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.

Early recognition of this apparent paradox played a major role in spurring research into non-lipid effects of statin therapy and the search for inflammatory biomarkers that might be strong determinants of stroke. In this regard, data for C-reactive protein (CRP) have been particularly informative. Not only has CRP been shown in several studies to predict incident stroke independent of LDL cholesterol, but statins have been shown to reduce CRP in an LDL-independent fashion. Moreover, differences between cholesterol and CRP in terms of predictive value provide considerable insight into the paradox facing the epidemiology of stroke. In the Physicians’ Health Study of healthy middle-aged men and in the Women’s Health Study of healthy postmenopausal women, total cholesterol and CRP both predict incident myocardial infarction, yet only CRP predicts incident stroke.

Almost identical data regarding CRP and thromboembolic stroke have now been presented in cross-sectional data from the National Health And Nutrition Examination Survey (NHANES) as well as in two prospective cohorts, the Leiden 85-Plus Study and the Framingham Heart Study. In Framingham, for example, baseline CRP proved to be a strong linear predictor of incident stroke even after adjustment for other atherothrombotic risk factors, data that confirm the utility of CRP as an adjunct in the global prediction of cardiovascular risk. These findings, in concert with laboratory evidence of novel pathways by which statins exert direct anti-inflammatory effects, have led to an alternative view of the stroke paradox. With plaque rupture increasingly seen as a critical feature of thromboembolic stroke, the concept of plaque stabilization through anti-inflammatory mechanisms provides a viable hypothesis as to why statins might reduce cerebrovascular risk even in the absence of elevated LDL cholesterol.

In this issue of Circulation, Engström and colleagues further explore this conundrum in a large-scale study of 6063 Swedish men who were monitored over a period of 19 years for incident cardiovascular events, including stroke. In contrast to prior studies of CRP, Engström and colleagues measured 5 inflammation-sensitive proteins (ISPs): α1-antitrypsin, haptoglobin, ceruloplasmin, orosomucoid, and the hemostatic marker fibrinogen. As would be expected, given the roles of inflammation and hemostasis in the genesis of atherothrombosis, those individuals with 4 of these 5 ISPs in the top quartile or higher had significantly increased risks of developing future vascular events. However, although hyperlipidemia was associated with an increased risk of coronary events among those with high as well as low ISP profiles, this was not the case for stroke. After risk factor adjustment, men with hyperlipidemia and high ISP levels had significantly increased risks of ischemic stroke (RR=2.1, 95% CI 1.4 to 3.3). By contrast, in the absence of high ISP levels, hyperlipidemia was no longer significantly associated with ischemic stroke (RR=1.2, 95% CI 0.8 to 2.0). With appropriate caution, the authors suggest that their observational data yet again support the hypothesis that inflammation (and perhaps hemostatic function) may play a larger role in stroke than in myocardial infarction. They further suggest that prior epidemiological studies of cholesterol and stroke may have resulted in null findings precisely because they failed to simultaneously assess the inflammatory component of this disease.

The results from Engström and colleagues deserve careful consideration for several reasons. Most importantly, the study is well designed, the sample size is large, and the follow-up period is long. However, it is equally important to put these data into a larger perspective. It is only in hindsight that we can conceptualize fibrinogen as a primary inflammatory-sensitive protein. As the precursor to fibrin, fibrinogen plays a fundamental role in hemostasis, thrombosis, and clot formation, and it remains at least equally plausible that the relationship between fibrinogen and vascular events first described by Wilhelmsen et al 15 years ago.
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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