

Ischemic stroke: A cardiovascular risk equivalent? Lessons learned from the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial

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Statin therapy in patients with coronary artery disease or in those at risk for cardiovascular disease is associated with a reduced incidence of ischemic stroke. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial showed treatment with atorvastatin 80 mg daily in patients with a recent stroke or transient ischemic attack (TIA) reduces the incidence of fatal and nonfatal stroke by 16%. In this population with a recent stroke or TIA, coronary artery disease events and the need for revascularization were a frequent occurrence. Furthermore, the relative reduction of noncerebrovascular events and the need for revascularization was greater with atorvastatin than the reduction of stroke. A patient with a recent ischemic stroke or TIA is at high risk for fatal and nonfatal coronary events (approximately 4% per year), and according to most guidelines for the management of coronary artery disease, such patients should be in the high risk category. Consequently, ischemic stroke should be considered to be a coronary risk equivalent with a prognosis similar to that of a patient with coronary artery disease. Furthermore, both the stroke and coronary artery disease prognoses are improved by treatment with atorvastatin 80 mg daily.

Key Words: *Atorvastatin; Cholesterol; Coronary artery disease; Stroke*

Cholesterol lowering with statins is one of the most effective measures in preventing recurrent ischemic events in patients with established coronary artery disease or in patients at high risk, such as those with diabetes or hypertension. Recent clinical trials have shown the added benefit of achieving lower levels of low-density lipoprotein (LDL) cholesterol with high-dose statin treatment. The relationship between cholesterol levels and stroke has been controversial and does not appear to be as strong as that observed for coronary artery disease. Furthermore, the benefit of cholesterol lowering in patients with ischemic stroke or transient ischemic attack (TIA) was unproven until the recently reported Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial showed that in these patients, atorvastatin 80 mg daily reduced the incidence of stroke and cardiovascular events.

Cholesterol and stroke

There is a strong epidemiological link between cholesterol levels and the risk of coronary artery disease; however, similar studies in stroke have shown less convincing evidence (1,2). This difference is likely due to the different pathogenetic mechanisms of most strokes from that of acute

Les accidents ischémiques cérébraux : Un équivalent du risque cardiovasculaire ? Des leçons tirées de l'essai SPARCL sur la prévention des AVC par réduction énergique des taux de cholestérol

Une thérapie aux statines chez les patients atteints d'une coronaropathie ou vulnérables à une maladie cardiovasculaire s'associe à une diminution de l'incidence d'accidents ischémiques cérébraux. L'essai SPARCL sur la prévention des accidents vasculaires cérébraux (AVC) par réduction énergique des taux de cholestérol a révélé qu'un traitement quotidien de 80 mg d'atorvastatine chez des patients qui avaient récemment subi un AVC ou un accident ischémique transitoire (AIT) réduit de 16 % l'incidence d'AVC fatal ou non fatal. Au sein de cette population ayant récemment subi un AVC ou un AIT, les événements reliés à la coronaropathie et la nécessité de revascularisation étaient courants. De plus, la réduction relative d'événements non vasculaires cérébraux et la nécessité de revascularisation étaient plus élevées avec l'atorvastatine que la réduction des AVC. Un patient ayant récemment subi un AVC ou un AIT court un risque élevé d'événement coronarien fatal ou non fatal (environ 4 % par année), et d'après la plupart des lignes directrices sur la prise en charge des coronaropathies, ces patients devraient faire partie de la catégorie à haut risque. Par conséquent, les accidents ischémiques cérébraux devraient être considérés comme un risque coronarien équivalent, au pronostic similaire à celui du patient atteint d'une coronaropathie. De plus, tant le pronostic d'AVC que celui de coronaropathie s'améliorent grâce à un traitement quotidien de 80 mg d'atorvastatine.

coronary occlusion. The Prospective Studies Collaboration (1) reviewed 45 prospective observational studies that included 450,000 subjects with over 13,000 strokes during the five to 30 years of follow-up. After adjustment for age, sex, race, blood pressure and history of coronary disease, there was no relationship between total cholesterol level and stroke, except in patients younger than 45 years of age. Unfortunately, most studies in this analysis recorded only fatal stroke, and there was no distinction between the types of stroke. The EUROSTROKE project (2) was a nested case-control study that also found no association among total cholesterol and fatal, nonfatal hemorrhagic or ischemic stroke.

A study of over 350,000 men (3) suggested a positive relationship between total cholesterol and ischemic stroke. The same study indicated that the risk of intracranial hemorrhage was three times higher when total cholesterol was below 4.14 mmol/L than for subjects with higher levels, especially when diastolic blood pressure was higher than 90 mmHg. From a public health perspective, the positive association of higher cholesterol and nonhemorrhagic stroke overwhelms the risk of hemorrhagic stroke associated with lower cholesterol levels. A case-control study (4) of 1242 patients with ischemic stroke and 313 cases of hemorrhagic stroke was compared with controls in a

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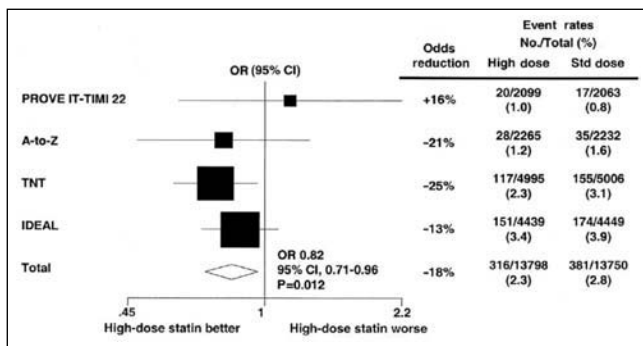


Figure 1) Meta-analysis of studies comparing high-dose statin therapy with standard or low-dose therapy on the incidence of stroke in patients with coronary artery disease. A-to-Z Aggrastat to Zocor; IDEAL Incremental Decrease in Events through Aggressive Lipid Lowering; PROVE IT-TIMI 22 Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction 22; TNT Treating to New Targets. Reproduced with permission from reference 7

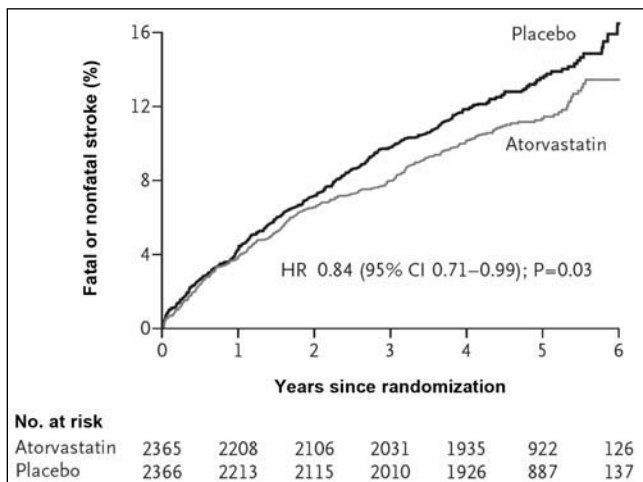


Figure 2) Kaplan-Meier curves for the first occurrence of fatal or nonfatal stroke and the effect of treatment with atorvastatin. Reproduced with permission from reference 9

myocardial infarction study. The study showed that patients in the highest quintile of total cholesterol had a 1.6-fold (95% CI 1.2 to 2.0) greater risk of ischemic stroke compared with patients in the lowest quintile. The strongest association was with atherosclerotic stroke (OR 3.2) and lacunar stroke (OR 2.4), and with patients with high-density lipoprotein cholesterol lower than 1.3 mmol/L. The lowest quintile of total cholesterol was associated with an increased risk of hemorrhagic stroke. Analysis of the Apolipoprotein-Related Mortality Risk (AMORIS) study (5) showed that the risk of fatal stroke is related to the apolipoprotein B to apolipoprotein A-1 ratio, although the slope of the relationship is less than that with fatal myocardial infarction.

Statins and stroke reduction

Treatment with statins reduces the risk of stroke among patients with coronary artery disease or those at risk for atherosclerotic disease. A systematic review and meta-analysis (6) of 90,000 patients enrolled in statin trials published before 2003 showed that statin treatment was associated with a 21% RR reduction of stroke (OR 0.79, 95% CI 0.73 to 0.85). However, neither fatal strokes (OR 0.91, 95% CI 0.76 to 1.10) nor hemorrhagic stroke (OR 0.90, 95% CI 0.65 to 1.22) was significantly altered by statin treatment. For every 10% reduction of LDL cholesterol, the risk of ischemic stroke was reduced by 15.6% (95% CI 6.7 to 23.6). The findings from a recent meta-analysis (7) also showed

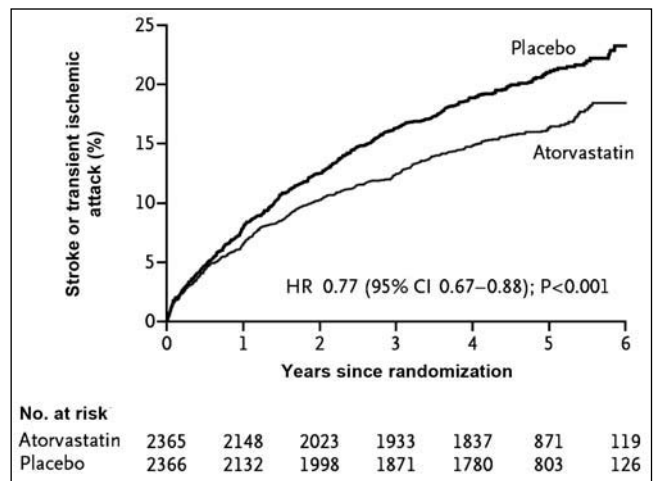


Figure 3) Kaplan-Meier curves for the first occurrence of stroke or transient ischemic attack and the effect of treatment with atorvastatin. Reproduced with permission from reference 9

that high-dose statin therapy has a greater benefit in stroke reduction than low-dose therapy (Figure 1).

Recent studies have suggested that the reduction of stroke by statin therapy is apparent within one to three months of starting treatment (8), and the benefit remains constant during the period of prolonged treatment. This is in contrast to the effect of statin therapy after myocardial infarction, when an early benefit decreases with time. The difference in the time course of the benefit of statins for coronary artery disease and ischemic stroke has suggested different mechanisms of action of statins in the two diseases.

Benefits of statins after stroke or TIA

SPARCL (9) was the first to examine whether a statin reduces the risk of stroke in patients with either a stroke or TIA within the past six months with no history of coronary artery disease. The 4731 patients were randomly assigned by a double-blind design to either atorvastatin 80 mg or placebo, and observed for the median follow-up period of 4.9 years. LDL cholesterol on entry into the study was 2.6 mmol/L to 4.9 mmol/L and was reduced by 38% in patients receiving atorvastatin 80 mg daily and 7% in those receiving placebo. During treatment, 11.2% of patients receiving atorvastatin and 13.1% taking placebo had either a fatal or a nonfatal stroke (Figure 2). The five-year absolute reduction of risk for the primary composite end point of fatal and nonfatal stroke was 2.2% with an adjusted hazard ratio (HR) of 0.84 (95% CI 0.71 to 0.99). Fatal stroke was significantly reduced (1.0% versus 1.7%, HR 0.57 [95% CI 0.35 to 0.95]), whereas the reduction of nonfatal stroke did not achieve statistical significance (10.4% versus 11.8%, HR 0.87 [95% CI 0.73 to 1.03]). Overall mortality was similar in the two treatment groups (9.1% versus 8.9%). Post hoc analyses suggested a different treatment effect according to the type of stroke: ischemic stroke was reduced 22% (218 events versus 274 events, HR 0.78 [95% CI 0.66 to 0.94]), whereas hemorrhagic stroke was increased (88 events versus 55 events, HR 1.66 [95% CI 1.08 to 2.55]).

The SPARCL trial showed that treatment with atorvastatin 80 mg/day reduced recurrent stroke in patients with a recent stroke or TIA, with a modest increase in the rate of hemorrhagic stroke (Figure 3). However, the overall benefit was in favour of treatment, with a net reduction of the total number of recurrent strokes. No conclusions can be drawn about the effects of statins in patients with hemorrhagic stroke because only 93 patients were enrolled in the SPARCL trial. Furthermore, patients with cardioembolic stroke did not qualify for the study. Thus, the results of the SPARCL trial should only be applied to patients with ischemic stroke or TIA.

How do statins reduce the risk of stroke?

In contrast to myocardial infarction, ischemic stroke and TIA are not usually caused by large-vessel atherothrombosis. It is unknown whether the different types of ischemic stroke, such as atherosclerotic embolic, lacunar or cryptogenic stroke, have different responses to statin treatment. Although stroke prevention appears to be related to the degree of cholesterol lowering (6,7), the importance of the non-lipid-lowering properties of statins, such as from an anti-inflammatory or antithrombotic effect, is uncertain.

Do statins increase the risk of cerebral hemorrhage?

Epidemiological studies have observed an association between low cholesterol levels and the incidence of cerebral hemorrhage (10). However, trials in patients with coronary artery disease with high-dose statins that achieved very low cholesterol targets (1.8 mmol/L) have not shown any association between either treatment, or reduction of cholesterol levels and brain hemorrhage (11-13). However, patients with cerebrovascular disease enrolled in the Heart Protection Study (HPS) (14) who received simvastatin had an increase in hemorrhagic stroke. The SPARCL study showed an increase in hemorrhagic stroke in patients receiving atorvastatin 80 mg (atorvastatin 2.3% versus placebo 1.4% HR 1.66 [95% CI 1.08 to 2.55]). However, the increase of hemorrhagic stroke was overshadowed by the larger reduction in recurrent ischemic stroke resulting in a net 16% reduction of nonfatal or fatal stroke. A post hoc on treatment analysis (15) of the SPARCL study showed that patients with the greatest cholesterol reduction (more than 50%) had the largest reduction of recurrent stroke (31%), with no increase in hemorrhagic stroke. Despite this analysis, it is possible that patients with a history of cerebrovascular disease may have a small risk of hemorrhagic stroke provoked by lowering cholesterol. However, the benefits of treatment, with a major reduction of coronary events and recurrent stroke, far exceed the apparently small increased risk of cerebral hemorrhage.

Coronary events in patients with stroke

Patients with a previous stroke or TIA have a high incidence of coronary events and nonstroke vascular death. A systematic review and meta-analysis (16) of 39 studies published between 1980 and 2005 included 65,996 patients and showed a substantial risk for nonstroke vascular events. The annual risk of either myocardial infarction or nonstroke vascular death was approximately 2% for each outcome. Such risks alone would be considered to be a high absolute risk in guidelines that assess cardiovascular risk (17,18). Furthermore, these patients have a substantial risk of recurrent stroke. Consequently, patients with a previous stroke or TIA are at a high to very high risk for cardiovascular events.

In the SPARCL study, over the 4.9 years of follow-up, patients with recent stroke or TIA but no history of coronary artery disease had a 5.1% incidence of a major coronary event (death from cardiac causes [1.6%], nonfatal myocardial infarction [3.5%]), major cardiovascular event (17.2%), any coronary event (8.6%) and need for revascularization (coronary, carotid or peripheral) (6.9%). Atorvastatin 80 mg daily reduced major coronary events by 35% (HR 0.65 [0.49 to 0.87]), any coronary event by 42% (HR 0.58 [95% CI 0.46 to 0.73]) (Figure 4) and the need for revascularization by 45% (HR 0.55 [95% CI 0.43 to 0.72]).

The high incidence of coronary vascular events in patients with ischemic stroke, as well as the profound reduction of coronary artery disease events with statin treatment, have led to stroke and TIA being considered to be a coronary risk equivalent. The SPARCL study confirmed the high risk for nonstroke vascular events and their substantial reduction with atorvastatin.

Is stroke a coronary risk equivalent?

Although patients with a recent stroke or TIA are at high risk for acute myocardial infarction, it is controversial whether stroke is an independent risk factor beyond classic risk factors such as diabetes,

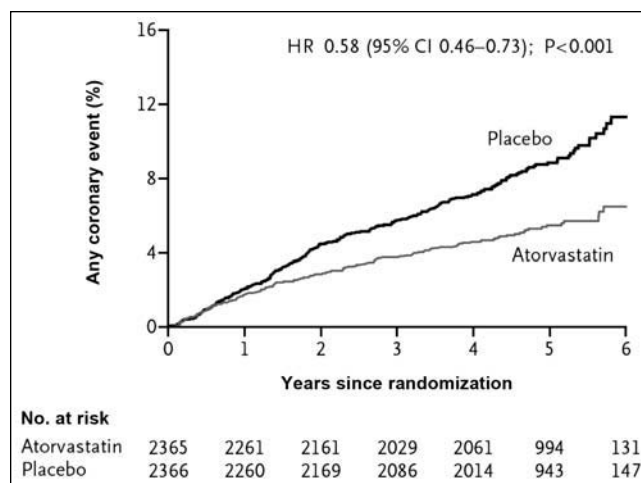


Figure 4) Kaplan-Meier curves for the first occurrence of any coronary event and the effect of treatment with atorvastatin. Reproduced with permission from reference 9

hypertension or hypercholesterolemia. In the SPARCL study, the average age was 63 years, 60% of patients were male, 16.9% had diabetes, 62% had hypertension, 19% were current smokers and baseline LDL cholesterol was 2.6 mmol/L to 4.9 mmol/L. Thus, a significant proportion of patients would have high-risk criteria by the Framingham risk score and qualify for statin therapy according to current guidelines (19,20).

Should patients with ischemic stroke undergo diagnostic tests to detect high-risk coronary artery disease and receive maximal vascular protective treatment with statins and angiotensin-converting enzyme inhibitors? An American Heart Association and American Stroke Association statement (21) has recommended individual risk assessment based on risk scores, but there is no reliable method to estimate the risk of myocardial infarction or vascular death after ischemic stroke. Furthermore, the SPARCL study has shown that atorvastatin reduced both recurrent stroke- and non-stroke-related vascular events, irrespective of risk scores. Thus, it is likely that future guidelines will suggest that ischemic stroke is a coronary risk equivalent and recommend a more widespread use of statins for the prevention of ischemic cardiac and cerebrovascular events.

CONCLUSIONS

- 1) Coronary artery disease events are common in patients who have had an ischemic stroke. The risk of fatal and nonfatal coronary artery disease is approximately 4% per year and places the patient in a high-risk category.
- 2) There is a weaker relationship between cholesterol levels and the risk of stroke than with coronary artery disease.
- 3) Lipid reduction with statins in patients with, and at risk for, coronary artery disease is associated with a reduction in the incidence of stroke. In this group of patients, there is no increase in cerebral hemorrhage associated with statin therapy.
- 4) Treatment with atorvastatin 80 mg daily in patients with recent stroke or TIA reduced the incidence of fatal and nonfatal stroke, as well as coronary artery disease events and the need for revascularization. The small increase in the risk of cerebral hemorrhage was overshadowed by the larger decrease in ischemic stroke and coronary artery events.
- 5) Patients with ischemic stroke or TIA have a high risk for recurrent stroke and coronary artery disease events, should be considered to have a coronary risk equivalent, and have a large overall benefit from statin treatment.

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