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Studies Identify A New Villain In Heart Disease

C-Reactive Protein May Play As Big a Role as 'Bad' Cholesterol; Could Affect Use of Statins

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In findings that could change medical care for heart patients and spur a new wave of drug development, two research groups reported compelling new evidence in the effort to prevent heart attacks: Reducing levels of a protein known as CRP may be just as important as fighting cholesterol.

Cardiologists who led the studies said the findings are likely to transform how doctors think about and use cholesterol-lowering statins, the world's top-selling class of drugs and a major weapon against the ravages of cardiovascular disease.

The results also amount to the strongest evidence yet that CRP, or c-reactive protein, is a cause of heart disease. That is likely to spur already heightened interest among drug companies to develop other medicines that would reduce levels of CRP.

In two separate studies on statin use, researchers found that statins produced more benefits for patients when they helped achieve low levels of CRP, regardless of how well the drugs reduced LDL, or bad cholesterol. The findings challenge widely held notions that statins save lives and reduce heart attacks solely by lowering LDL cholesterol, and suggest the drugs work by reducing CRP as well. The studies are being published today in the New England Journal of Medicine.

The researchers conclude that doctors and patients should aggressively target both CRP and LDL -- possibly by increasing doses or switching patients to different statins -- to achieve the best chance of avoiding heart attacks and other consequences of cardiovascular disease. Heart disease is the globe's leading killer. The findings also could spur expanded use of CRP blood tests to monitor whether a drug is sufficiently lowering CRP levels.

Both of today's studies compared results from using 80 milligrams of Pfizer Inc.'s Lipitor, the highest dose of one of the most potent statins, against results in patients who took 40 milligrams of Bristol-Myers Squibb Co.'s Pravachol, a weaker statin that reflected a moderate treatment strategy.

Currently, even for high-risk patients, many statin prescriptions are written for moderate doses, says Paul Ridker, a researcher at Brigham and Women's Hospital and Harvard Medical School, Boston, and lead author of one of the studies. By measuring and monitoring both indicators and raising doses if indicated, "physicians can do a better job immediately," he maintains. "That translates into tens of thousands of lives right away

just by doing better management of statin therapy." Dr. Ridker, whose study "Prove-It" was sponsored by Bristol-Myers, holds patents related to CRP testing that are held by Brigham and Women's Hospital.

The other study, called "Reversal," was sponsored by Pfizer and led by Steven Nissen, a cardiologist at the Cleveland Clinic in Ohio. In both cases, the more-aggressive treatment approach offered patients the better chance of getting both LDL and CRP to low levels. Also in both studies, Lipitor outperformed Pravachol, but Dr. Ridker says that some patients successfully achieved very low cholesterol and CRP levels with Pravachol. He adds that what mattered most wasn't the treatment used but the ability to get to low levels of both LDL and CRP.

TWO TARGETS

Rates of heart attacks or death from heart disease over 2.5 years, based on levels of LDL cholesterol and C-reactive protein taken 30 days after beginning treatment with a statin. Rates declined with lower levels of CRP, even when LDL was high.

LDL greater than 70 and CRP greater than 2	9.9%
LDL less than 70 and CRP greater than 2	7.1
LDL greater than 70 and CRP less than 2	7.0
LDL less than 70 and CRP less than 2	4.9

Source: "C-Reactive Protein Levels and Outcomes after Statin Therapy," by P.M. Ridker et al., New England Journal of Medicine

Some other scientists are skeptical. David Waters, chief of cardiology at San Francisco General Hospital, believes further studies are needed to confirm CRP's causative role in disease. "Before we target CRP as something to be treated, we should make sure it is actually a villain and not just some guy standing on a street corner in Queens looking guilty," he says.

For the past several years, researchers have debated the role of CRP in heart disease. Levels of the protein are known to rise when inflammation is present somewhere in the body. And a number of studies have associated inflammation and elevated CRP levels with a higher risk of heart attack. But many doctors have believed that high CRP is merely an indicator of disease -- a so-called marker whose presence in the blood can be measured with a simple, inexpensive test as a means of assessing heart risk.

What this new research suggests is that CRP is an agent of inflammation that helps cause heart disease and thus a potential target of therapy as well.

The data are fresh analyses of two studies that have had a major impact on heart treatment. After Dr. Ridker's Harvard and Brigham and Women's colleagues presented the main findings of the Prove-It study last March, a panel of experts issued an update of

cholesterol guidelines urging doctors to consider an LDL target below 70 for high-risk patients, a change from previous recommendations of below 100.

The new analysis supports that recommendation but now suggests that doctors also should look beyond cholesterol. Dr. Ridker and his colleagues divided the 3,745 patients in the study into four groups based on their LDL and CRP readings taken about 30 days after they were hospitalized for unstable chest pain called acute coronary syndrome.

The researchers found that 7.1% of those whose LDL was below 70 -- in accordance with what is the current treatment recommendation -- but whose CRP was above 2 had an additional heart attack or died from heart-related causes within 2.5 years, while just 4.9% of those whose LDL was below 70 and CRP was below 2 suffered a recurrent event.

Even when the LDL level was above 70, having a CRP below 2 was associated with a 7% chance of another major heart problem -- almost identical to the low LDL and high CRP group. For patients whose indicators were above the threshold in both cases, the event rate was 9.9%.

The findings indicate that reducing CRP independently gets about the same benefit as reducing LDL, says Dr. Ridker, who was expecting to find a small additional CRP effect after taking LDL into account. "To get a benefit that is at least as large is extraordinary," he says. "It tells you how powerful the inflammation component of heart risk is on top of an already powerful cholesterol component."

Dr. Nissen's paper, a reanalysis of his 502-patient Reversal study, used ultrasound imaging to measure the amount of plaque on artery walls and found that low LDL and low CRP each were linked to a slowing or stanching of progression and even a regression of cardiovascular disease. Whether this would translate into fewer heart attacks isn't known, but researchers say the findings are in line with those in the Prove-It study.

"If you want to reverse the disease, you've got to get the CRP down as well as the LDL," Dr. Nissen says.

How to do that is a challenge. Daniel Rader, director of preventive cardiology at University of Pennsylvania School of Medicine, Philadelphia, describes the new data as "very provocative" but isn't certain they apply widely yet to current clinical practice. "The biggest question is, if you're on a statin with optimal care and your CRP is still elevated, what you do about it?" he says.

Even at maximum doses of statins, getting LDL to below 70 is difficult for many patients and the strategy increases the likelihood that patients will suffer muscle pain called myalgia and other side effects of the drugs.

Dr. Ridker says some answers are for patients to lose weight, quit smoking and get regular exercise -- all of which can lower CRP. "You just can't play couch potato and trust the drugs to get you there," he says.

In addition, other drugs already on the market, including aspirin; Vytorin, a combination cholesterol remedy co-marketed by Merck & Co. and Schering-Plough Inc.; the diabetes drugs Actos, co-marketed by Eli Lilly & Co. and Takeda Pharmaceutical Co. of Japan; and GlaxoSmithKline PLC's Avandia all have been shown to reduce CRP levels. But there aren't any clinical-trial data available to guide their use or to demonstrate whether these specific drugs will reduce the risk of major heart problems by lowering CRP.

Meantime, Sanofi-Aventis SA's obesity drug called rimonabant, which is in late-stage development, appears to reduce CRP, though, similarly, there aren't any data indicating whether that would translate specifically into heart benefits.

Dr. Ridker's study included only patients with unstable heart disease when their statin treatment began, and some doctors caution against extrapolating the results to healthy people with lower risk.

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