

Testing for CRP may lead to treatment creep

If you pay attention to health news, you've probably heard about c-reactive protein (CRP). You may recall headlines touting a blood test for CRP; a 2002 story in the *New York Times*, for example, hailed it as "better than cholesterol in predicting heart disease risk." You may even have asked your doctor to test your CRP level.

Not so fast, caution several DMS researchers. They set out to study the impact that widespread CRP testing would have on the prescribing of lipid-lowering medication—and were alarmed by the results.

Harm: The investigators concluded that at least 25 million Americans at low risk for cardiac problems would suddenly become eligible for cholesterol-lowering drugs if today's criterion for elevated CRP were added to prescription guidelines. "This worries us," says Lisa Schwartz, M.D., one of the authors of the study, "because we don't know if exposing these people to cholesterol medications will do more good than harm." She concedes that some observational studies have found that reducing CRP levels led to improved outcomes for patients with established heart disease. But, she adds, there have been no randomized trials demonstrating that such drugs benefit those whose only indication for treatment is elevated CRP.

Furthermore, says coauthor Steven Woloshin, M.D., "nearly two-thirds of Americans at high risk for a myocardial infarction or cardiac heart disease death are *not* taking lipid-lowering medications. Before expanding treatment to include more *low*-risk patients for whom treatment benefit is not established," he adds, "we should ensure the treatment of *high*-risk patients where the benefit of therapy is clear." The study, also coauthored by H. Gilbert Welch, M.D., M.P.H., and Kevin Kerin, M.D., was published in the *Journal of General Internal Medicine*.

Liver: C-reactive protein, produced in the liver, is a marker for systemic inflammation. A study in the *New England Journal of Medi-*

cine in 2002 suggested that high CRP might be a stronger predictor of cardiovascular problems than LDL ("bad") cholesterol. What implicates CRP is that an inflammatory response may occur when LDL lodges in arterial walls. The inflammation, in turn, promotes LDL plaque that can rupture, creating clots and sparking heart attacks.

Since 2002, interest in CRP has soared. Use of the test among Medicare patients tripled from 145,000 in 2002 to 454,000 in 2004. And a consensus panel of the Centers for Disease Control and Prevention (CDC) and the American Heart Association (AHA), while not calling for universal CRP testing agreed that it might guide the prescribing of lipid-lowering drugs for some people at moderate risk for heart disease.

"We got interested in [CRP testing]," says Schwartz, "because we thought people were jumping on the bandwagon much too early," without understanding the pros and cons of screening. And there *are* cons, says Woloshin, to casting an ever-wider net for precursors to disease. "The downsides," he explains, "are that you scare people and maybe give them medications [that will do them no good]."

Sample: The study was based on the 1999-2002 National Health and Nutrition Examination Study (NHANES), an annual survey of a sample of the U.S. population. The team identified 2,778 participants with sufficient data to be assigned to one of four risk categories for coronary heart disease (CHD). To assign them, they used several resources, including a National Cholesterol Education Program (NCEP) algorithm. The two high-risk groups—including people with CHD or its equivalent—came to about 35% of the sample, which extrapolates to some 53 million adult Americans. The two low-risk groups came to about 65% of the sample, representing some 100 million individuals.

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Woloshin, Welch, and Schwartz (left to right) worry about overtesting those at low risk for heart disease.

Under current NCEP guidelines, which do not include a CRP criterion, most of the people in the two high-risk categories were already eligible for lipid-lowering drugs on the basis of their LDL levels. But only 12% of those in the two low-risk categories would qualify for drugs.

Drugs: Applying a conservative CRP criterion of 3 milligrams per liter of blood (mg/l) to those at intermediate risk of CHD—a "narrow" strategy, according to the CDC-AHA panel—would make 2.1 million more people eligible for lipid-lowering drugs. And under the "broad" strategy recommended by proponents of CRP tests—that is, treating anyone whose level exceeds 3 mg/l, whether or not they meet NCEP criteria—would make another 25.3 million individuals candidates for medication.

The magnitude of those numbers surprised the researchers, all of them members of the VA Outcomes Group. And they were even more startled by the discovery that while a majority of those in the high-risk groups are *not* being treated for their high LDL levels—a proven risk factor for CHD—more than 40% of those at lowest risk *are* taking cholesterol-lowering drugs. JAMES DiCLERICO