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Statins and Stroke: A Promising Approach Towards Stroke Prevention

M. Brainin

Stroke is a growing global health burden. Mortality is declining in most of the Western countries but incidence rates do not show a parallel decline. In East European countries both mortality and incidence are on the rise. In developing countries stroke has been emerging as a major disease. Measures to prevent first-ever or recurrent strokes therefore have a large, world-wide impact on health and economy. One of the most effective and promising agents are statins that seem to be effective also in many patients with normal lipids. Atherothrombotic strokes account for approximately half of all strokes and are probably effectively treated with statins especially when additional risks are present such as coronary heart disease or diabetes. In spite of a substantial risk reduction with statins there is at present only sufficient evidence to recommend statins for those stroke patients that have additional vascular risks including diabetes or hyperlipidaemia. *J Clin Basic Cardiol* 2002; 5: 159–62.

Key words: statins, stroke, cerebrovascular diseases, treatment, prevention

Ischaemic cardiac disease and stroke result in more deaths worldwide than any other disease. It is estimated that at least 15 million deaths annually are attributed to those diseases, that is 30 % of all deaths occurring globally. This is in spite of the fact that, in most industrialized countries, mortality from both diseases steadily declined during the 1970s and 1980s [1, 2]. As for stroke, this decrease was not paralleled by a similar decrease in incidence and some studies, including the WHO MONICA Study, show that incidence rates are not levelling off [3, 4]. Regional studies even indicate a small but steady increase in stroke rates in developed industrialized nations [5].

In addition, a new and disturbing trend is read from the epidemic proportions stroke and cardiac diseases are reaching in lesser developed countries as has been shown by the Global Burden of Disease Study [2]. According to these data it has been estimated that by 2020 both ischaemic cardiac diseases and stroke will become the leading cause of death in the developing world unless effective measures of prevention will be developed and implemented.

Secular Trends in Stroke Mortality and Incidence in Austria and Europe

In Austria, mortality from stroke has declined in the past decades but still ranges a little below 100 per 100,000 inhabitants per year (which is in contrast to US stroke mortality which has been reduced to 31.7 per 100,000 per year). Age-standardized mortality rates for men have shown a steep decline in stroke mortality between 1970 and 1994 from 201 per 100,000 to 92 per 100,000 (minus 54.7 %) and for women from 160 per 100,000 to 77 per 100,000 (minus 51.7 %). From 1970 to 1985 mortality has continuously declined for men and women by 1.5 % per year and since 1985 the risk of mortality has been continuously reduced by 4 % per annum [6]. On a European scale, the reduction of stroke mortality in Austria is considered only to be average compared to other countries with a stronger reduction as is the case in Western Europe, where some countries, eg Italy, France or Switzerland show an even steeper decline in mortality and this contrasts to other countries with no reduction or even an increase of mortality as is the case in Eastern European coun-

tries, such as Hungary, Poland or the Baltic States. For these countries in Eastern Europe there is clear evidence for an increase in stroke mortality. This has been described as a widening gap between East and West throughout Europe and points to an alarming growth of the disease burden [3–5, 7]. The reasons for this diverging development are not entirely clear. One possible reason is that countries with a reduced stroke mortality risk have populations that are increasingly elderly and bear only moderately expressed risk factors thus resulting in an increase of mild (and non-fatal) strokes in the very elderly population. In contrast, countries with a comparatively high mortality rate show a high prevalence as well as a high expression of stroke risk factors within their population and therefore also a higher rate of severe (and fatal) strokes [3].

Cholesterol and Stroke

Coronary artery disease and cerebrovascular disease share most of their risk factors leading to the clinical manifestation of disease. This holds for the most common risk factors, such as hypertension or diabetes, although their respective population attributable risks for each of the diseases differ quantitatively. It has been firmly established that arterial hypertension has a higher attributable risk for stroke than for coronary heart disease and prevalence of hypertension in any given population parallels stroke incidence much more closely than it mirrors coronary heart disease incidence [8].

In contrast, elevated levels of total cholesterol have not been associated with a substantial risk for stroke or for recurrent stroke. Most of the earlier data came from epidemiological surveys which were mostly based on Asian populations. Meta-analyses including several 100,000 individuals were performed in the following years and confirmed that raised cholesterol levels have a small or even negligible effect for the risk of stroke, the odds ratio amounting to only little above 1 for men as well as for women (for a complete review see [9]). It has been suggested, though, that the value of these observational studies is limited as they are only based on mortality data and the effect of hyperlipidaemia on non-fatal strokes might have been missed. In addition, elderly age groups, especially women, that are prone to suffer stroke events have

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not been included in a significant number. Interpretation of data might have been flawed as in most of these surveys no separate analysis was done for subtypes of strokes. Still, some studies suggested a small but notable risk of cerebral haemorrhage for persons with very low cholesterol levels. This has not been unequivocally accepted because of the possible confounding effect of a deprived socio-economic status accounting for malnutrition and alcohol abuse as the more causal factors for cerebral haemorrhages. It must be therefore stated that to date this suggested risk of low cholesterol and increased cerebral haemorrhage has not been replicated in a controlled clinical trial. In individual cases though we have seen elderly patients with a low cholesterol and a high prevalence of clinically silent cerebral haemorrhages as can be depicted by means of haemosensitive sequences on MRI (Figure 1). Considering the fact that such microbleeds can be seen in 3–6 % of the elderly population [10, 11] such anecdotal experiences might be of importance.

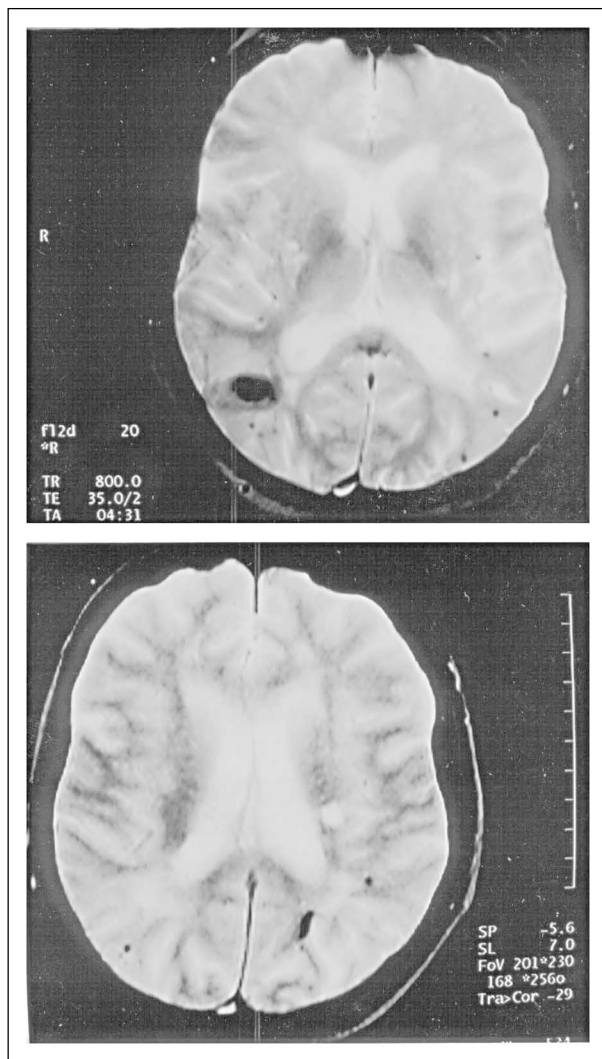


Figure 1. MR scans of a 74-year old patient with amyloidangiopathy-induced cerebral bleeding in the right parietal subcortex. In the haemosensitive scans (gradient-echo T2* sequences) numerous additional hypointense lesions are visible, indicating multiple silent cerebral "microbleeds". Such patients might bear an additional risk for a recurrent haemorrhage if cholesterol or LDL is markedly reduced below normal.

Statins and Stroke: The Evidence From Randomized Trials

Until the advent of statins there was no consistent evidence that cholesterol lowering reduces the risk of stroke. Several published meta-analyses demonstrate that statins reduce the risk of stroke up to 30 % in patients with coronary artery disease (for review see [12]). This reduction in stroke approximates that of antihypertensives and antiplatelet agents.

To date there are three published major randomized trials [13–15] that make evidence available including also secondary prevention of stroke. They are summarized in Table 1.

It can be seen that in all three trials the absolute risk reduction for stroke is about 1 %. It can also be seen that the age groups included in such studies are not typical for stroke populations and that the number of strokes seen in these trials probably strongly underestimate the importance for stroke prevention. It would be statistically appropriate to include also elderly patients that have a higher risk of suffering a stroke. Considering the enormous direct and indirect costs of stroke to a community it is surprising that no statin study has been completed to date that aims for a clear result also for stroke prevention.

Efficacy of statins are the sum of lipid as well as non-lipid effects [12]. The lipid-effects include that statins inhibit the cholesterol biosynthesis and they up-regulate LDL receptors in the hepatocytes with consecutive enhanced clearance of LDL from plasma. In addition, statins have a number of well-investigated and proven non-sterol effects on endothelial, macrophage, platelet, and smooth muscle cell function. Statins lower the levels of C-reactive protein which was first described in the CARE trial. Not surprisingly, also the levels of other inflammatory markers, such as IL-6, TNF- α , amyloid A, and fibrinogen are decreased and adhesion molecules, such as ICAM-1 and E-selectin are deactivated. It is held that these non-lipid effects effectively contribute to the stabilization of plaques and, therefore, account for up to 25 % of reduction of vascular events. This probably also accounts for the observation that statins are equally effective in preventing vascular events in individuals with cholesterol above 200 mg/dl as well as in individuals with values below 200 mg/dl.

Table 1. Stroke relevant data from the 3 large, randomized statin trials (modified from [12])

	4S	CARE	LIPID
Age (range), y	35–70	21–75	31–75
Mean age, y	58	59	62 (median)
Number of patients	4,444	4,159	9,014
Total enrollment \geq 65 y	1,021	1,283	3,514
Total enrollment \geq 70 y	0	NR	1,346
Intervention	Simvastatin 10–40 mg	Pravastatin 40 mg	Pravastatin 40 mg
Primary endpoint	Total mortality	MI and CHD death	Total mortality
Number of strokes (Placebo vs statins)	73 vs. 56	76 vs. 52	204 vs. 169
ARR % (stroke)	0.8	1.2	0.8
NNT to prevent one stroke	132	86	128
RRR % (stroke)	23, NS	32, p = 0.03	19, p = 0.022

ARR = absolute risk reduction; NNT = number needed to treat; RRR = relative risk reduction; NS = not significant; NR = not reported

Diet, Physical Exercise and Stroke

General recommendations for stroke patients include a healthy diet and physical exercise. These measures have not yet been tested for their individual and combined value for stroke prevention by means of properly designed intervention trials. In spite of this, indirect evidence from population surveys and from long-term observation of high risk patients supports the biological plausibility that physical exercise should be recommended also for stroke prevention [16]. In patients with impaired glucose tolerance two prospective studies have recently shown the combined measures of diet and physical exercise to be highly effective in preventing diabetes. The total reduction of diabetes was 58 % in both studies [17, 18]. This is of enormous importance also for stroke prevention because of the five-fold risk of stroke that diabetics carry compared to non-diabetics [19].

Due to these considerations 2 questions have to be answered:

1. If lifestyle interventions are so much effective in high risk populations (eg diabetics) why should they not also be effective in stroke patients or stroke prone individuals? The reduction of outcome events by means of lifestyle changes is about 60 % and this doubles the effects of statins.
2. If such lifestyle interventions are recommended to stroke patients or stroke prone individuals should these interventions be more or less automatically supplemented by statins or should statins be reserved for vascular high risk patients with hypercholesterolaemia? In other words: Should the indication for regular statin intake be based on the individual risk of developing a vascular event (eg coronary heart disease or stroke) or should the risk be stratified by total cholesterol or LDL plasma values and therefore only be applied to high risk individuals with hypercholesterolaemia?

Whereas lifestyle interventions which include a healthy diet, physical exercise, and, if necessary, antihypertensive treatment seem to be the primary and most effective intervention for the prevention of stroke it remains to be determined whether statins should be recommended for the secondary prevention of any kind of stroke.

Limitations to such general conclusions are based firstly on the fact that only little more than 50 % of all strokes are due to an acute atherothrombotic event. Atherothrombotic strokes consist of two defined ischaemic stroke groups. One group comprises all types of lacunar strokes which implies a vascular blockage on a microcirculatory level or on the level of arterioles of the brain, and the second group comprises strokes that are caused by atherothrombotic lesions of the large craniocervical vessels. Other non-atherothrombotic aetiologies include cardiogenic embolism which is due to atrial fibrillation or based on evidence of thrombi in the left atrium or left atrial appendage or any other source of embolism. Still other causes of stroke are cryptogenic or from rarer causes including genetic or coagulation disorders. This classification of ischaemic stroke subtypes has become well accepted and also mandatory for many clinical trials [8, 20, 21].

On the other hand, a considerable number of stroke patients already have a statin indication by nature of other risks or diseases. Approximately 15–20 % of all strokes have manifest diabetes, 15 % have atrial fibrillation, additional 15 % a history of myocardial infarction or cardiac insufficiency. Thus, such patients do not need additional evidence for an atherothrombotic risk in order to indicate the intake of a statin.

The Heart Protection Study Advocates Treatment of Risk Equivalents Over Cholesterol Levels: Also for Stroke?

The ongoing discussion whether the decision should be made to treat any high vascular risk by means of statin drugs (similar to the indication for aspirin) or to limit such decisions to treat only patients that also have hyperlipidaemia has recently been challenged by the (as yet not completely published results of the) MRC/BHF Heart Protection Study (HPS) [22]. The HPS has included more than 20,000 high risk patients and 28 % of them (5805 patients) were older than 70 years. The including qualifying event were either a history of myocardial infarction (42 %), other vascular events (including stroke) (24 %), or a diagnosis of diabetes or treated hypertension (35 %). By a factorial design (which also considered treatment by vitamins, the results of which are not reported here) the patients were randomized to treatment with either simvastatin 40 mg daily or matching placebo. Among the primary endpoints were fatal/non-fatal coronary heart disease rate as well as fatal/non-fatal strokes. It is of interest that 33 % of all patients included had an LDL value within normal range (below 3 mmol/l = 116 mg/dl). The differences obtained in the treatment group resulted in LDL values of 2.3 mmol/l whereas the LDL values in the placebo group remained at 3.3 mmol/l. Thus, there was a group difference of 0.96 ± 0.02 mmol/l. One of the intriguing results of this trial was that the extent of LDL lowering was of the same magnitude irrespective of pretreatment LDL values at the time of randomization. The overall results of this trial clearly favoured statin treatment showing a highly significant reduction for all outcome measures. The rate for all vascular events was 7.7 % (791/10,269) versus 9.2 % (943/10,269) corresponding to a 17 ± 4.4 % risk reduction, $2p = 0.0002$. Significant differences were also found for the stroke outcome measure. In the statin treatment group versus the placebo treatment group the strokes observed within the follow-up period of up to 6 years were 4.4 % (456/10,269) and 6.0 % (613/10,269) respectively, with a risk reduction of 27 ± 5.3 %, bearing a significance of $2p = 0.00001$. The largest difference was seen in the group of ischaemic strokes (242 and 376, respectively), with no significant differences between other stroke subtypes. No excess of subarachnoid haemorrhage or haemorrhagic stroke was seen. Once the complete data will be available, especially the data concerning the stroke subtype diagnosis, it will be possible to give an estimate whether group differences for stroke rates occurring over time resulted from differences due to treatment allocation or some other clinical or therapeutic difference. Such possibilities include differences in rates of patients being anticoagulated for atrial fibrillation or other proven preventive measures.

Outlook

One of the major future hopes for deciding whether stroke *per se* justifies treatment with statins or whether additional risks such as coronary heart disease, diabetes or other risk equivalents have to be present will come from the results of the SPARCL study (Stroke Prevention by Aggressive Reduction in Cholesterol Levels [23]). In this study, acutely administered atorvastatin 80 mg will be compared to placebo in 4200 stroke patients. The follow-up period for the stroke study will end in 2005. In a very similar study in coronary heart disease patients, the MIRACL study, the same medication has been tested and was shown highly effective [24]. In this study the stroke rate was a secondary outcome measure

and shown to be reduced by 50 % within 16 weeks. In spite of this impressive result, no definite conclusions or recommendations for the treatment of stroke patients can be drawn due to the small absolute numbers of strokes in this study.

This study will also shed some light on the hopes that acute interventions with statins might be an effective treatment for early stroke recurrence. Until now only anecdotal evidence exists that show efficacy of statins for recurrent cerebral ischaemic episodes.

Statins also give some hopes in being effective in vascular dementia. It is not yet clear in which stages of dementia the most effect is to be expected. Probably the initial stages of dementia will be a target for therapy.

Other hopes include the improvement of cerebral autoregulation as well as safety during carotid endarterectomy or during other vascular operative procedures.

In general, statins give hope for the future also for stroke patients. There is no reason to doubt the efficacy of statin treatment for stroke patients. Once efficacy is shown also for these patients, the numbers needed to treat to avoid one stroke, especially one disabling stroke, will have to be added up against the total costs of stroke which is one of the most expensive diseases in all health regions worldwide. Safety issues have not been discussed in this review but they do not differ for stroke patients. Fatal adverse reactions have been reported (mostly for cerivastatin) but a review of these cases has shown that statins can be considered quite safe, with fatal rhabdomyolysis being much lower than 1 death per 1 million prescriptions [25]. More recently, statins have been connected to polyneuropathies, with a number-needed-to-harm rate of 2.200 over the age of 50 years [26].

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