

## Review Article

# Use of Statins for Secondary Prevention and Primary Prevention of Ischemic Stroke

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### Abstract

Numerous randomized, double-blind, placebo-controlled studies and observational studies have shown that statins reduce ischemic stroke in high-risk persons with hypercholesterolemia. The 2013 American College of Cardiology (ACC)/American Heart Association guidelines on treatment of hypercholesterolemia supports the use of statins in 4 major groups. Patients with clinical atherosclerotic cardiovascular disease including those with stroke or transient ischemic attack should be treated with high-dose statins. High-dose statins reduce serum LDL cholesterol  $\geq 50\%$  and include atorvastatin 40 to 80 mg daily and rosuvastatin 20 to 40 mg daily. Patients with a serum LDL cholesterol  $\geq 190$  mg/dl should also be treated with high-dose statins. The ACC/AHA guidelines recommend for primary prevention in diabetics with a serum LDL cholesterol between 70 to 189 mg/dl moderate-dose statins. If the 10-year risk of developing atherosclerotic cardiovascular disease (coronary heart disease, stroke, transient ischemic attack, or atherosclerotic peripheral arterial disease) by the Pooled Cohort Equations is  $\geq 7.5\%$ , high-dose statins should be administered. Persons aged 40 to 75 years without atherosclerotic cardiovascular disease or diabetes mellitus with a serum LDL cholesterol between 70 to 189 mg/dl and an estimated 10-year risk of developing atherosclerotic vascular disease of  $\geq 7.5\%$  should be treated with high-dose statins. It is reasonable to treat persons aged 40 to 75 years without atherosclerotic vascular disease or diabetes mellitus with serum LDL cholesterol between 70 to 189 mg/dl and an estimated 10-year risk of developing atherosclerotic cardiovascular disease of 5% to 7.4% with moderate-dose statins.

**Keywords:** Lipids; Statins; Lipid-lowering drugs; Atherosclerotic cardiovascular disease; Stroke; Transient ischemic attack; Serum low-density lipoprotein cholesterol

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### Introduction

Hypercholesterolemia was a risk factor for stroke in 1,834 elderly persons [1]. There was a 1.06 times higher probability of developing an Atherothrombotic Infarction (ABI) for an increment of 10 mg/dl of serum total cholesterol after controlling for other prognostic variables. A low serum High-Density Lipoprotein (HDL) cholesterol is also a risk factor for stroke [1,2]. There was a 1.27 times higher probability of developing an Atherothrombotic Infarction (ABI) for a decrement of 10 mg/dl of serum HDL cholesterol after controlling for other prognostic variables. Statins are the only lipid-lowering drugs that have been shown to reduce the incidence of ischemic stroke in patients at risk for ischemic stroke. This review article will discuss the studies demonstrating the efficacy of statins in preventing ischemic stroke and the current guidelines supporting this use of statins. The search strategy for this review article included a review of all articles on this topic published in PubMed. The search terms used were stroke, transient ischemic attack, atherothrombotic brain infarction, statins, lipid-lowering drugs, hypercholesterolemia, dyslipidemia, serum lipids, serum low-density lipoprotein cholesterol atherosclerotic cardiovascular disease, hypertension, and diabetes mellitus.

### Randomized, Double-Blind Clinical Trials

At 5.4-year median follow-up of 4,444 men and women (of whom 1,021 were 65 to 70 years of age at study entry) with Coronary Heart Disease (CHD) and hypercholesterolemia in the Scandinavian Simvastatin Survival Study, compared with double-blind placebo, simvastatin 20 mg to 40 mg daily significantly reduced cerebrovascular events by 30% [Table 1] [3,4]. The reduction in stroke was similar in older and in younger men and women. At 5-year median follow-up of 1,283 patients aged 65 to 74 years at study entry in the Cholesterol and Recurrent Events study involving pravastatin treatment for a period of 5 years in post-myocardial infarction patients and serum total cholesterol levels less than 240 mg/dl and serum Low-Density Lipoprotein (LDL) cholesterol levels of 115 to 174 mg/dl, compared with double-blind placebo, pravastatin 40 mg daily significantly decreased stroke by 40% [Table 1] [5].

The Heart Protection Study randomized 20,536 men and women (5,806 of whom were aged 70 to 80 years) with prior myocardial infarction (8,510 persons), other CHD (4,876 persons), and no CHD (7,150 persons) and a serum total cholesterol level of 135 mg/dl or higher to simvastatin 40 mg daily or to double-blind placebo [6] of the 7,150 persons without CHD, 25% had cerebrovascular disease. At 5-year follow-up, compared to placebo, simvastatin significantly decreased any stroke by 25% [Table 1] [6]. The significant reduction in stroke occurred regardless of initial levels of serum lipids, age, or gender. In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering study, 3,086 persons, mean age 65 years, with an acute coronary syndrome and a mean serum LDL cholesterol level of 124 mg/dl were randomized to atorvastatin 80 mg daily or to double-blind placebo 24 to 96 hours after hospitalization for 16 weeks [7]. At 16-week follow-up, compared with placebo, atorvastatin significantly decreased stroke by 50% [Table 1] [7].

Double-Blind, Placebo-Controlled, Randomized Clinical Trials				
Number	Follow-up	Statin	Reduction in Stroke (%)	Reference
4,444	5.4 years	simvastatin	30	[3,4]
1,283	5.0	pravastatin	40	[5]
20,536	5.0 years	simvastatin	25	[6]
3,086	16 weeks	atorvastatin	50	[7]
10,305	3.3 years	atorvastatin	27	[8]
2,838	3.9 years	atorvastatin	48	[9]
4,731	4.9 years	atorvastatin	16	[10]
17,082*	1.9 years	rosuvastatin	48	[11]
Observational Studies With Different Statins Prescribed By Physicians				
1,410	3.0 years		60	[16]
529	29 months		47	[17]
449	26 months		87	[18]

**Table 1:** Use of Statins for Secondary Prevention and Primary Prevention of Ischemic Stroke.

\* primary prevention trial

In the Lipid Lowering Arm of the Anglo-Scandinavian Cardiac Outcomes trial, 10,305 persons (6,570 aged 61 to 79 years) with hypertension and at least 3 other cardiovascular risk factors with no history of CHD and a mean serum LDL cholesterol of 133 mg/dl were randomized to atorvastatin 10 mg daily or to double-blind placebo [8]. At 3.3-year follow-up, compared with placebo, atorvastatin significantly decreased fatal and nonfatal stroke by 27% [Table 1] [8]. In the Collaborative Atorvastatin Diabetes Study, 2,838 patients (62% older than 60 years) with diabetes mellitus, no cardiovascular disease, and a serum LDL cholesterol less than 160 mg/dl were randomized to atorvastatin 10 mg daily or to double-blind placebo [9]. At 3.9-year median follow-up, compared with placebo, atorvastatin significantly reduced stroke by 48% [Table 1] [9].

In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels study, 4,731 patients, mean age 63 years, who had a stroke or transient ischemic attack within 1 to 6 months prior to study entry, a serum LDL cholesterol of 100 to 190 mg/dl, and no CHD were randomized to atorvastatin 80 mg daily or to double-blind placebo [10]. At 4.9-year median follow-up, atorvastatin significantly reduced the incidence of new stroke by 16% [Table 1] [10]. In the Justification for the Use of Statins in Prevention: an Intervention Trial evaluating Rosuvastatin, 17,082 apparently healthy persons, median age 66 years, with a serum LDL cholesterol of less than 130 mg/dl and high-sensitivity C-reactive protein levels of 2.0 mg/L or higher were randomized to rosuvastatin 20 mg daily or to double-blind placebo [11]. At 1.9-year median follow-up, rosuvastatin significantly reduced the incidence of any stroke by 48% [Table 1] [11].

A meta-analysis was performed in 9 randomized trials of statins for secondary prevention in 19,569 patients aged 65 to 82 years [12]. Over 5 years, statins significantly reduced the incidence of stroke by 25% [12]. A meta-analysis performed in 26 randomized trials of 170,000 patients showed that compared with less intensive statin therapy, intensive statin therapy significantly reduced ischemic stroke further by 16% [13]. A meta-analysis was performed in 14 randomized trials of statins in 18,686 diabetics, mean age 63 years, (1,466 with type 1 diabetes and 17,220 with type 2 diabetes) [14]. After 4.3-year mean follow-up, statins significantly reduced the incidence of stroke by 21% [14].

Randomized placebo-controlled trials have not demonstrated a significant reduction in stroke by other lipid-lowering drugs. Among 3,414 patients, mean age 64 years, with atherosclerotic cardiovascular disease and low serum HDL cholesterol levels treated with simvastatin plus ezetimibe if needed to maintain the serum LDL cholesterol less than 70 mg/dl, at 36-month follow-up, patients randomized to niacin had improvements in serum HDL cholesterol and triglyceride levels but no clinical improvement compared to patients randomized to placebo [15]. In this study, patients treated with niacin had a 67% increase in ischemic stroke or stroke of uncertain origin ( $P=0.09$ ) [15].

## Observational Studies

In all of the observational prospective studies performed by this author, the attitude of the different physicians toward treating hypercholesterolemia in high-risk older persons determined whether or not statins were prescribed. In an observational prospective study of 488 men and 922 women, mean age 81 years, with prior myocardial infarction and a serum LDL cholesterol of 125 mg/dl or higher, 48% of persons were treated with statins [16]. At 3-year follow-up, compared to no treatment with statins, use of statins significantly decreased the incidence of stroke by 60% [Table 1] [16]. Statins significantly decreased new stroke in persons aged 90 years and younger but not in persons older than 90 years [16]. Decreasing serum LDL cholesterol to less than 90 mg/dl was associated with a 7% incidence of new stroke, whereas decreasing serum LDL cholesterol to 90 to 99 mg/dl was associated with a 16% incidence of new stroke [16]. The lower the serum LDL cholesterol in elderly persons treated with statins, the greater was the decrease in new stroke [16].

In an observational prospective study of 171 men and 358 women, mean age 79 years, with prior myocardial infarction, diabetes mellitus, and a serum LDL cholesterol of 125 mg/dl or higher, 53% of persons were treated with statins [17]. At 29-month follow-up, compared with no treatment with statins, use of statins significantly decreased in elderly diabetics with prior myocardial infarction the incidence of stroke by 47% [Table 1] [17]. Of 449 patients, mean age 72 years, with severe carotid arterial disease who did not undergo revascularization, 298 (66%) were treated with statins [18]. Follow-up was 26 months in patients treated with statins and 21 months in patients not treated with statins. Stepwise Cox regression analysis showed that use of statins reduced the time to development of new stroke or new myocardial infarction or death by 87% ( $p<0.0001$ ) [Table 1] [18]. Randomized clinical trials need to be performed to confirm the validity of these data [18].

## Treatment Guidelines

Lifestyle measures are important in the treatment of dyslipidemia. The person should achieve and maintain a desirable weight. The diet should be low in cholesterol (less than 200 mg daily). Less than 30% of total caloric intake should be fatty acids. Saturated fatty acids should comprise less than 7% of total calories, polyunsaturated acids up to 10% of total calories, and monounsaturated fatty acids 10% to 15% of total calories. The diet should also be high in fiber and high in fruits and vegetables. There is no strong evidence to support any dietary supplements. A more liberalized diet is warranted in elderly persons prone to malnutrition. Moderate intensity exercise is recommended for 30 to 60 minutes daily. Smoking should be stopped, hypertension treated, and diabetes controlled. Secondary causes of dyslipidemia should be treated.

The 2013 American College of Cardiology (ACC)/American Heart Association guidelines on treatment of hypercholesterolemia support the use of statins in 4 major groups [19]. Patients with clinical atherosclerotic cardiovascular disease including those with stroke or transient ischemic attack should be treated with high-dose statins. High-dose statins reduce serum LDL cholesterol  $\geq 50\%$  and include atorvastatin 40 to 80 mg daily and rosuvastatin 20 to 40 mg daily. Patients with a serum LDL cholesterol  $\geq 190$  mg/dl should also be treated with high-dose statins. The ACC/AHA guidelines recommend for primary prevention in diabetics with a serum LDL cholesterol between 70 to 189 mg/dl moderate-dose statins. If the 10-year risk of developing atherosclerotic cardiovascular disease (coronary heart disease, stroke, transient ischemic attack, or atherosclerotic peripheral arterial disease) by the Pooled Cohort Equations is  $\geq 7.5\%$ , high-dose statins should be administered. Persons aged 40 to 75 years without atherosclerotic cardiovascular disease or diabetes mellitus with a serum LDL cholesterol between 70 to 189 mg/dl and an estimated 10-year risk of developing atherosclerotic cardiovascular disease of  $\geq 7.5\%$  should be treated with high-dose statins. It is reasonable to treat persons aged 40 to 75 years without atherosclerotic cardiovascular disease or diabetes mellitus with a serum LDL cholesterol between 70 to 189 mg/dl and an estimated 10-year risk of developing atherosclerotic cardiovascular disease of 5% to 7.4% with moderate-dose statins [19].

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