

Studies See New Way to Reduce Heart Risk Halting inflammation may be as crucial as lowering cholesterol. In each case, statins are key.

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Researchers have found the first direct evidence that reducing inflammation in coronary arteries decreases the risk of heart attacks as powerfully as the conventional strategy of reducing cholesterol levels — a finding that offers a new approach to preventing heart disease.

Two studies published today show that inflammation of the arteries can be reduced by more aggressive use of statins, a family of drugs already used to lower cholesterol.

But more significantly, the findings are likely to set off a frantic search by the pharmaceutical industry for other drugs more powerful and more specifically targeted against inflammation.

Statins are already the most widely sold family of drugs in the world and have provided a major reduction in heart attack risk. New drugs that target inflammation — as measured by a marker called C-reactive protein, or CRP — could have an equally large financial and health impact, experts said.

"All of a sudden, we have a revolution," said Dr. Steven Nissen of the Cleveland Clinic, who led one of the studies published today in the *New England Journal of Medicine*. "It's not enough to follow patients with heart disease by measuring cholesterol levels. We need to attack CRP with the same aggressiveness that we have used for cholesterol."

If cardiologists started routinely monitoring levels of CRP in patients at risk and treating them aggressively, tens of thousands of lives could be saved over the next few years, Nissen said.

CRP levels can be lowered through diet, exercise and quitting smoking, and researchers are studying a variety of drugs that they think might reduce inflammation, but for now the best hope for most patients is statins, which are rapidly becoming the next wonder drug.

"If ever there were a perfect marriage of drug with disease, it might be between statins and atherosclerosis," researchers from University College London wrote in an editorial in the same issue of the journal.

Atherosclerosis — often referred to as hardening of the arteries — is caused by the accumulation of cholesterol-laden plaque on the interior of the arteries leading to the heart. The buildup reduces blood flow, forcing the heart to work harder. If the artery is completely blocked, a heart attack is the result.

High cholesterol levels are the chief cause of atherosclerosis, but researchers have long known that as many as half of heart attacks occur among patients who do not have high levels. There has thus been a search for other factors that increase the risk.

Some researchers have speculated that low-grade infections, such as chlamydia, can irritate artery walls, accelerating the buildup of plaque even when blood levels of cholesterol are not unusually high.

The body mounts an immune response to the infection, a process known as inflammation. The inflammation also could be caused by some other, as yet unknown, process.

Cardiologists speculate that inflammation causes plaque to break off from artery walls, triggering potentially life-threatening blood clots.

In the late 1990s, Dr. Paul Ridker and his colleagues at Brigham and Women's Hospital in Boston identified C-reactive protein as a marker for inflammation, and they subsequently demonstrated that high CRP levels were a risk factor for heart attacks and death.

Both of the new studies involve the reanalysis of data from large studies that looked at the effects of varying levels of statins on the reduction of heart attack risk.

The initial analyses looked only at the reductions of levels of low-density lipoproteins, or LDL, the so-called bad cholesterol.

Ridker and his colleagues studied two drugs, pravastatin (trade named Pravachol) and atorvastatin (Lipitor), in patients who had already had a heart attack.

They initially reported that the greatest reductions in LDL levels were associated with the greatest reduction in heart attack risk.

But because of the other studies that had shown that high levels of CRP appeared to indicate an increased risk for heart attacks, they reanalyzed the data to study how CRP levels were affected by the treatment.

They found that reductions in C-reactive protein had a beneficial effect independent of reductions in LDL cholesterol.

In the 2 1/2 years following an initial heart attack, researchers found that the risk of recurrence was 9.9% among patients whose LDL remained above a healthy target level of 70 milligrams per deciliter, or mg/dl, and whose CRP was higher than 2 milligrams per

liter, or mg/l.

If the CRP level was lowered below 2 mg/l, the risk of heart attacks fell to 7%, even when cholesterol levels remained high.

Lowering cholesterol levels while CRP remained high produced the same drop in risk.

Lowering levels of both reduced the risk to 4.9%. And lowering CRP levels below 1 mg/l reduced the risk even further — to 4%.

"This is a very powerful statement about the importance of inflammation in atherosclerosis," Ridker said.

Nissen and his colleagues used the same two drugs in a study of patients with chronic heart disease who had not had a heart attack. They obtained similar results, showing that the greatest reduction in risk of a heart attack was among patients with the greatest reduction in both LDL and CRP.

In the patients with the greatest lowering of cholesterol and CRP, the researchers actually saw a regression of plaque in the coronary arteries, indicating that the disease process had been reversed.

"We must now begin to think of CRP as an accelerator of disease activity, not just a marker associated with high risk," Nissen said.

"These are very compelling, very important studies," said Dr. Sidney Smith of the University of North Carolina at Chapel Hill, the chief scientific advisor for the American Heart Assn. "The real question now is: How do we take this information and couple it with therapeutic strategies?"

Ridker and Nissen indicated that a first step was to increase the dosage of a patient's statin when possible.

The studies looked at statin dosages as high as 80 milligrams, about twice the normally prescribed dose.

Long-term use of statins has been associated with a risk of liver and muscle damage that increases with dose. The new studies found a small increase in risk of such damage associated with the higher doses, but the overall risk was small compared to the heart attack risk.

"There is a very powerful benefit-to-risk ratio," Nissen said.

If increasing the dose doesn't work, changing statins also is a possibility.

"All statin drugs lower CRP," Ridker said, but individual patients often responded better

to one drug than to another.

The new findings are certain to accelerate the search for other drugs that can reduce arterial inflammation.

Nissen is already testing some diabetes drugs that seem to have a beneficial effect, and some experts have speculated that the benefits of daily doses of aspirin in heart patients may arise, in part, from its effects on inflammation.