



By
Navin S. Nikam, M.D.
Nik Nikam, M.D.

Heart disease is the number one cause of overall morbidity and mortality in the US. Despite significant advances in the understanding of traditional cardiac risk factors such as high cholesterol, hypertension, smoking, diabetes among others in the diagnosis and management of cardiovascular diseases, it is perplexing to note that more than 40% of the people who have heart attacks, have cholesterol in the normal range. This has energized the researchers to look at indicators, beyond the traditional risk factors, to identify those people who maybe at an increased risk of developing future cardiovascular events and take measures to reduce those events.

An observational study involving more than 85,000 nurses showed that those who had elevated levels of C-Reactive Protein (CRP), a marker for low level inflammation, had higher incidence of vascular events compared to those with normal CRP levels.

Several small scale studies have shown that those who were getting statins for high LDL levels benefited more when they had elevated CRP levels in comparison to those with normal CRP levels.

A landmark study that was reported at the American Heart Association annual meeting this month sheds some light on one such

indicator that might identify people with minimal traditional risk factors such hypertension, diabetes, high cholesterol, who may be at an increase risk for developing heart disease in the future.

This study called JUPITER (acronym for Justification for the Use of statins in Prevention and Intervention Trial Evaluating Rosuvastatin), involved 17,802 patients. It was based on the hypothesis that people with elevated levels of "C-reactive protein (CRP)," may be at an increase risk of developing cardiovascular disease in the future. C-reactive protein, a marker of low-grade inflammation, can readily be measured in any laboratory.

They selected 17,802 people with no history of hypertension, diabetes, or normal LDL cholesterol levels. The only inclusion criterion was that they had a CRP level above 2.0 mg/L. The mean CRP in the treated group was 4.2 mg/L in comparison to 4.3 mg/L in the placebo group. It also excluded people with known history of heart disease, or those who were already on statins. The study population included a wide spectrum of people including, whites, women, blacks, Hispanics, and others.

Half the people in the group (8901) received 20 mg Rosuvastatin (cholesterol reducing drug) while the other half received a placebo. These patients were followed for four years. The study was prematurely terminated in March 2008 because of overwhelmingly positive result in favor of the Rosuvastatin treated group.

In the Rosuvastatin treated group there was a 50% reduction in the LDL cholesterol, 4% increase in the HDL cholesterol, 17% decrease in the triglyceride, and a 37% decrease

in the CPR levels. The LDL level was less than 50 mg/dL in the treatment group.

At the end of four years cardiovascular endpoints such as heart attack, stroke, unstable angina (chest pain), revascularization, and cardiovascular related deaths were monitored. In the placebo group 251 out of 8901 people experienced the above mentioned event(s). In the Rosuvastatin treated group there were only 142 such incidences. Overall, the Rosuvastatin treated group experienced a 44% reduction in these end points. These benefits were noted across the board in men, women, smokers, non-smokers, people less than 65 and people more than 65, people with or without hypertension, people with or without family history of heart disease, and in people who were normal weight and who were overweight. There was a 20% reduction in mortality in the treated group. There was also a 47% reduction in the rates of hospitalization or revascularization in the Rosuvastatin group over a two year period.

There was a slight increase in the incidence of diabetes; 3% in the treated group in comparison to 2.4% in the placebo group. Overall, the drug was well tolerated by the group.

Another study (AFCAPS/TEXCAPS) randomized 5740 men and women with average cholesterol levels, low HDL, and absence of cardiovascular diseases, to lovastatin and placebo. The treatment group showed a 37% reduction in the risk of first coronary events. Here also they noted an increased incidence of cardiac events in those who had higher CRR levels. Those who had higher levels of CRP, but low levels of LDL cholesterol had cardiac events equal to those who had higher LDL levels suggesting that high levels of

CRP were as risky as the elevated levels of LDL in predicting future cardiac events. The treated group also noted a 15% reduction in the CRP levels in the treated group.

Another inflammatory marker that has gained attention is the Lipoprotein-associated Phospholipase A2 (Lp-PLA2). It has been shown to recognize the presence or formation of rupture-prone plaque. It has also been shown that lifestyle modification including diet and exercise along with lipid lowering agents can be effective in lowering the Lp-PLA2.

WASCOPS (West of Scotland Coronary Prevention Study Group), reported in 1995, was an earlier study that looked at using cholesterol lowering drug Pravastatin in reducing cardiovascular events. This study involved 6595 men without a history of heart attack. At the end of five years the combined cardiovascular events were 5.5% in the treatment group compared with 7.9% in the placebo group.

There were two additional points of information derived from this study that are noteworthy. After the study was stopped, the same people were followed for the next five years. Interestingly, the group that received the Pravastatin continued to show lower cardiovascular events compared to those who received placebo during the study, despite many in the treatment group were no longer taking the drug. One explanation was that by reducing the LDL levels, they were perhaps able to stabilize the plaque that provided long term benefit, long after the drug was discontinued. The second point related to the CRP. When the researchers went back and looked at the CRP data they had gathered from the study population, found that the combination of elevated Lp-PLA2

cholesterol and high CRP levels were highly correlated with increased future cardiovascular events.

Cardiac imaging is an another area of interest in detecting a vulnerable plaque that is likely to rupture and cause a heart attack. The CT scanners available today can identify the coronary arteries and plaques buildup within those arteries. However, the present day CT scanners are not able to differentiate the plaques in various stages of formation. We can detect calcium buildup within a plaque. However, we are not yet able to tell the difference between a stable and an unstable plaque. It is the unstable plaque that is of a greater concern because the cap can rupture and lead to thrombus formation that eventually occludes the coronary arteries resulting in a heart attacks.

These studies have enabled us to take a step further in identifying people who might be a risk of developing cardiovascular problems in the future and trying to reduce such events before they have an effect on the patients. This will change the way we will look at existing risk factors while taking into account the new identifiers when we see patients for the first time or those who had a negative cardiac workups. The new prudent approach in the treatment of heart disease risk factors would be to use statins if someone has elevated LDL cholesterol, diabetes, or CRP of greater than 2.0 mg/L along with diet, weight control, and exercise.

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Nik Nikam, M.D.

P: 281-265-7567

nikam@alltel.net