Vanderbilt now also routinely gene testing for clopidogrel metabolizer status

OCTOBER 21, 2010 | Sue Hughes

Nashville, TN - Vanderbilt University Medical Center has now joined the Scripps Clinic in starting to routinely test for variations in the *2CYP19* gene, which controls the conversion of **clopidogrel** into its active metabolite, in patients before they receive antiplatelet therapy [**1**].

But whereas Scripps is testing patients just before they receive a stent, Vanderbilt is going much further and aims to test all patients who have a high likelihood of receiving antiplatelet therapy sometime in the future. The results would then be incorporated into their electronic medical records and would therefore be available to guide therapy decisions when the time comes for antiplatelet therapy to be started,

And this is just the first step in a much larger scheme in which Vanderbilt aims to test all their patients for many single nucleotide polymorphisms (SNPs), which can be used in different areas of medicine and will be kept in their notes for future use.

Different treatment strategies recommended

Dr John McPherson, an interventional cardiologist at Vanderbilt, told heartwire that this was a hospitalwide initiative for all departments, but the clopidogrel test is leading the way as a pilot project. Any practicing physician at the hospital will be able to order the genetic test for any inpatient or outpatient on clopidogrel or any patient with a high likelihood of needing an antiplatelet agent in the future—that is, most patients with heart disease. The test will give information on the wild-type *1 allele, *2 and *3 loss-of-function alleles, and the *17 gain-of-function allele. It is then up to the individual clinician to decide which treatment to give, although some recommendations will be provided. McPherson gave the example of a patient who is found to be homozygous for the loss-of-function alleles: "We know they are at a very high risk of being a poor metabolizer and having a bad outcome on clopidogrel, so we would recommend **prasugrel** in this case in the absence of contraindications. If there are contraindications to prasugrel then an increased dose (150 mg) of clopidogrel will be recommended. When **ticagrelor** becomes available that will be another option for those patients."

He says for patients with the wild-type genes the test will be a reassurance that clopidogrel is probably working well for them. "For patients heterozygous for a loss-of-function allele, the outcomes data are a little less clear, but we may prompt clinicians to use an increased dose of clopidogrel or monitor the platelet function in these cases."

Used in outpatient setting

McPherson believes the real utility of this strategy will be in the outpatient setting. "They can have the test well in advance of needing an antiplatelet agent and then when the time comes for them to have a stent, we have advance notice of whether they need a different therapeutic option to regular-dose clopidogrel."

Asked how he would respond to skeptics of this approach, who say it is too early to use such genetic testing, McPherson said: "While this test doesn't explain all the platelet variability in response to clopidogrel, it does explain some of it and therefore is an important tool. I don't think it is premature. Okay, we don't have all the outcomes data we need to make treatment decisions, but we do have access to this one piece of information on how well different patients are likely to metabolize clopidogrel into its active form. So we should use it.

"We know that *2 homozygotes will have a worse outcome on regular clopidogrel, and although this probably applies only to about 3% of the population, it is probably worth doing just to pick these patients

up. At the same time, we get some information on everyone else that we can use to guide therapy. And we will be following these patients and tracking outcomes, so this initiative also has a research purpose, although we consider it primarily as a quality-improvement initiative."

On some other gene tests in cardiology that may be included in the overall strategy in future, McPherson suggested that these may include one to detect the predisposal to myalgia with statins.

Vanderbilt is the first medical center in the country to deliver this form of "decision-supported, personalized" drug therapy, said **Dr Jeff Balser** (vice chancellor for health affairs and dean of the school of medicine). The new program is known as **Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment** (PREDICT), according to a Vanderbilt press release. It was developed by a team of experts led by **Drs Dan Roden**, **Jim Jirjis**, and **Jill Pulley**, all at Vanderbilt, and it is hoped that the scheme may substantially decrease the cost of care for patients by reducing the incidence of cardiac events.

Scripps now doing point-of-care tests

Dr Eric Topol, who pioneered the use of the clopidogrel gene test at the Scripps Clinic, applauds the Vanderbilt approach. "The fact that Vanderbilt is now doing this is a pretty significant development. It is the pharmacogenomic capital of the US. So now we have another major academic center routinely genetically testing their stent patients. That is a real step forward." And he describes the Vanderbilt strategy of testing all their patients and having the pharmacogenomic data in their records as "way ahead of the curve."

Topol said he would like to see that happening at Scripps too, someday. But at the present time, they are routinely conducting the *CYP2C19* gene test in patients who are actually undergoing stenting. He says it is this group where there is the best evidence that carriers of the *CYP2C19* loss-of-function alleles are at increased risk. "The reason that systematic *CYP2C19* variant assessment is being done at Scripps for stented patients is that it provides some important information about risk that is actionable, but this does not represent the complete story. Stent thrombosis, while infrequent, is potentially fatal. The evidence that carriers of *CYP2C19* loss-of-function alleles are at increased risk of stent thrombosis is incontrovertible. There will be more gene variants validated in the future, but at this juncture, with multiple alternative treatments (double-dose clopidogrel, prasugrel, and ticagrelor soon to be available), it is well suited for implementation to routine practice."

In a new development, Scripps is now starting to perform these tests in a "point-of-care" setting. "We are now starting to do these gene tests in the cath lab, with the results analyzed in-house and available in about 20 minutes. It can be set up in any hospital and will cost only about $1 per test," Topol reports.

Source

1. Snyder B. Patient genotypes guide drug therapy in new VU program. *Reporter* [Vanderbilt University Medical Center's weekly newspaper], September 23, 2010. Available here.

Related links

- New PLATO data: No need for gene testing in PCI patients
  [*Acute Coronary Syndromes* > *Acute coronary syndromes*; Aug 29, 2010]
- CURE ACTIVE: No effect of loss-of-function clopidogrel gene on event rates in ACS or AF
  [*Acute Coronary Syndromes* > *Acute coronary syndromes*; Aug 29, 2010]
- Platelet assay betters clopidogrel gene testing: Study published
  [*Interventional/Surgery* > *Interventional/Surgery*; Aug 11, 2010]
- New meta-analysis: *CYP2C19*2* carriers at higher risks of events on clopidogrel
  [*Interventional/Surgery* > *Interventional/Surgery*; Jul 05, 2010]

- No routine genetic or platelet-function testing for clopidogrel nonresponsiveness: ACC, AHA
[*Acute Coronary Syndromes* > *Acute coronary syndromes*; Jun 30, 2010]
- Skip the clopidogrel gene test, just assay the platelets, new data suggest
[*Interventional/Surgery* > *Interventional/Surgery*; May 28, 2010]
- Personalizing antiplatelet therapy: Could platelet-function tests help?
[*Thrombosis* > *Thrombosis risk*; May 14, 2010]
- Cardiologists voice concern on FDA clopidogrel warning
[*Interventional/Surgery* > *Interventional/Surgery*; Mar 16, 2010]
- Clopidogrel receives boxed warning for reduced benefit in poor metabolizers
[*heartwire* > *Medscape Medical News*; Mar 12, 2010]
- Scripps starts routine genetic testing for clopidogrel responsiveness
[*Interventional/Surgery* > *Interventional/Surgery*; Oct 14, 2009]
- CHARISMA Genomics Substudy links loss-of-function allele and bleeding
[*Acute Coronary Syndromes* > *Acute coronary syndromes*; Sep 28, 2009]
- First genomewide data on gene variant affecting clopidogrel response
[*Acute Coronary Syndromes* > *Acute coronary syndromes*; Aug 25, 2009]
- Genotyping info now in US clopidogrel label
[*Thrombosis Risk* > *Thrombosis risk*; May 21, 2009]
- Evidence growing for personalized antiplatelet therapy
[*Interventional/Surgery* > *Interventional/Surgery*; Mar 28, 2009]
- Clopidogrel gene mutation linked to higher rate of stent thrombosis
[*Acute Coronary Syndromes* > *Acute coronary syndromes*; Feb 12, 2009]
- Genetic variant linked with worse clinical outcomes in MI patients treated with clopidogrel
[*Acute Coronary Syndromes* > *Acute coronary syndromes*; Dec 24, 2008]