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Atorvastatin
Its Clinical Role in Cerebrovascular Prevention

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Abstract

An association between hypercholesterolaemia and ischaemic stroke has not yet been clearly defined by observational studies. In clinical trials, however, cholesterol-lowering treatments appear to consistently reduce stroke risk. Data are now available from various primary prevention studies – ALLHAT-LLT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack, Lipid-Lowering Therapy), ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial, Lipid-Lowering Arm), CARDS (Collaborative Atorvastatin Diabetes Study, WOSCOPS (West of Scotland COronary Prevention Study) – and secondary prevention studies – 4S (Scandinavian Simvastatin Survival Study), CARE (Cholesterol and Recurrent Events), GREACE (GREek Atorvastatin and Coronary-heart-disease Evaluation), HPS (Heart Protection Study), LIPID (Long-term Intervention with Pravastatin in Ischaemic Disease), MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering), SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels), TNT (Treating to New Targets) – confirming the ability of statins to reduce stroke risk.

Regarding primary prevention, *post hoc* analyses showed pravastatin reduced the relative risk of stroke by 9–11% (not statistically significant) in the ALLHAT-LLT and WOSCOPS trials, whereas atorvastatin reduced this risk by 27–48% in the ASCOT-LLA ($p = 0.024$) and CARDS trials. It remains to be established in prospective studies whether cholesterol-lowering is effective in the primary prevention of stroke. Regarding secondary prevention, in five placebo-controlled studies (4S, CARE, HPS, LIPID, MIRACL) involving a total of >40 000 patients with coronary heart disease (CHD), statin therapy reduced the relative risk of fatal or nonfatal stroke by 19–50% ($p \leq 0.048$); the largest decrease was produced by atorvastatin in the MIRACL study (−50%, $p = 0.045$). In addition, high-dosage atorvastatin reduced stroke risk by 25% ($p = 0.02$) relative to lower-dosage therapy in the TNT trial, and by 47% ($p = 0.034$) relative to 'usual' care in the GREACE study. A *post hoc* analysis of data for 3280 HPS study participants who had had a previous stroke revealed that simvastatin reduced major vascular events by 20% ($p = 0.001$).

The SPARCL study assessed the secondary preventive efficacy of atorvastatin versus placebo in 4731 patients with a history of stroke or transient ischaemic attack (TIA), but without CHD. Atorvastatin reduced the adjusted relative risk of fatal or nonfatal stroke by 16% ($p = 0.03$), and that of fatal stroke alone by 43%

(p = 0.03). Among secondary study endpoints, atorvastatin reduced the relative risks of stroke and TIA (−23%; p < 0.001), TIA alone (−26%; p = 0.004), and ischaemic stroke (−22%; p = 0.01). Overall, SPARCL study findings suggest that intensive atorvastatin therapy should be started immediately after a stroke or TIA.

In summary, atorvastatin has developed a well defined role in the primary and secondary prevention of cerebrovascular disease, and appears to have a particularly prominent place in preventing such disease in CHD patients, and in the post-stroke and post-TIA setting in patients without CHD.

While the association between hypercholesterolaemia and risk of myocardial infarction (MI) has been well characterised, the aetiology of stroke is multifactorial, and a link between hypercholesterolaemia and ischaemic stroke has not yet been clearly defined. Currently available data are controversial. For instance, an overview of 45 observational studies, involving a total of 450 000 individuals followed up for 5–30 years, revealed no significant association between plasma total cholesterol concentration and stroke;[1] the same was true in EUROSTROKE, a nested case-control trial.[2] Indeed, in pooled analyses of EUROSTROKE data, the odds ratio of stroke was 0.98 for each 1 mmol/L increase in plasma total cholesterol concentration.[2] Nested case-control analyses of data from the PROGRESS (Perindopril Protection Against Recurrent Stroke) trial also revealed no associations between plasma total cholesterol, high-density lipoprotein cholesterol (HDL-C) or triglyceride levels and the risks of haemorrhagic or ischaemic stroke.[3]

Other case-control evaluations seem to confirm a relationship between the risk of ischaemic stroke and plasma HDL-C levels.[4,5] That is, an HDL-C concentration ≥35 mg/dL (0.91 mmol/L) was associated with a 47% decrease (adjusted for various risk factors) in the risk of ischaemic stroke;[4] conversely, lower HDL-C levels were associated with an increased risk of ischaemic stroke, particularly in patients with atrial fibrillation or diabetes mellitus.[5]

From the clinical standpoint, cholesterol-lowering therapies appear to consistently reduce stroke risk.[6] For instance, a meta-analysis of 41 randomised clinical trials involving about 80 000 participants revealed a 16% reduction in stroke risk among patients given cholesterol-lowering therapy versus controls. A statistically significant 23% decrease in stroke risk was evident in the constituent studies that employed statin therapy specifically.[6] Additional meta-analyses also indicate that statins are more effective than other interventions in reducing plasma total cholesterol and low-density lipoprotein-cholesterol (LDL-C) concentrations and, consequently, stroke risk.[7,8] For example, in an analysis of data from >80 000 patients, statins significantly reduced the relative risk of stroke by 26%, compared with a decrease of only 17% for all lipid-lowering therapies, including statins (p < 0.001).[8] Another analysis of >90 000 randomised patients showed that statins reduced the relative risk of stroke by 21% (p < 0.0001), with no significant increase in the risk of haemorrhagic stroke (odds ratio 0.9); furthermore, a significant relationship (p = 0.002) was identified between plasma LDL-C level and stroke risk, such that each 10% decrease in LDL-C was associated with a 15.6% decrease in stroke risk.[7]

The Cholesterol Treatment Trialists' Collaborators also reported, from a large analysis of ≈90 000 individuals involved in statin studies, that 5 years' statin therapy reduced the overall risk of major vascular events (including fatal or nonfatal stroke) by about 20% for each 1 mmol/L decrease in plasma LDL-C level; this effect was largely unrelated to patients' initial lipid profiles.[9] Statins appeared to have a greater stroke-reducing effect in patients with previous cardiovascular disease (i.e. patients more susceptible to ischaemic stroke), since the relative risk of confirmed ischaemic stroke was reduced by 22% (p < 0.0001) per mmol/L decrease in LDL-C, while statins had no major influence on haemorrhagic stroke (relative risk 1.05).[9]

The effect of statin therapy on cognitive function is controversial; although pravastatin had no effect on cognitive function in the PROSPER (PROspective Study of Pravastatin in the Elderly at Risk) study,[10] other analyses have shown that statins may reduce cognitive decline in elderly patients,[11-13] and therefore may have additional potential benefits as cerebrovascular preventive therapies. A meta-analysis of seven observational studies, for instance, showed that statins significantly reduced the relative risk of cognitive impairment by 57%,[12] whereas an analysis of data from the Cardiovascular Health Study in elderly individuals (aged ≥65 years) showed that the rate of decline in mean Modified Mini-Mental State Examination score was approximately 0.5 points/year less in patients receiving, versus those not receiving, statin therapy.[11]

Data are available from various primary prevention (i.e. in patients with no evidence of cardiovascular disease)[14-17] and secondary prevention studies (i.e. in patients with a history of cardiovascular, coronary, and/or cerebrovascular disease)[18-24] to corroborate the favourable impact of statins in reducing stroke risk. Therefore, this review focuses on the clinical utility of statins in general, and of atorvastatin in particular, in these settings, with major emphasis on the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) study[25] (see section 3).

1. Statins and Primary Stroke Prevention

Four major trials warrant consideration under the heading of primary stroke prevention. It must be noted, however, that none of them was primarily designed to evaluate the effects of statins on stroke prevention:

- ALLHAT-LLT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack–Lipid-Lowering Therapy)[14]
- ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm)[16]
- CARDS (Collaborative Atorvastatin Diabetes Study)[15]
- WOSCOPS (West of Scotland COronary Prevention Study)[17]

Pravastatin 40 mg/day did not significantly reduce the risk of stroke relative to usual care or placebo in hypercholesterolaemic patients in the ALLHAT-LLT[14] or WOSCOPS[17] trials (−9% and −11%, respectively) [table I]. Conversely, atorvastatin 10 mg/day markedly reduced the risk of fatal or nonfatal stroke (vs placebo) by 27% (p = 0.024) in hypertensive patients in the ASCOT-LLA trial,[16] and by 48% in patients with type 2 diabetes and raised LDL-C concentrations in the CARDS trial.[15] The apparent lack of pravastatin efficacy regarding reduced stroke risk in the ALLHAT-LLT trial, compared with considerable atorvastatin efficacy in the ASCOT-LLA and CARDS studies, can perhaps be

Table I. Relative reductions in stroke (fatal or nonfatal) risk in primary prevention studies of statins

Study	Patient characteristics	Regimen (mg/day)	Median follow-up (years)	No. of patients randomised	End-of-study LDL-C difference (statin vs comparator; mg/dL)	Relative stroke risk (95% CI) for statin therapy	p-Value
ALLHAT-LLT[14]	HT, mod HC	PRA 40 Usual care	4.8 (mean)	5710 5185	−17	0.91 (0.75, 1.09)	NS
ASCOT-LLA[16]	HT, ≥3 CV risk factors	ATO 10 PL	3.3	5168 5137	−37	0.73 (0.56, 0.96)	0.024
CARDS[15]	T2DM, LDL-C ≤160 mg/dL	ATO 10 PL	3.9	1428 1410	−39	0.52 (0.31, 0.89)	
WOSCOPS[17]	Men with HC	PRA 40 PL	4.9 (mean)	3302 3293	−50[a]	0.89 (0.60, 1.33)	NS

a Approximate value.

ALLHAT-LLT = Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack–Lipid-Lowering Therapy; **ASCOT-LLA** = Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm; **ATO** = atorvastatin; **CARDS** = Collaborative Atorvastatin Diabetes Study; **CV** = cardiovascular; **HC** = hypercholesterolaemia; **HT** = hypertension; **LDL-C** = low-density lipoprotein-cholesterol; **mod** = moderate; **NS** = not significant; **PL** = placebo; **PRA** = pravastatin; **T2DM** = type 2 diabetes mellitus; **WOSCOPS** = West of Scotland COronary Prevention Study.

Table II. Relative reductions in stroke (fatal or nonfatal) risk in secondary prevention studies of statins

Study	Patient characteristics	Regimen (mg/day)	Median follow-up (years)	No. of patients randomised	LDL-C difference (statin vs comparator; %)	Relative stroke risk (95% CI) for statin therapy	p-Value
4S[22]	CHD	SIM 20–40 PL	5.4	2 221 2 223	−36[a]	0.70 (0.52, 0.96)	0.024
CARE[23]	CHD	PRA 40 PL	5.0	2 081 2 078	−28[b]	0.69 (0.48, 0.97)	0.030
GREACE[18]	CHD	ATO 10–80 Usual care	3.0 (mean)	800 800	−43[b]	0.53 (0.30, 0.82)	0.034
HPS[19]	CHD, OAD, DM or HT	SIM 40 PL	5.0 (mean)	10 269 10 267	−29[b]	0.75 (0.66, 0.85)	<0.0001
LIPID[21]	CHD	PRA 40 PL	6.1 (mean)	4 512 4 502	−25[c]	0.81 (0.66, 1.00)	0.048
MIRACL[24]	Early ACS	ATO 80 PL	16 weeks (scheduled)	1 538 1 548	−47[a]	0.50 (0.26, 0.99)	0.045
TNT[20]	CHD	ATO 80 ATO 10	4.9	5 006 4 995	−24[b,d]	0.75 (0.59, 0.96)[d]	0.020[d]

a End-of-study differential.

b Mean difference throughout follow-up.

c Mean difference over the first 5 years of follow-up.

d Intensive vs lower-dosage ATO therapy.

4S = Scandinavian Simvastatin Survival Study; **ACS** = acute coronary syndrome; **ATO** = atorvastatin; **CARE** = Cholesterol And Recurrent Events; **CHD** = coronary heart disease; **DM** = diabetes mellitus; **GREACE** = GREek Atorvastatin and Coronary heart disease Evaluation; **HPS** = Heart Protection Study; **HT** = hypertension; **LDL-C** = low-density lipoprotein-cholesterol; **LIPID** = Long-term Intervention with Pravastatin in Ischaemic Disease; **MIRACL** = Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering; **OAD** = occlusive arterial disease; **PL** = placebo; **PRA** = pravastatin; **SIM** = simvastatin; **TNT** = Treating to New Targets.

attributed to the markedly smaller end-of-study statin-comparator LDL-C differential in the former trial; however, this explanation does not account for the statistically insignificant decrease in stroke risk produced by pravastatin in the WOSCOPS study, since pravastatin reduced mean LDL-C level by approximately 50 mg/dL in the latter trial.[17]

2. Statins and Secondary Stroke Prevention

Several secondary prevention studies of statins have focused on patients primarily with existing coronary heart disease (CHD; table II). In five large-scale comparisons of statins with placebo in a total of >40 000 patients, statin therapy reduced mean plasma LDL-C concentration by approximately 25–50% more than that in placebo recipients, and significantly reduced the relative risk of fatal or nonfatal stroke by 19–50% ($p \leq 0.048$).[19,21-24] In these five placebo-controlled trials, the greatest decrease in relative stroke risk (−50%, $p = 0.045$) was attained in the MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) study of intensive atorvastatin therapy in patients with recent acute coronary syndrome (ACS); corresponding relative risk reductions were 19–31% for pravastatin in the CARE (Cholesterol And Recurrent Events)[23] and LIPID (Long-term Intervention with Pravastatin in Ischaemic Disease)[21] studies, and 25–30% for simvastatin in the 4S (Scandinavian Simvastatin Survival Study)[22] and HPS (Heart Protection Study)[19] trials.

Furthermore, in the TNT (Treating to New Targets) trial,[20] intensive atorvastatin therapy (80 mg/day), compared with lower-dosage therapy (10 mg/day), reduced the relative risk of fatal or nonfatal stroke by 25% ($p = 0.02$); and in the GREACE (GREek Atorvastatin in Coronary heart disease Evaluation) trial,[18] high-dosage atorvastatin therapy, compared with 'usual' care, reduced this risk by 47% ($p = 0.034$).

Regarding secondary stroke prevention, specifically in patients with a history of stroke, data for

statins are rather limited and are taken almost entirely from a *post hoc* analysis in 3280 patients with stroke before enrolment in the HPS trial.[26] In this subgroup of participants in the HPS trial, simvastatin did not significantly reduce the relative risk of recurrent stroke, i.e. the incidence of new cerebrovascular events was 10.4% in simvastatin-treated patients versus 10.5% in placebo recipients. This lack of difference between treatment groups may have resulted from patients being enrolled in the HPS trial a mean of 4.3 years after the index stroke, although it is known that the greatest risk of stroke recurrence is in the first few years after stroke. Nonetheless, simvastatin did significantly reduce the relative risk of any major vascular event (−20%; p = 0.001) in the aforementioned subgroup analysis, thus corroborating the clinical benefit of statin therapy in patients with pre-existing cerebrovascular disease.[26]

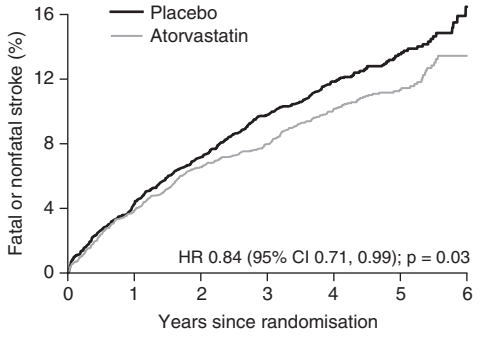
3. Atorvastatin in Stroke Prevention: the SPARCL Study

To date, SPARCL is the only trial to have directly evaluated the ability of high-dosage statin therapy to reduce the risk of fatal or nonfatal stroke in patients with a stroke or transient ischaemic attack (TIA) in the previous 6 months, but without definitive evidence of CHD.[25] SPARCL was a prospective, double-blind, placebo-controlled trial conducted at 205 centres, in which 4731 patients with a history of stroke or TIA were randomised to receive atorvastatin 80 mg/day (n = 2365) or placebo (n = 2366) for a median follow-up period of 4.9 years. Ischaemic or haemorrhagic stroke, or a TIA, had to be diagnosed by a neurologist ≤30 days after the event, but 1–6 months before randomisation, and all patients had to be ambulatory (modified Rankin score ≤3) and have an LDL-C concentration of 100–190 mg/dL. Any lipid-altering treatments had to be discontinued ≥30 days before the first study screening visit. After randomisation, fewer atorvastatin than placebo recipients withdrew their consent to participate (p = 0.07), or permanently stopped study medication (p = 0.07). However, a similar proportion of patients in each group received concurrent therapy with aspirin (≈94%), angiotensin-converting enzyme inhibitors (≈47%), dihydropyridine calcium channel antagonists (≈29%), β-adrenoceptor antagonists (≈32%), angiotensin II-receptor antagonists (≈14%), and/or vitamin K antagonists, including warfarin (≈12%). Approximately half as many atorvastatin as placebo recipients received open-label statin therapy (11.4% vs 25.4%), and, in both study groups, atorvastatin was the most widely used non-study, open-label statin.[25]

Mean plasma levels of LDL-C were similar in the two treatment groups at baseline (atorvastatin 132.7 mg/dL; placebo 133.7 mg/dL).[25] However, 1 month after randomisation, the mean LDL-C concentration in atorvastatin-treated patients was 61.3 mg/dL (−53% vs baseline; p < 0.001), whereas it was unchanged in placebo recipients (133.5 mg/dL). Corresponding mean LDL-C values over the course of the trial were 72.9 mg/dL and 128.5 mg/dL (p < 0.001), whereas HDL-C levels were 52.1 mg/dL and 51.0 mg/dL (p = 0.006), total cholesterol concentrations were 147.2 and 208.4 mg/dL (p < 0.001), and triglyceride levels were 111.5 and 145.0 mg/dL (p < 0.001) for atorvastatin and placebo, respectively.[25]

Importantly, the primary study endpoint of fatal or nonfatal stroke was significantly less frequent in atorvastatin than placebo recipients (11.2% vs 13.1% of patients; unadjusted p-value [log-rank test] = 0.05), thus representing a relative risk reduction of 16% (p = 0.03; figure 1).[25] The latter statistic was derived from a prespecified Cox regression model that accounted for baseline variables, comprising age, sex, geographical origin, initial event (i.e. stroke or TIA), and time since the initial event. Moreover, atorvastatin reduced the adjusted relative risk of fatal stroke alone by 43% (p = 0.03), but had no significant effect on nonfatal stroke (−13%; p = 0.11).[25]

Concerning secondary study endpoints, atorvastatin (vs placebo) reduced the relative risks of stroke and TIA (−23%; p < 0.001), TIA alone (−26%; p = 0.004), major coronary events (−35%; p = 0.003), nonfatal MI (−49%; p = 0.001), major cardiovascular events (−20%; p = 0.002), acute coronary events



No. at risk							
Atorvastatin	2365	2208	2106	2031	1935	922	126
Placebo	2366	2213	2115	2010	1926	887	137

Fig. 1. Incidence of the primary endpoint in the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) study (reproduced from Amarenco et al.,[25] with permission). **HR** = hazard ratio.

(−35%; p = 0.001), any coronary events (−42%; p < 0.001), revascularisation (−45%; p < 0.001), and any cardiovascular event (−26%; p < 0.001).[25] No significant difference was noted between the atorvastatin and placebo groups regarding the incidence of total mortality (9.1% vs 8.9%), including cancer-related mortality (2.4% vs 2.2%). Interestingly, *post hoc* analyses based on stroke type revealed that atorvastatin reduced the relative risk of ischaemic stroke by 22% (p = 0.01), and that of unclassified stroke by 45% (p = 0.01). However, the incidence of haemorrhagic stroke was significantly greater in atorvastatin than placebo recipients (2.3% vs 1.4%; p = 0.01), although the number of patients who died from haemorrhagic stroke was not significantly different between the two groups (17 vs 18 patients).[25]

It is difficult to explain the excess incidence of haemorrhagic stroke in atorvastatin versus placebo recipients in the SPARCL study.[25] Nonetheless, epidemiological studies have reported an association between low levels of plasma total cholesterol and an increased risk of haemorrhagic stroke.[27-29] The HPS trial also documented an increased risk of haemorrhagic stroke in simvastatin-treated patients with previous cerebrovascular disease.[26] It was therefore suggested that any excess risk of haemorrhagic stroke during statin therapy might be related to marked reduction of plasma total cholesterol levels, although recent secondary prevention studies, such as MIRACL[30] and TNT,[31] in which an LDL-C goal well below 70 mg/dL was attained, and recent meta-analyses of statin studies,[7,9,32] have questioned this hypothesis.

Data presented at the World Congress of Cardiology in Barcelona (2006), which focus on the approximately one-third of SPARCL study participants who attained an LDL-C reduction of >50%, also provide some clarification.[33] Almost all of the previously mentioned one-third of SPARCL subjects received atorvastatin 80 mg/day, the relative risks of all stroke, major vascular events and revascularisation procedures were reduced by 31%, 37% and 47%, respectively, and atorvastatin was not associated with an increased risk of haemorrhagic stroke.[25] Another detailed analysis assessed the potential association between baseline variables, including lipid profile and blood pressure values, and the risk of haemorrhagic stroke in the SPARCL study.[34] Thus, a Cox regression model outlined that the risk of haemorrhagic stroke was elevated in patients with a history of such stroke (hazard ratio [HR] 6.17; p < 0.0001) or hypertension (HR 1.56; p = 0.061), and in elderly patients (HR 1.40; p = 0.018 per each 10-year increment in age) or those with stage II hypertension (HR 2.22; p = 0.035); conversely, the risk of haemorrhagic stroke was reduced in women (HR 0.63; p = 0.045). No statistically relevant, overall association was noted between baseline variables, atorvastatin therapy, and haemorrhagic stroke risk.[34] Altogether, therefore, there would seem to be no causal link between reduced plasma total cholesterol concentrations attained with statin therapy and an increased risk of haemorrhagic stroke. That said, however, further investigation would be useful to determine an exact explanation for the increased risk of haemorrhagic stroke that manifested in the SPARCL study.

Atorvastatin was generally well tolerated in the SPARCL trial.[25] That is, no significant difference was evident between atorvastatin and placebo recipients regarding the incidence of serious adverse events (41.8% vs 41.2%), myalgia (5.5% vs 6.0%), myopathy (0.3% vs 0.3%), or rhabdomyolysis

(0.1% vs 0.1%). Moreover, few patients (2.2% vs 0.5%; $p < 0.001$) had persistent elevation of hepatic transaminase levels (i.e. ALT or AST >3-fold greater than the upper limit of normal on two consecutive occasions) or creatine kinase level (i.e. >10-fold greater than the upper limit of normal on two consecutive occasions; 0.1% vs 0.0%), and no patients had liver failure. Few patients had persistent elevation of hepatic transaminase levels (i.e. ALT or AST >3-fold greater than the upper limit of normal on two consecutive occasions), even though this was more frequent in atorvastatin than placebo recipients (2.2% vs 0.5%; $p < 0.001$). Overall, the SPARCL study confirms that high-dosage atorvastatin is a safe and effective treatment option for reducing the risks of fatal or nonfatal stroke, major coronary events, and revascularisation procedures in patients with a recent stroke or TIA, but without definitive evidence of CHD. SPARCL findings therefore support the commencement of intensive atorvastatin therapy immediately after a stroke or TIA.[25]

4. Conclusions

Atorvastatin significantly reduced the relative risk of stroke by 16–50% in several large-scale primary and secondary prevention studies (the latter in CHD patients), and in a large-scale secondary prevention trial in patients with pre-existing cerebrovascular disease. Although further clarification of the effects of statin therapy on haemorrhagic stroke incidence is now warranted, there appears to be no definitive, causal link between statin-induced reduction of plasma total cholesterol concentration and an increased risk of haemorrhagic stroke. Moreover, atorvastatin is generally well tolerated, with no dose-dependent increase in adverse events up to the maximum daily dosage of 80 mg/day. Thus, atorvastatin has developed a well-defined role in the primary and secondary prevention of cerebrovascular disease, and appears to have a particularly prominent place in preventing such disease in CHD patients, and in the post-stroke or post-TIA setting in patients without CHD.

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