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Pharmacogenetic Analysis of *CYP2C19* for Clopidogrel: Ready for Prime Time

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Guest: Dr. Joshua Miller, a post-doctoral clinical chemistry fellow at the Mayo Clinic in Rochester, Minnesota.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett. Clopidogrel, sold under the brand name Plavix, is an oral antiplatelet prodrug that minimizes the risk of stroke or other adverse cardiac events in patients at high risk, such as those with acute coronary syndrome or those who have undergone percutaneous coronary intervention.

In 2010, the United States Food and Drug Administration [FDA] added a boxed warning to clopidogrel's label advising healthcare professionals to consider alternative therapies for patients who are poor metabolizers of the drug as they are unable to convert clopidogrel to its active form. Despite this boxed warning, the American Heart Association [AHA] and the American College of Cardiology were initially reluctant to recommend pharmacogenetic screening to identify poor metabolizers. However, the American Heart Association has changed their position following the publication of several studies supporting a precision medicine approach, improvements in genetic testing, and Medicare coverage of medically necessary *CYP2C19* testing beginning in 2021.

A new scientific statement from the AHA published in 2024 now recommends pharmacogenetic screening to help physicians select the appropriate antiplatelet therapy for their patients. Appearing in the March 2025 issue of *Clinical Chemistry* is a News & Views article summarizing this new AHA statement, written by Dr. Joshua Miller, a postdoctoral clinical chemistry fellow at the Mayo Clinic in Rochester, Minnesota. Dr. Miller is our guest in this podcast.

So, Doctor, let's get the basics first, why is clopidogrel clinically useful? How does it work and why would the FDA add the boxed warning in the first place?

Joshua Miller: Certainly, Bob. That's a great question. So, this drug, clopidogrel, inhibits platelet aggregation and so by preventing platelet aggregation, it prevents blood clots from forming. And this is useful in patients who are high risk at forming these clots in the arteries. So, namely, this has been shown to reduce the risk of myocardial infarction and strokes in

those with acute coronary syndrome, peripheral artery disease, those who have recently experienced a myocardial infarction or those who have undergone percutaneous coronary intervention, otherwise known as PCI, or coronary artery bypass graft surgery, otherwise known as CABG.

However, clopidogrel is actually a prodrug. Meaning that the form of the drug administered is not active and actually doesn't cause the desired therapeutic effect of preventing these clots from forming. Instead, clopidogrel requires endogenous oxidation to a metabolite that actually inhibits platelet function. So, this metabolite is known as R130964, which can irreversibly bind and inhibit a platelet chemoreceptor known as $P2Y_{12}$. So, by inhibiting this ADP chemoreceptor, it prevents platelets from aggregating together. Although there are several enzymes which can perform this oxidation to this active metabolite, the most salient one is cytochrome P450 2C19, also known as CYP2C19.

And so, patients who exhibit loss of function alleles with the *CYP2C19* gene, they have a reduced capability to produce this R130964 metabolite leading to a lack of therapeutic effect. So, this led to the FDA cautioning providers to consider an alternative therapy if their patients have a loss of function allele with *CYP2C19*. The most common loss of function alleles are *2 and *3. These are both guanine to adenine point mutations at positions 681 and 636 in the coding region, respectively, of DNA for this gene.

Bob Barrett: If the FDA added a warning in 2010, why were professional organizations like the American Heart Association and the American College of Cardiology hesitant to screen patients for loss of function *CYP2C19* genetic variants prior to prescribing platelet inhibitors?

Joshua Miller: Great question, Bob. So, you can imagine if this problem exists, right, and the FDA added this warning label, why are we just now having this update in 2024 from the American Heart Association? So, first and foremost, even if this problem is known, there needs to be demonstrable clinical utility showing that pharmacogenic screening actually leads to better outcomes, and this was lacking around 2010. Namely, there were no prospective random clinical trials at the time that showed the use of genetic screening to guide antiplatelet therapy actually led to improved outcomes. Furthermore, at the time, in around 2010, the turnaround time required for those testing to be practical just wasn't available.

So, you can imagine that without a same-day turnaround time, a provider may be hesitant to order genotyping if it means that they have to wait up to a week for a result. So,

at that length of time, patients will have already left the clinic by the time the results are received by the provider. And so, if there was a change in therapy that was required, providers would have to communicate this to the patient remotely, which could lead to confusion or anxiety and the patient may not understand why there's a need for new medication.

So, without this data to show that this therapy leads to improved outcomes and this long turnaround time, there is no uniformly established method to evaluate a patient's response to clopidogrel.

In essence, it was known this loss of function, the presence of these loss of function alleles may not achieve the desired therapeutic outcome when given clopidogrel. There just wasn't the information or infrastructure at the time to support the wide adoption of pharmacogenetic screening prior to choosing an antiplatelet therapy.

Bob Barrett: So, is clopidogrel the only anti platelet drug available, and if not, why not just universally prescribe those other drugs instead?

Joshua Miller: That's an excellent point. You can imagine if there's alternative therapies that don't have this loss of function allele problem, why not just prescribe those instead? And there are alternatives to clopidogrel, such as prasugrel or ticagrelor. However, these medications are more potent inhibitors of $P2Y_{12}$. Again, that's the platelet surface ADP chemoreceptor that's responsible for platelet aggregation. And there's a fine balance you have to maintain when choosing antiplatelet therapy. If you have too weak of an effect, as in those patients who have loss of function alleles for *CYP2C19*, that means an undesired clot can form. But on the other end, a stronger than desired effect could lead to an inability to clot effectively at all, and this inability of the clot could cause massive blood loss if there are challenges to hemostasis.

So, because these other alternative drugs, such as prasugrel or ticagrelor, are more potent inhibitors, a blanket universal prescription of these drugs could lead to unnecessary higher bleeding risk in patients. In addition, clopidogrel is actually a desirable drug to prescribe. A generic equivalent is available in the United States, and it only needs to be taken once daily, leading to higher compliance.

Bob Barrett: Doctor, what's changed since 2010 to persuade the American Heart Association to now recommend screening for *CYP2C19* genetic variants?

Joshua Miller: So what's really changed in the last decade or so, Bob, is that there's now an abundance of clinical evidence to support the

use of screening for these, you know, genotypes prior to choosing an antiplatelet therapy. So, there's been…some of the most important clinical trials of interest is the 2011 Individual Applications of Clopidogrel after Percutaneous Coronary Intervention, also known as the IAC PCI. This was a randomized clinical trial from China that followed two cohorts of patients after receiving percutaneous coronary intervention and stent implantation.

One cohort included 301 individuals who received precision medicine, i.e., they received genetic screening for the *CYP2C19* genotype and would subsequently have a modified antiplatelet therapy. So, they had personalized medicine. The other cohort of 299 patients all received the same conventional clopidogrel based therapy. So, we have these two cohorts, right? One has the precision medicine, genetic guided therapy approach, and one followed the traditional no genetic screening for *CYP2C19*.

So, after about a 180-day follow up, there was a statistically significant reduction in major adverse cardiovascular events in the group receiving genetic guided therapy. So the right we have some data showing that if you screen for these loss of function alleles prior to choosing antiplatelet therapy and then change therapy accordingly, there is a reduction in adverse cardiovascular events. Another really salient trial is the Tailored Antiplatelet Therapy Following PCI, or the TAILOR PCI. This was a larger multicenter study, which included over 2,500 patients in both the genetic guided and conventional therapy cohort. So, this multinational, multicenter study demonstrated that there was actually a 34% reduction in cardiovascular events when assessed as time to the first event and a 40% reduction in cumulative ischemic events per patient in the genetic guided group. So again, the TAILOR PCI study is also showing that there is a reduction in major adverse cardiovascular events when you screen for loss of function alleles prior to choosing antiplatelet therapy and adjusting accordingly to other alternatives for antiplatelet drugs.

So, alongside this new evidence, remember we discussed earlier how the turnaround time is a critical aspect of this, right? You don't want to order a test that's going to take a week to get results back from and then you lose the patient to follow up. So, we now have point-of-care testing with rapid turnaround time, which allows providers to easily and quickly choose the appropriate therapy in near real time, and finally, medically necessary *CYP2C19* genetic testing has been covered by Medicare since 2021. And so, this further lowers the cost barrier for pharmacogenomic screening.

Bob Barrett: So, how do point-of-care tests compare to traditional genotyping methods? Are there any limitations to this methodology?

Joshua Miller: Sure. So, firstly, genomic DNA for point-of-care testing is typically acquired via a buccal swab. So, that's like a swab to your inner cheek, compared to EDTA whole blood, which is the preferred specimen for traditional genotyping methods. Although in recent years, most labs accept saliva samples for sequencing and genotyping.

So after DNA extraction, PCR amplification of targeted DNA sequences are what are detecting the single nucleotide polymorphisms corresponding to the *2 and *3 alleles. And again, these *2 and *3 alleles are the most common loss of function alleles for *CYP2C19*.

And detecting the presence of these *2 and *3 loss of function alleles can help determine whether or not the patient is going to be a poor metabolizer of clopidogrel. The presence of the *17 allele, which is actually a gain of function allele, is also detected in point-of-care testing for this drug. However, this method does not detect every loss of function allele that exists. For example, a more traditional laboratory-based instrument that can detect *CYP2C19* single nucleotide polymorphisms can also detect the *4, the *7, and *8 alleles, among others. Regardless, because this assay amplifies targeted sequences of DNA that can detect single nucleotide polymorphisms rather than truly sequencing the entire gene, other variants of significance cannot be identified using this method. So novel or unexpected variants can't be identified, nor can structural variations like insertions or deletions.

And so, providers should be aware of these limitations when they're performing point of care testing. It's really only looking for targeted DNA sequences of interest rather than a true sequencing in the entire gene. So you're not going to be able to detect every mutation of interest. However, despite these limitations, the rapid turnaround time for point-of-care testing is really its biggest boon. Again, providers can order this point-of-care testing, they can receive a result in approximately an hour, and then decide which antiplatelet therapy to use, you know, all before the patient leaves the hospital, which is incredible, where you no longer have to worry about the results coming back in a week, and then having to, you know, discuss the changes in therapy once the patient has left the clinic.

Bob Barrett: Doctor, given all of this information presented, could you succinctly summarize the new suggestions from the AHA?

Joshua Miller: Absolutely, Bob. So the recommendations from the American Heart Association is quite simple. Patients with acute

coronary syndromes should be screened for *CYP2C19* loss of function alleles prior to prescription of a $P2Y_{12}$ inhibitor. Patients who are *carriers* of loss of function alleles should be prescribed another drug like ticagrelor or prasugrel, while non-carriers are prescribed clopidogrel. This minimizes the risk of ischemic events while balancing bleeding complications.

Bob Barrett: Well, finally, Dr. Miller, what barriers, if any, are there to adopting genetic guided antiplatelet therapy? Is there still provider hesitancy to use genetic guided therapy?

Joshua Miller: That's an excellent question, Bob. Just because this new statement is out there and we have all this data, it doesn't mean that providers will adopt, there will be a universal adoption, or an instant adoption by all providers. So, for example, the National Institute for Health and Care Excellence from Britain, also known as NICE, they published similar guidelines to the American Heart Association last year related to stroke and transient ischemic attack. And they suggest implementing testing in a stepwise manner while laboratory and point-of-care testing capacity for this genetic testing improves. This transition cannot occur overnight, right? It takes time for healthcare systems to not only purchase this equipment, but also develop the infrastructure to be able to interpret this information in a real time manner, you know, push it to their digital medical records and so on.

So, you know, it's important that this point-of-care testing integration into the electronic medical record [EMR] is a logistical consideration, that's very key here because with main laboratory testing or traditional laboratory testing, integration to the EMR is more straightforward. Information integration into the electronic medical record is a challenge with point of care in general. So it's going to take time for clinics to implement this new workflow. In addition, provider perception and utilization of this information is key. For example, in the TAILOR PCI study, that was the larger multi scenario study I mentioned earlier, 20% of patients in the genetic guided group with loss of function alleles who experience ischemic events were paradoxically switched to clopidogrel or aspirin. So they, they were known to have loss of function alleles and were actually switched back to clopidogrel after experiencing an ischemic event. So not only must providers be willing to adopt a persistent medicine approach, but provider education is also important to ensure proper utilization of pharmacogenetic information.

Finally, while *CYP2C19* pharmacogenomic point-of-care devices, they have received 510(k) clearance by the FDA, they are high complexity test. This means that these point-of-care testing can only be run in labs that have a certificate of compliance or a certificate of accreditation and these

require additional expertise in personnel training compared to labs which only hold a certificate of waiver, and this ultimately limits which hospitals and clinics can adopt this testing in-house. So sort of the, the final to providers here is that one, they need to be able to properly interpret this information, there needs to be a slow adoption of this technology into clinics, and then finally, from a high complexity, you know, regulatory role, it limits which hospitals and clinics can adopt this testing.

Bob Barrett: That was Dr. Joshua Miller from the Mayo Clinic in Rochester, Minnesota. He authored a News & Views article in the March 2025 issue of *Clinical Chemistry*, summarizing the new AHA statement promoting genetic testing to identify clopidogrel poor metabolizers.

I'm Bob Barrett. Thanks for listening.