THERAPEUTIC INTERVENTIONS

INTRODUCTION

Worldwide, stroke is the second most common cause of death and the sixth most common cause of disability (Murray and Lopez 1997). By 2020 it is projected to remain the second most common cause of death but to rise to the fourth most common cause of disability. During the second half of the 20th century death rates due to stroke declined by about half in Western Europe and the USA, even more in Japan (Sarti 2000 *et al*). However, in Eastern European countries (Levi *et al* 2002) and China (Chinese Ecological Study 2003), rates have been gradually increasing over the last 20 years. These mortality trends are likely to be related to changes in the known risk factors for stroke, including smoking, blood pressure and diabetes, and they may also reflect changes in cholesterol levels. These trends broadly parallel those of coronary heart disease (Lawlor *et al* 2003), reminding us of the generalised nature of atherosclerotic vascular disease.

As with the other manifestations of atherosclerosis, the incidence of stroke increases markedly with age, so that approximately three-quarters of all strokes occur in those aged over 65 years of age, and after age 55 the risk of stroke doubles with each successive decade (Warlow *et al* 2001). Therefore, with an increasing proportion of the world population living into old age, *primary* prevention of stroke should be a major priority. Furthermore, stroke survivors (two-thirds of whom are functionally independent at one year; Bamford *et al* 1990) are at greatly increased risk of subsequent strokes, and those with a transient ischaemic attack (TIA) are at increased risk of a first stroke (~5–7% per annum) (Hankey *et al* 1999). Hence *secondary* prevention of stroke is also important and, given the very high risk of other vascular events among stroke survivors, about half of whom die of coronary heart disease (Warlow *et al* 2001),

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Practical Neurology, 2003, **3**, 224–233

Cholesterol lowering for the prevention of stroke

this needs to be part of a strategy for secondary prevention of vascular disease in general.

In this article I shall review the epidemiological basis and the randomised trial data for cholesterol lowering in both the primary and secondary prevention of stroke. In addition I shall cover some practical aspects of prescribing statins for vascular risk reduction.

STROKE AND CHOLESTEROL – IS RAISED BLOOD CHOLESTEROL LEVEL A RISK FACTOR FOR STROKE?

There is no clear relationship between total cholesterol levels and subsequent risk of death from stroke (Fig. 1) although there does appear to be an increased risk of stroke deaths with higher cholesterol levels among younger individuals (Fig. 2). However, stroke is a heterogeneous disease and the different types of stroke may have different underlying relationships to risk factors. So the two main causes of stroke, ischaemic

Figure 1 Risk of death from stroke by usual blood cholesterol in five categories defined at baseline among 450 000 people in 45 observational cohort studies, amongst whom 13 000 stroke deaths occurred. To derive 'usual' cholesterol, total cholesterol levels have been corrected for regression to the mean. Squares represent stroke risks relative to the risk in the whole study population with 99% confidence intervals (CI). Adapted with permission from the Prospective Studies Collaboration 1995.

Figure 2 Risk of death from stroke by usual blood cholesterol in five categories defined at baseline among 450 000 people in 45 cohorts subdivided by age at screening (in the same study as illustrated in Fig. 1). Squares represent stroke risks relative to the risk in the whole study population with 95% confidence intervals (CI). Adapted with permission from the Prospective Studies Collaboration 1995.

Figure 3 Overall relative risk of non-haemorrhagic stroke (494 events) by usual cholesterol in five categories defined at baseline among 60 750 participants in 11 studies. Solid squares represent stroke risks relative to the risk in the whole study population; their size is proportional to the number of strokes in each usual cholesterol category. Vertical lines represent 95% confidence intervals. Adapted with permission from the Eastern Stroke and Coronary Heart Disease Collaborative Research Group 1998.

stroke (due to either thrombosis or embolism) and intracranial haemorrhage (either intracerebral or subarachnoid) may differ in their relationship to cholesterol levels. Similarly *total* cholesterol is made up of different lipoprotein sub-fractions – predominantly low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol – and these may have opposite associations with stroke risk (as they do for coronary heart disease risk). Hence a positive association between ischaemic stroke and LDL-cholesterol and a negative association between ischaemic stroke and HDL-cholesterol may not be apparent when looking at crude associations between total stroke and total cholesterol.

An additional difficulty is that the epidemiological data largely describe stroke *death* rather than stroke *incidence*. The majority of incident strokes are due to ischaemia (about 80% in Western and 60% in Asian populations), but about 50% of stroke deaths in Western and two-thirds in Asian populations are due to haemorrhagic strokes because these are more likely to be fatal. In the collaborative meta-analysis of observational studies from China and Japan (Eastern Stroke and Coronary Heart Disease Collaborative Research Group 1998), which included non-fatal as well as fatal stroke events, there did appear to be a higher risk of non-haemorrhagic stroke with higher blood cholesterol levels, even without data on lipid sub-fractions (Fig. 3), and possibly an inverse association with haemorrhagic stroke (Fig. 4). Similarly in the large MRFIT cohort of 350 000 middle-aged American men, there was a positive association between deaths from ischaemic stroke over 6 years and total cholesterol levels (Iso *et al* 1989). Limited data from other prospective studies (Wannamethee *et al* 2000, Lindenstrom *et al* 1994) also suggest that HDL is inversely related to the risk of stroke (as for coronary heart disease too).

In summary, although blood cholesterol levels have not traditionally been considered a risk factor for stroke, careful consideration of the observational data is consistent with cholesterol being an important contributor to ischaemic stroke risk, as might be expected given the very strong relationship between coronary heart disease risk and lipid levels. The observational data also raise the possibility of an increased risk of haemorrhagic stroke with low blood cholesterol levels.

Figure 4 Overall relative risk of haemorrhagic stroke (404 events) by usual cholesterol in five categories defined at baseline among 60 750 participants in 11 studies. Solid squares represent stroke risks relative to the risk in the whole study population; their size is proportional to the number of strokes in each usual cholesterol category. Vertical lines represent 95% confidence intervals. Adapted with permission from the Eastern Stroke and Coronary Heart Disease Collaborative Research Group 1998.

LDL-CHOLESTEROL LOWERING REDUCES THE RISK OF STROKE

Initially, given the lack of any definite relationship in the observational data, no trials were designed to address whether cholesterol-lowering would reduce stroke risk. Rather, during the late 1980s and 1990s a series of large-scale trials were initiated to assess whether substantial cholesterol-lowering would reduce *coronary* events with the, then, newly available statins, much more potent cholesterol-lowering agents than those used in earlier trials. The 4S Study (Scandinavian Simvastatin Survival Study Group 1994) in hypercholesterolaemic, middle-aged people with coronary heart disease was the first trial to raise the possibility that cholesterol lowering with a statin might reduce the risk of stroke as well as coronary events. Consistent effects on stroke then emerged in the three large pravastatin trials (Byington *et al* 2001) and led to stroke being included as a pre-specified outcome in later trials. Indeed, there is now no doubt from these and later randomised trials and meta-analyses that lowering blood cholesterol with a statin really does reduce the risk of stroke (Bucher *et al* 1998, Mascio *et al* 2000, Heart Protection Study Collaborative Group 2002, ALLHAT Collaborative Research Group 2002, Sever *et al* 2003).

The MRC/BHF heart protection study

The MRC/BHF Heart Protection Study (HPS) (Heart Protection Study Collaborative Group

2002) was the first large-scale study (of about 20 000 high vascular risk patients followed for about 5 years) to show unequivocally that cholesterol lowering with a statin reduced the risk of stroke, as well as other major vascular events. There was a highly significant 25% risk reduction (95% confidence interval (CI) 15 to 34) in first fatal or non-fatal stroke among those allocated simvastatin 40 mg daily compared to placebo (Fig. 5), which appeared to be entirely due to the 30% (95% CI 19 to 40) reduction in ischaemic stroke [290 (2.8%) simvastatin allocated versus 409 (4.0%) placebo allocated]. There was no adverse effect on haemorrhagic stroke (51 versus 53). Taking account of the two-thirds trial medication compliance in HPS, this suggests that 40 mg simvastatin daily or equivalent reduces the risk of ischaemic stroke by almost one-half ($30\% \times 1.5 = 45\%$). This gives an approximate number needed to treat (NNT) over 5 years to prevent one stroke of about 44 among the sort of high vascular risk patients in HPS (with a stroke rate of about 1% per annum), but an NNT of only 10 to 15 to prevent a first major vascular event.

Subsequent large trials of statins

Since HPS, three further large statin trials have provided data on stroke. PROSPER (Shepherd *et al* 2002) randomised about 6000 elderly patients to pravastatin 40 mg daily versus placebo and showed a reduction in coronary events of about one-quarter with the 1 mmol/L reduction in

Figure 5 The Heart Protection Study. Rate ratios (numerically the same as odds ratios) are plotted as black squares, which are proportional to the amount of information, comparing first stroke rates among those allocated simvastatin and those allocated placebo. For each type of stroke the figure shows the number of patients having the first stroke of that type, and for stroke severity the most severe stroke that a patient experienced. Horizontal lines represent 95% confidence intervals. The overall result and its 95% confidence interval is represented by a diamond.

LDL-cholesterol but *no* difference in the risk of stroke. This lack of effect is likely to reflect the play of chance given the relatively small number of first strokes (266 compared with over 1000 in HPS), the relatively short duration of follow-up (just 3.2 years), and that the other trials of pravastatin have all shown reductions in stroke risk. The ALLHAT trial (The ALLHAT Collaborative Research Group 2002) of pravastatin versus usual care in an open design showed only a non-significant 9% (95% CI 25% reduction to 9% increase) relative risk reduction in stroke over 4.8 years. However, a substantial proportion of those allocated usual care in this open trial were prescribed statins, producing only a relatively small difference in blood cholesterol of about 0.6 mmol/L between the randomised groups. Adjusting this 9% reduction in stroke risk with the 0.6 mmol/L difference in LDL-cholesterol to a per mmol/L reduction brings the result more in line with the other trials as discussed below. The Anglo-Scandinavian Cardiovascular Outcomes Trial – Lipid-Lowering Arm (ASCOT-LLA) (Sever *et al* 2003) was the first

large randomised trial of atorvastatin to assess hard clinical outcomes. In over 10 000 patients with hypertension and at least three other risk factors, there was a clear reduction in the risk of stroke (as well as in coronary events) with a 1.1 mmol/L difference in LDL-cholesterol and 3.3 years of follow-up.

Putting all the statin trials together

Table 1 includes published data from all the large randomised trials of statins that reported on total stroke separately as an outcome. The results are remarkably consistent across the different trials giving an overall highly significant reduction in stroke risk of 19% (95% CI 13 to 25). The underlying stroke rate in these trials varied from very low (~0.3% per annum) in middle-aged men without coronary disease in the WOSCOPS trial to higher rates (~1% per annum) among the older high-risk patients recruited into HPS and PROSPER. Nevertheless, in the same way as is seen for the reduction in coronary events, the *proportional* (ie relative) reductions in stroke risk (as expressed by the odds

Table 1 The effect of cholesterol-lowering on total stroke (i.e. fatal and non-fatal, ischaemic and haemorrhagic) in the principal large-scale statin trials.

TRIAL NAME	STATIN USED IN TRIAL	ALLOCATED STATIN (NUMBER WITH STROKE/ NUMBER RANDOMISED)	ALLOCATED PLACEBO (NUMBER WITH STROKE/ NUMBER RANDOMISED)	ODDS RATIO (95% CONFIDENCE INTERVAL)
4S	Simvastatin 20–40mg	51/2221 (2.5%)	69/2223 (3.3%)	0.74 (0.51 to 1.06)
CARE	Pravastatin 40 mg	52/2081 (2.5%)	76/2078 (3.7%)	0.69 (0.48 to 0.97)
LIPID	Pravastatin 40 mg	169/4512 (3.7%)	204/4502 (4.5%)	0.82 (0.67 to 1.01)
WOSCOPS	Pravastatin 40 mg	46/3302 (1.4%)	51/3293 (1.5%)	0.89 (0.60 to 1.33)
HPS	Simvastatin 40 mg	444/10269 (4.3%)	585/10267 (5.7%)	0.75 (0.66 to 0.85)
PROSPER	Pravastatin 40 mg	135/2891 (4.7%)	131/2913 (4.5%)	1.03 (0.81 to 1.31)
ASCOT	Atorvastatin 10 mg	89/5168 (1.7%)	121/5137 (2.4%)	0.73 (0.56 to 0.96)
ALLHAT	Pravastatin 40 mg	209/5170 (4.0%)	231/5185 (4.5%)	0.90 (0.75 to 1.09)
Pooled overall result		1195/35614	1468/35598	0.81 (0.75 to 0.87)*

* $P < 0.00001$

Note: the pooled overall odds ratio of 0.81 gives a relative odds reduction of $(1.0 - 0.81) \times 100 = 19\%$, which is numerically almost the same as the relative risk reduction given the small proportion of patients who had a stroke during follow up (generally $< 5\%$).

From Mascio *et al.* 2000, HPS Collaborative Group 2002, Shepherd *et al.* 2002, Sever *et al.* 2003 and ALLHAT Collaborative Research Group 2002.

ratios) were similar among those with differing underlying risks of stroke at baseline (with no significant heterogeneity), implying that larger absolute benefits will be seen in those at higher absolute risk of stroke (such as those with a previous history of stroke or TIA, or because of age or other risk factors).

The average reduction in cholesterol in most of the trials was about 1 mmol/L (somewhat more at 1.7 mmol/L in 4S and somewhat less at about 0.6 mmol/L in ALLHAT). Overall, the trial data show that reducing LDL-cholesterol by 0.6–1 mmol/L reduces the relative risk of fatal or non-fatal stroke by about one-fifth, with reductions of about 1 mmol/L reducing risk by about one-quarter. The effect is primarily on ischaemic stroke with no adverse effect on haemorrhagic stroke. Recommended statin doses (e.g. simvastatin 20–40 mg or atorvastatin 10–20 mg daily) in a population eating a mixed 'western' diet and with an average total blood cholesterol of about 6 mmol/L will typically reduce LDL-cholesterol by about 1.5 mmol/L, suggesting that the observed benefits with routine treatment should be a relative reduction in risk of stroke of about one-third (i.e. $1.5 \times 25\%$).

Other drugs for cholesterol lowering

It is not clear whether cholesterol-lowering by other means (ie non-statins) has the same effect. Early trials of various cholesterol-lowering interventions (before statins were introduced) failed to demonstrate a clear effect on stroke (Hebert *et al.* 1995, Mascio *et al.* 2000). However,

they lacked statistical power (partly due to the small cholesterol reductions achieved in low vascular risk populations) and stroke outcomes were not collected systematically and consistently. The pooled data from the two recent large trials of fibrates [Veterans Administration HDL Intervention trial (VA HIT; Rubins *et al.* 1999) and the Bezafibrate Infarction Prevention Study (The BIP Study Group 2000)] among patients with coronary heart disease gives a non-significant odds reduction of 16% (95% CI 34% to 7% increase), but this is based on only about 300 strokes. This is consistent with the statin effect but not conclusive and further large-scale trial data are awaited.

DOES CHOLESTEROL LOWERING AFFECT COGNITIVE FUNCTION?

Despite the reduction in the risk of stroke and the observational evidence linking cognitive impairment to vascular risk factors (Hofman *et al.* 1997, Kivipelto *et al.* 2001), there is no effect of cholesterol lowering with either simvastatin or pravastatin on cognitive function, at least not as measured by a variety of validated scores either in HPS or PROSPER.

WHICH PATIENTS SHOULD BE OFFERED CHOLESTEROL-LOWERING TREATMENT?

There is now a general consensus reflected in national and international guidelines that patients with established vascular disease (history of coronary heart disease, cerebrovascular disease or peripheral vascular disease) are all

at sufficiently high risk of recurrent vascular events that cholesterol-lowering with a statin is recommended e.g. National Cholesterol Education Programme (NCEP) guidelines (Expert panel on Detection, Evaluation, and treatment of high blood cholesterol in adults 2002), AHA Guidelines (Pearson *et al* 2002) and the Joint British Guidelines (British Cardiac Society, British Hyperlipidaemia Association) British Hypertension Society, British Diabetic Association 2000). Most guidelines advocate the use of LDL-cholesterol targets, NCEP giving LDL-cholesterol < 100 mg (2.6 mmol/L) for those at highest risk as optimal and the Joint British Recommendations advocate achieving an LDL-cholesterol < 3.0 mmol/L, or at least a 30% reduction. However, HPS established that those at increased vascular risk and with a total blood cholesterol level above 3.5 mmol/L will gain benefit from further cholesterol lowering (but most guidelines have yet to be modified to incorporate this evidence). One caveat is that the trials on which these recommendations are based were largely conducted in western populations. However the overall consistency of the results, and the consistency of benefit across all levels of baseline cholesterol level, suggests that these results are applicable globally.

The recommendation in secondary prevention is therefore straightforward, that ischaemic stroke survivors and TIA patients are generally given a statin to reduce LDL-cholesterol to the target levels, or by at least 30%. For most people this can be achieved with a statin in the doses that have been well tested in clinical trials (i.e. atorvastatin 10 mg, pravastatin 40 mg or simvastatin 20–40mg daily). For those failing to attain the targets, the statin dose can sometimes be increased (but with the possibility of more adverse effects), or additional drugs added such as fibrates, resins or niacin.

Patients with hypertension or diabetes are at increased risk and will benefit from cholesterol lowering irrespective of baseline cholesterol

Patients being treated for hypertension are being treated primarily to reduce their risk of stroke (although there will be additional benefits on coronary events and other vascular outcomes). The decision has already been taken that they are at sufficient vascular risk to merit therapeutic intervention. Logically such patients should also be routinely prescribed a statin because the randomised evidence shows that this will addi-

tionally reduce their risk of ischaemic stroke by about one-third.

People with diabetes are at 2–4-fold higher risk of vascular events than comparable non-diabetic populations. The combination of established vascular disease and diabetes puts people at particularly high risk. Clear evidence from HPS and the other statin trials shows that diabetics gain the same proportional (relative) benefits from cholesterol-lowering as other groups, arguing for routine cholesterol-lowering in all diabetics who have already had a stroke or other vascular event irrespective of the baseline cholesterol level. Even among people with diabetes and no clinically evident vascular disease there is now clear evidence that cholesterol lowering will reduce the risk of major vascular events regardless of baseline lipid levels (HPS Collaborative Group 2003).

The decision to initiate treatment in other primary prevention settings depends on estimated future vascular risk. The level of risk (e.g. 15, 20 or 30% serious vascular events such as stroke and myocardial infarction over 10 years) at which to initiate drug treatment that will reduce that risk then becomes a cost-effectiveness decision. However, accurate estimation of risk is difficult from the currently available charts, most of which only provide coronary risk, and so these estimates need to be approximately doubled to account for total vascular risk including stroke and the need for revascularisation procedures.

USE OF STATINS IN ROUTINE CLINICAL PRACTICE

Choice of drug and dose

Most of the randomised data showing that statins reduce the risk of stroke come from trials of pravastatin and simvastatin with information recently emerging for atorvastatin (Table 1). Table 2 gives the relative cholesterol-lowering potency of the different statins at usual doses. In general, doubling the dose of a statin will provide about 6% additional LDL-cholesterol lowering and 5% additional total cholesterol lowering. Given the strength of the data for stroke, simvastatin should probably be the drug of first choice in stroke survivors and TIA patients. In HPS it was given at a dose of 40 mg daily with no titration up to this dose and there were no clear problems from this simple – and simple to remember – strategy.

The lower the cholesterol the better?

The relationship between blood pressure (BP) and stroke and the relationship between cholesterol and coronary heart disease are both approximately log-linear; for the same absolute difference in BP or cholesterol a similar proportional difference in risk is observed. It seems likely, but is not proven, that the relationship between LDL-cholesterol and risk of ischaemic stroke is similarly log-linear with an inverse association with HDL-cholesterol. This implies that to minimise the risk of vascular events all patients should have their LDL-cholesterol lowered as far as possible and their HDL-cholesterol raised. However, no completed studies have directly addressed whether more intensive cholesterol lowering with higher doses of statins achieves further reductions in risk compared with standard doses. Statins have only very small effects on HDL-cholesterol and, as discussed above, although fibrates raise HDL there is insufficient evidence from current trials to advocate their routine use for stroke prevention. At present the best available evidence suggests that lowering cholesterol by 1–1.5 mmol/L will reduce stroke risk by one-quarter to one-third and this should therefore be the minimum target of treatment.

Safety of statins

Statins are safe and well tolerated at the doses used in the large randomised trials. The only important adverse effect is both rare and largely unpredictable: myopathy, defined as muscle pain or weakness with a raised plasma creatine kinase (CK) more than 10 times the upper limit of normal. In the randomised trials no other adverse effects were clearly more common in those on a statin compared with placebo. Importantly, there is no convincing evidence that statins cause muscle pain (when the CK is normal). Therefore, given that muscle pain is so common (about one-third of patients in HPS reported muscle pain at some time during the trial but with similar proportions among those on active and placebo statin), it is extremely important that muscle symptoms in the absence of myopathy do not lead to patients having their statin inappropriately stopped. Statins are safe in the elderly with no need for dose adjustment or any special consideration.

Myopathy if unrecognized can lead to rhabdomyolysis (usually defined as a CK greater than 10 000 IU/L) with its concomitant risks of myoglobinuria and acute renal failure. With simv-

Table 2 Lipid lowering effects and UK cost of currently available statins at doses used in the randomised trials or typical recommended doses

STATIN	LDL-CHOLESTEROL		28 DAY COST (£*)
	DOSE	REDUCTION	
Atorvastatin	10mg	38%	18.03
Fluvastatin	40mg	24%	12.72
Lovastatin	40mg	34%	NA
Pravastatin	40mg	34%	29.26
Rosuvastatin	10mg	45%	18.03
Simvastatin	40mg	41%	29.69

* September 2002 costs. NA, not available in UK.

Doubling the dose of statin increases the LDL reduction by about 6% and the total cholesterol reduction by 5% (Potencies from Shepherd 2001 and Data Sheet for rosuvastatin).

astatin 40 mg daily in HPS the excess myopathy risk was about 1 in 10 000 per annum, with other published data suggesting incidence of about 0.08% with various statins (Pasternak 2002). Myopathy risk probably does vary between different statins and is dose related but limited published data are available. Other cholesterol-lowering drugs such as fibrates, high dose niacin and resins can also cause myopathy and the risk appears to be increased when combinations of these and statins are prescribed. Certain other concomitant medications also increase the risk of myopathy when given with statins, the most important of these being ciclosporin, systemic azol anti-fungals (such as itraconazole and fluconazole), macrolide antibiotics (erythromycin and clarithromycin) and the calcium channel blocker verapamil (Pasternak 2002).

On starting treatment with any statin, patients should be warned about the rare risk of myopathy and asked to report unusual or unexplained muscle pain or weakness and the CK should be measured. If the CK is > 5 times the upper limit of normal then the test should be repeated and if > 10 times then the statin should be stopped. At usual statin doses routine monitoring of CK is not helpful in identifying those at risk of myopathy.

Some statins (simvastatin and atorvastatin) have a small effect on anti-coagulant control in patients on warfarin. Measuring the International Normalised Ratio (INR) is recommended when statin treatment is started, stopped or the dose altered.

Monitoring during statin treatment

Once patients are established on statin treatment the most important monitoring is to

ensure continued compliance. Statins are contra-indicated in the presence of active hepatic disease and liver function should be checked before starting treatment, but despite current recommendations on-going monitoring of liver function is not necessary, based on the HPS and other trial results. Reversible increases in liver transaminases are seen in about 1% of patients after starting statins (although no significant excesses have been seen in the large statin trials) and a similar effect is seen with other classes of cholesterol-lowering drugs. There is no evidence from the large randomised trials that statins are liver toxic, suggesting that the liver enzyme effects may reflect some non-specific hepatic reaction to cholesterol lowering.

Is it safe to lower a low cholesterol?

No adverse effects have been seen in the randomised trials from lowering cholesterol in people with baseline levels already below average. Concerns had been raised from observational data both about possible increased risks of cancer and of haemorrhagic stroke with very low cholesterol levels but the trials have not provided any support for these concerns. In the randomised trials there was no excess cancer risk either overall or for any particular cancers (Shepherd *et al* 2002). Extended follow-up for 2 years beyond the end of the trial has been reported for the 4S (Pedersen *et al* 2000) and LIPID (The LIPID Study Group 2002) trial populations. These provide further reassuring safety information.

Costs of treatment

The costs of the statins that remain in patent vary from about £0.5 to £1 per day. Generic lovastatin is available in some countries (although not in the UK) at lower prices and simvastatin is now off patent in the UK and several other European countries with the expectation of cheaper versions. Estimates of the cost-effectiveness of statin treatment vary widely. One particular UK study estimated a cost-per-life-year gained for treating a high-risk vascular patient of around £5 000 at a coronary risk of 4.5% per annum, with costs up to £12 500 for primary prevention at an event rate of 1.5% per annum (Pickin *et al* 1999). Other estimates based on US data give estimates of \$10 000 per quality-life-year gained for post myocardial infarction patients but, as expected, with lower cost-effectiveness at lower levels of risk, and these authors argue that statin use in secondary prevention is cost-effective (Prosser *et al* 2000). However, these estimates

involve several assumptions and fail to take into account savings due to prevention of strokes as well as coronary events. Cost-effectiveness estimates are also critically dependent on the price of the statin and so will need revising when generic preparations become available. A particular difficulty of assessing the true cost-effectiveness of statin treatment is the uncertainty surrounding future benefits from preventing disabling events and the probability that benefits of taking statins will increase with time (HPS Collaborative group 2002).

CONCLUSIONS

- Cholesterol-lowering with a statin should be routinely used for anyone at sufficient risk of ischaemic stroke or other vascular disease to warrant reduction in that risk, regardless of their blood cholesterol levels. This includes anyone with a history of ischaemic stroke or TIA or other vascular disease, and those at high risk of stroke because of hypertension or other disease such as diabetes.
- Overall, the trial data show that reducing LDL-cholesterol by about 1 mmol/L reduces stroke risk by about one quarter.
- Treatment should be started at the earliest opportunity with a dose sufficient to reduce total and LDL-cholesterol by 1–1.5 mmol/L (e.g. atorvastatin 10 mg, simvastatin 20–40 mg, pravastatin 40 mg daily) and continued life-long. Treatment should be continued even if patients have recurrent vascular events but more intensive cholesterol lowering and/or control of other risk factors should then become a priority.
- These statin doses in a population eating a mixed 'western' diet and with an average total blood cholesterol of about 6 mmol/L will typically reduce LDL-cholesterol by about 1.5 mmol/L, which should lead to a relative reduction in risk of stroke by about one-third.
- Compliance should be monitored but other monitoring is not generally required.
- Statins appear safe and well tolerated over 5 to 10 years, and the benefits are additional to those of the other cardio-protective agents including aspirin and anti-hypertensive medications.
- It is extremely important that muscle symptoms in the absence of myopathy (ie plasma CK > 10 times upper limit of normal) do not lead to patients having their statin inappropriately stopped.
- Given the necessity of polypharmacy in many of these patients and the importance of compliance, it is hoped that combinations of statins with other commonly prescribed medications, such as aspirin, will become available in future. These combinations will be more convenient than having to take several separate pills.

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