Genotyping Reveals CHD Risk in Type 2 Group

BY BRUCE JANCIN
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NEW ORLEANS — The cardiovascular mortality rate was more than fivefold higher in type 2 diabetic patients who possessed the haptoglobin 2-2 genotype than in those who did not in a large, prospective, Israeli study.

Another analysis based on the same study population showed that tight glycemic control reduced the incidence of myocardial infarction—but only in those type 2 diabetic patients with the haptoglobin 2-2 genotype.

Taken together, these findings suggest an important role for haptoglobin genotyping in assessing cardiovascular risk and guiding management strategies in patients with type 2 diabetes, Dr. Uzi Milman said at the annual scientific sessions of the American Heart Association.

Haptoglobin is a serum protein that binds extracellular hemoglobin, a potent source of oxidative tissue damage in the bloodstream and in vascular endothelium. The haptoglobin arising from the haptoglobin (Hp) 2-2 genotype is a much less efficient antioxidant than are the forms of the protein present in individuals who are Hp 1-1 or Hp 1-2. Thus, haptoglobin typing permits identification of a diabetic subgroup with chronically high oxidative stress, explained Dr. Milman, a family physician at Clalit Health Services and the Technion-Israel Institute of Technology, Haifa.

The Hp 2-2 variant is quite common. In most Western populations, its prevalence is 36%, compared with 16% for Hp 1-1 and 48% for Hp 1-2.

These findings suggest an important role for haptoglobin genotyping in assessing cardiovascular risk and guiding management strategies in patients with type 2 diabetes.

Dr. Milman reported on 2,241 type 2 diabetes patients age 55 years or older who participated in a registry created at 47 primary care clinics in northern Israel as part of the Israel Cardiovascular Events Reduction with Vitamin E (ICARE) study. The double-blind randomized portion of ICARE, which was presented at the 2007 scientific sessions of the American Heart Association, showed a halving of cardiovascular death, MI, and stroke with 18 months of 400 IU/day of vitamin E, compared with placebo.

The 2,241 registry participants were not part of the vitamin E randomized trial. They underwent haptoglobin genotyping, then were followed prospectively for 3 years, with all treatment decisions left to the discretion of their primary care physicians. Patients in the three groups with regard to haptoglobin genotype did not differ in terms of baseline duration of diabetes, glycosylated hemoglobin values, or prevalence of known cardiovascular disease, which was roughly 25% across the board.

The key finding was that the incidence of cardiovascular death during the 3-year follow-up was 1.1% in the 708 Hp 2-2 patients, more than fivefold greater than the 0.2% rate in Hp 1-1 or 1-2 individuals. The rate of nonfatal MIs was 3.9% in the Hp 2-2 patients and 2.5% in the others, a difference that did not reach statistical significance.

The other ICARE substudy Dr. Milman presented looked at the impact of haptoglobin genotype on the success of tight glycemic control to prevent MI. He found that the rate of MI during follow-up was 5% in Hp 2-2 patients whose average glycosylated hemoglobin was greater than 7.0%, compared with 1.8% in Hp 2-2 individuals who maintained an HbA_{1c} of 7.0% or less. The number of Hp 2-2 type 2 diabetic patients who needed to be on tight glycemic control for 3 years in order to prevent one MI was 31.

In contrast, MI rates were similar in Hp 1-1 or Hp 1-2 individuals regardless of whether their average HbA_{1c} was greater or less than 7.0%.

This finding may explain the lack of consistent clinical trials evidence that tight glycemic control reduces cardiac events in diabetic patients. The benefit of tight control in terms of reduced macrovascular events appears to be restricted to the subgroup with high oxidative stress, as reflected in the Hp 2-2 genotype. These are the diabetic patients in whom aggressive risk factor modification is warranted; they also are the ones who will benefit from 400 IU/day of vitamin E, he continued.

Dr. Milman and coinvestigators recently demonstrated that the mechanism for vitamin E's benefit in Hp 2-2-positive patients with type 2 diabetes involves the antioxidant vitamin's ability to correct the HDL dysfunction present in such individuals (Diabetes 2008;57:2794-800).

Synvista Therapeutics is developing a simple diagnostic kit to determine haptoglobin genotype. Until the kit receives marketing clearance from the Food and Drug Administration, physicians can order haptoglobin genotype testing from ARUP Laboratories, a national clinical reference laboratory, under a license agreement with Synvista.

Interested physicians can call ARUP's 24-hour service line at 800-522-2787 and should refer to ARUP test #0040116).

The ICARE trial was sponsored by the Technion-Israel Institute of Technology. ■

GENOMIC MEDICINE

Risky Business

Age, sex, body mass index, smoking status, hypertension, diabetes, family history, and cholesterol levels are the heavy hitters of risk assessment for coronary heart disease, especially in patients of a certain age. Combined, these risk factors explain a considerable amount of population risk; but in isolation, each is merely a weak predictor of risk, so that making risk predictions at the individual level is a complex and risky process.

BY GREG FEERO, M.D., PH.D.

Recently, biomarkers such as homocysteine levels and C-reactive protein (CRP) have been added as considerations in predicting individual risk. Their inclusion has sparked considerable debate, and things could heat up yet, given that, as of last month—December 2008—genome-wide association studies have identified at least 22 new genetic markers for coronary heart disease (CHD) risk.

These markers provide novel insights on pathways and mechanisms for cardiovascular disease pathogenesis and will prove invaluable over time in developing new approaches for the prevention and treatment (think "statins") of the disease. Many of these associations are related to lipid profiles and other known and already measurable risk factors. Some may eventually prove useful in clinical care, given that your DNA sequence is not much affected by transient factors such as diet or the presence of a cold. And at least some of the markers seem to be independent of all currently measurable markers of cardiovascular disease risk.

The markers are those near the 9p21 locus. The presence of certain variants at this locus increases an individual's risk for CHD by about 1.3 fold over the average individual, whereas protective variants at the locus will diminish risk for the disease.

Can these genetic risk markers for coronary heart disease be used to improve the prediction of disease risk and health outcomes? In our attempts to answer this question we cannot lose sight of our goal: We consider using new risk markers in clinical medicine to improve health outcomes, not to refine current models for predicting risk.

Remember, too, that the process of analyzing the usefulness of these markers is occurring within the context of a health care system in which cost consciousness is mandatory and cost savings would be a huge benefit. It may turn out that adding markers to existing risk models makes little sense unless the new markers dramatically improve risk discrimination.

Consider a recent area under the curve (AUC) analysis of the potential for improved risk prediction for CHD: Adding 22 genetic cardiovascular risk markers to the conventional risk factors increases the AUC from 63% to 66%. Although this small change is significant, it is not transformative for the individual patient.

Future guidelines will incorporate at least some elements of genetic risk assessment. The big question is whether that addition transforms or simply tweaks health care.

An incremental improvement on CHD risk assessment could conceivably drive up health care costs with little return on the investment. Transformation would therefore best be achieved by discovering additional genetic contributors to risk as well as rethinking the way in which we use the information to care for individual patients and populations.

For example, it is possible that those identified as having increased risk by virtue of these genetic markers at 9p21 may be subject to more-intense management. Using the information this way may improve health outcomes and is a hypothesis that should be tested. Alternatively, health benefits and cost savings may be achieved if those individuals shown to be at reduced risk had less-aggressive management with expensive drugs and laboratory tests.

Most scientists and providers agree that it is too early to recommend using the new CHD risk markers in routine care. However, CHD risk evaluation is rapidly evolving, and you can expect that future guidelines will incorporate at least some elements of genetic risk assessment. The big question is whether such guidelines will transform or simply tweak cardiovascular health care. ■

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