygous carriers be treated with the more potent drugs.

Bob Barrett: Finally, doctor, what do you think are the current obstacles preventing implementation of guidelines into practice at this point?

Dr. Derek So: In regards to the obstacles, part of it also surrounds the controversy. First and foremost would be cost. I think right now, genetic testing is certainly getting cheaper. I think it's one consideration that as the cost comes down, more and more people would be able to afford genetic testing. The other big concept in terms of cost of course would be the difference between the pricing of the generic clopidogrel as opposed to ticagrelor so there has to be a consideration in terms of where exactly the cost between paying for the more expensive drug versus upfront paying for the genetic testing.

I think another obstacle in terms of all this is that right now we still don't have definitive evidence that prospectively testing and then subsequently changing therapy is going to actually alter clinical outcomes. I think from a clinical cardiology point of view, that's going to be a very important aspect, is to actually be able to prove that prospectively testing patients and then changing therapy, we're going to overall lower morbidity and mortality for all patients.

And so there's actually a number of large studies coming down the pipeline, one of which is the Tailor-PCI, On which our group is working with a number of centers around the world and the study is led by the Mayo Clinic and hopefully, this is going to be the world's biggest study where we enroll 5,000 patients and that's going to give us more insights in terms of whether this type of strategy is going to work. Along with those lines is once we have these bigger studies, that potentially is going to help change guidelines and by having alteration in guidelines, that of course is going to help in terms of moving physicians to actually applying this into everyday practice.

And then I think the last bit in terms of obstacles and controversy is that one of the things we have to remember is that although genetics plays a big part in terms of impaired response to the clopidogrel, there other risk factors

that also impair response to clopidogrel, an example would be diabetes, so that by doing genetic testing alone, we account for a large part of that variability but we're not able to account for all causes of clopidogrel non-responsiveness.

I think we just need to be very careful moving forward to say that this alone is not going to be able to protect all patients, that we still have a lot to go in terms of understanding other potential mechanisms that predispose patients to clopidogrel non-responsiveness and hopefully, in the future, by applying a combination of genetics and other novel risk factors, we're able to then better personalize therapy for patients that are receiving these P2Y12 inhibitors.

Bob Barrett: That was Dr. Derek So, a staff cardiologist at the University of Ottawa Heart Institute and Associate Professor in the Department of Medicine at the University of Ottawa. He was joined by Dr. Michael Knauer, a Clinical Chemistry fellow in the Department of Pathology and Laboratory Medicine at the University of Toronto. They've been our guests in this podcast from *Clinical Chemistry*. I'm Bob Barrett. Thanks for listening.