Cholesterol as a Risk Factor for Stroke

The Fugitive?

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The burden of stroke is unquestionable in a myriad of aspects. Multiple stroke risk factors are known, and some of them are considered strong and primary while others are considered uncertain and secondary. Among the latter, there is hyperlipidemia. As the acute stroke treatment is costly, the saying that prevention is better than treatment bears a special meaning here. In this discussion, as prosecutors from our bar we stand to plead, “Cholesterol – guilty for stroke.”

Several epidemiological studies demonstrated a correlation between increased blood total cholesterol levels and risk of myocardial infarction.1,2 The association between cholesterol levels and stroke occurrence is debated in the literature. In the Framingham cohort no connection was found between the levels of cholesterol and the incidence of stroke.1 Nonetheless, in young women, a positive correlation between total cholesterol levels and stroke-related mortality was observed, while in subjects in 6th and 7th decade of age, an inverse correlation between these parameters was found.3 The combined analysis of cohort trials showed no significant association between the increased level of serum cholesterol and stroke rate, except for patients younger than 45 years.4 However, this analysis did not stratify into stroke subgroups and thus a positive association with ischemic stroke might be offset by a negative association with hemorrhagic stroke. This was confirmed in a longitudinal study on men screened for multiple risk factors, as a positive correlation between total cholesterol levels and ischemic stroke risk, and a negative association between cholesterol level and occurrence of all hemorrhagic strokes was demonstrated. Serum cholesterol levels under 4.14 mmol/L increased the risk of fatal intracranial hemorrhage while the levels above 7.23 mmol/L increased the risk of death from ischemic stroke.5 An overview of Asian subjects showed a trend toward increased risk of hemorrhagic stroke in subjects with decreased cholesterol level.6 A positive correlation between very high total cholesterol levels >8 mmol/L, and the risk of nonhemorrhagic stroke was demonstrated in a prospective community based study.7 At this point we can state that there is indeed a convincing point for elevated cholesterol levels to be linked with increased risk of ischemic stroke. The reasons for not finding the clear-cut relationship between cholesterol level and stroke occurrence may be multiple. The longitudinal cohort studies were predestined to evaluate the role of cholesterol in coronary atherosclerosis, but not to investigate its role in stroke. Therefore, by selecting middle-aged subjects for cardiac studies, the older subjects, who were more susceptible to cerebral infarction, were undoubtedly lost. Moreover, analysis of the occurrence of stroke subtypes and differentiation between cholesterol components was not done. Additionally, the prophylactic treatment used might also influence the incidence of stroke. While there may be some missing epidemiological evidence for the correlation between hypercholesterolemia and stroke occurrence, should we stop at this point and set our defendant free? With some circumstantial evidence we would like to prove its guilt.

The Heart Protection Study tested the effectiveness of simvastatin in patients with coronary disease, other occlusive disease, or diabetes in conjunction with LDL cholesterol levels at least 3.5 mmol/L.8 A 24% reduction in the rate of all-cause mortality and fatal or nonfatal vascular events between simvastatin and placebo groups was shown. There was a 25% reduction in the all-cause stroke incidence rate and a 30% reduction in the ischemic stroke incidence rate. Transient ischemic attacks were also significantly less frequent in the simvastatin versus placebo group (2% versus 2.4%). In this trial, there was a subgroup of patients with the history of cerebrovascular disease without coronary heart disease. However, there was no stratification for the past medical events, thus yielding the interpretation of the effects of simvastatin in subgroups untrustworthy. In this subgroup, a 21% relative risk reduction of major vascular events was demonstrated. However, no effect of simvastatin on stroke recurrence was observed.

A few meta-analyses on lipid-lowering therapy and coronary prevention were published in the past decade. The most recent one included all randomized trials, published between 1966 and 2001, testing statins, resins, fibrates, niacin, surgical interventions, and diet.9 There were 10 primary and 28
secondary prevention trials. This analysis showed a significant (17%) relative risk reduction of stroke incidence. There was no significant heterogeneity between trials either in intervention tested (primary versus secondary prevention) or type of lipid-lowering therapy examined. When analyzing subgroups, only statins yielded a significant (24%) relative risk reduction of stroke. When analyzing by type of intervention, the significant effect of statins on stroke incidence was present only in secondary prevention, with a 26% relative risk reduction of stroke. However, the incidence of fatal strokes was not influenced by lipid-lowering therapy. Lipid-lowering therapy did not change the incidence of hemorrhagic stroke.

A strong evidence for the role of cholesterol in stroke comes with the documented correlation of stroke incidence and the degree of cholesterol reduction, baseline cholesterol level, and final cholesterol level. The final cholesterol level of ≥6 mmol/L, achieved with lipid-lowering therapy, separated between absence and presence of stroke risk reduction and thus exposed an accused correlation between elevated serum cholesterol levels and reduction of stroke incidence.

Is elevated cholesterol a risk factor for stroke? While the evidence is mostly indirect for stroke, it is not disputable for coronary heart disease. This must be remembered when patient management is addressed, since prevention of atherothrombotic events should be a global effort.

**Cholesterol Is Associated With Stroke, but Is Not a Risk Factor**

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Proponents of cholesterol as a risk factor for stroke usually support their argument by citing evidence from clinical trials of the beneficial effects of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors ("statins") in reducing stroke risk among people with prior cardiovascular disease. Although such studies may provide some supportive evidence, causation can really only be established between a risk factor and a disease when certain criteria are met. These include the criteria that the association between the risk factor and the disease must be temporal and biologically plausible. Although there may be little or no debate about whether cholesterol is a biologically plausible risk factor for stroke or that high cholesterol levels precede (rather than follow) stroke, some of the other criteria are more ambiguous. These other "guidelines for causation" are discussed below:

1. **Strong Association Between Risk Factor and Disease**

   There have been numerous major prospective epidemiological studies of cholesterol and the risk of stroke. However, at best, the results have provided evidence for a minimal association. Initially, part of this may have been because stroke was treated as a homogeneous entity. This may have resulted in an association being masked by the opposing effects of cholesterol on ischemic stroke and intracerebral hemorrhage. In a meta-analysis that was limited to ischemic stroke, cholesterol levels of more than ≈5.7 mmol/L were associated with a relative risk of ischemic stroke of 1.3. One must be extremely cautious in interpreting findings with such weak associations as they could be influenced by confounding factors or bias. This is particularly important given that this risk ratio is unadjusted for any potentially confounding factors.

2. **Consistency of Results Between Studies**

   The association between cholesterol and stroke has not always been consistent. In an analysis of the results of 45

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**References**


**Key Words:** stroke ■ incidence ■ lipid-lowering therapy ■ statins
cohort studies, no association was found between cholesterol and stroke. However, the fact that many of these studies included only fatal strokes as an endpoint may have resulted in bias. In contrast, authors of a recent meta-analysis of 7 cohort studies reported a positive association between cholesterol and ischemic stroke. The fact that the former analysis of cohort studies mainly included fatal events, and that there was no differentiation between ischemic and hemorrhagic stroke, may explain these disparate findings.

3. Dose–Response Relationship
In a recent meta-analysis of cohort studies conducted in the Asia-Pacific region, there was a positive association between cholesterol levels and ischemic stroke. Each increase of 1 mmol/L to the “usual cholesterol” level was associated with a 25% greater risk of fatal or nonfatal ischemic stroke. Although adjusted for the important and potentially confounding factors of age, systolic blood pressure, and smoking status, other equally important confounding factors have not been considered. Such factors may include the so-called inflammation-sensitive plasma proteins. In the Framingham study, cholesterol was associated with ischemic stroke among people who had high levels of inflammation-sensitive plasma proteins, but not among people with low levels of these markers. Thus, cholesterol may not be a risk factor in isolation, but may interact with other factors to aid the progression of atherosclerosis.

4. Removing the Risk Factor Reduces Disease Risk
Meta-analysis of early trials of lipid-lowering therapy with the use of dietary or drug intervention (eg, fibrates and resins) provides evidence that, among people with elevated cholesterol levels, reducing cholesterol levels per se does not reduce the risk of stroke. In contrast, use of HMG-CoA reductase inhibitors (“statins”) among such patients has been reported to produce about a 24% relative risk reduction of all stroke and a 30% relative risk reduction of ischemic stroke. The disparity between the dramatic effects of statins in reducing stroke risk compared with the more modest effects of other methods of reducing cholesterol levels may reflect the possibility that statins have greater cholesterol-lowering efficacy. However, it is also likely that other pharmacological effects of statins such as amelioration of endothelial dysfunction, promotion of atherosclerotic plaque stability, and modification of both inflammatory responses and thrombus formation play a major role.

Further evidence for a major role of nonlipid properties is provided by the observation that, among high risk patients with average or below-average cholesterol levels, both the development of carotid atherosclerosis and coronary and stroke events can be reduced by statins.

In summary, the prevailing evidence is not supportive of the hypothesis that cholesterol is an important risk factor for stroke. This is based on the observation that the association between cholesterol and stroke is weak, inconsistent, and that lowering cholesterol levels does not necessarily result in a reduction in the risk of stroke. It is clear that this issue has been clouded by the observation of a reduced risk of stroke with use of statins.

References
Stroke and Cholesterol
Weakness of Risk Versus Strength of Therapy
Geoffrey A. Donnan, MD, FRACP; Stephen M. Davis, MD, FRACP

This is one of the most tortured issues yet debated by our team of experts. Each of our protagonists has identified the key points, but naturally has selectively cited those more likely to advance their argument. Let us review the facts, as we see them.

1. Cholesterol is a very weak risk factor for ischemic stroke, in contrast to coronary artery disease.

2. Cholesterol reduction with diet and nonstatin drugs is not effective in stroke prevention, although reductions in levels of cholesterol are modest.

3. Statins have potent treatment effects in stroke prevention, although most of the evidence to date is in patients with coronary artery disease.

4. There is some evidence that statins are also effective in secondary stroke prevention, with pivotal trial results awaited.1

Because of the systemic nature of atherosclerosis, it may at first seem counterintuitive that cholesterol is not a potent risk factor for stroke, as it is for coronary artery disease. An obvious explanation for this difference is the heterogeneous nature of stroke, although even when homogenous cohorts of ischemic stroke have been studied, the association remains weak. Thrift argues that cholesterol cannot be unequivocally condemned as a stroke risk factor, because the “guidelines for causation” are not strictly fulfilled. Piechowski-Jóźwiak and Bogousslavsky want cholesterol “found guilty,” although they acknowledge that there appears to be some missing epidemiological evidence and rely on the circumstantial evidence provided by therapeutic weapon of statins.

So what do we think? There seems to be an unacceptable dichotomy between the weakness of cholesterol as a stroke risk factor and the potent effects of statin therapy. For example, the benefits of statins in many trials appear to be as great in those with “normal” cholesterol levels compared with those with higher cholesterol levels, similar to the effect seen with blood pressure lowering.1,2 As with blood pressure, the trials suggest that clinicians change their concepts of normal versus abnormal levels to a more continuous benefit. Interestingly, although statins have been shown to attenuate the progression of carotid atherosclerosis,3 even this biological effect may not be related to cholesterol reduction.4 Hence, it seems hard to escape the idea that the protective effect of statins may be largely due to their non–cholesterol-lowering effects.

While this is where we stand at the moment, the issue is still perplexing enough to keep this debate alive for some years to come.

References

Key Words: cholesterol ■ risk ■ statins ■ stroke
Stroke and Cholesterol: Weakness of Risk Versus Strength of Therapy
Geoffrey A. Donnan and Stephen M. Davis

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