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Statins and stroke prevention

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The primary goal of β-hydroxy-β-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) is to reduce the plasma total cholesterol (TC) and LDL-cholesterol (LDL-C), but the relationship between hyperlipidemia and ischemic stroke remains controversial. Such an association has been reported in some observational studies (Iso *et al.*, 1989 ; Benfante *et al.*, 1994), but not in others (Wolf *et al.*, 1991). The conflicting results of these studies might be explained by a masking effect due to the inclusion of patients with cerebral hemorrhage for which an inverse correlation with hyperlipidemia has been reported (Law *et al.*, 1994). Another possible reason is that the impact of hyperlipidemia may be different according to ischemic stroke subtype. Thus, an association between large vessel atherosclerosis and hyperlipidemia has been reported in several studies (Bogousslavsky *et al.*, 1985 ; Ford *et al.*, 1985 ; Palomaki *et al.*, 1993 ; Fine-Edelstein *et al.*, 1994 ; Fabris *et al.*, 1994 ; O'Leary *et al.*, 1996 ; Wilson *et al.*, 1997 ; Amarenco *et al.*, 1998), although in some of them this association disappeared after adjustment for confounding factors (Palomaki *et al.*, 1993 ; Fabris *et al.*, 1994). In a review of 45 prospective observational studies with a mean follow-up of 16 years and a high number of stroke (Prospective Studies Collaboration, 1995 ; Crouse *et al.*, 1997), there was no independent association between baseline TC and the risk of stroke across the entire range of cholesterol values. However, most of the studies did not record nonfatal strokes. The results might have been different for less severe strokes.

The Second Joint Task Force of European Societies (Wood *et al.*, 1998) has determined the target levels of lipids to be reached by therapeutic interventions to prevent coronary heart disease. However, we do not know if these target levels also apply to ischemic stroke.

Statins

The available statins in Belgium are simvastatin (Zocor®), pravastatin (Pravasine®), fluvastatin (Lescol®), and atorvastatin (Lipitor®). Pravastatin is fermentation-derived or "natural" statin. Simvastatin has a similar chemical structure but is semi-synthetic. Fluvastatin and atorvastatin are synthetic statins which are chemically distinct from the natural statin and from each other. Pravastatin is the most hydrophilic of the statins and this may account for the low incidence of elevated creatine kinase levels and myopathy.

Statins and atherosclerosis

Atherosclerosis is a chronic inflammatory disorder which may lead to fissure and rupture of a vulnerable atherosclerotic plaque, thereby resulting in mural thrombus formation (Delanty and Vaughan, 1998 ; Rabbani and Topol, 1999 ; Drouet, 2002). Statins inhibit HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis, leading to a depletion of intracellular cholesterol in hepatocytes. This in turn induces an upregulation of hepatic LDL receptors, which promotes a lowering of LDL-C levels. Statins produce dose-dependent reductions in LDL-C of up to 60%, but reductions of 25-40% were commonly reported in the placebo-controlled trials with the doses used in clinical practice (Farnier and Davignon, 1998). Reduction of plasma LDL-C levels decreases the lipid and foam cell content of plaque by reducing cholesterol deposition and by promoting cholesterol efflux from plaque. These induced changes in plaque architecture make it less prone to disruption and acute thrombosis. However, in statins trials for coronary ischemic disease, there is a discrepancy between coronary angiography showing rather small regression of plaques and clinical data showing significant decrease of ischemic heart disease. Moreover, whereas there is a weak correlation

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Table 1

Characteristics of the randomized, placebo-controlled trials reporting on stroke

Trials	Reductase inhibitors	Number randomized	Age years	Male %	Hypertension %	Mean TC mg/dl	Mean LDL-C mg/dl	TC reduction %	LDL-C reduction %
CARE	Pravastatin	4 159	20-75	86	43	209	139	20	32
LIPID	Pravastatin	9 104	31-75	83	41	220	150	18	25
4S	Simvastatin	4 444	35-70	81	26	263	189	25	35
MIRACL	Atorvastatin	3 086	> 18	65	55	206	124	–	40
HPS	Simvastatin	20 536	40-80	75	41	227	131	- 44 mg/dl*	- 37 mg/dl*
PROSPER	Pravastatin	5 804	70-82	48	62	307	204	–	34

TC, total cholesterol ; LDL-C, LDL-cholesterol. Mean total and LDL cholesterol refer to baseline mean levels.

* In the HPS trial, reduction of total and LDL-cholesterol is reported as the level observed in the simvastatin group minus the level observed in the placebo group.

Table 2

Effects of statins on the reduction of stroke incidence in secondary prevention

Trials	Number of events		RRR	Events avoided / 1000 treated**	Follow-up
	Statin n (%)	Placebo n (%)	%		
CARE					5 years
stroke	52 (2.5)	76 (3.7)	32	12	
stroke or TIA	92 (4.4)	124 (6.0)	27	16	
LIPID	127 (3.4)	161 (4.4)	23	10	6 years
4S					6 years
stroke	56 (2.5)	73 (3.3)	24	8	
stroke or TIA	75(3.4)	102 (4.6)	28	12	
MIRACL	10 (0.6)*	20 (1.3)*	46	7	16 weeks
HPS	290 (2.8)	409 (4.0)	30	12	5 years
Hx. of CVD	406 (24.7)	488 (29.8)	17	51	
PROSPER					3 years
stroke	74 (5.6)	69 (5.5)	0●	–	
TIA	47 (3.6)	64 (5.1)	25●	15	

RRR, relative risk reduction ; TIA, transient ischemic attack ; Hx. of CVD, patients with a history of cerebrovascular disease.

* MIRACL, after calculation of the relative risk for ischemic stroke only.

** The events avoided refer to ischemic stroke for CARE, LIPID, 4S, and MIRACL, and to any major vascular events, including stroke for HPS.

● The difference was not statistically different between the treatment and placebo group.

between hypercholesterolemia and ischemic stroke, statins significantly reduce the risk of cerebrovascular events. These observations suggest that statins have additional protective effects other than lowering cholesterol levels : improvement of plaque stability, restoration of endothelial function, and decrease of platelet activity (Delanty and Vaughan, 1998 ; Rabbani and Topol, 1999).

Prevention of ischemic stroke

Meta-analyses of the early clinical trials with older lipid-lowering agents, such as diet or fibrates, have concluded that modest reductions of cholesterol did not reduce stroke (Atkins *et al.,* 1993 ; Hebert *et al.,* 1995 ; Di Mascio *et al.,* 2000). However, these trials had some methodological weakness : lack of brain CT scan or neurological exam and inclusion of young patients with a lower risk of cerebral atherosclerosis.

Efficacy of HMG-CoA inhibitors in reducing the risk of ischemic stroke has been evaluated in primary and secondary prevention. The characteristics and results of the 6 randomized, placebo-controlled trials reporting on stroke in secondary prevention are reported in Table 1 and 2.

Primary prevention

In the West of Scotland Coronary Prevention Study (WOSCOPS) (Shepherd *et al.,* 1995), pravastatin reduced the relative risk of ischemic stroke by 10%, but the difference was not significant. In a meta-analysis pooling all trials, there was a non significant reduction of 11% (95% CI, -31 to 40%) (Stein *et al.,* 1998). In the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) (Shepherd *et al.,* 2002), pravastatin (40 mg) therapy did not reduce the risk of transient ischemic attack (TIA) and the risk of fatal and non fatal

stroke in primary prevention in elderly individuals, but the number of stroke was particularly small.

Secondary prevention after myocardial infarct

The Cholesterol And Recurrent Events (CARE) placebo-controlled study evaluated pravastatin (40 mg) treatment in 4 159 patients with a history of coronary artery disease, who had average cholesterol levels (TC < 240 mg/dl), and who were well matched for stroke risk factors and the use of antiplatelet agents (85% of subjects in each group) (Sacks *et al.,* 1996).

A small proportion of patients had also a history of stroke or TIA (pravastatin, 5.3% ; placebo, 4.8%). In a further analysis (Plehn *et al.,* 1999), this trial showed that pravastatin reduced the frequency of ischemic stroke or TIA by 27% (95% C.I., 4-44 ; p = 0.02) and the frequency of all stroke by 32% (95% C.I., 4-52 ; p = 0.03), over a median 5-year follow-up period. There was a reduction in all stroke etiologic subtypes, but statistical power was inadequate to test for significance due to the limited number of events in each class. There was no increase of intracerebral hemorrhage on pravastatin. There were too few fatal strokes to conclude to a beneficial effect of pravastatin in the prevention of death from stroke (pravastatin, 5 ; placebo, 1). The study does not provide data about the reduction of stroke in the subgroup of patients having also a history of cerebrovascular disease.

The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) placebo-controlled study evaluated pravastatin (40 mg) treatment in 9 104 patients with a history of coronary artery disease, who had a broad range of cholesterol levels (155-270 mg/dl) (The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group, 1998). The proportion of patients having also a history of stroke or TIA (pravastatin, 7.2% ; placebo, 8.3%) was higher in this study than in the CARE trial. Eighty-three percent and 82% of patients were taking aspirin in the pravastatin and placebo group, respectively. In a further analysis (White *et al.,* 2000), pravastatin reduced the risk of ischemic stroke by 23% (95% C.I., 5-38 ; p = 0.02) over a mean follow-up period of 6.1 years. Pravastatin had no effect on hemorrhagic stroke. There was no reduction in risk of fatal stroke (pravastatine, 22 ; placebo, 27 ; OR, 0.81 ; 95% CI, 0.46-1.43). Data in the patients with a history of cerebrovascular are lacking.

The Scandinavian Simvastatin Survival Study (4S), a placebo-controlled trial, evaluated simvastatin treatment (20 mg or 40 mg in 37% of patients) in 4 444 patients with a history of coronary artery disease with high levels of cholesterol (212-309 mg/dl) (The Scandinavian Simvastatin Survival Study (4S), 1994). Patients with a history of stroke were excluded. Only 37% of all patients were receiving aspirin at baseline, whereas comparatively more than 80% of all patients in CARE and LIPID received aspirin. A post-hoc analysis (Pedersen *et al.,* 1998) reported a 28% (p = 0.033) reduction of total stroke (fatal and non fatal stroke, TIA) and a 24% reduction of stroke (TIA excluded) over a median follow-up period of 5.4 years. There were 14 fatal stroke in the simvastatin group and 12 in the placebo group (OR, 1.17 ; 95% CI, 0.54-2.52). Two hemorrhagic strokes occurred in the treatment group and none in the placebo group.

The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) placebo-controlled study (Waters *et al.*, 2002) evaluated the efficacy of high dose of atorvastatin (80 mg) in 3 086 patients with a history of coronary artery disease and presenting a broad range of cholesterol levels (< 270 mg/dl, no lower limit). The proportion of patients with a history of cerebrovascular disease was 8.4% in the atorvastatin group and 8.7% in the placebo group. Before randomization, only 18% of patients were taking aspirin. In this study, non fatal stroke, as a predetermined secondary endpoint, included both ischemic and hemorrhagic strokes. In contrast to CARE and LIPID, MIRACL was a short term trial with a follow-up period of 16 weeks. Atorvastatin significantly reduced the relative risk of non fatal stroke by 40% (95% CI, 0.19-0.88 ; p = 0.02) and that of fatal and non fatal stroke by 49% (95% CI, 0.24-0.98 ; p = 0.04). Cerebral hemorrhage was reported in 3 patients in the placebo group. After exclusion of the 3 hemorrhagic strokes and the 5 ischemic strokes which occurred after a coronary bypass surgery, the relative risk of thrombotic/embolic stroke was reduced by 46%. The risk of experiencing a non fatal stroke for patients with a history of cerebrovascular disease was 3.44 times the risk for those without this history (95% CI, 1.50-7.87 ; p = 0.004).

Secondary prevention after any cardiovascular events (high risk patients)

The MRC/BHF HPS trial (Heart Protection Study Collaborative Group, 2002) was a placebo-controlled study planned to evaluate the effects of simvastatin (40 mg) in 20 536 high-risk individuals (aged 40-80 years) with a plasma cholesterol level ≥ 135 mg/dl, and defined as having either a history of coronary disease, or occlusive disease of non coronary arteries (non disabling ischemic stroke ; leg artery stenosis ; carotid endarterectomy ; other arterial surgery or angioplasty), or diabetes mellitus, or treated hypertension. The follow-up period was 5 years. Physicians in charge of the patients were allowed to treat with a non study statin those they judged to be at high risk for a major cardiovascular event. At the end of the fifth year, 82% of patients allocated in the simvastatin

group were still compliant, while 3% were using a non study statin and 2% both. In the placebo group, a high number of patients were taking a non study statin (32%) at the end of follow-up. As one third of patients were taking statin in the placebo group, this means that the LDL difference and the risk reduction observed in HPS represents two third of the actual difference which could have been observed from a direct comparison between simvastatin and placebo.

The mean difference in concentrations (simvastatin minus placebo) was – 44 mg/dl for TC and – 37 mg/dl for LDL-C. The proportional reduction in LDL-C was independent of the presenting cholesterol concentrations (< 193 mg/dl, 193-323 mg/dl, or ≥ 323 mg/dl), and even for those presenting a low baseline LDL-C (< 116 mg/dl), the average LDL-C difference during the trial was still – 35 mg/dl.

In this high-risk population, simvastatin significantly produced a 25% reduction in the incidence rate of any stroke (ischemic and hemorrhagic) (95% CI, 0.66-0.85 ; $p < 0.0001$), a 30% reduction in the incidence of ischemic stroke (95% CI, 19-40 ; $p < 0.0001$), and a 17% reduction in the incidence of TIA (204 [2.0%] vs. 250 [2.4%] ; $p = 0.02$). There was a non-significant trend towards a 25% decrease of fatal stroke. The incidence of hemorrhagic stroke was not significantly different (0.5% in each group). There was a non-significant trend towards fewer major vascular events (myocardial infarct, stroke, revascularization) in the first year of follow-up, but subsequently, for each year, the reductions were highly significant to reach 24% in the end of follow-up. Most notably, the proportional reductions in risk did not appear to be influenced by the pre-treatment TC or LDL-C level. Indeed, even with a level of LDL-C < 116 mg/dl and TC < 323 mg/dl, the rates of any major vascular events were reduced by 21% and 23%, respectively. Also, similar reductions were observed when simvastatin was added to other effective therapies, such as aspirin, β-blockers, or ACE inhibitors, and when age was higher or lower than 70 years.

Secondary prevention in high risk elderly patients

The MRC/BHF HPS study included 5 806 (28%) high-risk patients aged at least 70 years. In this trial, simvastatin (40 mg) reduced the risk of stroke by 29% (simvastatin, 5.8% vs. placebo, 8.2% ; $p = 0.0003$) (Heart Protection Study Collaborative Group, 2002).

The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) (Shepherd *et al.*, 2002) evaluated the efficacy of pravastatin (40 mg) in 5 804 patients aged 70-82 years with a history of, or risk factors for, vascular disease. Baseline cholesterol levels ranged from 155 mg/dl to 484 mg/dl. Mean follow-up was 3.2 years (range 2.8-4.0). In the placebo and pravastatin groups, 277 (10%) and 131 (5%) individuals, respectively, initiated non-study statin therapy. The number of patients taking aspirin or other antiplatelet agents was not reported. In secondary prevention, there was no significant effect on the occurrence of fatal or non fatal stroke. Transient ischemic attacks were reduced by 30%, but this effect was not significant. This apparent reduction in TIAs suggests that the lack of efficacy on stroke might be the consequence of a lack of statistical power, since the stroke rate at 4.5% in the whole pravastatin group was about half of that predicted. The too short follow-up period (3-2 years vs. 5 years in HPS) might be another reason.

Secondary prevention after ischemic stroke

The MRC/BHF HPS trial is the only ever published study in secondary prevention after ischemic stroke. However, in this subpopulation of patients, the trial recorded the first occurrence of any major vascular events mixing major coronary disease, any stroke, and revascularization in a composite endpoint, and did not single out recurrent stroke separately (Heart Protection Study Collaborative Group, 2002). Of the 7 150 participants without diagnosed coronary disease, 1 820 had cerebrovascular disease (simvastatin, 8.9% ; placebo, 8.7%), whereas among the 13 386 with known coronary disease, 1 460 had also a history of ischemic stroke (simvastatin, 7% ; placebo, 7.1%). In the population of patients with a history of cerebrovascular and coronary heart disease, there was a significant 13% reduction in any major vascular events. In the population of patients with a history of cerebrovascular disease and no prior coronary heart disease, the relative risk of any major vascular events was reduced by 21%. Overall, in those patients with a history of cerebrovascular disease, the risk to present a new major vascular event was significantly reduced by 17%.

The SPARCL study is another ongoing trial to evaluate the benefits of atorvastatin in the prevention of stroke in patients with a history of cerebrovascular disease.

Safety

The large scale randomized trials such as CARE, LIPID, and PROSPER for pravastatin, 4S and HPS for simvastatin, reported elevated serum alanine aminotransferase and creatine kinase levels, liver disease, and myopathy, more often in the treatment group, but the differences were not significant as compared to the control groups. However, in the MIRACL study, abnormal liver transaminases (> 3 times upper limit of normal) were more common in the atorvastatin group than in the placebo

group (2.5% vs 0.6% ; p <.001), but this may be due to the high dose (80 mg) used in this trial.

Conclusions

The WOSCOPS and PROSPER study as well as a meta-analysis indicate that statins have no preventive effects on stroke incidence in primary prevention, and should not be recommended in this setting.

In secondary prevention, the different trials have shown that statins can significantly reduce the long-term incidence of stroke in patients with a history of coronary disease and in high-risk patients presenting one or several risk factors. Interestingly, the HPS trial shows that the risk of any major vascular events including stroke is reduced whatever the baseline cholesterol values (even in those with normal levels) and whatever the patients are hypertensive, diabetic or not. As neurologists are mainly concerned by patients with a history of stroke, it is interesting to point the HPS data in this subcategory of patients, in which simvastatin reduces the risk of any major vascular events by 17% and avoids 51 of these major events for 1 000 patients treated.

However, the results provided by the secondary prevention trials have some limitations. First, the number of stroke events avoided per 1000 patients treated over 5 to 6 years is relatively low, between 10 and 16, and the reduction of stroke incidence is only apparent after 1 to 2 years with simvastatin or pravastatin. This may be due to the weak association between ischemic stroke and hypercholesterolemia. Data about the differential effects of statins on the various subtypes of ischemic stroke are still lacking, and this is due to the low number of ischemic stroke observed in the randomized trials. Thus, although statins can reduce large vessel cerebral atherosclerosis, the issue of whether cholesterol-lowering therapy can also prevent lacunar infarctions remains unsettled. The currently available trials do not show any reduction in risk of fatal stroke. This may be the consequence of the low number of fatal stroke observed in these trials. In addition, the clinical characteristics of some trials do not match those of a common stroke population. LIPID, CARE, and 4S included younger patients (20-75 years) than in a general stroke population, but the HPS trial showed a 29% reduction in risk of stroke in patients aged at least 70 years followed over a period of 5 years. A similar reduction was not observed in PROSPER with a follow-up period of 3 years only. The proportion of male subjects in CARE, LIPID, 4S, and HPS was higher (75-86%) and that in PROSPER lower (48%) than the proportion of male patients usually observed in a stroke population (61% in the Mont-Godinne Stroke database). Also, the prevalence of hypertension (26-43%), a risk factor associated more often with ischemic stroke than coronary disease, was lower in CARE, LIPID, 4S, and HPS than in a general stroke population (49%, Mont-Godinne Stroke database).

All statins are well tolerated, so that it seems sufficient to check creatine kinase concentrations only when definite unexplained muscle symptoms are reported, unless patients are using other drugs known to increase the risk of myopathy. Likewise, there is no need for routine liver function checks, except for patients with a pre-existing liver disease. There were no more hemorrhagic strokes in the patients on statins, which is against the view that lowering cholesterol would be potentially harmful by increasing the risk of cerebral hemorrhage (Law *et al.*, 1994).

Recommendations

Primary prevention : statins do not prevent stroke.
Secondary prevention after ischemic heart disease : pravastatin, simvastatin, and atorvastatin prevent stroke.
Secondary prevention in high-risk patients : simvastatin prevent stroke.
Secondary prevention in high-risk elderly patients : simvastatin prevent stroke over a follow-up period of 5 years ; pravastatin does not prevent stroke over a follow-up period of 3 years.
Secondary prevention after cerebrovascular disease : simvastatin prevent any major vascular events, including stroke.

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