The role of statin therapy in preventing recurrent stroke

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Several interventions may be used to prevent recurrent stroke. The role of statins was recently clarified by a large double-blind trial comparing atorvastatin with placebo. This article outlines the study results and implications for practice.

Stroke is the third largest cause of death and a leading cause of adult disability in the UK. There are approximately 66,000 deaths every year, plus around 300,000 non-fatal events mostly in people over the age of 60 years. Those who have suffered a stroke have a 30–43% risk of a further stroke within five years (Wolfe, 2000).

The incidence of stroke is predicted to rise due to the ageing population but several interventions have been found to reduce the human, social and economic burden of cerebrovascular disease. Table 1, p26 lists known important measures for secondary stroke prevention, although the role of cholesterol-lowering has not been clear.

The role of reducing cholesterol

Hypercholesterolaemia is not established as a risk factor for first or recurrent stroke, though it is for coronary heart disease (CHD). The Heart Protection Study (HPS) looked at 3,280 patients with cerebrovascular disease randomly allocated to 40mg simvastatin daily or placebo. While there was no apparent reduction in the stroke rate, there was a highly significant reduction in major vascular events such as myocardial infarction or coronary death (HPS Collaborative Group, 2004). There were similar findings in the Cholesterol and Recurrent Events (CARE) trial (Sacks et al, 1996), and simvastatin and pravastatin are already licensed for the prevention of stroke in patients with prior coronary disease.

Guidelines on stroke prevention from the American Heart Association (Sacco et al, 2006) reflect this and recommend that patients with ischaemic stroke or transient ischaemic attack (TIA) and coronary artery disease be treated with a statin. They also suggest that those without coronary disease be considered for statin therapy to reduce the risk of vascular events, although not specifically recurrent stroke, a potential benefit that until recently has been unproven.

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial was designed to ascertain whether a more potent statin (atorvastatin) would help prevent stroke recurrence in patients with previous stroke or TIA (SPARCL, 2006). The sample consisted of 4,731 patients who had suffered a stroke or TIA in the past 1–6 months, had low-density lipoprotein (LDL) cholesterol levels of 2.6–4.9mmol/L, and no known CHD. They were randomised into two groups and given double-blind treatment with 80mg atorvastatin daily or placebo. As its primary endpoint the study was looking at the incidence of fatal or recurrent non-fatal stroke.

The mean LDL cholesterol level fell to 1.9mmol/L in those treated with atorvastatin and remained at 3.3mmol/L in the placebo group. Over a median follow-up of 4.9 years, 265 patients (11.2%) receiving atorvastatin and 311 (13.1%) receiving placebo had a fatal or nonfatal stroke, an absolute reduction in risk over five years of 2.2%, a modest
but significant reduction. The atorvastatin group had 218 ischaemic strokes and 55 haemorrhagic strokes, while the placebo group had 274 ischaemic strokes and 33 haemorrhagic strokes. The incidence of fatal haemorrhagic stroke did not differ significantly between the groups (17 in the atorvastatin and 18 in the placebo group).

In common with other statin trials, there was a reduction in other major cardiovascular events by 3.5%, although total mortality was not affected.

Practice implications

These positive results support the initiation of atorvastatin treatment soon after a stroke or TIA. Hospitalisation provides an excellent opportunity for initiation of all preventative therapy, and is associated with better compliance than when such measures are instigated in primary care (Ovbiagele et al, 2004). Primary care nurses involved with chronic disease management can ensure the dose of the chosen statin is maintained and titrated to achieve optimum blood cholesterol levels, as in the follow-up of other patients with cardiovascular disease.

Limitations

Patients with atrial fibrillation and other cardiac sources of emboli were excluded from the trial, so the SPARCL results cannot apply to the roughly one in five ischaemic strokes where emboli originate in the heart. There is also some concern for patients who present with cerebral haemorrhage. The relative risk of haemorrhagic stroke was increased by 66% in those patients in the atorvastatin group.

The speed of intervention is also likely to be important. TIs and minor strokes are considered a medical emergency. The risk of completing a stroke after a TIA may be as high as 20% within the first month, with half occurring within the first two days.

Whether the benefits of statins are as great in this early, vulnerable phase is not known. Patients in SPARCL entered the trial 1–6 months after their first stroke, while in the HPS this was on average 4.3 years later. This delay may have adversely affected outcome. The ongoing Fast Assessment of Stroke and Transient Ischaemic Attack to Prevent Early Recurrence (FASTER) trial is focusing on the initial period of high risk, starting patients on stroke prevention treatments (aspirin, clopidogrel, statin) in the hours following a TIA or minor stroke. While these drugs have been shown to reduce recurrent cardiac events in patients with unstable angina when commenced early, strokes are a diverse group of conditions, and only a minority are caused by large-vessel thrombosis.

Is the statin or dose important?

This is the first trial to show the benefits of statin therapy in preventing recurrent stroke. Whether a lower dose of atorvastatin or an alternative statin would also reduce the risk is unknown. It is possible that other less potent generic statins may have similar benefits. The UK stroke guidelines published prior to SPARCL already recommend treatment with a statin for all patients with ischaemic stroke or TIA, and total cholesterol of >3.5mmol/L, unless contraindicated.

Conclusion

Current UK stroke guidelines on lipid management have been supported by SPARCL (RCP, 2004). Lipid-lowering therapy should aim to reduce total serum cholesterol to <4mmol/L, or LDL cholesterol to <2mmol/L, or to reduce total cholesterol by 25% or LDL cholesterol by 30%, whichever results in the lower cholesterol level. A multifaceted approach to the prevention of stroke recurrence remains important, and all patients with TIA or cerebral infarction should be offered a statin to prevent further cardiovascular events.

**TABLE 1. SECONDARY PREVENTION OF STROKE OR TRANSIENT ISCHAEMIC ATTACK**

<table>
<thead>
<tr>
<th>An individualised prevention strategy should be implemented within seven days of acute stroke or TIA</th>
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<tbody>
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<td>General measures</td>
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<tr>
<td>Blood pressure</td>
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<td>Anti-platelet therapy</td>
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<td>Treatment with a statin</td>
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