

Program Genotypes All Cardiac Cath Patients

BY MITCHEL L. ZOLER

FROM THE ANNUAL SCIENTIFIC SESSIONS OF THE AMERICAN HEART ASSOCIATION

CHICAGO – Last fall, physicians at Vanderbilt University Medical Center began routinely testing all patients who were scheduled for coronary catheterization with a broad genotyping screen that – among other things – would identify whether they had a problem activating clopidogrel.

By mid-November, the program had tested about 300 patients, including 10 found to have a poor-metabolizer genotype in the hepatic-enzyme gene CYP2C19 that would likely blunt the efficacy of a conventional clopidogrel dose. Many of the 10 patients received a dou-

bled dose to compensate, whereas others who weren't aged 75 or older received the pricier, alternative agent prasugrel.

This experience marked the first phase of a new Vanderbilt program that will expand over time to include other patients in line to receive a drug with a pharmacogenetic dimension, Dr. Dan M. Roden said at the meeting.

The genotyping program will soon expand to include patients who are scheduled for knee- or hip-replacement surgery, anticipating their need to start on warfarin. Genotype data can also help physicians select the best dosage for starting a warfarin regimen, said Dr. Roden, a cardiologist and assistant vice chancellor for personalized medicine at Vanderbilt in Nashville, Tenn.

Subsequent expansion plans are not yet set, but other candidates for genotyping include patients who are either already on or at an increased risk for soon starting tamoxifen, abacavir, azathioprine, 6-mercaptopurine, codeine, or "virtually any antidepressant or most antipsychotics," Dr. Roden said in an interview.

"In the long perspective, every 50-year-old" is a good bet to eventually

receive at least one drug for which a dosage adjustment based on genotype is warranted, but – stopping short of such global use right now – the Vanderbilt program will instead gradually phase in new groups of patients to the offer of genotyping.

The program identified 10 patients whose genotype would likely blunt the efficacy of clopidogrel.

DR. RODEN

ought to work is, a physician prescribes a drug and the electronic system recognizes [that] the drug has a genetic element and goes into the patient's record and finds the genotype information" to decide whether to flash a screen alert about the patient's genotype and the implications.

The program, known as PREDICT (Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment) launched on Sept. 15.

It uses a genotyping panel sold on the U.S. market by Illumina that screens for 184 different genetic polymorphisms in 34 genes that affect the absorption, distribution, metabolism, or excretion of various drugs. Test results get posted into the record within a day of specimen collection.

So far, Vanderbilt itself has completely funded the program, which involved a year of planning and "a huge amount of money," said Dr. Roden, adding that the program is the first of its kind worldwide.

PREDICT is expected to improve patient outcomes, and its developers hope to eventually convince payers to cover the cost.

Dr. Roden reported that he is or has been a consultant to Merck, Novartis, Sanofi-Aventis, Daiichi Sankyo, and Astellas and has received royalties from Clinical Data.



Scyble Van Cleve, right, is the first patient at Vanderbilt to benefit from a program that helps physicians like Dr. John McPherson choose the best drug and dose.

COURTESY SUSAN URMY

High-Dose Clopidogrel Ineffective in Nonresponsive Patients

BY BRUCE JANCIN

FROM THE ANNUAL SCIENTIFIC SESSIONS OF THE AMERICAN HEART ASSOCIATION

CHICAGO – Six months of high-dose clopidogrel were no better than standard-dose clopidogrel for preventing cardiovascular events in patients with high residual platelet reactivity after percutaneous coronary intervention in the GRAVITAS trial.

This large randomized study does not support the common practice of doubling the standard 75-mg/day dosing of clopidogrel as a default strategy in patients who are nonresponsive to the drug, Dr. Matthew J. Price said at the meeting.

"The high dose of clopidogrel doesn't appear to improve outcomes, so alternative treatment strategies should be tested," according to Dr. Price, chair of GRAVITAS (Gauging Responsiveness With a VerifyNow Assay—Impact on Thrombosis and Safety) and director of the cardiac catheterization laboratory at the Scripps Clinic, La Jolla, Calif.

The GRAVITAS trial included 2,214 patients who displayed high residual platelet reactivity on the Accumetrics VerifyNow P2Y12 test 12-24 hours after undergoing elective or urgent PCI with

stenting. They were randomized to 6 months of clopidogrel (Plavix) at the standard dose of 75 mg daily or to a 600-mg loading dose followed by high-dose therapy at 150 mg/day.

The primary study end point of cardiovascular death, nonfatal MI, or stent thrombosis at 6 months occurred in 2.3% of patients in each study arm. On the plus side, at least there was no significant difference in moderate to severe GUSTO (Global Use of Strategies to Open Oc-



A high dose isn't better than the standard dose, so 'alternative treatment strategies should be tested.'

DR. PRICE

cluded Coronary Arteries) bleeding, which occurred in 1.4% of patients on high-dose clopidogrel and 2.3% on standard-dose therapy, he noted.

High-dose therapy provided what the cardiologist deemed a "modest" but statistically significant pharmacodynamic effect in the form of an absolute 22% re-

duction in persistently high platelet reactivity at 30 days, compared with the 62% rate in the standard-dose arm.

Discussant Dr. Jessica L. Mega said one possible explanation for the neutral results in GRAVITAS is that high residual platelet reactivity is a risk marker but not a modifiable risk factor. It's not



Perhaps an even higher dose of clopidogrel, or a more powerful agent, would be beneficial for these patients.

DR. MEGA

known yet whether that's true.

Another possibility worthy of future study is that a tailored approach to antiplatelet therapy would be beneficial in patients with high residual reactivity if an even higher dose of clopidogrel or an alternative, more potent agent were to be employed, added Dr. Mega of Brigham and Women's Hospital, Boston.

The GRAVITAS trial was sponsored by Accumetrics. Dr. Price said that he serves as a consultant to the company as well

as to Sanofi-Aventis and Bristol-Myers Squibb, which provided the clopidogrel used in the study. Dr. Mega has received clinical research grants through the TIMI Study Group from Accumetrics and other companies, and has served as a consultant to Sanofi-Aventis and Bristol-Myers Squibb.

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