GENETICS IN YOUR PRACTICE

Pharmacogenetics of Clopidogrel

One promise of the Human Genome Project was that an understanding of genetic differences between individuals would move medical practice away from "one-size-fits-all" medicine, toward a personalized medicine approach. Most drug prescription practices today still fit a "reactive" paradigm in that patients are prescribed a medication first and knowledge of their response is learned secondarily as patients respond, favorably or otherwise, to each medication. Knowledge of a patient's genetic makeup before prescribing could allow for a "predictive" model in which expected response could guide medication selection and dosing, potentially increasing efficacy and reducing adverse events.

BY MATTHEW R.G. TAYLOR, M.D., PH.D.

But personalized medicine and individualized management plans require the kind of pharmacogenetic models that are currently known and understood for only a few drugs, and widespread use in clinical practice has yet to occur. In a previous column, Dr. Michael Murray reviewed pharmacogenetic principles and challenges to the field (June 1, 2009, p. 32). Dr. Murray noted that one barrier to broader application of pharmacogenetics in clinical practice was that few pharmacogenetic models were relevant to widely used drugs.

In 2007, the landscape began to change when the Food and Drug Administration (FDA) added language to warfarin's label regarding genetic differences predicting response to the drug. Because of warfarin's widespread use and narrow therapeutic window, genetic differences in response are a common cause of adverse events.

In March 2010, a second commonly used medication, clopidogrel (Plavix), was relabeled by the FDA to reflect potentially important pharmacogenetic differences in patient response to the drug. The label now warns of reduced effectiveness in patients who are "poor metabolizers" of clopidogrel, gives information about the availability of genetic testing for clopidogrel metabolism, and advises physicians to consider alternative therapies in poor metabolizers. Although the FDA did not mandate any specific testing, some patient advertisements for clopidogrel already include language about the possibility of genetic testing being needed. Thus, physicians can expect to be asked by their patients to evaluate the role of genetic testing when prescribing clopidogrel.

The label change was in response to various studies showing that a subset of patients have "clopidogrel resistance," which manifests biochemically as modest changes in platelet aggregation behavior and clinically as recurrent ischemic events. Because clopidogrel requires conversion to an active metabolite by the liver cytochrome P450 (CYP) enzyme system, it was hypothesized that some patients may harbor genetic variants in CYP genes that can lead to absent or reduced metabolism.

A number of studies have identified CYP2C19 as the principal gene system involved in the variation in clopidogrel metabolism, and the evidence that CYP2C19 has a biologic effect on clopidogrel metabolism is quite strong. A study of 2,208 patients with acute myocardial infarction who received clopidogrel noted a higher rate of subsequent cardiovascular events in those with CYP2C19 low-function alleles (N. Engl. J. Med. 2009;360:363-75). Similar findings were seen in 259 young patients who received clopidogrel after their first myocardial infarction. The low-function CYP2C19*2 allele was the only independent predictor of subsequent cardiovascular events in the study (Lancet 2009;373:309-17). Reduced adenosine diphosphate (ADP)–stimulated platelet aggregation responses were demonstrated in carriers of CYP2C19 low-function alleles in a study of 429 Amish patients (JAMA 2009;302:849-57).

Two alleles of this gene (*2 and *3) are the most common genetic causes of low clopidogrel metabolism. Ethnic variation may also be a factor, as fewer low-metabolism variants have been found in whites (around 25%), compared with East Asians (around 50%).

Overall, the findings in these studies suggest that CYP2C19 genotyping could identify patients who may not respond optimally to clopidogrel. Newer ADP-receptor antagonists that are not subject to extensive CYP2C19 metabolism (such as prasugrel, ticagrelor, and elinogrel) are possible alternatives for patients with unfavorable clopidogrel-metabolizing genotypes. Challenges remain, however, including a lack of large prospective trials showing that preemptive genotyping for CYP2C19 low-function variants can be leveraged to improve outcomes.

The amount of variable response that is controlled by CYP2C19 variation is also under debate. A recent analysis of 760 patients undergoing elective coronary stent implantation found CYP2C19 genotype to be an important statistical predictor, although it accounted for only about 5% of the actual platelet response to clopidogrel (J. Am. Coll. Cardiol. 2010;55:2427-34).

The speed of genetic assays has been a hurdle for point-of-care testing until quite recently. But rapid-turnaround assays are now available that directly test CYP2C19 alleles, as are functional tests that can provide timely results.

It is likely that debate will continue on the role of genetic and/or functional testing for clopidogrel resistance. The new black-box warning added by the FDA should alert physicians to the possibility of clopidogrel resistance being explained by pharmacogenetic principles. As rapid testing enters the marketplace and additional studies of prospective populations are completed, physicians who care for patients with cardiovascular disease will need to determine when and how to integrate this new knowledge into their clinical practices. ■

DR. TAYLOR is associate professor and director of adult clinical genetics at the Health Sciences Center of the University of Colorado, Aurora. To provide feedback or suggest future topics of interest, write to Dr. Taylor at our editorial offices or imnews@elsevier.com.

Hiatal Hernia Ups Risk of A-Fib, Subsequent Heart Failure

BY BRUCE JANCIN

FROM THE ANNUAL MEETING OF THE HEART RHYTHM SOCIETY

DENVER — Hiatal hernia is associated with sharply increased risk of atrial fibrillation, according to a large Mayo Clinic study.

The mechanism of the increased prevalence of atrial fibrillation in patients with hiatal hernia is not known but likely involves the direct mechanical effects of the hiatal hernia pressing on the left atrium or indirect effects through activation of the autonomic nervous system or inflammation, Dr. Komandoor Srivathsan said at the meeting.

"Of course, it would be nice to show that if you treat the hiatal hernia with modified fundoplication, the atrial fibrillation rate goes down. We're looking into that now in our database. We should have the answer in the next 6 months," added Dr. Srivathsan of the Mayo Clinic, Rochester, Minn.

The study was undertaken after he and his coinvestigators formed an impression that a disproportionate number of patients at the clinic's large-volume atrial ablation center had hiatal hernias on their preablation CT scans, echocardiography, or both. So the investigators used the Mayo Clinic's electronic medical records system to identify the 111,429 adults diagnosed with hiatal hernia during 1976-2006. Among this group were 5,929 patients diagnosed with new-onset atrial fibrillation after they had already received a diagnosis of hiatal hernia.

For comparison, the investigators turned to published data on the Olmsted County and statewide Minnesota general populations. In this way, they determined that the prevalence of atrial fibrillation in men under age 55 with hiatal hernia was 13-fold greater than in the age-matched general population. Among women under age 55, atrial fibrillation was 15-fold more likely if they had a hiatal hernia.

Within 10 years of receiving the dual diagnosis, roughly half of patients had heart failure, compared with about one-tenth of the age-matched general population.

Moreover, the prevalence of atrial fibrillation in men with hiatal hernia remained several-fold greater than in men without this abdominal defect up until about age 80. Among women, this remained the case even beyond age 80, Dr. Srivathsan continued.

Patients with hiatal hernia and atrial fibrillation were a mean of 73 years old at the time of their dual diagnosis, compared with 61 years for those with either diagnosis alone. The dual-diagnosis group had significantly more hypertension, diabetes, hyperlipidemia, coronary artery disease, heart failure, and sleep apnea.

The dual-diagnosis group had markedly worse long-term outcomes than did the general population.

"Once you have the combination, it seems to be a strong predictor of congestive heart failure," the cardiologist observed.

Indeed, within 10 years of receiving the dual diagnosis, roughly half of patients had heart failure, compared with about one-tenth of the age-matched general population of Olmsted County. And the all-cause mortality rate within 10 years following dual diagnosis was significantly greater than in the general Minnesota population.

One audience member observed that some patients with hiatal hernia never receive the formal diagnosis, but instead are told they have reflux and put on a histamine-2 receptor blocker. He asked whether the use of these drugs in such patients may lessen their risk of developing atrial fibrillation.

Dr. Srivathsan replied that he and his coworkers are examining that in a subgroup analysis. They are also interested in learning whether atrial fibrillation is more severe in patients with hiatal hernia. ■

Disclosures: *Dr. Srivathsan reported no conflicts of interest.*