Risk Score's Validity Debated

C-Reactive Protein *from page 1*

people without a history of clinical disease was in the spotlight twice at the annual scientific sessions of the American Heart Association. Once was when the Reynolds Risk Score for men was unveiled in a report at the meeting by one of its developers, Dr. Paul M. Ridker, director of the Center for Cardiovascular Disease Prevention at Brigham and Women's Hospital in Boston. And hsCRP was the key enrollment criterion in the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study, the results of which showed that people with high hsCRP levels but normal serum levels of LDL cholesterol had a marked benefit when put on statin treatment (INTERNAL MEDICINE NEWS, Dec. 1, 2008, p. 1).

The Reynolds Risk Score for women was introduced nearly 2 years ago, in a February 2007 journal report (JAMA 2007;297:611-9). "The Reynolds Risk Score for men confirms in a second major cohort that the addition of the same two risk factors—hsCRP, representing inflammation, and family history, representing genetics—improve our overall ability to predict risk when compared to the covariates used in Framingham," Dr. Ridker said in an interview.

The Reynolds Risk Score was derived for women using a randomly selected, 16,400-person subgroup from the 24,558 women who were enrolled in the Women's Health Study and were followed for a median of about 10 years.

In validity testing that involved the remaining 8,158 women, predicted outcome rates were compared with actual rates. The simplified risk score accurately reclassified about half of these women, compared with their classification using the Framingham Risk Score. On the basis of this evidence, Dr. Ridker and his associates made the Reynolds Risk Score for women available online in 2007 at www.reynoldsriskscore.org.

"We have been quite pleased with the widespread positive reception it has gotten from many within the prevention community," Dr. Ridker said.

Other experts say the Reynolds Risk Score for women has not caught on, in part because of limited validation, in part because of its reliance on hsCRP levels.

"The Reynolds Risk Score was not very well validated," in contrast to the Framingham Risk Score, which underwent validation in 2001, commented Dr. Peter W.F. Wilson, a cardiology epidemiologist and professor of medicine at Emory University, Atlanta. Most people want to see a validation before using the Reynolds Risk Score, he said in an interview.

"The Reynolds Risk Score requires getting an hsCRP, and it's not currently recommended to universally screen for this," commented Dr. Lori Mosca, a professor of medicine at Columbia University and director of preventive cardiology at New York–Presbyterian Hospital in New York. Measuring hsCRP in a lot of people "could greatly increase the cost of risk assessment, and it has not yet been shown to improve clinical outcomes compared with the Framingham Risk Score." What's needed is a study to prove that getting a Reynolds Risk Score leads to better outcomes, she said in an interview.

An hsCRP test is currently reimbursed at about $18, nearly the same amount as a standard lipid panel.

The Reynolds Risk Scores "need validation in a lot of other settings before they are as robust as the Framingham Risk Score," commented Dr. Donald Lloyd-Jones, a cardiologist at Northwestern University, Chicago.

In defense of the Reynolds Risk Score, Nancy R. Cook, Sc.D., noted that "the Reynolds Risk Score for women was internally validated. This is a higher standard than that faced by the Framingham models." In addition, "the model for men serves as a type of external validation," said Dr. Cook, a biostatistician at Brigham and Women's Hospital and a codeveloper of the Reynolds Risk Score.

After publication of the Reynolds Risk Score for women, the score was tested using data on 10,724 initially healthy, American, nondiabetic men aged 50 or older in the Physician's Health Study, who were followed for a median of 10.8 years.

When risk assessment by the Reynolds Risk Score was compared with the Framingham Risk Score, about 19% of all the men, and about 20% of those with an intermediate risk, were reclassified by the Reynolds formula. The reclassifications were correct (based on actual outcomes) for 90% of all men, and for 100% of the intermediate-risk men, Dr. Ridker reported at the meeting. This analysis was published simultaneously with his talk (Circulation 2008;118:2243-51). Also concurrently with his talk, the Reynolds Risk Score for men became available at the same Web site that has carried the Reynolds Risk Score for women.

The difference between the two risk scoring systems can have a substantial clinical impact, Dr. Ridker said. Take the case of a 65-year-old, nonsmoking man with a systolic blood pressure of 130 mm Hg, a total cholesterol of 205 mg/dL, an HDL cholesterol of 45 mg/dL, an hsCRP of 4.0 mg/dL, and a positive family history of an early myocardial infarction. When scored by the Framingham criteria, this man's 10-year risk for a cardiovascular event would be 11.6%, an intermediate risk level. But because of the man's high level of hsCRP and positive family history, his Reynolds Risk Score jumps to 20.4%, placing him in a high-risk category and making him eligible for more aggressive risk-reduction treatment with a statin.

Dr. Ridker cautioned that the Reynolds score for men had been tested in a cohort of physicians, who have a relatively high socioeconomic status and generally excellent access to health care. This group was also predominantly white, with low numbers of African Americans, Hispanics, and Asians.

On the basis of these limitations, he acknowledged that it might be premature to use the Reynolds Score for nonwhite men without additional confirmation. But, he added, data from the JUPITER study provided "for the first time hard evidence that statin therapy reduces vascular risk in women and minorities. Since the same entry criteria were used for women, minorities, and men in JUPITER, these data demonstrate that the strategy of screening for hsCRP and treating with a statin works very well for women and minorities as it does for men," he said.

A major factor in determining which risk-scoring method U.S. physicians will use over the next several years will likely be the next revision of the Adult Treatment Panel guidelines from the National Cholesterol Education Program. "I suggest waiting until the Reynolds Risk Score is reviewed by a guidelines-writing committee and is recommended before using it in general practice," Dr. Lloyd-Jones said.

Dr. Ridker is listed as a coinventor on patents held by Brigham and Women's Hospital that relate to the hsCRP test, and he has received research support from Astra-Zeneca. The company sponsored JUPITER and markets rosuvastatin (Crestor), the statin used in that study. ■

Risk Scores Rarely Used in Practice

Contention over which cardiovascular risk scoring method to use—Framingham or Reynolds—misses a critical issue: Many physicians don't use any formal scoring method.

Despite guidelines that call for Framingham Risk Scoring when deciding whether to start primary prevention treatment with a statin, many if not most physicians use a much simpler approach.

"There is a disconnect between what the ATP [Adult Treatment Panel] advocates and what happens in the real world," Dr. Mosca said. "The Framingham Risk Score may be advocated, but it's not used."

That's OK, experts say, as long as physicians keep in mind some general guidelines on primary prevention.

"Just counting up risk factors is not so bad," Dr. Wilson said. "A physician who doesn't use a risk score is like someone walking through the woods without a map. They're OK as long as they know the overall geography and where they're going."

Dr. Ridker said that "a simpler, primary prevention screen that is fully evidence based for men over 45 and women who are postmenopausal is as follows: If they have diabetes, treat [with a statin]. If not, but their LDL cholesterol is greater than 160 mg/dL, treat. If not, then if their hsCRP is greater than 3.0 mg/dL, treat. If none of the above, get their blood pressure to goal and don't worry about statin therapy."

Metabolic Syndrome Blunts Aspirin's Antiplatelet Activity

BY MITCHEL L. ZOLER
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NEW ORLEANS — Apparently healthy people with a family history of coronary artery disease who also had metabolic syndrome showed elevated platelet aggregation and reduced platelet responsiveness to aspirin in a study of more than 2,000 people.

These findings suggest that "low-dose aspirin therapy alone may not be sufficient to provide optimal antiplatelet protection" in people with metabolic syndrome and an increased risk for coronary artery disease, Dhananjay Vaidya, Ph.D., and his associates reported in a poster at the annual scientific sessions of the American Heart Association.

The link between metabolic syndrome and aspirin resistance in platelets was examined because metabolic syndrome is known to be proinflammatory and prothrombotic, they said.

The study involved 2,088 apparently healthy siblings, sibling offspring, and coparents of the sibling offspring of more than 500 patients younger than 60 years and hospitalized for coronary artery disease. The average age of the relatives was about 44 years, and about 58% were women. Overall, 28% of the group had metabolic syndrome.

The aggregability of each person's platelets was tested before and after 2 weeks of treatment with 81 mg/day of aspirin. Before starting aspirin, the platelets of the people with metabolic syndrome showed significantly more aggregation than the platelets from people without metabolic syndrome, after adjustment for age, gender, race, smoking status and baseline levels of LDL cholesterol and high sensitivity C-reactive protein, reported Dr. Vaidya, a vascular researcher in the department of medicine at Johns Hopkins University, Baltimore, and his associates.

Immediately after 2 weeks of daily aspirin treatment, the platelets of the people with metabolic syndrome continued to show a significantly higher level of aggregation, compared with platelets from those without metabolic syndrome, again after adjustment.

This finding has clinical implications because aspirin prophylaxis for coronary artery disease is recommended in people with metabolic syndrome, the researchers noted. ■