MINDFUL PRACTICE

Treating Elevated Biomarkers to Lower CV Risk

BY JON O. EBBERT, M.D., AND ERIC G. TANGALOS, M.D.

The Problem

A 50-year-old physician presents to your office for a routine physical examination. His past medical history is significant for adenoidectomy. He jogs 3 miles five times a week. He is a never tobacco user, and his family history is negative for coronary heart disease (CHD). His body mass index is 26 kg/m^2, and his blood pressure is 110/60 mm Hg. His total cholesterol is 204 mg/dL, with an HDL cholesterol level of 51 mg/dL and LDL of 136 mg/dL, and his triglyceride level is 85 mg/dL. You put his information in your Framingham CHD risk calculator, which tells you that his 10-year "hard" CHD risk (i.e., risk of heart attack plus risk of CHD death) is 5%. He asks about your opinion regarding C-reactive protein (CRP) level as an additional risk factor for heart disease. One of his business associates had a complete risk factor profile done and was advised to take a statin because of an elevated CRP level. You tell him that you've been overwhelmed with work and have been unable to read the most recent publications on this issue. You promise to review the matter and get back to him.

The Question

In patients with minimal risk factors for cardiovascular disease whose LDL cholesterol level is at goal, does treatment of an elevated CRP with a statin decrease the risk for adverse cardiovascular events?

The Search

You log on to Google (www.google.com) and use C-reactive protein, rosuvastatin, and randomized controlled trial as your search terms. You find a relevant study. (See box at right.)

Our Critique

The study was large and well conducted, with a long duration of follow-up. The trial was stopped early for efficacy, which may tend to overestimate treatment effects. The enrolled participants do not resemble those in our practice, and we were impressed that the investigators were able to find such healthy people with an average age of 66 years.

It would be challenging to incorporate testing for CRP into routine clinical practice, and the "medicalization" of biomarkers is a concern. Patients who thought they were healthy now run the risk of being diagnosed with nonspecific biomarker elevations (i.e., "biomarkeritis"). The unintended consequences and the cost-effectiveness of increasingly widespread use of statins need to be considered.

Clinical Decision

After reviewing the information, you tell the patient that statins decrease the risk for cardiovascular disease in patients with elevated CRP levels. You note that he would have been excluded from this study because his LDL cholesterol level was too high. He is not excited about being on a statin for the rest of his life, so he is satisfied with the current information.

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P.M. Ridker, et al.

Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N. Engl. J. Med. 2008;359:2195-207.

► **Design and Setting:** Randomized, blinded, placebo-controlled clinical trial conducted at 1,315 clinical sites in 26 countries.

► **Subjects:** Eligible patients were men at least 50 years of age and women at least 60 years who did not have a history of cardiovascular disease and who had an LDL cholesterol level under 130 mg/dL, a high-sensitivity CRP concentration of 2 mg/dL, and a triglyceride level under 500 mg/dL. Potential subjects were excluded if they previously or currently used lipid-lowering therapy; currently used postmenopausal hormone therapy; had evidence of liver dysfunction, an elevated creatine kinase level, or an elevated creatinine level; had diabetes, uncontrolled hypertension, or cancer within 5 years of enrollment; had uncontrolled hypothyroidism; abused alcohol or drugs; had an inflammatory condition such as severe arthritis, lupus, or inflammatory bowel disease; or were taking immunosuppressants.

► **Intervention:** Subjects were randomized to rosuvastatin 20 mg daily or matching placebo.

► **Outcomes:** The primary outcome was the first major cardiovascular event (i.e., nonfatal MI, nonfatal stroke, hospitalization for unstable angina, an arterial revascularization procedure, or death from cardiovascular causes). Secondary end points included the components of the primary end point considered individually. End points were adjudicated by a blinded committee.

► **Results:** The study randomly assigned 17,802 people to rosuvastatin or placebo. Groups were similar at baseline, with baseline median CRP levels of 4.2 mg/dL in the rosuvastatin group and 4.3 mg/dL in the placebo group. Median follow-up was 1.9 years, and the trial was stopped early. At 12 months, the rosuvastatin group had a 50% lower median LDL cholesterol level and a 37% lower median CRP level, compared with the placebo group. The rates of the primary end point were 0.77 and 1.36 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio for rosuvastatin, 0.56; 95% confidence interval: 0.46-0.69). Rosuvastatin also decreased the likelihood of an MI (HR 0.46; 95% CI: 0.30-0.70), stroke (HR 0.52; 95% CI: 0.34-0.79), revascularization or unstable angina (HR 0.53; 95% CI: 0.40-0.70), and death from any cause (HR 0.80; 95% CI: 0.67-0.97). The rosuvastatin group was not observed to have a significant increase in myopathy or cancer rates but did have a higher incidence of physician-reported diabetes.

Score Can Gauge Risk Of Atrial Fibrillation

BY MITCHEL L. ZOLER
Philadelphia Bureau

NEW ORLEANS — Eight easily obtained clinical variables together formed a risk score that could predict a person's risk for developing atrial fibrillation with reasonable reliability, on the basis of an analysis using data from the Framingham Heart Study.

"The next step is to show the transportability [of this risk score] to other cohorts," Dr. Renate B. Schnabel said at the annual scientific sessions of the American Heart Association.

This tool for predicting atrial fibrillation is 'easily applicable for clinical assessment.'

DR. SCHNABEL

This is the first reported tool for assessing atrial fibrillation risk, and it is simple enough to be "easily applicable for clinical assessment," said Dr. Schnabel, a researcher at Boston University and with the Framingham Heart Study. The risk formula has the potential to identify high-risk patients and to help in communicating risk information to patients. Further study is needed to determine whether modifying some of the component risk factors can result in a reduced incidence of atrial fibrillation, she said.

The formula was derived from data on 4,764 women and men enrolled in either the original Framingham Heart Study, which began in 1948, or in the Framingham Offspring Study, begun in 1971. The participants were aged 46-95 years at enrollment, with an average age of 61. Records from more than 8,000 clinical examinations were reviewed. Incident atrial fibrillation was identified on the basis of records in participants' charts, including ECG data.

The eight factors identified as significant determinants of risk for developing atrial fibrillation were age, gender, body mass index, systolic blood pressure, treatment for hypertension, PR interval, significant heart murmur, and heart failure. Together, these eight factors could account for 78% of incident atrial fibrillation cases.

The risk for atrial fibrillation was higher in men than in women, Dr. Schnabel said. Risk was also elevated with increases in age, body mass index, systolic blood pressure, and the duration of the PR interval. And risk was higher in people being treated for hypertension, those who had a significant heart murmur, and those with heart failure.

An example of a low-risk person is a woman aged 60 with a body mass index of 20 kg/m^2, a systolic pressure of 120 mm Hg, and a PR interval of 160 msec who also was not on antihypertensive treatment and did not have a heart murmur or heart failure. This relatively low-risk woman had a 10-year risk for developing atrial fibrillation of about 2%. A man with a similar low-risk profile would have a 10-year risk of about 4%.

In contrast, a high-risk woman would be 70 years old with a body mass index of 35, a systolic pressure of 150 mm Hg, and a PR interval of 210 msec who was also on an antihypertensive regimen and had either a heart murmur or heart failure. This woman would have a 10-year risk for developing atrial fibrillation of about 28%. A man with a similar clinical profile would have about a 29% 10-year risk.

The analysis also examined whether adding three variables obtained from an echocardiographic examination could further improve the risk score. The echo variables tested were left atrial size, left ventricular wall thickness, and fractional shortening. But even using all three of these variables together led to only a slight improvement in predictive accuracy, and they were judged to not be worth including in the risk formula, Dr. Schnabel said. Future studies will look at whether other ECG findings can make a more substantial difference.

Dr. Schnabel and her associates plan to post a calculator on the Framingham Heart Study's Web site (www.framinghamheartstudy.org/risk/index.html) soon that will accept a person's eight variables and provide 10-year atrial fibrillation risk. ■