# Lowering lipids after a stroke or transient ischaemic attack

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***There is a lot of clinical uncertainty about how to aggressively pursue elevated cholesterol levels in patients following stroke or transient ischaemic attack. This article reviews the evidence linking cholesterol level with stroke and looks at whether treatment with lipid-lowering drugs can be justified.***

There are two major issues for physicians concerning lipid levels in the patient who has had a stroke or transient ischaemic attack (TIA). The first is whether measuring blood lipid levels is in any way useful, i.e. does an abnormal blood lipid result tell us anything about the risk of a future stroke or other vascular events? The second is whether treatment to lower blood lipid levels can modify the risk of a future stroke or other vascular events. There has been no general consensus reached on either issue, and the varying views and what evidence there is will be presented here.

## ABNORMAL BLOOD LIPIDS AS A RISK FACTOR FOR STROKE

There is convincing evidence from large prospective cohort studies that an elevated blood cholesterol level is associated with a greater risk of cardiovascular and peripheral vascular disease (Wilson et al, 1998). Given that the underlying disease process is largely similar (i.e. atherosclerosis), it might be reasonable to assume that elevated blood cholesterol would also be associated with a higher risk of stroke. This is not necessarily so. In the Framingham study (Kannel et al, 1965), there was no overall correlation between cholesterol level and stroke. Some of the results in that study, such as the inverse correlation between low density lipoprotein cholesterol and stroke in women, are at variance with the data for cholesterol and coronary artery disease (Gordon et al, 1981).

In the Framingham study, an inverse relationship of increasing fat intake with ischaemic stroke incidence was seen (Gillman et al, 1997). In the Honolulu Heart Study (Kagan et al, 1980), which involved American men of Japanese origin, there was no significant association between cholesterol and ischaemic stroke, although there was an inverse relationship between cholesterol levels and intracerebral haemorrhage. However, when the study participants were followed up for 15 or more years (Benfante et al, 1994), a significant relationship between elevated cholesterol level, coronary artery disease and thromboembolic stroke was seen.

In another trial of 350 000 men, death from ischaemic stroke was correlated with elevated cholesterol (Iso et al, 1989). A meta-analysis of trials in China and Japan involving 70 000 subjects revealed a non-significant trend towards higher risk of ischaemic stroke with elevated cholesterol (Eastern Stroke and Coronary Heart Disease Collaborative Research Group, 1998). Considering all the available evidence at that time, a systematic review published in 1995 (Prospective Studies Collaboration, 1995) found no significant association between cholesterol level and stroke.

## CHOLESTEROL LEVEL AND STROKE RECURRENCE

There is little or no evidence outside treatment trials (considered below) which supports the role of cholesterol as an independent risk factor for stroke recurrence, i.e. once a stroke or TIA has already occurred. Given that this is often a situation where physicians might be measuring cholesterol levels and considering whether or not treatment might be indicated, this lack of information is problematic. In particular, as patients in this situation are at high risk of recurrent stroke (up to 10% or so in the first year following TIA or minor stroke; Dutch TIA Trial Study Group, 1991), how much does the cholesterol level influence the overall risk of stroke for that individual? The current answer is, unfortunately, a 'don't know'. Data from the Framingham study indicate that blood lipids form one of the risk factors for subsequent coronary artery disease following ischaemic stroke (D'Agostino et al, 2000).

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## WHY THE APPARENT DIFFERENCE BETWEEN CORONARY ARTERY DISEASE AND STROKE?

Atherosclerosis is a multifactorial process, and single factors were never likely to easily explain the variation that occurs within individuals, between individuals and between populations in clinically important vascular events. The cerebral circulation is different in important respects from the coronary and peripheral vascular circulation. However, methodological issues in some of the studies might also be important. In many of the studies, the distinction between ischaemic and haemorrhagic strokes was not always (clearly) made, and different types of blood lipids were tested in different studies (Demchuk et al, 1999; Landau, 1999).

On the basis of the studies of people without prior stroke or TIA, it seems reasonable to conclude that there is some relationship between elevated cholesterol level and (first) ischaemic stroke. Nevertheless, the evidence is sufficiently inconclusive to allow well-regarded authorities to come to opposite conclusions about whether or not cholesterol is a risk factor for stroke (Demchuk et al, 1999; Landau, 1999). It also seems reasonable to conclude that, in comparison with other established risk factors for stroke, such as hypertension, age and smoking, abnormal cholesterol (or other lipid substance) levels are likely to have a relatively small impact on risk of future stroke events (Hankey, 1999).

## SO WHY THE FUSS?

The renewed interest in cholesterol lowering for stroke prevention largely stems from the results of intervention trials appearing to show better outcomes for patients treated with cholesterol-lowering agents. These trials have studied different populations of patients and used different classes of lipid-lowering agents.

## DOES CHOLESTEROL LOWERING REDUCE THE INCIDENCE OF STROKE AS PRIMARY PREVENTION?

The answer to this question is probably 'yes', particularly if the agent used is a 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitor (statin). Reductions in stroke rate were seen in large trials using various statins in patients with coronary artery disease and varying levels of cholesterol. The results of these trials have been combined into various meta-analyses (Blauw et al, 1997; Hebert et al, 1997; Bucher et al, 1998). The relative risk reduction for stroke is of the order of 20–25%, although the absolute risk reduction is only a little over 1%. A more recent trial (Long-term Intervention with Pravastatin in Ischaemic Disease [LIPID] trial; White et al, 2000b) showed a similar risk reduction, and incorporation of that trial's results into the meta-analysis made no substantial difference (White et al, 2000a). Treating 1000 patients with statin drugs for 3–6 years might prevent 9–15 strokes, although the LIPID investigators also estimate that 30 deaths and 28 non-fatal myocardial infarctions would be prevented by 6 years of treatment (White et al, 2000a).

Interestingly, in the LIPID trial, the cholesterol level (or levels of subfractions) was not an independent risk factor for stroke in multiple logistic regression analyses (White et al, 2000b). This also was the case for changes in low-density lipoprotein cholesterol levels during the first year after enrolment, implying that the beneficial effect of pravastatin in that study was independent of the baseline cholesterol or magnitude of cholesterol lowering.

A meta-analysis of various non-statin cholesterol-lowering agents showed no benefit for stroke reduction (Hebert et al, 1995). Since then, the Veterans Affairs HDL (high density lipoprotein) Intervention trial using gemfibrozil (Rubins et al, 2001) has shown a benefit for gemfibrozil on stroke incidence.

## DOES CHOLESTEROL LOWERING REDUCE THE INCIDENCE OF STROKE AS SECONDARY PREVENTION?

The answer to this question is definitely 'don't know'. It is tempting to extrapolate the findings of trials with statin drugs in patients with coronary artery disease to patients with completed stroke or TIA. However, there is currently no evidence from randomized controlled trials in this patient population. With recent publication of the results of the PROGRESS (perindopril protection against recurrent stroke study) trial (MacMahon et al, 2001), renewed emphasis on treatment of blood pressure following stroke or TIA appears justified, even in patients with blood pressure in the normal range.

It will take a further trial comparing a cholesterol-lowering agent (probably a statin) with placebo in patients following stroke or TIA to inform us whether measuring and treating elevated (or even normal) cholesterol levels in these patients is worthwhile. All patients enrolled in that trial should receive the best medical and surgical management of risk factors, including aggressive blood pressure lowering and carotid endarterectomy where appropriate. In the meantime, some physicians will no doubt use additional information from some of the statin trials

showing regression of intima-media thickness in the carotid arteries (MacMahon et al, 1998) along with the evidence from primary prevention trials to justify treatment with statin drugs for many (or all) patients following stroke or TIA.

## WHAT ABOUT THE RISK OF HAEMORRHAGIC STROKE?

Some studies have suggested an inverse relationship between cholesterol levels and risk of haemorrhagic stroke (Iso et al, 1989). In the LIPID trial, there were twice as many haemorrhagic strokes in the pravastatin group, although the absolute numbers were small and the difference was not significant ($P$=0.28; White et al, 2000b). Uncertainty exists as to whether this relationship is a real one and, if so, whether decisions about treatment should be influenced by it.

## DOES THE TIMING OF CHOLESTEROL MEASUREMENT MATTER?

The facetious answer to this question might be that it only matters if you intended to do anything with the result. There is evidence that cholesterol levels fall in the immediate post-stroke period, stabilizing by 3 months post-stroke (Butterworth et al, 1997).

## WHAT ABOUT THE ACTUAL LEVEL?

There is insufficient evidence to know whether the level of cholesterol (or subfractions) matters when considering treatment for secondary prevention of stroke. As indicated above, treatment with cholesterol-lowering agents for people with stroke or TIA is speculative, and any benefit might be independent of the starting cholesterol level. There is some basis for believing that statin drugs might have other functions independent of cholesterol lowering that might contribute to a lower stroke risk (Landau, 1999; White et al, 2000b). In New Zealand, the cost of some statins (none of which have been tested in trials measuring stroke as an endpoint) is subsidized for patients following stroke and TIA so long as the serum cholesterol level is greater than 6.0 mmol/litre, a level chosen purely to ration the supply of the drug.

## A RATIONAL APPROACH TO CHOLESTEROL IN THE PATIENT WITH STROKE OR TIA

Based on the available evidence, in the author's opinion, it would be reasonable to take one of three approaches to the issue of cholesterol following stroke or TIA, accepting that the first two are somewhat nihilistic and the third is speculative:

1. Until better information becomes available, cholesterol levels following stroke or TIA should not be routinely measured and treatment with cholesterol-lowering drugs only considered if there is a history of coronary artery disease, or
2. Base measurement and management decisions on existing guidelines for primary and secondary prevention of coronary artery disease, e.g. Wood et al (1998), Anonymous (2000), understanding that these are largely consensus documents and that significant differences exist between various guidelines (Unwin et al, 1998). Given that the cholesterol level tends to fall in immediately post-stroke, it makes sense to wait 3 months before measuring the cholesterol level in this situation
3. Measure cholesterol level 3 months following stroke and prescribe a statin drug if the total cholesterol level is greater than 4.0 mmol/litre (the level for entry into the LIPID trial).

As the third option is speculative and associated with considerable cost, in a cost-restrained environment, one of the first two options seem the most prudent until better information is available. Even option two would benefit from more high quality information and consistency of recommendations to allow sensible decision making. In the meantime, physicians should continue to aggressively pursue secondary prevention programmes with proven benefit for patients following stroke and TIA. HM

*Conflict of interest: none.*

### KEY POINTS

- There is probably a relationship between elevated cholesterol and first ischaemic stroke.
- There is insufficient evidence to say that elevated cholesterol has an important relationship with stroke recurrence in people who have had a stroke or transient ischaemic attack (TIA).
- Treating people with coronary artery disease with 'statin' drugs reduces the rate of new strokes in that population, although the absolute benefit is small.
- Treating people with cholesterol-lowering drugs for stroke prevention following stroke or TIA is speculative, based on currently available evidence.
- Physicians should focus efforts on available evidenced-based treatments for the secondary prevention of stroke, particularly management of hypertension, atrial fibrillation, antiplatelet agents and symptomatic carotid stenosis.


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