Exploring Jupiter

By Gregory S. Cohn, M.D.

A very controversial topic in the field of preventive cardiology concerns the "pleotropic" (plee-o-tro-pick) effects of the statin drugs (Zocor, Lipitor, etc…). Simply put, do all of the cardiovascular benefits derived from these medications occur solely due to their cholesterol-lowering effects? Currently there is no definitive answer to this question, but accumulating evidence suggests that statins do much more than simply affect lipid levels. Other reputed benefits derived from these drugs include decreases in the tendency to form blood clots, improvements in arterial (endothelial) structure and function, and perhaps most importantly, reduction in levels of inflammation. Recall that the processes behind the development, growth, and subsequent rupture of atherosclerotic plaques (causing heart attacks, strokes, etc…) are largely inflammatory in nature. In the past, I have informed you that the plaques most likely to rupture are generally **not** the largest (i.e. causing the greatest degree of blood flow limitation), but those that are the most **unstable** due to high levels of inflammation. Insight into the amount of inflammation that is occurring inside our bodies can be gained by measuring blood levels of certain inflammatory markers, most commonly **high-sensitivity CRP**. Several studies have strongly suggested that elevated levels of this marker (indicating high levels of inflammation) are associated with an increased risk for cardiovascular disease events, **even when cholesterol levels are normal**.

It is for the above reasons that the results of the JUPITER study were so highly anticipated. These results were recently announced at the 2008 American Heart Association meeting, and made headlines across the country. In this study, almost 18,000 men and women **without** a known history of cardiovascular disease were enrolled if they had an LDL ("bad")-cholesterol **less than 130 mg/dl** (i.e. normal levels) and **at least average levels of inflammation**, as indicated by a high-sensitivity CRP of 2 mg/L or more (low levels are less than 1; high levels are greater than 3). These subjects were randomly assigned to receive either Crestor (a statin) or a matching placebo, and followed until the first occurrence of a major cardiovascular event (heart attack, stroke, etc…). In other words, a powerful cholesterol-lowering medication was being given to people with normal cholesterol levels, but with evidence of active inflammation, thus providing more direct insight into the potential anti-inflammatory effects of this medication. Not surprisingly, compared to those assigned to placebo, the subjects receiving Crestor had 50% lower median LDL-C and 37% lower median high-sensitivity CRP levels. What was striking was a **44% reduction** in the incidence of major cardiovascular events among those receiving this medication. This benefit was so strong that the study, which was originally planned to last for 5 years, was terminated after a median follow up of only 1.9 years!

The implications of this study are profound, and will be debated for a long time to come. However, I think a few pearls can be gleaned from the results at this time. First, those

among us who have neither elevated lipid nor inflammation levels have the lowest cardiovascular risk, but those with high levels of inflammation are at increased risk even if they have normal lipids. Second, in some cases, measurement of inflammatory markers, like high-sensitivity CRP, may help in an overall cardiovascular risk assessment. Finally, anything that has been proven to have a cardiovascular benefit has a direct or indirect anti-inflammatory effect. This would include diet, exercise, weight loss, omega-3 fish oil, aspirin, and other medications. Needless to say, the converse of this is also true: anything that promotes cardiovascular disease also fosters inflammation, either directly or indirectly.

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