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Drug Insight:

statins and stroke

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SUMMARY

Stroke is the third leading cause of death in the US and a common cause of long-term disability worldwide. Ischemic strokes, which are often atherothrombotic, account for more than 80% of all strokes. Current stroke prevention focuses on optimizing the treatment of modifiable risk factors, such as hypertension, diabetes and dyslipidemia. The epidemiologic association between serum cholesterol levels and adjusted stroke rates is not as strong as the link between serum cholesterol levels and coronary heart disease. Clinical trials of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins), which are potent inhibitors of cholesterol synthesis, have demonstrated, however, a marked reduction in stroke risk in hypercholesterolemic and atherosclerotic individuals, with benefits extending to normocholesterolemic individuals. These findings suggest that statins might have additional effects in stroke protection beyond cholesterol reduction. Because statins inhibit the synthesis of isoprenoid intermediates in the cholesterol biosynthetic pathway, which are important lipid attachments for intracellular signaling molecules, they might have direct noncholesterol-dependent effects on inflammatory and endothelial cells. Here we discuss data from clinical trials assessing the effects of statins on stroke risk, as well as outline the mechanisms evidence-based recommendations for stroke prevention, based on achieved underlying the cholesterol-independent effects of statins and provide serum cholesterol levels in patients at risk of stroke.

Keywords

cholesterol; endothelium; nitric oxide; statins; stroke

INTRODUCTION

Stroke has a major impact on the public health of every nation. In the US, stroke is the third leading cause of death, accounting for 160,000 deaths per year, and is the most common cause

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Competing interests

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REVIEW CRITERIA

All articles were identified by searching the MEDLINE and PubMed databases. The search keywords used were "statins" and "stroke". All articles were full-text, English-language clinical trials and meta-analyses based on human studies.

of long-term disability. Each year, 700,000 Americans suffer a new or recurrent stroke. Nearly two-thirds of ischemic strokes are atherothrombotic, resulting from atherosclerosis of large arteries, or vasculopathy of small arteries.¹ Cerebral ischemia results from reduced blood flow in a narrowed or occluded artery, or an embolism from a complex atherosclerotic plaque. The cause of the narrowing is most often atherosclerosis, a process involving endothelial injury, inflammation, lipid deposition, smooth-muscle-cell proliferation, plaque formation, fibrin, platelets and thrombin.

LIPIDS AND RISK FACTORS FOR STROKE

Abnormal levels of serum lipids, including triglycerides, LDL and HDL cholesterol, are regarded as greater risk factors for coronary artery disease (CAD) than for cerebrovascular disease. Hypercholesterolemia might promote atherosclerosis, because elevated concentrations of oxidized or modified LDL cholesterol contribute to endothelial dysfunction.^{2,3} The association between hypercholesterolemia and stroke has become more apparent because of data from prospective cohort studies that show higher risks of ischemic stroke with increasing levels of total cholesterol in both men and women.⁴⁻⁷ Increased HDL cholesterol levels have a protective effect against the occurrence of ischemic stroke,^{8,9} but the association between LDL cholesterol and stroke is less clear. Elevated triglyceride levels have also been reported as a risk factor for stroke.^{7,10} Overall, elevated total cholesterol confers an approximately twofold relative increase in stroke risk for men and women.¹¹ Moreover, the high prevalence of this condition in the population translates into a larger proportion of strokes potentially attributable to dyslipidemia and, therefore, a greater relative importance in public health.¹¹

Thus, current stroke-prevention strategies include management of modifiable risk factors, including hypertension, diabetes and hypercholesterolemia, which affect atherosclerosis and thrombus formation.¹¹⁻¹³ Evidence from clinical trials indicates that statins lower serum cholesterol levels and reduce the risk of stroke. The primary mechanism of action of statins is the competitive inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, the enzyme that catalyzes the rate-limiting step in cholesterol biosynthesis. Inhibition of this enzyme results in increased expression of the LDL cholesterol receptor in the liver, leading to increased clearance of LDL cholesterol and its precursors, as well as protection against oxidized LDL cholesterol. In addition to their actions on cholesterol biosynthesis, statins might have other effects, including improvements in endothelial function, reduction of inflammation, stabilization and regression of atherosclerotic plaques, attenuation of thrombogenic responses and increases in circulating endothelial progenitor cells. Indeed, in a study of patients with heart failure that compared the vascular protective effects of a statin and ezetimibe (an inhibitor of intestinal cholesterol absorption), the statin group demonstrated improved endothelial function, enhanced antioxidative properties and increased circulating endothelial progenitor cells, despite similar reductions in LDL cholesterol of 15% that were seen in both groups.¹⁴ These findings suggest that there are beneficial effects with statin use beyond lowering LDL cholesterol that could contribute to their effects on stroke protection.

CLINICAL TRIALS OF STATINS IN STROKE PREVENTION

Statins and subclinical carotid disease

Statins decrease the risk of various cardiovascular outcomes, particularly stroke (Table 1). Indeed, several clinical trials with statins have shown delayed progression or even regression of subclinical carotid disease assessed by measurement of intima-media thickness. These clinical trials were designed to determine whether control of modest elevations of LDL cholesterol would retard the progression of asymptomatic carotid atherosclerotic plaques. A

small reduction in carotid artery intima-media thickness has been documented with aggressive lowering of lipid levels in various trials with different statins.¹⁵⁻¹⁷

Statins and the risk of stroke in patients with coronary disease

Early clinical trials demonstrated that statin therapy decreased the risk of stroke, particularly among patients with CAD. This reduction was significant in the three major trials that evaluated statin use in patients with existing CAD: the Scandinavian Simvastatin Survival Study (4S),¹⁸ the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trial,¹⁹ and the Cholesterol And Recurrent Events (CARE) trial.²⁰ In the 4S trial, 4,444 patients with angina pectoris or previous myocardial infarction (MI) and total serum cholesterol levels of 5.5-8.0 mM/l (212.4-308.9 mg/dl) on a lipid-lowering diet were randomized to double-blind treatment with 20-40 mg simvastatin or placebo. Post hoc analysis showed a significant reduction in fatal and nonfatal stroke among patients with hyper cholesterolemia who were treated with simvastatin in comparison with those receiving placebo, as well as a reduction in total mortality and cardiac events in this patient group. The risk of stroke was reduced by 30% in patients receiving simvastatin who had suffered a single MI and had elevated cholesterol levels.

The risk of stroke was also significantly reduced following treatment with pravastatin in the CARE and LIPID trials, in which stroke was prespecified as a secondary endpoint. In the CARE trial,²⁰ the effect of lowering cholesterol with 40 mg pravastatin daily on the incidence of vascular events was assessed in patients with a total cholesterol level of less than 6.2 mM/l (240 mg/dl) and an LDL cholesterol level of 2.98-4.51 mM/l (115-174 mg/dl; $n = 4,159$: 3,583 men and 576 women). The risk of stroke in patients receiving pravastatin was reduced by 31% (95% CI 3-52; $P = 0.03$) in comparison with those receiving placebo. In addition, this study randomized patients without elevated baseline blood cholesterol levels, and the results suggest that all survivors of a first MI should be considered for cholesterol-lowering therapy to reduce the risk of stroke and ischemic heart disease. The LIPID trial¹⁹ randomized 9,014 men and women aged 31-75 years with pre-existing coronary heart disease (CHD), either acute MI or unstable angina, and total cholesterol levels of 4-7 mM/l (155-270 mg/dl). Patients in the LIPID trial who received pravastatin (40 mg daily) achieved reductions of 24% in CHD mortality, 22% in total mortality and 19% in the incidence of stroke ($P = 0.048$) in comparison with patients who received placebo. Moreover, 82% of participants were taking aspirin; therefore, pravastatin reduces the risk of these events even in patients who are already receiving antiplatelet therapy.

The benefits of statins for stroke and cardiovascular disease prevention were more broadly evaluated in the large-scale, long-term Heart Protection Study (HPS).^{21,22} In this study, 20,536 adults aged 40-80 years with coronary disease, other occlusive arterial disease, diabetes or treated hypertension were randomly allocated to 40 mg simvastatin daily or placebo. All-cause mortality was reduced among patients receiving simvastatin in comparison with those receiving placebo (1,328 [12.9%] deaths versus 1,507 [14.7%] deaths, $P = 0.0003$), the rate of nonfatal MI or coronary death was reduced (898 [8.7%] versus 1,212 [11.8%], $P < 0.0001$). Fewer patients receiving simvastatin had a nonfatal or fatal stroke than patients receiving placebo (444 [4.3%] versus 585 [5.7%] patients, $P < 0.0001$).

In a subgroup analysis from the HPS of the 3,280 individuals with cerebrovascular disease, there was no apparent reduction in the stroke rate, which challenged the efficacy of statins in the secondary prevention of stroke. In the HPS,²² however, there was a 20% reduction in the rate of any major vascular event among cerebrovascular disease patients receiving statin therapy rather than placebo (406 [24.7%] versus 488 [29.8%] events, $P = 0.001$). The risk of stroke was reduced by about 25% in many other subgroups, including those with coronary disease or diabetes, those who were younger or older than 70 years of age at study entry, and those presenting with various levels of blood pressure or lipids, even when pretreatment LDL

cholesterol was below 3.0 mM/l (116 mg/dl). The reduction in stroke incidence was not significant during the first year, but was significant ($P = 0.0004$) by the end of the second year. The HPS was notable because it showed benefits of statin use in a wide range of high-risk patients, including those without a diagnosis of CHD.

Primary prevention trials also showed protective effects for statins that were more pronounced for CAD endpoints than for stroke. In the West of Scotland Coronary Prevention Study (WOSCOPS),²³ 6,595 men with hypercholesterolemia (mean cholesterol level 7.05 mM/l [272 mg/dl]) were randomized to pravastatin or placebo to determine the effects of these regimens on the incidence of nonfatal MI and death from CHD. The incidence of these primary endpoints was significantly reduced; however, stroke, which was a secondary endpoint and underpowered for the study, was only reduced by a nonsignificant 11%. In the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial,²⁴ the benefits of pravastatin (40 mg daily) or placebo treatment were evaluated in an elderly cohort of 5,804 men and women aged 70-82 years with a history of, or risk factors for, vascular disease. The primary endpoint was a composite of coronary death, nonfatal MI and fatal or nonfatal stroke. Those patients who were randomized to receive pravastatin had a significantly reduced incidence of the primary composite endpoint in comparison with patients receiving placebo (408 events versus 473 events, hazard ratio (HR) 0.85, 95% CI 0.74-0.97; $P = 0.014$). The risk of coronary disease and nonfatal MI was significantly lower in the pravastatin-treated patients than in those receiving placebo (HR 0.81, 95% CI 0.69-0.94; $P = 0.006$). The risk of stroke was not significantly different between the two treatment groups (HR 1.03, 95% CI 0.81-1.31; $P = 0.8$), but the HR for transient ischemic attack was 0.75 (95% CI 0.55-1.00; $P = 0.051$).

Statins and the risk of stroke in patients with hypertension or diabetes

Beneficial effects on the primary prevention of stroke have been observed for statin use among patients with hypertension or diabetes. The Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA) study²⁵ evaluated the benefits of cholesterol lowering in the primary prevention of CHD among hypertensive patients who were not classified as dyslipidemic. Of 19,342 hypertensive patients (aged 40-79 years, with at least three other cardiovascular risk factors), 10,305 with nonfasting total cholesterol concentrations of 6.5 mM/l (251 mg/dl) or less were randomly assigned to receive atorvastatin 10 mg or placebo daily. The primary endpoints were prespecified as nonfatal MI and fatal CHD. The trial was stopped after a median follow-up of 3.3 years. The occurrence of primary events was significantly reduced in the atorvastatin group in comparison with the placebo group (100 versus 154 events, HR 0.64; 95% CI 0.50-0.83; $P = 0.0005$). Fatal and nonfatal stroke were also significantly reduced in the atorvastatin group compared with the placebo group (89 versus 121 events, HR 0.73; 95% CI 0.56-0.96; $P = 0.024$).

In the Collaborative Atorvastatin Diabetes Study (CARDS),²⁶ 2,838 patients from 132 centers in the UK and Ireland, who were aged 40-75 years and had type 2 diabetes but no cardiovascular disease, were randomized to placebo ($n = 1,410$) or 10 mg atorvastatin daily ($n = 1,428$). The trial was stopped early after finding clear efficacy in an interim analysis after a median follow-up duration of 3.9 years. Patients allocated to receive atorvastatin had a significantly lower rate of cardiovascular events than those who received placebo (37% relative rate reduction; 95% CI -52 to -17; $P = 0.001$) and a 48% relative reduction in the stroke rate (95% CI -69 to -11).

The effect of pravastatin on all-cause mortality was evaluated in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)²⁷ in 10,355 patients over 55 years of age who were hypertensive and moderately hypercholesterolemic with at least one additional risk factor. Pravastatin did not significantly reduce all-cause mortality, or the incidence of coronary events or stroke, when compared with usual care (in this trial, usual care was defined as including other measures to reduce cholesterol but excluding statin therapy).

In the course of the study, however, nearly one-third of those allocated to usual care were treated with lipid-lowering drugs, which resulted in a smaller differential in total cholesterol reduction between the two groups.

Early effects of statin therapy

Most long-term trials assessing statin therapies have shown benefits in terms of stroke reduction within the first year of treatment. Among high-risk patients with unstable angina or non-Q-wave MI, the benefits of statin therapy were demonstrated within 16 weeks in the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial.²⁸ The primary endpoint—a composite of death, nonfatal MI, resuscitated cardiac arrest or recurrent symptomatic myocardial ischemia—was reduced from 17.4% in the placebo group to 14.8% in the atorvastatin group over the 16 weeks of the trial ($P = 0.048$). Stroke was a secondary endpoint, and the incidence of nonfatal stroke was reduced in the statin treatment group (relative risk 0.40, 95% CI 0.19-0.88; $P = 0.02$), as was the combined incidence of a fatal or nonfatal stroke (relative risk 0.49, 95% CI 0.24-0.98; $P = 0.04$).

Results from meta-analyses and other studies

Meta-analyses have demonstrated an overall reduced incidence of stroke with statin therapy.²⁹⁻³¹ In a systematic review and meta-analysis of all randomized statin trials published before August 2003, which included over 90,000 patients, the relative risk reduction for stroke was 21% (odds ratio 0.79, 95% CI 0.73-0.85) with no heterogeneity between trials.³² For each 10% reduction in LDL cholesterol (i.e. 1 mM/l), there was an estimated reduction in the risk of stroke of 15.6% (95% CI 6.7-23.6) and a 0.73% reduction in carotid intima-media thickness per year (95% CI 0.27-1.19).

The benefits of statins for secondary stroke prevention among patients with normal cholesterol levels and without CAD remain unclear. The ongoing Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial³³ is addressing this question. This trial has enrolled 4,700 patients with previous stroke or transient ischemic attack who have been randomized to atorvastatin (80 mg daily) or placebo. The primary endpoint for SPARCL is fatal or nonfatal stroke, and the planned follow-up for the trial is 5 years.

STATIN PLEIOTROPY AND POTENTIAL NONCHOLESTEROL-RELATED EFFECTS ON STROKE

As mentioned previously, an elevated level of LDL cholesterol has not traditionally been considered an important risk factor for stroke; for example, in the Framingham Heart Study or the Multiple Risk Factor Intervention Trial (MRFIT).^{34,35} Indeed, a review of 45 prospective observational cohorts involving 450,000 individuals failed to find an association between adjusted stroke rates and serum cholesterol levels.³⁶ Furthermore, cholesterol reduction in numerous nonstatin trials has generally failed to reduce the incidence of fatal strokes significantly.²⁹ Meta-analyses of clinical trials^{30,31} and a post hoc analysis of the data from 4S¹⁸ have, however, shown a clear association between statin therapy and a reduced incidence of cerebrovascular events. Furthermore, data from the HPS^{21,22} have shown a 27% reduction in total stroke incidence (including ischemic stroke) in patients treated with simvastatin 40 mg daily compared with those receiving placebo, a finding that was independent of age, sex and baseline cholesterol level. Collectively, these data suggest that statins might reduce stroke incidence by mechanisms beyond cholesterol lowering. Some of these mechanisms include improvements in endothelial function, reduced inflammation, stabilization and regression of atherosclerotic plaques, and attenuation of thrombogenic responses (Box 1).

Improved endothelial function

One of the best-characterized benefits of statin therapy is an improvement in endothelial function, which can occur through a cholesterol-dependent or a cholesterol-independent mechanism. In this context, cholesterol apheresis alone can improve endothelial function within hours of lowering LDL cholesterol levels.³⁷ The mechanism by which statins improve endothelial function is thought to involve a nitric oxide (NO)-dependent process. Withdrawal of statin therapy leads to decreased endothelial NO production.³⁸ NO regulates the paracrine antiatherosclerotic functions of the endothelium. Reducing NO synthesis with an inhibitor of endothelial nitric oxide synthase (eNOS) promotes the progression of atherosclerosis³⁹ and increases stroke size.⁴⁰

By inhibition of mevalonate synthesis, statins prevent the production of biologically active intermediates, such as the isoprenoids, farnesylpyrophosphate and geranylgeranyl pyrophosphate (Figure 1). Farnesylpyrophosphate and geranylgeranylpyrophosphate have important roles in the post-translational modification of proteins, such as the γ -subunit of heterotrimeric G PROTEINS and members of the RAS SUPERFAMILY of GTP-binding proteins, including Ras, Rho, Rap, Ral, Rab and Rac. Members of the Ras superfamily function as molecular switches that cycle between the inactive GDP-bound state and the active GTP-bound state. Statins inhibit the ISOPRENYLATION of Ras and Rho, thereby promoting an accumulation of the inactive forms of these proteins within the cytoplasm of endothelial cells. It is the inhibition of Rho isoprenylation by statins that is largely responsible for the upregulation of eNOS expression within the endothelium.^{41,42} Statins can, however, also directly activate eNOS through additional post-translational mechanisms involving activation of the PHOSPHATIDYLINOSITOL 3-KINASE/ PROTEIN KINASE AKT PATHWAY.⁴³ Statins can also inhibit GERANYLGERANYLATION of Ras superfamily members, including Rho; however, activation of eNOS occurs much more rapidly via the phosphatidylinositol 3-kinase/protein kinase AKT signaling pathway, for which lower statin concentrations are required.⁴⁴

The inhibitory effect of statins on Rac1 geranylgeranylation, which is involved in the production of reactive oxygen species by NADPH oxidase, is thought to maintain NO availability by preventing it from being degraded by free-radical molecules. Indeed, preclinical studies suggest that the effects of statin therapy in enhancing levels of NO might translate into important benefits for cerebral ischemia, by increasing blood flow⁴⁵ and reducing neutrophil infiltration.⁴⁶ In addition, the preservation of NO levels is implicated in additional effects of statin therapy on vascular cells, including promotion of angiogenesis and

Box 1 Potential benefits and effects of statins in stroke

Improvement of endothelial dysfunction

- Increased synthesis of nitric oxide
- Decreased synthesis of endothelin 1
- Inhibition of LDL cholesterol oxidation

Reduced inflammatory response

- Reduced number and activity of inflammatory cells
- Reduced levels of C-reactive protein

Stabilization of atherosclerotic plaques

- Reduced serum cholesterol levels
- Reduced production of metalloproteinases

Reduced thrombogenic response

Inhibition of platelet adhesion or aggregation

Reduced fibrinogen concentration

Reduced blood viscosity

attenuation of endothelial cell apoptosis.⁴³ These effects might also lead to increased cerebral blood flow through increased collateral vessel formation.

FUTURE APPROACHES WITH STATINS FOR STROKE PREVENTION AND TREATMENT

Although statins reduce serum cholesterol levels and inflammation, the effects on each of these processes appear to be independent of one another.^{47,48} This might have important clinical implications, as epidemiology studies, as well as clinical trials with statins, have shown that inflammation correlates better with stroke incidence than serum cholesterol levels.⁴⁹ In the Pravastatin Inflammatory/CRP Evaluation (PRINCE) trial,⁴⁹ pravastatin therapy resulted in reduced levels of C-reactive protein, which is a marker of inflammation. The reduced levels of C-reactive protein were observed soon after pravastatin initiation (within 12 weeks) and occurred independently of effects on LDL cholesterol levels. Preclinical studies of stroke in animal models have demonstrated that statin therapy can provide neuroprotective benefits, as well as improved neurorecovery. Simvastatin administered either before or 3-25 h after middle cerebral artery occlusion in a rodent model of stroke resulted in a dose-dependent decrease in the size of the infarction.^{45,50} Similarly, statins protected against ischemic stroke by decreasing the thrombogenic response in a thromboembolic model of stroke.⁵¹ In another laboratory, atorvastatin therapy initiated 24 h after middle cerebral artery occlusion in rats resulted in improved function and neurologic recovery, including evidence of angiogenesis, neurogenesis and synaptogenesis.⁵² Evidence of anti-inflammatory and neuroprotective effects of statins, as well as improved neuro-recovery, have led to the design of early phase-IB dose-escalation studies to evaluate the use of high-dose statins in acute stroke.

EVIDENCE-BASED RECOMMENDATIONS FOR STROKE PREVENTION

The American Heart Association and the National Stroke Association guidelines for the prevention of primary ischemic stroke focus on optimizing the management of modifiable risk factors, as well as identifying individuals with nonmodifiable risk factors.^{11,13} Both the American Heart Association and the National Stroke Association recommend using statins to prevent stroke for patients with elevated cholesterol concentrations and those with known CAD. The recommendations follow the National Cholesterol Education Program/Adult Treatment Panel III approach for managing elevated cholesterol levels, which includes lifestyle modifications.⁵³

Although the lipid-modifying effects of statin therapy have been well documented, there is increasing evidence that statins might have other beneficial effects, such as improving endothelial function and anti-inflammatory effects, which could contribute to stroke risk reduction. Stroke prevention guidelines have not yet been updated to reflect the results of some of the newer clinical trials showing benefits for those at risk of stroke with normal cholesterol, hypertension or diabetes. On the basis of these data, optimum therapies for stroke prevention might include a statin in high-risk individuals, such as those with either hypertension or diabetes, irrespective of their serum cholesterol levels. Furthermore, serum biomarkers, such as C-reactive protein, which are independent of cholesterol levels, could potentially be used in conjunction with standard risk assessments in order to provide a better evaluation of which

individuals will benefit from statin therapy. Further studies will be needed, however, to determine the relative utility of C-reactive protein measurements over other traditional risk factors for stroke. Undoubtedly, future guidelines will have to reconsider these recommendations and consider making broader groups eligible for treatment with statins, on the basis of results from new trials.

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GLOSSARY

G PROTEINS, GTP-binding regulatory proteins in the cell membrane that act as intermediaries between cell-surface receptors and intracellular enzymes, enabling regulation of enzyme activity in response to extracellular signals; **RAS SUPERFAMILY**, A superfamily of GTP-binding hydrolysis-coupled signal-transduction relay proteins that includes the Ras, Rho, Rab and Rap families; **ISOPRENYLATION**, Modification of intracellular signaling molecules by intermediates of the cholesterol biosynthesis pathway; **PHOSPHATIDYLINOSITOL 3-KINASE/PROTEIN KINASE AKT PATHWAY**, Intracellular signaling pathway that mediates the effects of most growth factors; **GERANYLGERANYLATION**, An intermediate step of the cholesterol biosynthesis pathway, which is used to modify the Rho GTPase family of signaling molecules.

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Figure 1.

Mechanisms underlying the pleiotropic effects of statins in stroke. A schematic of the cholesterol biosynthesis pathway showing the effects of inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase by statins. Decreased isoprenylation of signaling molecules, such as Ras, Rho and Rac, leads to modulation of various signaling pathways. Reproduced with permission from reference ⁵⁵ © (2005) Annual Reviews. BMP2, bone morphogenetic protein 2; Cdc42, cell division cycle 42 GTP-binding protein; CoA, coenzyme A; eNOS, endothelial nitric oxide synthase; ET1, endothelin-1; HMG, 3-hydroxy-3-methylglutaryl; HO, hydroxy group; OPP, ether-linked pyrophosphate form of the isoprenoid; PAI1, plasminogen activator inhibitor 1; PI3 phosphatidylinositol 3; PP, pyrophosphate; tPA, tissue-type plasminogen activator.

Table 1

Stroke endpoints in selected statin trials

Trial name (number of patients)	Age range (years)	Study criteria	Primary endpoint	Follow-up (years)	Stroke rate (%)		Risk reduction		Number of strokes prevented per 1,000 people per 5 years	
					Control	Statin	P value	Absolute		Relative (range)
Atorvastatin										
ASCOT-LLA ²⁵ (10,305)	40-79	Baseline TC <6.5 mM/l (<251.0 mg/dl); high-risk hypertensive	CHD death, nonfatal MI	3.3	2.4	1.7	0.024	0.7	27 (4-44)	7
CARDS ²⁶ (2,838)	40-75	Baseline LDL <4.14 mM/l (<159.8 mg/dl); diabetes, no CHD	CHD or stroke	3.9	2.8	1.5	0.001	1.3	48 (11-69)	16
TNT ⁵⁴ (10,001)	35-75	Baseline LDL <3.4 mM/l (<131.3 mg/dl); CHD	CHD death, MI, cardiac arrest, stroke	4.9	3.1	2.3	0.02	0.8	25 (4-41)	8
Pravastatin										
ALLHAT-LLT ²⁷ (10,355)	>55	Baseline TC 3.1-4.9 mM/l (119.7-189.2 mg/dl) or 2.6-3.3 mM/l (100.4-127.4 mg/dl) if CHD; hypertension	All-cause mortality	4.8	4.5 ^a	4.1	0.31	0.4	9 (-25 to 9)	4
CARE ²⁰ (4,159)	31-75	Baseline TC <6.2 mM/l (<240 mg/dl)	CHD events	5.0	3.8	2.6	0.03	1.2	31 (3-52)	12
LIPID ¹⁹ (9,014)	31-75	Baseline TC 4.0-7.0 mM/l (155-270 mg/dl)	CHD death	6.0	4.5	3.7	0.048	0.8	19 (0-34)	8
PROSPER ²⁴ (5,804)	70-82	Baseline TC 4.0-9.0 mM/l (154.4-347.5 mg/dl); high-risk elderly	CHD death, nonfatal MI, stroke	3.2	4.5	4.7	0.81	0.2	3 (-19 to 31)	ND
Simvastatin										
HPS ²² (20,536)	40-80	Baseline TC >3.5 mM/l (>135.1 mg/dl);	Total mortality	5.3	5.7	4.3	<0.0001	1.4	25 (15-34)	14

Trial name (number of patients)	Age range (years)	Study criteria	Primary endpoint	Follow-up (years)	Stroke rate (%)		Risk reduction		Number of strokes prevented per 1,000 people per 5 years
					Control	Statin	Absolute	Relative (range)	
4S ¹⁸ (4,444)	35-70	high-risk hypertensive Baseline TC 5.5-8.0 mM/l (212-308.9 mg/dl)	Total mortality	5.4	4.3	2.7	1.6	30 (4-48)	16

^aIn these open-label trials, the control group was 'usual care' not placebo treatment. ALLHAT-LLT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm; CARDS, Collaborative Atorvastatin Diabetes Study; CARE, Cholesterol and Recurrent Events; CHD, coronary heart disease; HPS, Heart Protection Study; LIPID, Long-term Intervention with Pravastatin in Ischemic Disease; MI, myocardial infarction; ND, not determined; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; 4S, Scandinavian Simvastatin Survival Study; TC, total cholesterol; TNT, Treat to New Targets.