New Tool Predicts CV Risks

Heart Disease *from page 1*

ic if we could identify more people as being at high lifetime risk and get them to understand that even though they might be at low risk now, they need to do something more," explained Dr. Amanda K. Marma, an intern in pediatrics at Children's Hospital, Boston.

She presented an analysis of 10-year and lifetime predicted risks for cardiovascular disease in U.S. adults based on extrapolation from 6,329 cardiovascular disease-free participants in the National Health and Nutrition Examination Survey for 2003-2004 and 2005-2006. The purpose of the study, which she worked on while a medical student at Northwestern University in Chicago, was to demonstrate the need for greater public health efforts addressing lifetime risk.

The study showed, for example, that among Americans aged 40-59 years—a group of particular interest in terms of cardiovascular prevention efforts—80% have a low short-term predicted risk—that is, less than a 10% chance of developing coronary heart disease or diabetes within the next 10 years. But three-quarters of those in this low short-term-risk group are at high lifetime predicted risk as defined by a 39% or greater estimated likelihood of developing cardiovascular disease, including stroke.

Lifetime risk was estimated using an algorithm previously developed by Dr. Marma's coinvestigators and validated in the Framingham Study population (Circulation 2006;113:791-8). The algorithm showed, for example, that the predicted lifetime risk of a 50-year-old, nonsmoking, nondiabetic man with optimal blood pressure and a total cholesterol below 180 mg/dL was 5%, but with one major risk factor his lifetime risk would soar to 50%.

As an example of how knowledge of lifetime estimated risk might serve as extra motivation for risk factor modification, Dr. Marma cited the example of a 50-year-old, nondiabetic, nonsmoking woman with a total cholesterol of 240 mg/dL, an HDL of 58 mg/dL, and an untreated systolic blood pressure of 160 mm Hg. Her 10-year predicted risk of MI or coronary death using the ATP III algorithm is just 2%. But her lifetime risk of cardiovascular disease is 50%.

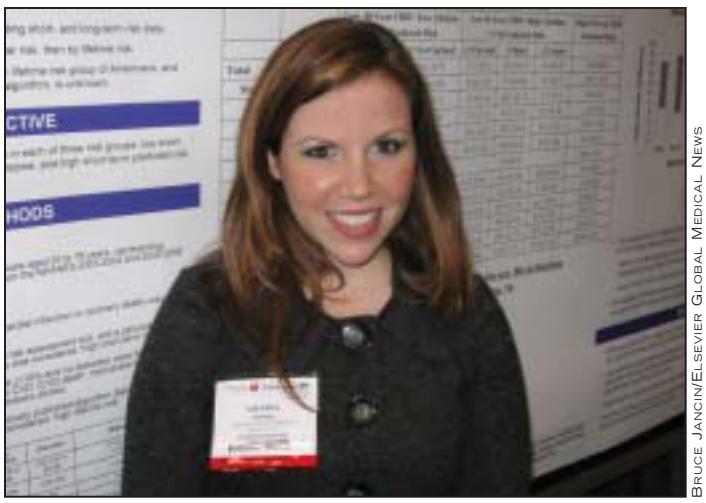
Among other key findings from the analysis of lifetime cardiovascular risk:

► Just 18% of adults—28 million Americans—are at high short-term predicted risk, defined as 10% or greater in the next 10 years.

► Only 11.4% of adults are at both low short-term and lifetime predicted risk.

► Two-thirds of all individuals at low short-term risk are at high lifetime predicted risk.

► Many women and younger men identified as low risk using the ATP III tool turn out to be at high lifetime risk. That's important in light of criticism that the ATP III tool does a relatively poor job of discriminating risk in those groups.



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Two-thirds of all adults at low short-term risk for CV disease are at high lifetime predicted risk, Dr. Amanda K. Marma found.

In an interview, former AHA president Raymond J. Gibbons said he strongly favors incorporating routine assessment of lifetime risk into prevention efforts.

"There are many patients who you would think of differently if you looked at them from a lifetime risk standpoint versus a 10-year-risk standpoint," said Dr. Gibbons, professor of medicine at the Mayo Clinic, Rochester, Minn.

"If we just look at 10-year risk in, say, a 40-year-old, we're in effect saying it's okay if you die at 52. That's not acceptable to my 40-year-old patients," the cardiologist added.

The data were published online simultaneously in Circulation Cardiovascular Quality and Outcomes (doi: 10.1161/circoutcomes.109.869727).

The work was funded by the National Heart, Lung, and Blood Institute. ■

Trial Halted With Niacin Found Superior to Ezetimibe

BY MARY ANN MOON

Extended-release niacin was clearly superior to ezetimibe when combined with statin therapy in patients who had or were at high risk for atherosclerosis in a prospective study in 363 patients.

Niacin caused the regression of carotid intima-media thickness, a surrogate marker for atherosclerosis progression, while ezetimibe caused no significant change in the first clinical trial to directly compare the two secondary agents in combination with a statin.

In addition, fewer adverse cardiovascular events developed with niacin than with ezetimibe during 14 months of follow-up. Perhaps most important, "We found an unexpected paradoxical relationship of a greater degree of atherosclerosis progression in patients with larger, ezetimibe-induced reductions in LDL cholesterol level," wrote Dr. Allen J. Taylor, director of advanced cardiac imaging at Washington Hospital Center in Washington, and his associates in the ARBITER 6-HALTS (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies) study. The findings were presented concurrently at the annual scientific sessions of the American Heart Association.

The prospective, open-label study, sponsored by Abbott, the maker of the extended-release niacin used in the trial, was designed to randomly assign 363 patients to receive either extended-release niacin or ezetimibe (Zetia, manufactured by Merck–Shering-Plough Pharmaceuticals) in addition to statin therapy. The study was halted early when an interim analysis showed a clear advantage with niacin, and the trial included complete data from only 208 patients (N. Engl. J. Med. 2009:doi:10.1056/NEJMoa0907569).

Critics have charged that this "premature" termination was "unfortunate and may exaggerate any potential benefit of niacin therapy," because "more than 40% of the patients did not undergo the measurement at 14 months of the carotid intima-media thickness (the primary end point)," Dr. Roger S. Blumenthal and Dr.

'We believe that prudent clinical practice currently favors the avoidance of ezetimibe.'

DR. TAYLOR

Erin D. Michos of Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Baltimore, said in an editorial comment accompanying the report.

"A larger sample size may have either strengthened the provocative results regarding the major adverse cardiovascular events or, alternatively, reduced any evidence of meaningful clinical differences," they wrote (N. Engl. J. Med. 2009:doi:10.1056/NEJMe0908838).

The ARBITER 6-HALTS trial enrolled 363 men and women, including 279 with known atherosclerotic coronary or vascular disease. In addition, there were 84 patients with a coronary heart disease risk equivalent such as diabetes (38 patients), a 10-year Framingham risk score of 20% or more (26 patients), and/or a high coronary calcium score (20 patients).

The study subjects (80% male, mean age 65 years) were randomly assigned to receive the maximum tolerated dose of extended-release niacin up to 2,000 mg/day or 10 mg of ezetimibe daily. All had already been taking a statin for a mean of 6 years, usually simvastatin or atorvastatin.

Niacin bested ezetimibe in improving both mean and maximal carotid intima media-thickness on ultrasonography at both 8 months and 14 months, Dr. Taylor and his colleagues said.

In addition, the rate of major adverse cardiovascular events was significantly lower with niacin (1%) than with ezetimibe (5%). Both of these benefits were consistent across all subgroups studied, without regard to gender, the presence or absence of diabetes, or baseline HDL cholesterol levels.

A post-hoc analysis showed a significant inverse relation between a decrease in LDL cholesterol and an increase in carotid intima-media thickness only in the ezetimibe group. The reason for this paradoxical effect is not yet known, but the researchers proposed that it is biologically plausible: Ezetimibe may have the unintended effect of disrupting the HDL-mediated reverse transport of cholesterol.

"We believe that prudent clinical practice currently favors the avoidance of ezetimibe, with consideration of further restriction on its use in lieu of clinically validated regimens, until its net effect on clinical outcomes can be fully ascertained," Dr. Taylor and his associates said.

The two patient groups did not differ in quality of life measures at the end of the study. More subjects in the niacin group (63%) than in the ezetimibe group (33%) withdrew from the study because of adverse drug effects, however.

In their editorial comment, Dr. Blumenthal and Dr. Michos said that using carotid intima-media thickness as a surrogate for coronary atherosclerosis is "controversial."

It is unknown whether arresting the progression of carotid intima-media thickness, or even reversing it, is consistently associated with a reduction in risk of CV events. "Furthermore, there are therapies other than niacin that retard the progression of carotid intima-media thickness (i.e., estrogen and thiazolidinediones) but do not reduce the incidence of cardiovascular events," they noted.

"The putative negative effects of ezetimibe (i.e., increase in the carotid intima-media thickness) espoused by the authors are unsubstantiated. In the 111 patients in the ezetimibe group with data reported in the study, the carotid intima-media thickness at 14 months was not significantly different from the thickness at baseline," Dr. Blumenthal and Dr. Michos added.

"Unfortunately, the premature termination of the ARBITER 6-HALTS trial, the small number of patients studied, and the limited duration of follow-up preclude us from conclusively declaring niacin the adjunctive agent of choice on the basis of the evidence. A decrease of 0.014 mm in the carotid intima-media thickness over 14 months does not necessarily merit changes in our lipid-lowering guidelines at this time," they said.

Dr. Taylor reports receiving lecture fees from Abbott. Dr. Blumenthal and Dr. Michos report no relevant conflicts of interest. ■