Stroke Prevention, Blood Cholesterol and Statins

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Abstract- Statins have a good overall safety profile to date, with no increase in haemorrhagic stroke or cancer. They have favourable effects in the primary prevention of cardiovascular disease in high-risk young as well as elderly populations. Statins reduce the incidence of stroke in high-risk populations (mainly CHD patients, diabetics and hypertensives) even with a normal baseline blood cholesterol level, which argues for a global cardiovascular risk-based treatment strategy. As for CHD, stroke reduction was mainly observed in studies with large between-group LDL cholesterol difference. In patients with prior strokes, statins reduce the incidence of coronary events, but it is not yet proven that they actually reduce the incidence of recurrent strokes in secondary prevention.

From a practical point of view, since there was a favourable treatment effect overall in stroke and TIA patients in HPS, it seems reasonable to treat stroke patients with a statin and total cholesterol >135 mg/dL (3.5 mmol/dL). On-going research is aiming to refine patient selection. As anticipated by current US recommendations, patients who are likely to benefit most are those with carotid atherosclerosis, diabetes mellitus, previous coronary heart disease, hypertension, hypercholesterolaemia, or cigarette smoking and LDL cholesterol >100 mg/dL.

Key Words: Statins, Cholesterol, Stroke, Stroke prevention

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INTRODUCTION

Before the statin era, any attempt to reduce total blood cholesterol levels, either by a diet approach or a fibric acid agent-based lipid lowering therapy, failed to significantly reduce the incidence of stroke[1]. Indeed, although blood cholesterol has been closely associated with carotid atherosclerosis, which causes atherothrombotic strokes, paradoxically, the link between serum cholesterol level and all strokes has never been fully established[2]. Consequently, reducing cholesterol levels after a stroke was not often considered a valuable objective by most clinicians.

In the past decade, 9 large-scale trials have demonstrated that cholesterol-lowering treatment using HMG-CoA reductase inhibitors (statins) significantly reduces vascular events in primary as well as secondary prevention of myocardial infarction[3-12]. All these studies but

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three[6,7,10] also showed a reduction in the risk of strokes, including brain infarctions, transient ischaemic attacks and brain haemorrhages, as a secondary endpoint in the population studied.

Are blood lipids a recognized risk factor for stroke?

The meta-analysis of 45 prospective cohorts including 450,000 subjects, a follow-up of 16 years on average (a total of 7.3 million patient-years) and 13,000 incident strokes found no association between total cholesterol and stroke[2]. These cohorts were primarily designed to study the incidence of coronary heart disease, and therefore included middle-aged subjects at risk of myocardial infarction; thus, since brain infarction occurs far later than myocardial infarction, at a mean age of 70 years (compared with 55-60 years for MI), these subjects presented a higher risk of having fatal recurrent MI before a stroke; however, they were more likely to have aggressive risk factor management, which may have accounted for a lower incidence of stroke, and cerebrovascular events were not analyzed according to stroke subtypes (e.g. haemorrhagic vs. ischaemic strokes). In particular, atherothrombotic brain infarction may have been underrepresented in these studies.

The MRFIT study showed that the risk of death from non-haemorrhagic (i.e., ischaemic) stroke increased in proportion to serum cholesterol in 351,000 men aged 35 to 57 years[13]. Conversely, there was a negative association with haemorrhagic stroke for cholesterol levels under 200 mg/dL: the lower the total cholesterol levels, the higher the risk of haemorrhagic stroke, thus suggesting a U-shaped relationship between cholesterol and stroke. Therefore, in the cohorts examined in the Prospective Study Collaboration, counting haemorrhagic strokes together with ischaemic strokes may have masked a small, true relationship with ischaemic stroke.

In the Copenhagen City Heart Study, total cholesterol was positively associated with risk of non-haemorrhagic stroke, but only for levels above 8 mmol/l (320 mg/dL), corresponding to the upper 5 per cent of the distribution in the study population[13]. Another prospective community-based study found a significant relationship between LDL cholesterol levels and dementia with stroke in 1,111 people without initial dementia (average age, 75 years)[14].

To sum up, most prospective observational cohorts were not representative of the whole population at risk for stroke, and did not identify blood cholesterol as a risk factor for all strokes, except those which considered stroke subtypes, particularly ischaemic and atherothrombotic strokes. No epidemiological studies have considered the relationship between blood cholesterol as a continuous variable and the risk of incident strokes in a high-risk cohort selected on the basis of global cardiovascular risk approaches (high Framingham or PROCAM risk score, increased carotid IMT, or presence of carotid artery atherosclerotic plaques).

USE OF STATINS IN STROKE PREVENTION: THE FACTS

The Scandinavian Simvastatin Survival Study (4-S) trial

This secondary prevention trial showed that simvastatin 10-40 mg/day given 6 months after a myocardial infarction or unstable angina in men with serum total cholesterol above 270 mg/dL reduced mortality by 30% (15 to 42%; P=0.0003) and major coronary events by 34% (25 to 41%; P<0.00001) after 5 years[3]. Post-hoc analysis showed that the incidence of strokes and TIAs was reduced by 30% (4 to 48%; P=0.024), but this was mainly due to the reduction in TIAs, which is considered a rather soft secondary endpoint because of the difficulties in differential diagnosis with other transient neurological conditions (e.g., migraine attack, focal epilepsy, hypoglycaemia, etc.). When TIAs were excluded from the analysis, the difference was no longer significant[3].

The Cholesterol and Recurrent Event (CARE) study

The CARE trial was a secondary prevention trial using pravastatin 40 mg/day in patients with myocardial infarction[4]. The results concurred with those of the 4-S trial. However, the CARE patients had cholesterol levels within the normal range or moderately elevated (total cholesterol less than 240 mg/dL and LDL cholesterol

between 115 and 174 mg/dL). Among the 2078 patients in the placebo group and 2081 in the pravastatin group who had suffered a myocardial infarction between 3 and 20 months before randomization, the relative risk reduction of a fatal coronary event or non-fatal myocardial infarction was 24% in the pravastatin group after 5 years of treatment[4]. On the basis of this combined criterion, event reduction was greatest in women (45%) and in elderly subjects aged 60 to 75 years, representing a total of 2129 patients (26%).

In CARE, a stroke occurred in 78 patients in the placebo group (3.7%) and 54 patients in the pravastatin group (2.5%), yielding a relative risk reduction of 31% (3 to 52%; P=0.03) with P=0.03. In a second analysis, the CARE investigators found a 27% reduction in stroke or TIA, and that all categories of stroke were reduced, although there was inadequate power to detect a significant result in each class[15]. For example, there was a 21% reduction (-20 to 48%, P=0.268) for atherothrombotic strokes. Unlike the 4-S trial, in which only 37% of patients received aspirin, 85% of the CARE patients received antiplatelet therapy, so that the stroke risk reduction achieved by pravastatin was added to that obtained by the antiplatelet agents.

The Long Term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial

The LIPID trial confirmed the efficacy of pravastatin 40 mg/day after MI and unstable angina occurring between 3 and 36 months before entry to the study, in patients who had a total cholesterol level between 155 and 271 mg/dL, i.e. a broad spectrum including high-risk and low-risk patients. After a 6-year period, the relative reduction in risk of death from coronary heart disease was 24% in the pravastatin group[5].

The special design of the LIPID trial was that cerebrovascular events were pre-specified and analyzed and validated by an end-point committee composed of vascular neurologists. The results for brain infarction were a relative risk reduction of 19% and an absolute risk reduction of 0.8% over a 6-year period of treatment with pravastatin[5,16]. These results were obtained in all ischaemic stroke subtypes (lacunar, cardioembolic and atherothrombotic strokes), mainly in the group of patients with low LDL (<138 mg/dL) and low HDL (<39 mg/dL) [109].

WOSCOP and AFACPS/TexCAPS trials

These were primary prevention trials, one in high-risk (WOSCOP) and another in low-risk patients (AFCAPS/TexCAPS). The first trial demonstrated that pravastatin reduced the incidence of fatal and non-fatal coronary events by 31%, all cardiovascular deaths by 32%, and death from any cause by 22% in hypercholesterolaemic men (272 $\pm$ 23 mg/dL on average)[6]. In the other trial, lovastatin reduced major coronary events (fatal and non-fatal MI, unstable angina and sudden cardiac death) by 27% in men and women with average total and LDL -cholesterol levels and below-average HDL cholesterol levels[7].

AFCAPS/TexCAPS did not report on stroke endpoint. In WOSCOP, there was no significant reduction in the incidence of stroke. However, the mean age of the patients included was low, accounting for a low incidence of stroke and consequently for lack of power to detect a significant difference[6,7].

The Heart Protection Study (HPS) trial

The HPS trial included 10,269 patients receiving simvastatin 40 mg/day and 10,267 patients receiving a placebo[8]. This trial included 13,379 patients with established CHD (65%), and 3280 patients with stroke prior randomization (no TIAs), including 1822 strokes without established CHD. There was a 24% relative risk reduction for major vascular events (major coronary events, stroke and revascularization), and the incidence of ischaemic stroke was reduced by 25% (4.3% in the simvastatin group and 5.7% in the placebo group), yielding an absolute stroke risk reduction of 1.4%, which essentially confirmed the results of the other 3 statin trials. Reduction of stroke incidence was observed with the same magnitude in diabetic patients[17]. Furthermore, in 3280 patients with stroke prior randomization, there was a 19% relative risk reduction for major vascular events (HR=0.81 [0.71-0.93], and in the 1822 stroke patients without an established CHD, the reduction in major vas-

cular events was 23% [HR=0.77 [0.63-0.94]). However, this reduction of the composite end-point (major coronary events, stroke or revascularization) was entirely due to the reduction of major coronary event and revascularization since there was 10.4% recurrent strokes in the simvastatin group and 10.5% recurrent strokes in the placebo group[9]. Therefore, simvastatin had virtually no effect on stroke recurrence, which may be due to the play of chance (subgroup analysis) or the fact that it was not a pre specified analysis and concerned only 300 strokes, lacking power to detect a difference. Patients were included with a mean of 4.3 years after the qualifying event meaning that the risk of recurrent stroke had already dramatically decreased.

The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial

The PROSPER trial included 5804 elderly men and women (52%) aged 70-82 years with a total cholesterol level between 155 and 350 mg/dL, receiving pravastatin 40 mg/day or a placebo[10]. Half were selected on the basis of a high-risk profile (62% were hypertensives, 11% diabetics and 28% current smokers), and half on the presence of established vascular disease (44% had a cardiovascular disease and 11% had stroke prior randomization). After a mean follow-up of 3.2 years, there was a significant 15% reduction in the primary composite endpoint (CHD death, non-fatal MI, fatal and non-fatal strokes) with 16.2% events in the placebo group and 14.1% in the pravastatin group (P=0.014). However, there was no effect on stroke incidence, with 4.5% strokes (131/2913) in the placebo group and 4.7% strokes (135/2891) in the pravastatin group. In addition, the cognitive functions declined at the same rate in both treatment arms, as in the HPS trial (in which the MMS was only evaluated at the end of the trial).

In summary, PROSPER confirmed that statins could be used in elderly patients, as in younger patients, to prevent any cardiovascular events, but did not confirm a favourable effect on the incidence of stroke in this population.

Why did PROSPER fail to show a reduction in stroke and cognitive impairment?

(1) One explanation may be the duration of the trial, which only lasted for 3 years. If the stroke endpoint in earlier pravastatin trials (CARE and LIPID) is considered, the Kaplan-Mieir curves started to diverge after the third year, and if the analyses had been performed after 3 years, these trials would also have had a neutral effect on the incidence of stroke[15,16].
(2) Another explanation is lack of power, since the hypothesis was an 8% stroke rate in the placebo group[18], whereas the actual rate was 4.5%. Although this is a rather soft endpoint, it may be worth noting that there was a trend towards a reduction in TIAs (P=0.051).
(3) Another factor is the design of the trial and the population selected which, as in the HPS trial, was based on 'no true indication for a statin'. The patients were selected in the primary care setting. We have no information about important baseline characteristics such as the presence of carotid stenosis, which are important for evaluation of the risk of stroke in the population included[18] as a result, it is not known whether this population was really representative of the entire elderly population at risk for stroke. Only 11% percent of patients had had a stroke at least 6 months before randomization. No documentation of carotid/vertebral atherosclerosis was required[18].
(4) In this trial, pravastatin 40 mg per day was used; once again, a higher dosage might have worked better, as suggested by the results of the ARBITER trial, which showed a regression of carotid atherosclerosis with atorvastatin 80 mg and progression of carotid atherosclerosis with pravastatin 40 mg/day[19].

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial - Lipid Lowering Treatment (ALLHAT-LLT)

The ALLHAT-LLT trial included 40,000 hypertensive patients aged 55 or older[20]. Those with an LDL cholesterol level of 120 to 189 mg/dL (100 and 129

mg/dL if known CHD) and a triglyceride level of less than 350 mg/dL were randomized to pravastatin 40 mg/day (n=5170) or usual care (n=5135). After a mean follow-up of 4.8 years, there was no significant difference in all-cause mortality, CHD mortality, the CHD event rate or stroke incidence (4.07% in the pravastatin group and 4.5% in the usual arm group, RR=0.91 [0.75-1.09]; P=0.31).

However, (1) this trial was not placebo-controlled, (2) the power calculation was based on the inclusion of 20,000 patients to detect a 12.5% reduction in mortality rate that provided 80% power, and only 10,000 were randomized, (3) 26.1% of patients in the usual care arm were treated with statins by the end of the trial, and finally (4) the confidence interval did not exclude a powerful effect of pravastatin in stroke prevention.

The KYUSHU Lipid Intervention Study (KLIS)

The KLIS trial is the only large statin trial ever conducted on a Japanese population[21]. KLIS included men aged 45-74 years with a total cholesterol level greater than 220 mg/dL and without a history of myocardial infarction or coronary revascularization. Of the 3,061 subjects assigned to pravastatin 10-20 mg/d and 2,579 assigned to usual care, 2,219 and 1,634 respectively were analyzed). After a 5-year follow-up, the primary endpoint (fatal and non-fatal MI, CABG, PTCA, cardiac death, sudden and unexpected death) occurred in 2.9% of patients. There was a non-significant reduction of 14% in the pravastatin group (0.86 [0.61-1.20]), and a non-significant 22% stroke risk reduction (0.78 [0.54-1.13]).

The non-significant effects in the KLIS trial were due to (1) the absence of a placebo group and of intention-to-treat analysis due to a failure in the randomization process; (2) the fact that the power calculation was based on the inclusion of 3,000 patients in each group to detect a 30% reduction in coronary events that provided 80% power with an estimated rate of 3.5% of coronary events in the usual care group after 5 years; (3) only 2,219 patients in the pravastatin arm and 1,634 in the usual care arm were analyzed, because many patients were excluded a posteriori (because of a total cholesterol level ≥ 300 mg/dL, protocol violations such as use of lipid-lowering agents, a history of endpoint disease, consent withdrawn, no contract with participants or missing data); (4) the coronary event rate was 2.9% in both groups, and (5) the low pravastatin dosage used (10-20 mg/d) accounted for an LDL reduction of only 15% in the pravastatin group.

The Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Trial

The GREACE trial randomized 1600 patients with an established coronary heart disease and LDL>100 mg/dL to atorvastatin or usual care[11]. The patients on atorvastatin (10 to 80 mg, mean 24 mg/d) were titrated to the NECP goal of LDL <100 mg/dL. After a 3-year follow-up, the primary endpoint (death, non-fatal MI, UA, CHF, revascularization or stroke) was reduced by 51% (0.49 [0.27-0.73]), and all components of the primary endpoint were significantly reduced; stroke in particular was reduced by 47%. By the end of the follow-up, 26% of patients in the usual care arm were receiving some form of lipid-lowering therapy.

The Anglo-Scandinavian Collaborative Trial (ASCOT)

In this primary prevention trial, 19,342 hypertensive patients (SBP>160 or DBP>100 mm Hg) who also had at least 3 risk factors (LVH, ECG abnormalities, non-insulin dependent diabetes mellitus, PVD, TIA, man>55 years, microalbuminuria, smoker, TC/HDL>6, early CHD) were randomized to s-blockers±diuretics or amlodipine±ACE inhibitor[12]. The patients who had a total cholesterol level of less than 6.5 mmol/dL were offered randomization in a factorial design to either atorvastatin 10 mg or placebo. A total of 10,297 patients were randomized in the lipid arm, and the follow-up was scheduled to be 5 years. However, on the recommendation of the independent DSMB committee of the study, the lipid arm was stopped early because of the great efficacy of the atorvastatin group on the primary endpoint. Stroke reduction was 27%, and the Kaplan-Meier curves diverged very early and constantly during the follow-up. This stroke reduction was obtained in addition to the

40% stroke reduction obtained in a population of patients who are well controlled for their hypertension after the blood pressure goal (<140/90 mmHg) is achieved. This trial emphasizes the need for a global cardiovascular risk approach, since statin treatment of these patients, who had 'normal' cholesterol levels but were hypertensives, was very effective.

Pravastatin or Atorvastatin Evaluation and Infection Therapy Thrombolysis in Myocardial Infarction 22 (PROVE-IT - TIMI 22) trial

The PROVE-IT trial randomized 4162 patients who had an acute coronary syndrome within 10 days into pravastatin 40 mg/d or atorvastatin 80 mg/d. The mean LDL cholesterol throughout the trial was 95 mg in the pravastatin arm and 66 mg/dL in the atorvastatin arm. After a mean of 24-month follow-up, the primary endpoint (any cardiovascular events including stroke) was 16% less in the atorvastatin arm than in the placebo arm (5 to 26%, P=0.005). Strokes were equaly frequent in the two arms. However stroke rate was very low (1% in each group) reflecting the short duration of the trial, and pravastatin has already shown to significantly reduced stroke in this CHD population against placebo, therefore a longer duration of the trial is likely to be necessary to show a further reduction in stroke incidence with a more aggressive lipid lowering therapy; finally, there was no heterogeneity between each part of the composite endpoint, meaning that stroke incidence might well be reduced in the same way than in the other part of the composite, and the confidence interval does not exclude a potential for a very large reduction of stroke in the atorvastatin arm[22].

The Treating to New Targets (TNT) trial

The Treating to New Targets Trial randomized 10,001 patients with coronary heart disease and cholesterol levels less than 130 mg/dL to receive 10 mg or 80 mg atorvastatin daily. LDL cholesterol levels were 101 mg in the 10 mg group and 77 mg in the 80 mg group throughout the trial. After a mean follow-up of 4.9 years, there was a 22% reduction in major vascular events. There were 3.1% and 2.3% fatal and nonfatal strokes in the 10 and 80 mg atorvastatin groups respectively, yielding a 25% relatiove risk reduction of stroke (P=0.02) [23].

Collaborative Atorvastatin Diabetes Study (CARDS)

In 2838 normocholesterolemic (LDL < 160 mg/dL) diabetics free of vascular events, there were 2.8% fatal and nonfatal strokes in the placebo group and 1.5% strokes in the atorvastatin (10 mg) group, yielding a 48% relative risk reduction of stroke in the atorvastatin arm (95% CI, 11 to 69%)[24].

Meta-analysis

The meta-analysis of all randomised trials testing statin drugs published before August 2003 now includes over 90,000 patients (Table 1)[25]. We analyzed statin effect on incident strokes according to LDL-C reduction. The relative risk reduction for stroke was 21% (OR 0.79 [0.73-0.85]) with no heterogeneity between trials (Fig. 1). Fatal strokes were reduced, but not significantly, by 9% (OR 0.91 [0.76-1.10]) (Fig. 2)[25]. Statin size effect was closely associated with LDL-C reduction (Fig. 3). Each 10% reduction in LDL-C was estimated to reduce the risk of all strokes by 15.6% (95%CI, 6.7-23.6). In terms of absolute stroke risk reduction there was a modest 0.9% risk reduction, i.e. approximately 9 strokes prevented per 1000 patients who would be treated during a 5-year period. By comparison, meta-analyses have shown that in similar patients with known CHD, antiplatelet agents prevent 17.3 strokes and ramipril prevents 17 strokes per 1000 patients treated for 5 years; in patients with prior stroke, antiplatelet agents prevent 27 strokes per 1,000 patients treated for 29 months (136 projected at 5 years).

Haemorrhagic stroke

One concern, because of the observational cohort data mentioned above, was an increased risk of haemorrhagic strokes with lipid-lowering therapy. In the Honolulu Heart Program, during an average 18-year follow-up of 7850 Japanese-American men living in Hawaii, 116 haemorrhagic strokes occurred, and there was an inverse relationship between serum cholesterol

Table 1. *Characteristics of the selected statin trials*

Trial	Year	Treatment	Mean Follow-up y	Randomised Patients, (A/C)	Mean† Age, y	Male† Gender, %	Baseline †, Mean LDL-C, mg/dl	Between group LDL-C ‡ reduction, %	All strokes (A/C)	Fatal stroke (A/C)	Haemorr-hagic stroke, (A/C)
ASCOT-LLA[56]	2003	Atorvastatin	3.3††	5168 / 5137	63	81	133	- 32	89 / 121	...	...
ALLHAT-LLT[13]	2002	Pravastatin	4.8	5170 / 5185	66	50	146	- 16	209 / 231	53 / 56	...
PROSPER[12]	2002	Pravastatin	3.2	2891 / 2913	75	48	147	- 27$	135 / 131	22 / 14	...
HPS[10]	2002	Simvastatin	5.0	10269 / 10267	65††	75	131	- 29	444 / 585	96 / 119	51 / 53
GREACE[11]	2002	Atorvastatin	3.0	800 / 800	59	79	180	- 41	9 / 17	0 / 1	1 / 1
HTAS[57]	2001	Simvastatin	3.0	80 / 80	53	87	125	- 33	0 / 4	0 / 0	0 / 0
MIRACL[14,15]	2001	Atorvastatin	0.3	1538 / 1548	65	65	124	- 52 §	12 / 24	3 / 2	0 / 3
L-CAD[58]	2000	Pravastatin	2.0	70 / 56	56	80	174††	- 28	2 / 1	1 / 0	0 / 0
GISSI[17]	2000	Pravastatin	2.0	2138 / 2133	60	86	152	- 12	20 / 19	4 / 4	...
KLIS*[9]	2000	Pravastatin	5.0	2219 / 1634	58	100	165	- 11	47 / 41	...	10 / 9
SCAT[59]	2000	Simvastatin	4.0	230 / 230	61	89	130	- 34	4 / 7	3 / 6	...
LIPID[6,16]	1998	Pravastatin	6.1	4512 / 4502	62	83	150	- 25	169 / 204	22 / 27	14 / 7
AFCAPS/ TexCAPS[8]	1998	Lovastatin	5.2	3304 / 3301	58	85	150	- 26	14 / 17	...	...
Post-CABG[60]	1997	Lovastatin	4.3	676 / 675	62	92	155	- 25	18 / 16	...	...
CARE[2,25]	1996	Pravastatin	5.0††	2081 / 2078	59	86	139	- 32	52 / 76	5 / 1	2 / 6
WOSCOPS[7]	1995	Pravastatin	4.9	3302 / 3293	55	100	192	- 26	46 / 51	6 / 4	...
PLAC I[18]	1995	Pravastatin	3.0	206 / 202	57	77	164	- 29	0 / 2	0 / 0	...
KAPS[19]	1995	Pravastatin	3.0	224 / 223	57	100	189	- 29	2 / 4	0 / 1	...
REGRESS[20]	1995	Pravastatin	2.0	450 / 434	56	100	165	- 29	1 / 2	0 / 0	0 / 0
CCAIT[21]	1995	Lovastatin	2.0	165 / 166	53	81	178	- 27	1 / 0	0 / 0	...
PLAC II[61]	1995	Pravastatin	3.0	75 / 76	63	85	166	- 30	1 / 2	0 / 1	...
SSSS[1]	1994	Simvastatin	5.4††	2221 / 2223	59	81	188	- 36	56 / 78	14 / 12	0 / 2
LRT[26]	1994	Lovastatin	0.5	203 / 201	62	72	129	- 36 §	0 / 1	0 / 0	...
MAAS[27]	1994	Simvastatin	4.0	193 / 188	56	89	171	- 31	1 / 2	0 / 0	...
ACAPS[28,29]	1994	Lovastatin	3.0	460 / 459	62	52	156	- 28	0 / 4	0 / 2	0 / 3
MARS[62]	1993	Lovastatin	2.2	134 / 136	58	91	153	- 37	0 / 3	0 / 0	...
PMNSG[63]	1993	Pravastatin	0.5	530 / 532	55	76	181	- 26 §	0 / 3	0 / 0	0 / 0
Mean or Total, A/C			4.3	49309 / 48672	62	77	149	- 27	1332 / 1646	229 / 250	78 / 84

* Unsuccessful randomised trial excluded from the main analysis; †Means of age, LDL-C value, and percentage of male gender on entry to study in all randomised patients. ‡Difference of the mean percentage LDL-C reduction during treatment period between active treatment (A) and control group (C) (§ at the end of the study, $ on the 2-year visit as published[12]); ††The median values are presented.

A: Active treatment; C: Control group; CHD: Coronary Heart Disease; LDL: low density lipoprotein cholesterol; ACAPS: Asymptomatic Carotid Artery Progression Study; AFCAPS/TexCAPS: Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASCOT-LLA: Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm; CARE: Cholesterol and Recurrent Events; CCAIT: Canadian Coronary Atherosclerosis Intervention Trial; HPS: Heart Protection Study; GISSI: Gruppo Italino per lo Studio della Sopravvivenza nell' Infarcto Miocardico; GREACE: GREek Atorvastatin and Coronary-heart-disease Evaluation; HTAS: HDL-Atherosclerosis Treatment Study; KAPS: Kuopio Atherosclerosis Prevention Study; KLIS: Kyushu Lipid Intervention Study; L-CAD: Lipid-Coronary Artery Disease; LIPID: Long-Term Intervention with Pravastatin in Ischemic Disease; LRT: Lovastatin Restenosis Trial; MAAS: Multicentre Anti-Atheroma Study; MARS: Monitored Atherosclerosis Regression Study; MIRACL: Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering; PLAC-I: Pravastatin limitation of atherosclerosis in the coronary arteries; PLAC-II: Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries; PMNSG: Pravastatin Multinational Study Group; Post-CABG: the Post Coronary Artery Bypass Graft Trial; PROSPER: Prospective Study of Pravastatin in the Elderly at Risk; REGRESS: Regression Growth Evaluation Statin Study; SCAT: Simvastatin / Enalapril Coronary Atherosclerosis Trial; SSSS: Scandinavian Simvastatin Survival Study; WOSCOP: West of Scotland Coronary Prevention.

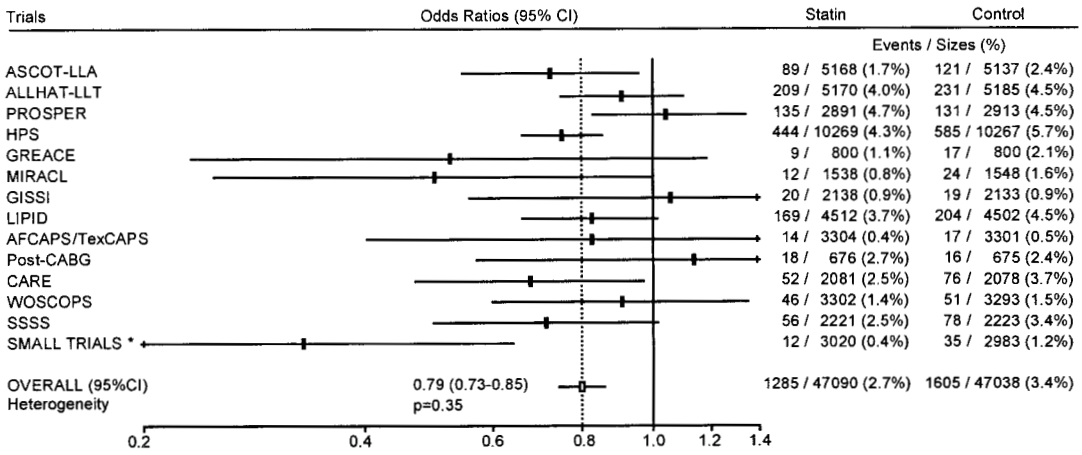

Figure 1. ORs for all strokes in individual trials, small trials[17-21,25,26,29,57-63] (data combined to simplify the presentation) and all trials.
* Pooled OR for all strokes in small trials[17-21,28,29,57-63] calculated with the Mantel-Haenszel method.

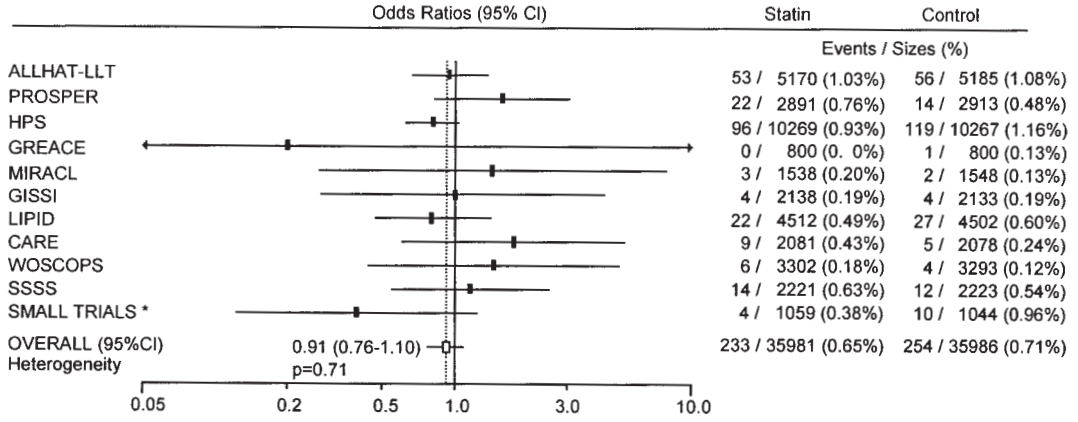

Figure 2. ORs for fatal strokes in individual trials, small trials[17-21,28,29,57-63] (data combined to simplify the presentation) and all trials. Fatal strokes were not available in the ASCOT-LLA, AFCAPS/TexCAPS, Post-CABG report.
* Pooled OR for fatal strokes in small trials calculated with the Mantel-Haenszel method.

and the risk of intracerebral haemorrhage, with a higher incidence rate only for the men with total cholesterol in the lowest quintile (less than 189 mg/dL) [26]. The relative risk in this group, compared with the other 4 quintiles, was 2.55 (1.58-4.12) after controlling for some confounding risk factors (age, blood pressure, serum uric acid, cigarette smoking and alcohol consumption) [26]. In 172 patients from Korea who underwent brain MRI to test for microbleeds (on T2*-weighted gradient-echo imaging, which shows the multifocal signal loss lesions that are believed to represent microbleeds histopathologically), the LDL concentrations were significantly lower in patients with a severe degree of microbleeding[27]. Multivariate analysis showed that microbleeds were significantly correlated with hypertension, leukoaraiosis, the lowest quartile of serum total cholesterol (<4.27 mmol/dL) and the highest quartile of HDL (>1.47 mmol/dL)[27]. However, such a potentially increased risk

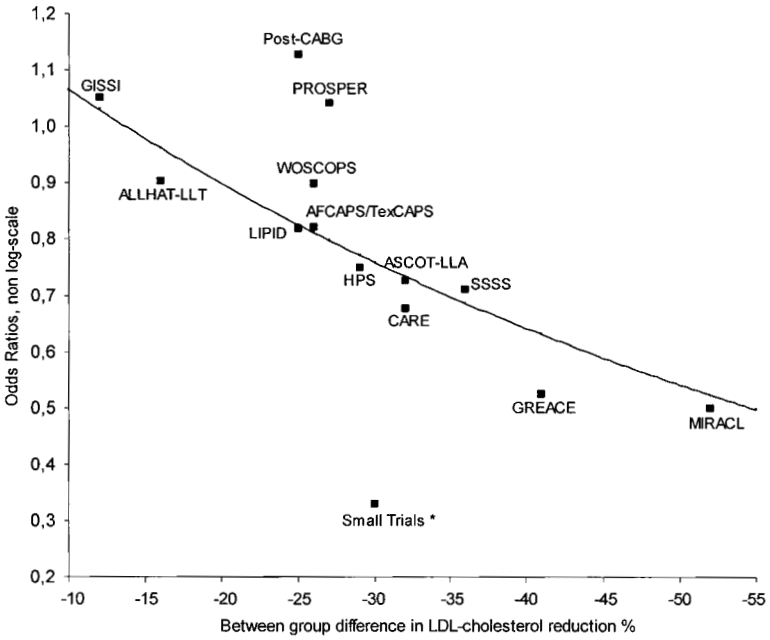

Figure 3. Relationship between ORs for stroke events and corresponding LDL-cholesterol reduction. The regression line has been plotted and weighted for the inverse of the variance of ORs.
* size-weighted combined estimates for the small trials

of haemorrhagic stroke was not observed overall in long-term clinical trials that looked at this secondary end-point. In the PPP project[28], combining the LIPID and CARE data, there were 19 haemorrhagic strokes (0.5%) in the pravastatin group and 15 (0.4%) in the placebo group (HR=1.25 [0.63-2.46]). In HPS, there were 51 haemorrhagic strokes (0.5%) in the simvastatin group and 53 (0.5%) in the placebo group[8]. These results, together with the nil increase in haemorrhagic strokes in the elderly population of the PROSPER trial, are reassuring. It is noteworthy that low cholesterol levels are frequent in patients in poor conditions such as loss of weight, severe handicap, severe and chronic illness, which may have constituted confounding factors for the relationship between the occurrence of a haemorrhagic stroke and low total cholesterol in observational studies. In a recent evaluation of all-cause mortality over 20 years in 3572 Japanese-Americans aged 71-93 years included in the Honolulu Heart Program, mean cholesterol fell significantly with increasing age[29]. Only the group with a low cholesterol concentration <4.65 mmol/dL at both examinations (20 years apart) had a significant association with mortality (RR=1.64 [1.13-2.36])[29]. One explanation is that the patients with high cholesterol died before the age of 75; weight loss ≥10% and poor physical function were more frequent in patients with a low serum cholesterol concentration.

In our meta-analysis, we found no increase in haemorrhagic strokes (OR 0.90 [0.65-1.22]) (Fig. 4)[25].

THE USE OF LIPID-LOWERING AGENTS IN STROKE PREVENTION, PENDING QUESTIONS

1. Why did statins show a stroke reduction? The stroke paradox Since observational studies have failed to find a clear association between cholesterol levels and stroke, it may seem paradoxical that cholesterol-lowering agents reduced the risk of suffering a stroke (Table 2).

(1) In reducing incident MI, statins reduced the occurrence of left ventricular mural thrombus and subsequent thromboembolic complications in the brain.

In the Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial, conducted on patients with unstable angina or non Q-wave MI immediately after the qualify-

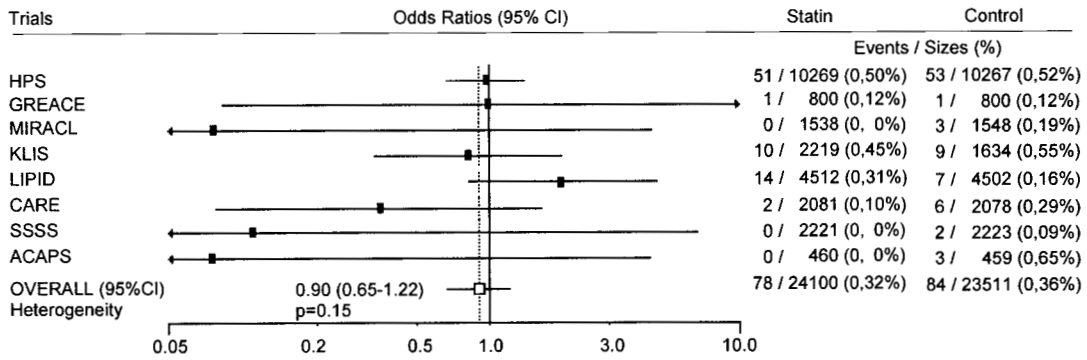

Figure 4. ORs for all haemorrhagic strokes in individual trials and all trials.

Table 2. *Potential mechanism of benefit of statin in preventing stroke*

- LDL cholesterol reduction
- Reduction in brain embolism in CHD patients (reduction of left ventricular thrombus with less myocardial infarction)
- Blood pressure lowering effect
- Regression of carotid/vertebral artery atherosclerosis and intima-media thickness
- Anti-inflammatory effect
- Plaque stabilisation (pleiotropic effects)
- Improved endothelial dysfunction (with improved cerebral vasoreactivity)
- Positive effect on fibrinolytic system and platelet function
- Neuroprotection (with up regulation of eNOS activity)

ing event[30], a total of 3086 patients were randomized to atorvastatin 80 mg/day or placebo and treated for 4 months. After 4 months, the composite end-point (death, non-fatal MI, resuscitated cardiac arrest or recurrent symptomatic myocardial ischaemia requiring emergency rehospitalization) was reduced from 17.4% to 14.8%, a relative risk reduction of 16% (p=0.048) in the atorvastatin group. As secondary end-point, there were 12 fatal and non-fatal strokes in 1538 (0.8%) patients in the atorvastatin group and 24 in 1548 (1.6%) patients in the placebo group, with all 3 haemorrhagic strokes occurring in the placebo group. The risk reduction was 51% (2 to 76%, p=0.04). As regards the stroke mechanism, there were 20 thromboembolic strokes in the placebo group compared with 10 in the atorvastatin group[31]. However, only 9 of the 36 strokes were preceded by a non-fatal MI, with the stroke occurring between 2 and 86 days after the MI[31]. Therefore, although the prevention of MI may in part prevent stroke by reducing the incidence of left ventricular thrombi, this is obviously not the only explanation.

(2) Statins may reduce the incidence of stroke by reducing blood pressure[32,33]. Lowering cholesterol may reduce the blood pressure by between 2 and 5 mmHg[34]. It is known that any blood pressure reduction results in a reduced incidence of stroke[35]. Even a difference of 2 mmHg could account for a 15% difference in the risk of stroke[36]. However, a careful post-hoc analysis of the LIPID trial[176] and the PPP[30] somewhat contradict this hypothesis. It is worth noting that in these pravastatin trials, the patients were not hypertensive at baseline, while the patients in the Glorioso et al. study[32] were hypertensive. Further studies, especially analyses of the ASCOT trial results, in

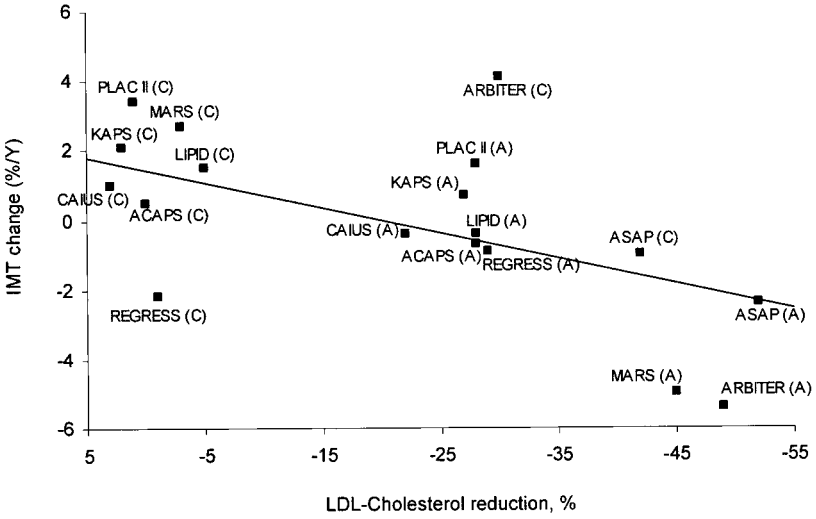

Figure 5. Relation between LDL-cholesterol reduction and carotid IMT change. The regression line has been plotted and weighted for the size of groups.

which all patients included were hypertensives, will shed light on this important, potent action mechanism of statin treatment.

(3) Another explanation is that statins reduce stroke simply by reducing cholesterol levels. Our recent meta-analysis showed that stroke risk reduction in all lipid-lowering trials depends on the extent of the reduction of LDL cholesterol levels (Fig. 3)[25]. Table 1 shows that positive studies have been those with a between-group difference in LDL cholesterol of at least 37 mg (except for PROSPER in which mean LDL reduction in the placebo group is not available in the publication). In the Framingham study there was a positive association between carotid stenosis, hypercholesterolaemia and coronary heart disease[37]. In the same epidemiological study of 449 men and 661 women who underwent B-mode ultrasound measurements of the carotid artery, with a mean age of 75 years, moderate stenosis greater than 25% was present in 189 men and 226 women. The baseline characteristics had been recorded 34 years earlier. Compared with minimal stenosis (less than 25%), moderate stenosis in men was associated with an increase of 20 mmHg in SBP (2.11 [1.51-2.97]), 10 mg/dL in total cholesterol level (1.10[1.03-1.16]), and five pack-years of smoking (1.08 [1.03-1.13]), a result which was similar in women[38]. These results clearly suggested that the cumulative effects of these important risk factors interfere with the development of carotid stenosis, and further argued for a global cardiovascular risk approach, based on the Framingham or PROCAM score, to prevent the development of atherothrombotic disease, even for carotid atherothrombosis.

(4) Statins may also directly act on atherosclerotic plaques in the carotid and vertebral basilar arteries, as shown by a slow progression or even regression of carotid wall thickness in the ACAPS study with lovastatin[39,40], the PLAC-II, KAPS and LIPID ancillary studies with pravastatin[41-43], the ASAP trial with atorvastatin and simvastatin[43], and the ARBITER trial[19] with atorvastatin and pravastatin. The two later trials showed that aggressive cholesterol reduction has a greater and more rapid effect on the development of carotid atherosclerosis than a more 'standard' dosage of statin therapy.

In our meta-analysis (Table 3), we analyzed statin effect on carotid IMT according to LDL-C reduction (Fig. 5)[25]. Each 10% reduction in LDL-C was estimated to reduce carotid IMT by 0.73%

Table 3. *Characteristics of the selected IMT studies*

Trial	Arteries	Regimen group		Randomised patients, (A/C)	Mean* age, y	Male* Gender, %	Baseline*, mean IMT (mm)	IMT change (%/yr) (A/C)	Baseline* mean LDL-C (mg/dl)	LDL-C reduction, % (A/C)
		Active (A)	Control (C)							
ARBITER	CCA † (Far wall)	Atorvastatin (80 mg/day)	Pravastatin (40mg/day)	70 / 68	60	71	0.62	- 5.4 / 4.1	151	-49 / -30
ASAP	CCA † (Near and Far wall)	Atorvastatin (80 mg/day)	Simvastatin (40 mg/day)	160 / 165	48	39	0.87	- 2.4 / -1.0	309	-52 / -42
LIPID §	CCA † (Far wall)	Pravastatin (40 mg/day)	Placebo + Diet	273 / 249	61	88	0.80	- 0.4 / 1.5	155	-28 / -5
CAIUS	CCA ‡ (Near and Far wall)	Pravastatin (40 mg/day)	Placebo	151 / 154	55	53	0.74	- 0.4 / 1.0	181	-22 / 3
KAPS	CCA ‡ (Far wall)	Pravastatin (40 mg/day)	Placebo	224 / 223	57	100	1.35	0.7 / 2.1	189	-27 / 2
REGRESS	CCA † (Far wall)	Pravastatin (40 mg/day)	Placebo + Diet	131 / 124	56	100	0.79	- 0.9 / -2.2	168	-29 / -1
PLAC II	CCA ‡ (Near and Far wall)	Pravastatin (20-40 mg/day)	Placebo + Diet	75 / 76	63	85	1.01	1.6 / 3.4	166	-28 / 1
ACAPS	CCA + CB + ICA ‡ (Near and Far wall)	Lovastatin (20-40 mg/day)	Placebo + diet	231 / 230	62	52	1.32	- 0.7 / 0.5	156	-28 / 0
MARS §	CCA † (Far wall)	Lovastatin (80mg/day)	Placebo + Diet	99 / 89	58	92	0.73	- 5.0 / 2.7	157	-45 / - 3

CCA: Common Carotid Artery; CB: Carotid Bulb; ICA: Internal Carotid Artery ; CFA: Common Fermoral Artery; SFA: Superficial Femoral Artery
* Means of age, IMT and LDL-C, and percentage of male gender on entry to study in all randomised patients. † the mean IMT value is given. ‡ the average of maximum IMT value is given. § the right side of the neck was examined only.
A: active treatment; C: control group; ARBITER: Arterial Biology for Investigation of the Treatment Effects of Reducing Cholesterol; ASAP: AggreSsive versus conventional lipid lowering on Atherosclerosis Progression; CAIUS: Carotid Atherosclerosis Italian Ultrasound Study; LIPID: Long-Term Intervention with Pravastatin in Ischemic Disease; KAPS: Kuopio Atherosclerosis Prevention Study; PLAC-II: Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries; ACAPS: Asymptomatic Carotid Artery Progression Study; REGRESS: Regression Growth Evaluation Statin Study; LDL: low density lipoprotein cholesterol.

per year (95% CI=0.27-1.19).

(5) The pleiotropic effect of statins on atherosclerotic plaques acting on biological promoters of plaque instability[44-48]. The magnitude of atherosclerotic plaque regression has never appeared parallel to the amplitude of the clinical benefit. This fact forms the basis for the hypothesis that statins may work through an action on other biological parameters within plaques, making them less active. A positive effect by statins on all these factors has been demonstrated in vitro[48]. It has also been shown in humans with pravastatin after a short-term lipid-lowering intervention. Of 24 patients scheduled for carotid endarterectomy, 11 were randomized to pravastatin and 13 to placebo. Carotid endarterectomy was performed after three months' treatment, and the material removed was analyzed. A positive effect of pravastatin was found on all biological parameters studied, included macrophage count, oxidized LDL, apoptotic cell count, metalloproteinases and smooth muscle cell proliferation[49].

(6) Statins may also have an impact on cerebral vasoreactivity[50], and have neuroprotective effects, mainly through upregulation of endothelial NO synthase[51,52].

2. What are the effects of statins in secondary prevention of stroke?

While HPS provided important information about

the effect of simvastatin in patients with stroke prior randomization, with a significant 19% reduction in major vascular events (major coronary events, revascularization and stroke) in this population, this reduction was entirely due to the reduction in coronary events, and not to the reduction in stroke recurrence[9]. In fact, in the 3280 patients with prior stroke randomization, the rate of recurrent stroke in the simvastatin group and the placebo group was equal (10.4% in each group)[9]. However, these results regarding recurrent strokes have to be considered in the light of the trial design[53]. This surprising HPS finding in secondary prevention of stroke is possibly due to the late inclusion of patients at a mean of 4.3 years after their stroke or TIA at a moment where patients were less likely to have stroke events and more likely to have coronary events[25]; thus speculation about the lack of reduction of recurrent stroke with statins in patients treated within 4 years post stroke or TIA would be premature[25]. What is reassuring in HPS is that of the 10,269 patients receiving simvastatin, 42 (0.4%) had a carotid endarterectomy or angioplasty, as against 79 (0.8%) of the 10,267 patients receiving the placebo, a significant relative risk reduction of 46% (0.54 [0.38-0.77])[8]. It is thus obvious that simvastatin had a clear impact by reducing the progression of carotid stenosis to surgical indication, and hence had the potential to reduce stroke recurrence.

Only a study dedicated to the secondary prevention of stroke/TIA (in patients without a past history of coronary events) can answer the question of the efficacy of statin therapy in preventing recurrent stroke. The Stroke Prevention with Aggressive Reduction of Cholesterol Levels (SPARCL) trial is ongoing, with 4700 stroke/TIA patients randomized to either atorvastatin 80 mg or placebo[54]. The strength of this study is that the patients were recruited in stroke departments (ensuring good representation of the entire population of stroke patients, as well as a good diagnosis of TIAs), within 6 months after the qualifying event (i.e., when the patients have the highest risk of recurrent stroke, contrary to HPS), the follow-up is 5 years, the primary endpoint is fatal and non-fatal stroke, but the power calculation has been effected so as to ensure a positive effect on the secondary endpoint (stroke, MI or vascular death), and the presence of carotid stenosis has been recorded[53]. The results should be available by 2005.

CONCLUSIONS

Statins have a good overall safety profile to date, with no increase in haemorrhagic stroke or cancer. They have favourable effects in the primary prevention of cardiovascular disease in high-risk young as well as elderly populations (Table 4). Statins reduce the incidence of stroke in high-risk populations (mainly CHD patients, diabetics and hypertensives) even with a normal baseline blood cholesterol level, which argues for a global cardiovascular risk-based treatment strategy. As for CHD, stroke reduction was mainly observed in studies with large between-group LDL cholesterol difference. In patients with prior strokes, statins reduce the incidence of coronary events, but it is not yet proven that they actually reduce the incidence of recurrent strokes in secondary prevention.

Table 4. *Populations in which statins have been studied*

- Coronary heart disease (SSSS*[3], CARE*[4], LIPID*[5], GREACE*[11], HPS*[8,9], KLIS[21])
- Hypercholesterolemia (WOSCOP[6])
- Normocholesterolemic (AFCAPS/TEXCAPS†[7])
- Hypertensives (ALLHAT[20], HPS*[8,9], ASCOT*[12])
- Diabetics (CARE[4], LIPID[5], HPS*[8], CARDS §)
- Elderly (PROSPER[10], HPS*[8,9])
- Stroke/TIA (HPS‡[8,9], SPARCL §[54])

* Positive results on stroke end-point. † Stroke end point not reported. ‡ Positive on combined primary end-point (major coronary events, stroke, revascularisation) but stroke recurrence not yet reported. §Pending results.

From a practical point of view, since there was a favourable treatment effect overall in stroke and TIA patients in HPS, it seems reasonable to treat stroke patients with a statin and total cholesterol >135 mg/dL (3.5 mmol/dL). On-going research is aiming to refine patient selection[53]. As anticipated by current US recommendations[55], patients who are likely to benefit most are those with carotid atherosclerosis, diabetes mellitus, previous coronary heart disease, hypertension, hypercholesterolaemia, or cigarette smoking and LDL cholesterol >100 mg/dL.

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