

## **Two Studies Suggest a Protein Has a Big Role in Heart Disease**

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Reducing the levels of a certain protein secreted by the body may be as powerful a tool in slowing heart disease and preventing heart attacks and cardiac-related death as lowering cholesterol, two teams of researchers are reporting today.

The studies, being published in *The New England Journal of Medicine*, provide the strongest evidence yet that the protein - known as CRP, for C-reactive protein - plays a role in heart disease.

The participants were patients with severe heart disease who were taking high doses of statin drugs, which reduce both cholesterol and CRP. Lower CRP levels, the researchers found, were linked to a slower progression of atherosclerosis and fewer heart attacks and deaths. And this effect was independent of the effect of lowering cholesterol.

"What we now have is hard clinical evidence that reducing CRP is at least as important as lowering cholesterol," said Dr. Paul Ridker of Brigham and Women's Hospital in Boston, the lead author of one of the studies.

But other heart disease researchers cautioned that more work was needed to prove that CRP directly causes heart disease. And most agreed that because the new studies involved only people with severe heart disease, it remained unknown whether healthy people would benefit from reducing their CRP levels.

Still, the study investigators said they suspected that the results would be shown to apply more broadly. If they are correct, a huge new market for the already popular statins could be opened among people whose cholesterol levels are normal but who have high levels of CRP. Of people stricken by heart attacks, half have normal cholesterol readings.

Dr. Ridker's study addressed the question of whether CRP levels independently predicted heart attacks and deaths.

The second study, by Dr. Steven E. Nissen of the Cleveland Clinic and his colleagues, asked whether CRP independently predicted heart disease progression.

In both cases, the investigators concluded, the answer was yes. (They, like most researchers in this field, have received support from drug companies, and Dr. Ridker is also an inventor of a test for CRP that his institution licensed. He and his laboratory profit from the use of the test.)

Some heart disease experts said the new studies offered persuasive evidence that doctors should focus on keeping CRP levels low in patients with severe heart disease.

"This is missing-link evidence," said Dr. Sidney Smith, a cardiologist at the University of North Carolina who is a past president of the American Heart Association and co-chairman of a committee of the heart association and the American College of Cardiology that sets treatment guidelines.

Others, though, said CRP could instead be a marker for something else being fought by statin drugs to reduce heart disease risk.

"These are very important papers," said Dr. James I. Cleeman, coordinator of the National Cholesterol Education Program at the National Heart, Lung and Blood Institute. "They are provocative. But we need to recognize that the relationship between CRP and heart disease is a developing story. This adds to the evidence, but I'm not sure it settles the issue."

CRP levels are low in healthy young people - usually less than one milligram per liter of blood - but they rise with age and with obesity, diabetes, smoking and a sedentary life. If people lose weight, stop smoking, exercise or take oral diabetes drugs, their CRP levels fall. But a third of the population has levels greater than three milligrams, and levels that high have been associated with heart disease risk, Dr. Ridker said.

Even before the new findings, evidence had been mounting that CRP and heart disease were somehow linked.

Scientists have developed hypotheses to explain why, proposing that the protein could cause plaque to develop in coronary arteries, lead plaque to burst open or bring on the formation of blood clots that then block arteries and cause heart attacks. Some drug companies have started programs to develop drugs that make a specific target of CRP and prevent its synthesis.

But what the findings of those studies mean remains uncertain. That CRP levels drop with exercise and weight loss, for example, has led some experts to argue that the protein is a marker of heart disease risk, not a cause, just as gray hair is a marker rather than a cause of aging.

CRP is made in the liver and also in the walls of coronary arteries and possibly elsewhere in the body. Its levels, which can be measured with a simple blood test, often rise and remain high in patients who have chronic inflammation from conditions like rheumatoid arthritis, for example, or periodontal disease. Patients with chronic inflammation also have an increased risk of heart disease.

Questions remain as to the protein's normal purpose in the body. CRP was discovered about 70 years ago by scientists who were trying to understand why some strep bacteria

caused disease and others did not. It is so called because it was found in the third band, which the scientists called Band C, in a gel used to separate proteins.

Then, about half a century ago, doctors noticed that after a heart attack, CRP flooded the patient's blood, and for a while the protein was used to help diagnose heart attacks.

Dr. Ridker's study involved 3,745 patients who had been hospitalized with heart attacks or with severe chest pain from the blocking of coronary arteries and who were then followed for two and a half years.

Dr. Ridker said that when the study, sponsored by Bristol-Myers Squibb, was being planned several years ago, the thought was that it would ask whether moderate statin therapy - 40 milligrams a day with Pravachol, a Bristol-Myers product - was as effective in preventing heart attacks as more intense therapy: 80 milligrams a day of Lipitor, a statin made by Pfizer Inc.

"I said, 'This is a good study, but it can be better,' " Dr. Ridker said.

He proposed also asking about CRP. Would there be fewer heart attacks and deaths among people in the study with lower levels of the protein?

Dr. Ridker said he would have been happy to find a benefit in lowering CRP levels that was only 10 percent or 20 percent that of lowering cholesterol, adding, "We never dreamed we'd get a risk reduction as large as the risk reduction from lowering LDL cholesterol" - that is, the "bad" type of cholesterol.

Dr. Nissen's study, sponsored by Pfizer, examined plaque in the coronary arteries of 502 patients with heart disease, comparing intense statin therapy against moderate and using the same doses of the same drugs as in Dr. Ridker's research.

Intense therapy resulted in lower cholesterol levels and slower growth of plaque, Dr. Nissen reported. But he also suspected that something else was going on, because some patients seemed to be doing much better than others with the same cholesterol levels.

Upon further analysis, Dr. Nissen found that levels of CRP dropped independently of cholesterol and that these reductions were independently associated with a slowing of disease progression. In patients who achieved low levels of both CRP and cholesterol, he found, plaque in the coronary arteries actually regressed.

"I'm looking right at the plaque, and when your CRP level is reduced, you are stopping the disease," Dr. Nissen said. "We are saying that CRP is a direct participant in atherosclerosis."

The next step, Dr. Ridker said, is to see if reducing CRP levels can prevent heart attacks in healthy people. His new study will enroll 15,000 people with normal cholesterol levels but higher-than-average levels of CRP, above two milligrams per liter of blood. The

participants will be randomly assigned to take either 20 milligrams a day of a statin - Crestor, made by AstraZeneca - or a placebo.

Some experts say the latest findings make it clear that doctors should monitor CRP levels in patients with severe heart disease and do whatever it takes, including giving high doses of the most powerful statins, to get levels below two milligrams per liter of blood.

"What these two papers are saying is that not only is CRP a risk factor on its own, but we should be aggressively treating it," said Dr. Valentin Fuster, former president of the American Heart Association and director of the cardiovascular institute at Mount Sinai School of Medicine in New York.

But Dr. Daniel Rader, a heart disease researcher at the University of Pennsylvania, said this might not be so easy in patients already doing everything possible.

"You've already counseled them about lifestyle, you've already given a statin, you're already targeting LDL cholesterol to less than 70," a very low level that is recommended by the current guidelines, he said. "So if you find a high CRP, what do you do? Do you tell the patient, 'Oh, this is bad. You're at high risk'?"

A difficult question, Dr. Ridker said, but one he predicted would not arise very often. Most patients with severe heart disease are not taking high doses of statins, he said, so there is room for doctors to experiment with higher doses and different drugs to reduce CRP levels if necessary.

"There is a huge payoff" if doctors understand that they need to test not just for cholesterol but also for CRP, Dr. Ridker said, adding, "That alone will save tens of thousands of lives right there."