CHARISMA Genomics Substudy Links Loss-of-Function Allele and Bleeding

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September 29, 2009 (San Francisco, California) **—** Stable cardiovascular patients taking **clopidogrel** may have a lower risk of bleeding if they are homozygous for the loss-of-function CYP2C19 variant, according to the **CHARISMA Genomics Substudy**. In a presentation at the **TCT 2009** meeting, **Dr Deepak L Bhatt** (Brigham and Women's Hospital, Boston, MA) explained that while such patients appeared to have an increased risk of ischemia when compared with patients with the wild-type (WT) allele, they also had fewer bleeding events.

"This is the first large study to establish a potential relationship between less bleeding and genotype," said Bhatt.

Interestingly, those who were homozygous for CYP2C19*2 were at increased risk for ischemic events, whether they were taking clopidogrel or placebo. Bhatt was quick to note, however, that the results were not statistically significant for the placebo group. But he hesitated to ignore the finding completely.

"It could be that the genotype affects other drugs or is independently affecting cardiovascular risk," Bhatt commented.

There has been much conversation recently regarding the antiplatelet agent clopidogrel and the CYP2C19 allele, which encodes the enzyme that metabolizes the drug into its active form. While there are several polymorphisms of the allele, the common CYP2C19*2 variant is thought to have a particularly strong association with the function of the drug. A recent study by **Dr Alan R Shuldiner** (University of Maryland School of Medicine, Baltimore) and colleagues found that clopidogrel had a diminished effect on people with two copies of CYP2C19*2 and that such individuals were more likely to sustain an ischemic event [1].

The prospective, placebo-controlled study, led by Bhatt, involved genotyping 4862 of the 15 603 patients enrolled in **CHARISMA** for CYP2C19 polymorphisms. Some 20.14% of participants had one copy of the CYP2C19*2 allele, while 2.37% had two copies. Patients were randomly assigned to take either aspirin and clopidogrel or aspirin and a placebo. Ischemic and bleeding events were evaluated to try to determine whether the polymorphism had an effect.

The study found that patients who were homozygous for the CYP2C19*2 allele had significantly less GUSTO bleeding if they were taking dual antiplatelet therapy instead of the placebo. Patients with the WT allele, in contrast, experienced more GUSTO bleeding with dual antiplatelet therapy.

CHARISMA Genomics Substudy: Effect of Genotype (CYP2C19*2 vs WT) on All GUSTO Bleeding Events

Effect	OR	95% CI	P
Treatment vs placebo	2.4110	1.978– 2.943	<0.0001
Placebo group: *2/*2 vs WT/WT	0.7250	0.340– 1.400	0.3528
Treatment group: *2/*2 vs WT/WT	0.3290	0.160–0.619	<0.001

Treatment Shouldn't Be Based on Genotype

Bhatt said he feels the findings aren't enough to warrant routine genomic analysis of CYP2C19. "The bottom line for clinicians is that it's likely premature to test for these genotypes because we don't know what to do with the information," Bhatt told **heart*wire*** . "Choices at this point should be made on the available clinical features and on the available data for the different compounds, but not based on genotype."

While findings from different studies tend to agree that homozygotes are at increased risk of ischemia, research on heterozygotes seems less clear. As previously reported in **heart*wire*** , the **TRITON-TIMI 38** study found that even one copy of the loss-of-function allele had a diminished response to clopidogrel. The CHARISMA Genomics Substudy found no such reduction in drug response in CYP2C19*2 heterozygotes.

Bhatt said he thinks a heterozygote might be at elevated risk for ischemia, but he wouldn't use the allele information as the "trigger" to change therapy. Switching the patient to another antiplatelet medicine might improve clinical outcome, but it might also increase bleeding.

The differences seen across studies might be attributable to the patient population, Bhatt explained. The CHARISMA Genomics Substudy dealt specifically with stable patients, while studies that showed a relationship between drug response and one copy of the common variant dealt with acute coronary disease. "I don't think the data necessarily negate other data sets. Lots of investigators have done careful analysis that I'm not dismissing," he said.

First Study of Its Kind With Placebo Group

Dr Shamir Mehta (McMaster University, Hamilton, ON) said the CHARISMA Genomics Substudy provided very important information. "One of the big strengths of this particular analysis is that we have a placebo group," Mehta said, noting that the TRITON-TIMI 38 study has no such group. "What we've learned that we didn't know before is that just having the CYP2C19 loss-of-function allele confers higher risk, irrespective of whether a patient is on placebo or thienopyridine." Mehta sees this insight as critical for guiding future research on the effect of CYP2C19 on other drugs.

Bhatt told ***heart*wire** that he too hopes the CHARISMA Genomics Substudy will lead to more research on the gene. "Further prospective study is needed in this field to determine the clinical relevance of CYP2C19 polymorphisms, not only on efficacy but on the bleeding part of the equation."

The CHARISMA study was funded by Sanofi-Aventis and Bristol-Myers Squibb, makers of clopidogrel. Bhatt was the principal investigator of the CHARISMA trial. He has served as a consultant to Arena, AstraZeneca, Bristol-Myers Squibb, Cardax Pharmaceuticals, Cogentus, Daiichi Sankyo, Eli Lilly, Eisai, GlaxoSmithKline, Johnson & Johnson, Medtronic, Millennium, Otsuka, Paringenix, PDL, Philips, Portola, Sanofi-Aventis, Schering-Plough, Takeda, the Medicines Company, and Vertex.

References

1. Shuldiner AR, O'Connell JR, Bliden KP, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. *JAMA* 2009; 302: 849-858. Abstract