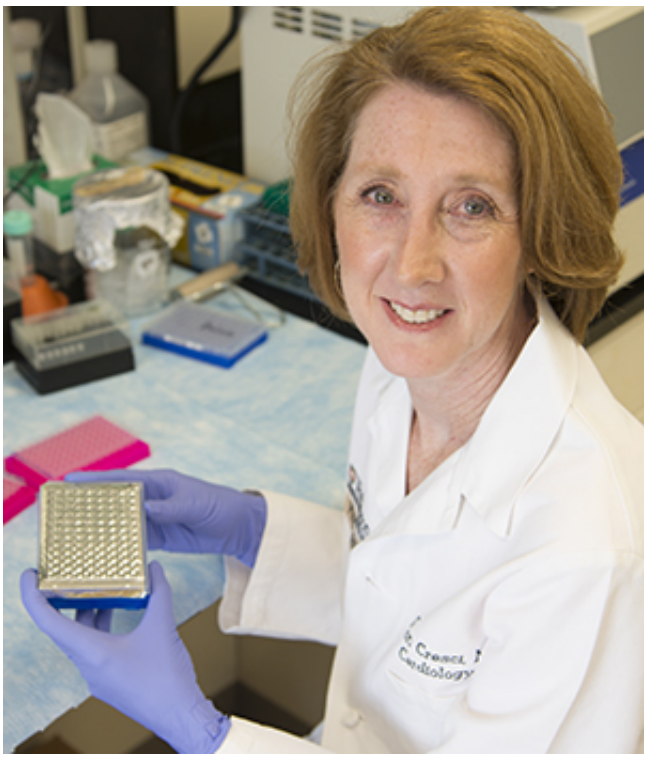
Genetic discovery shows racial differences a factor in mortality in heart attack patients on anti-clotting drug

June 18 2014, by Kristina Sauerwein



Cardiologist Sharon Cresci, MD, led a genetic study showing that racial differences account for a higher risk of mortality in some patients taking clopidogrel (Plavix) after a heart attack. Credit: Robert Boston

(Medical Xpress)—Researchers have identified the first genetic variations linked to race that begin to explain a higher risk of death

among some African American and Caucasian patients taking the anti-clotting drug clopidogrel (Plavix) after a heart attack.

These variants increased patients' risk of dying in the year following a first heart attack, but they appeared to do so for different reasons depending on race, according to a study at Washington University School of Medicine in St. Louis.

In particular, the team found that two DNA variants common in African Americans were associated with an increased risk of both bleeding and death. In Caucasians, a different variant was linked to additional heart attacks and a higher risk of death.

The research is published June 17 in the American Heart Association journal *Circulation: Cardiovascular Genetics.*

The variations influence the way people metabolize clopidogrel and can alter its effectiveness. The blood-thinning drug commonly is prescribed after a heart attack to reduce the likelihood of another heart attack or a stroke.

"The research is provocative," said the study's first author, cardiologist Sharon Cresci, MD, assistant professor of medicine and of genetics. "Knowing about potential genetic differences based on race can help physicians tailor drugs to patients based on their genetic makeup."

Clopidogrel is metabolized in the liver, where it is turned into its active form via a group of enzymes called cytochrome P450, or CYP for short. Although clopidogrel is effective in many patients, earlier studies determined that some people metabolize the drug better than others.

Indeed, in 2010, the Food and Drug Administration added a "black box" warning to labels of clopidogrel after research that primarily involved

Caucasians showed that people with a particular CYP genetic variant metabolized the drug poorly, which reduced the amount of the drug circulating in the blood. These patients had a higher risk of heart attack and stroke.

Additional studies showed that other CYP gene variants are linked to the rapid metabolism of clopidogrel and that patients with those variants had a higher risk of bleeding.

But it has not been clear until now that the effects of these particular gene variations can vary by race in patients taking clopidogrel after a heart attack.

For the study, the researchers analyzed CYP variants among 2,062 Caucasians and 670 African Americans who suffered heart attacks. Nearly 80 percent of the Caucasians and 65 percent of the African Americans were prescribed clopidogrel. The patients were enrolled in a major study known as TRIUMPH (Translational Research Investigating Underlying disparities in acute Myocardial infarction Patients' Health) conducted from 2005 to 2008 at 24 U.S. hospitals, including Barnes-Jewish Hospital in St. Louis.

Among patients taking clopidogrel, the one-year mortality rate for African Americans was 7.2 percent, compared with 3.6 percent for Caucasians.

Caucasians who carried the CYP2C19*2 variant, which has been linked to poor metabolism of the drug, had a higher rate of repeat heart attacks and death. The higher rate of heart attacks is consistent with the slower metabolism of clopidogrel.

However, among African Americans treated with clopidogrel, the CYP2C19*2 variant was not associated with a higher rate of death.

Rather, African Americans had higher rates of bleeding and death if they carried either of two other variants: CYP1A2*1C or CYP2C19*17, the latter of which has been associated with the rapid metabolism of clopidogrel. Among Caucasians on clopidogrel, neither variant increased the risk of death.

"This is very novel information that begs for more research," said cardiologist Richard G. Bach, MD, the study's senior author and an associate professor of medicine at Washington University.

Although genetic testing is available to identify CYP variants in a patient's DNA, these tests generally are not widely used by cardiologists. Results of the current study suggest this practice may need to be reconsidered.

"This research is an important addition to the field because previous studies looking at CYP gene variants and their effects on risks of repeat heart attacks, bleeding and death have included predominantly Caucasian patients of European ancestry," Cresci noted. "There is almost no data, until now, about these variants in African Americans."

Research examining how genetic variants alter the effectiveness of clopidogrel remains somewhat controversial, Bach said. Many physicians feel that before they can tailor medical therapy for heart attack patients, more data is needed to prove there is a clear link between genetic variants and negative health consequences and that tailoring therapy will improve patients' outcomes, he explained.

His hope is that additional research would provide more definitive conclusions to help physicians choose the best medications for patients after a heart attack and, ultimately, "to reduce the too-high rate of death and disability for patients after a heart attack," Bach said.

Cresci agreed, adding: "By focusing on genetic differences, we may be able to individualize therapies after heart attacks and achieve the best treatment for each patient."

More information: Cresci S, Depta JP, Lenzini PA, Li AY, Lanfear DE, Province MA, Spertus JA and Bach RG. "Cytochrome P450 gene variants, race and mortality among clopidogrel-treated patients following acute myocardial infarction." *Circulation: Cardiovascular Genetics*. In print, June 17, 2014.

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