GENOMIC MEDICINE

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 2007, the landscape began to change when the Food and Drug Administration 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 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 testing 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. ■

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Decrease in Heart Function Might Impact Brain Aging

BY HEIDI SPLETE

FROM CIRCULATION: JOURNAL OF THE AMERICAN HEART ASSOCIATION

Reduced heart function might be associated with signs of preclinical brain aging, based on a review of data from the observational Framingham Heart Study.

Investigators led by Angela Jefferson, Ph.D., of Boston University found that cardiac output, adjusted for body size, was significantly associated with the rate of change in brain volume as the study participants aged. The findings were published online.

Because initial research studies on the effects of cardiac output on brain aging were conducted on small samples of referred patients with clinical cardiovascular disease (CVD) and were not systematically adjusted for environmental risk factors known to contribute to both central nervous system and myocardial injury, Dr. Jefferson and her colleagues sought to determine if the relationship existed in patients who were free of clinical dementia or stroke. Based on previous findings from animal and clinical studies, they "hypothesized that MRI-assessed cardiac function is associated with cognitive and neuroimaging markers of preclinical Alzheimer's disease and cerebrovascular disease."

The investigators reviewed brain and heart MRI data from 1,504 adults aged 34-84 years, excluding individuals with a documented history of clinical stroke, transient ischemic attack, or dementia. The average age of the study group was 61 years, and 54% were women. In the ongoing study, participants are assessed every 4-8 years (Circulation 2010 Aug. 2 [doi:10.1161/circulationaha.109.905091]).

VITALS

Major Finding: Individuals in the highest tertile for cardiac index (indicating healthier heart function) had 0.35% and 0.36% greater total brain volume than did individuals in the middle and lowest tertiles, respectively.

Data Source: A cross-sectional review of brain and heart MRI data from 1,504 adults in the Framingham Offspring Cohort.

Disclosures: None of the investigators had financial conflicts to disclose. The research was supported in part by grants from the National Heart, Lung, and Blood Institute's Framingham Heart Study.

Low cardiac index (defined as less than 2.5 L/min per m^2) was identified in 415 individuals (28%) after the exclusion of 112 individuals with prevalent cardiovascular disease.

The researchers found that for every one standard deviation increase in cardiac index, the total brain volume (measured as a percentage of total cranial volume) increased by 0.30%. Cardiac index also increased as lateral ventricular volume decreased, but this relationship was not significant when individuals with CVD were excluded.

In a post hoc analysis, the researchers compared cardiac index tertiles and changes in brain volume. They used the highest tertile as the referent, given that higher cardiac index values reflect healthier heart function.

Individuals in the middle tertile for cardiac index had an average total brain volume that was 0.35% less than that of those in the top tertile. Those in the bottom tertile had average total brain volume of 0.36% less than that of those in the top tertile. These changes corresponded to an average difference in brain aging of 1.9 years (a total brain volume decrease of 0.19% per 1-year increase in age).

Cardiac index as a continuous variable was not significantly related to any of the neuropsychological factor scores. But low executive function and information processing nearly reached statistical significance in association with low cardiac index.

The association between cardiac index and brain volume was significantly stronger among adults who were younger than 60 years, compared with older adults, and in men compared with women. However, the association was not significantly modified by apolipoprotein E e4 allele status.

The results were limited by the observational nature of the study, which cannot establish causality. However, the findings were consistent with the hypothesis that decreasing cardiac function is associated with accelerated brain aging, and suggest that low and low-normal cardiac index values might be related to brain health, as measured by brain volume, the investigators said. ■