Inflammatory Biomarkers, Statins, and the Risk of Stroke
Cracking a Clinical Conundrum
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A central paradox of the cholesterol hypothesis is that long-term treatment with statins reduces the risk of stroke, yet LDL cholesterol is not a strong risk factor for stroke. In almost all major prospective epidemiological studies, relationships between any measure of cholesterol and the risk of incident stroke are minimal. Nonetheless, as clearly demonstrated in large-scale randomized trials, therapy with HMG-CoA reductase inhibitors reduces stroke risk by as much as 25%, a reduction similar to that for myocardial infarction and cardiovascular death.

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Relative risks of stroke in recent studies employing CRP (top) as compared with a combination of 5 inflammatory-sensitive proteins (ISPs) (bottom). PHS indicates Physicians’ Health Study; WHS, Women’s Health Study; Leiden, Leiden 85-Plus Study; NHANES, Third National Health and Nutrition Examination Survey; FHS, Framingham Heart Study; and Malmo, Malmo Preventive Project. Relative risks are based on the presence of 4 of 5 ISPs in the top quartile (Malmo) or on CRP levels alone in the top quartile (all other studies).

reflects a primary abnormality of fibrinolysis and a resultant hypercoagulable state. After all, several fibrinolytic proteins, including tissue-type plasminogen activator and plasminogen activator inhibitor, have also been shown to predict incident stroke. Furthermore, as a reflection of fibrin/fibrinogen degradation, plasma levels of D-dimer are known to be elevated among individuals at risk for initial as well as recurrent cardiovascular events.

In contrast to fibrinogen, the other inflammatory sensitive proteins measured by Engström and colleagues are not structural proteins implicated directly in clot formation. Like CRP, these other inflammatory sensitive proteins can be considered as classic acute phase reactants. The data of Engström et al thus provide strong confirmatory evidence that several nonspecific inflammatory markers are elevated among individuals at risk for stroke, data that resonate with studies using erythrocyte sedimentation rate or the white blood cell count as surrogates for low-grade systemic inflammation.

Engström and colleagues also address the clinical issue of whether or not multiple markers reflecting inflammation and hemostatic function add to our ability to detect vascular risk, an approach not widely tested in prior large-scale prospective settings. What their data demonstrate, however, is that simultaneous measurement of multiple markers reflecting a common pathophysiological pathway is unlikely to have additional clinical utility. As shown in the Figure, the magnitude of stroke risk among those in Malmo with 4 of 5 inflammatory-sensitive proteins elevated above the 75th percentile is virtually identical to risk ratios reported in other studies based on CRP evaluation alone. By contrast, as has been shown in several instances, the combination of a stable inflammatory biomarker (such as CRP) and an effective lipid marker (such as the total to HDL cholesterol ratio) improves the predictive value of either used alone. This latter observation is consistent with data indicating that inflammatory biomarkers are not related to lipid levels, yet that both are critically involved in the atherothrombotic process.

Post hoc analyses of both the Cholesterol and Recurrent Events (CARE) trial and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) suggest that statin therapy may be differentially effective among those with inflammation compared with those without. Despite these data, we must be careful not to assume that statins will reduce event rates among those with isolated elevations of CRP. After all, although the AFCAPS/TexCAPS analysis suggests that statin therapy may be effective among individuals with low LDL levels but increased CRP, the absolute difference in number of events between the placebo and statin arms in this subgroup was small. Because the public health implications of prescribing statins to low LDL/high CRP patients are wide ranging, a large-scale randomized trial in primary prevention directly testing this hypothesis is critically needed.

Interactions between inflammation, lipid lowering, and stroke may not be unique to HMG CoA reductase inhibitors. In the Veterans Administration HDL Intervention Trial (VA-HIT), random allocation to gemfibrozil led to a 59% reduction in transient ischemic attack and a 25% reduction in stroke among secondary prevention patients with low levels of LDL cholesterol. These reductions in cerebrovascular risk were achieved with a lipid-lowering regimen that had minimal effect on LDL cholesterol levels yet also reduced CRP. As CRP in turn can induce several interrelated inflammatory responses, it is becoming easier to conceptualize how pharmacological agents that modulate vascular inflammation might beneficially affect clinical outcomes without necessarily lowering LDL cholesterol.

Twenty-five years ago, the introduction of lipid screening served in part to teach physicians and patients about the importance of cholesterol in risk prediction. Today, in a similar manner, CRP evaluation may have the potential to translate the biology of inflammation into clinical practice. One and a half million myocardial infarctions and seven hundred thousand strokes will occur in the United States this coming year. If an inexpensive method to detect vascular risk can improve physician compliance with established prevention guidelines as well as increase patient motivation for diet, exercise, blood pressure control, and smoking cessation, then the goal of preventing atherothrombotic disease will be one step closer.

References


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