# The role of statins in the prevention of stroke

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## Abstract

Previous randomized trials have shown that statins may reduce the risk of stroke in high-risk patients. There were no evidences however that statins can reduce recurrent strokes. In the SPARCL trial, compared to placebo, the patients with a recent stroke or TIA randomized to atorvastatin 80 mg per day had a significant 16% relative risk reduction of stroke, and a 35% reduction in major coronary events. This was obtained despite 25% of patients allocated to placebo arm were prescribed a commercially available statin outside the trial. A post-hoc analysis used blinded LDL-C measurements (taken at study visits during the trial) as a marker of adherence to lipid lowering therapy. Compared to the group with no change or an increase in LDL-C (the group adherent to placebo or not taking a statin), the group with >50% reduction in LDL-C had a significant 31% reduction in stroke. The meta-analysis of trials that evaluated intensive LDL-C lowering (n=29,906 patients) shows that, compared to standard statin therapy, intense therapy reduced the risk of stroke by 17% (95% CI, 4 to 28%; p=0.01) with no heterogeneity between trials, and the risk of major cardiovascular events (stroke, myocardial infarction and vascular death) by 20% (95% CI, 14 to 26%; p<0.0001) with no heterogeneity between trials. Next step is to define whether achieving a LDL-C less than 70 mg/dL is better than a standard dose of statin (LDL around 100-110 mg/dL) in the secondary prevention of stroke. Other directions include evaluation of combination therapy (statin and ezetimide, statin and HDL-raising drugs), primary prevention of stroke and TIA as well as other cardiovascular events in patients at intermediate risk, and to evaluate the benefit/risk of PPAR agonist such as fibrate, alone or in combination with statins. Statins are effective in reducing both first-ever and recurrent stroke in high-risk patients, and this effect seems driven by the extent of LDL-C lowering.

Key words: stroke, stroke prevention, statin, lipid lowering therapy.

## Introduction

It is estimated that stroke affect 10 million people worldwide every year. Ischemic stroke is more frequent than myocardial infarction in Asia and we have now evidences that it has become also more frequent in Europe as well [1]. This should prompt considerable interest in both primary and secondary prevention of stroke in the next decades. The occurrence of stroke increases with age, particularly affecting the older elderly, a population also at higher risk for coronary heart disease (CHD). Regardless of stroke subtype, the prevalence of coronary atherosclerosis in patients with stroke is 75% [2]. After a first stroke, the 5-year risk of having another stroke is 20% and the 5-year risk of myocardial infarction is 10% [3], which qualifies stroke as a

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coronary heart disease risk equivalent (i.e., a 10-year risk of MI of 20%).

High blood pressure is the most important risk factor for stroke [4], and by controlling high blood pressure, it is well established that the risk of first-ever or recurrent stroke can be reduced by 40% [5]. Epidemiologic and observational studies have not shown a clear association between cholesterol levels and all causes of stroke [6]. Nonetheless, large, long-term statin trials in patients with established or at high risk of coronary heart disease have shown that statins decrease stroke incidence.

## Statins in prevention of stroke in high-risk patients

Statin trials have included over than 90,000 patients to determined the effect of statins on the incidence of major cardiovascular events in patients at high vascular risk [7]. In these trials stroke was a secondary endpoint. The relative risk reduction for stroke was 21% [OR 0.79 (0.73-0.85)] with no heterogeneity between trials [8]. Fatal strokes were reduced, but not significantly, by 9% [OR 0.91 (0.76-1.10)]. The extent of statin's effect was closely associated with LDL-C reduction. LDL reduction explained 34 to 80% of the observed benefit, leaving also room for other, pleotropic, effects. Each 10% reduction in LDL-C was estimated to reduce the risk of all strokes by 13.2% (95% CI, 4.8-20.6) and carotid intima-media thickness (IMT) by 0.73% per year (95% CI, 0.27-1.19). This meta-analysis showed that statins may reduce the incidence of all strokes, and this effect was mainly driven by the extent of between-group LDL-C reduction. Another meta-analysis, using individual data of 90,000 individuals, came to the same conclusion [9]. It showed a reduction in fatal and nonfatal stroke (0.83, 0.78-0.88; p<0.0001) and

Table I. Potential mechanisms whereby statins may reduce the risk of stroke

| Evidence-based |
| --- |
| LDL-C lowering |
| Reduction of carotid atherosclerosis progression (IMT studies) |
| Putative (not demonstrated) |
| Reduction of myocardial infarction and mural thrombus in the left ventricle (and subsequent thrombo-embolic complication) |
| Plaque stabilization |
| Anti-inflammatory effect |
| Anti-thrombotic properties |
| Blood pressure lowering effect |
| Improvement of endothelial dysfunction |
| Neuroprotective effect (up-regulation of nitric oxide) with increased cerebral blood flow |

that statin therapy can reduce the 5-year incidence of major coronary events, coronary revascularisation, and stroke by about one fifth per mmol/L reduction in LDL cholesterol, largely irrespective of the initial lipid profile or other presenting characteristics, and with a good overall safety profile with no increased incidence of hemorrhagic stroke and cancer [9].

More recent studies have confirmed that statins reduced the risk of first-ever stroke in patients with coronary artery disease in the Treat to New Target (TNT trial) and in other high risk populations – mainly diabetics in HPS and Collaborative AtoRvastatin Diabetes Study (CARDS) trial and hypertensives in Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) trial – even with a normal baseline blood cholesterol level, which argues for a global cardiovascular risk-based treatment strategy [10-12] (Table I).

## Statins in secondary stroke prevention

Statins had not been shown to prevent recurrent stroke in patients with prior stroke and additional studies in patients representative of the typical stroke population were needed. In the Heart Protection Study, the risk of recurrent stroke was 10.3% in the simvastatin group and 10.4% in the placebo group with a significant heterogeneity (p=0.002) with the group with no prior cerebrovascular disease at randomization, and there were 21 (1.3%) hemorrhagic strokes in the active group compared with 11 (0.7%) in the placebo group (p=0.03) [13]. The main explanation for this neutral effect was likely the fact that the study was not powered for this comparison, and that patients had their qualifying stroke on average 4.3 months prior randomization, at a time where the risk of stroke has naturally decreased to its lowest level. On the contrary, the risk of MI is continuously increasing overtime after a stroke or TIA.

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study was only dedicated trial to stroke patients. This unique, large randomized, placebo-controlled trials which evaluated atorvastatin 80 mg/day in patients with stroke or TIA [14].

In this study, patients with recent stroke or TIA within 1-6 months of study entry and low-density lipoprotein [LDL] cholesterol of 100-190 mg/dL without known coronary heart disease (CHD) (n=4731) were randomly assigned to double-blind treatment with atorvastatin 80 mg/day or placebo. The primary end point was occurrence of first fatal or nonfatal stroke.

Mean LDL cholesterol was 73 mg/dL on atorvastatin, and 129 mg/dL on placebo over the course of the trial. After 4.9 years median follow-up, a fatal or non fatal stroke occurred in 265 patients (11.2%) receiving atorvastatin and 311 patients (13.1%) receiving placebo (5-year absolute risk reduction 2.2%; adjusted hazard ratio – 0.84, 95% CI, 0.71 to 0.99, p=0.03). Two hundred

and eighteen ischemic and 55 hemorrhagic strokes occurred with atorvastatin and 274 ischemic and 33 hemorrhagic strokes with placebo. The absolute 5-year risk reduction in major cardiovascular events was 3.5% (hazard ratio – 0.80, 95% CI, 0.69 to 0.92, p=0.002). Overall mortality was unchanged (216 deaths, atorvastatin vs. 211 deaths, placebo, p=0.98). The rates of serious adverse events such as muscle pain, myopathy and rhabdomyolysis were similar.

Therefore this trial showed that in patients with recent stroke or TIA without known CHD, a 5-year treatment with atorvastatin 80 mg/day reduced the incidence of stroke and cardiovascular events (Figure 1).

### SPARCL subanalyses

#### Who benefited most?

This result was obtained despite a bad adherence to the allocated randomized treatment, particularly in the placebo group. On average, 25% of patients in the placebo group were prescribed a commercially available statin outside the trial. In a post-hoc analysis, LDL-C reduction was thus used as the best marker for being adherent to the allocated treatment with the hypothesis that patients with no change or an increase in LDL-C (compared to baseline) were not on statin or adherent to allocated placebo, while the group with a >50% LDL-C reduction from baseline were likely adherent to atorvastatin 80 mg/day. Based on 55,045 blinded LDL-C measurements (with an average 11.6 measurement/patient performed during the follow-up), percent change in LDL-C from baseline was classified – post hoc – as no change from baseline, <50% reduction or ≥50% reduction. Compared to the group with no change or an increase in LDL-C, the group with the deepest LDL-C lowering (>50% from baseline) had a 31% relative risk reduction in stroke and no increase in brain hemorrhage [15].

#### Hemorrhagic strokes

One other post-hoc analysis explored the factors associated with outcome hemorrhagic strokes [16]. It found that hemorrhagic stroke was more frequent in those treated with atorvastatin, in those with a hemorrhagic stroke as an entry event, in men, and increased with age. Those with stage 2 hypertension at the last visit prior to the hemorrhagic stroke were also at increased risk. Treatment did not disproportionately affect the hemorrhagic stroke risk associated with these other factors. There were no relationships between hemorrhage risk and baseline LDL-cholesterol level or recent LDL-cholesterol level in treated patients.

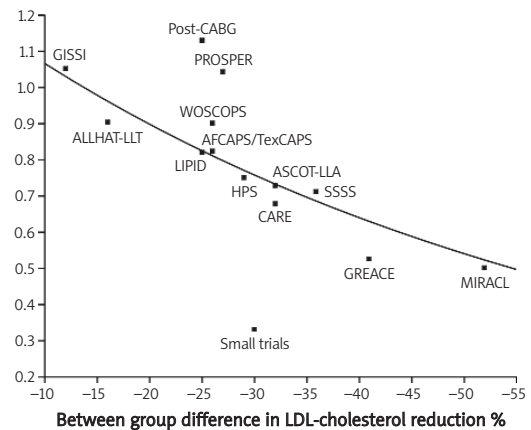Although the 1,409 patients with small vessel disease had a risk of hemorrhagic stroke over the



**Figure 1.** Stroke risk reduction according to LDL-cholesterol reduction (%) in statin trials

course of the trial similar to other ischemic stroke subgroups, the 708 patients with small vessel disease randomized in the atorvastatin arm were at higher risk of hemorrhagic stroke. The reported multivariate analysis [16] did not identify small vessel disease subgroup as an independent predictor of hemorrhagic stroke, meaning that there was no heterogeneity due to treatment in this subgroup. Data not collected in SPARCL, such as imaging data (e.g., extent of leukoaraiosis, cerebral microbleeding, multilacunes), might have confounded or explained some of the significant associations found. These patients with small vessel disease had a higher baseline systolic and diastolic blood pressure than other ischemic stroke subgroups. They also had an absolute event rate of recurrent stroke (14.3 and 15.9%, respectively) and outcome major cardiovascular events similar to patients with large vessel disease. This similarity between both subgroups was unexpected, though further confirmed recent autopsy data showing that small vessel disease patients (with no history of coronary heart disease) had coronary plaque in 79% of case and coronary stenosis >50% in 37% of cases as compared to 77 and 33% of cases respectively in atherothrombotic strokes and no history of symptomatic coronary heart disease [2]. Data from SPARCL clearly show that patients with small vessel disease had a long-term risk of MCVE similar to other ischemic stroke subtypes, and therefore must require the same intensive preventive strategies, including statin therapy. Indeed, atorvastatin in SPARCL was as effective in the small vessel disease subgroup as in the large vessel disease subgroup on MCVE.

### Next step

The same time-varying analysis of SPARCL showed that achieving LDL-C levels <70 mg/dL as compared to >100 mg/dL was followed by a 28%

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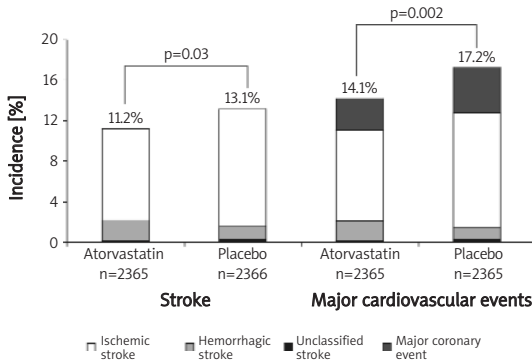
**Figure 2.** Net benefit of treatment with atorvastatin 80 mg/day in patients with recent stroke or transient ischemic attack (analysis of incidence of hemorrhagic stroke was post hoc) in the SPARCL trial.
Left panel: primary endpoint stroke fatal or non. Right panel: secondary endpoint major cardiovascular events (stroke fatal or non and major coronary events)

RRR in stroke [15]. This result was obtained post-hoc and therefore is hypothesis generating. Next would be to demonstrate in patients with stroke/TIA that low LDL-C target levels <70 mg/dL are associated with a lower incidence of recurrent stroke or other major vascular events than currently recommended LDL-C target after a stroke (<100 mg/dL).

Recent trials have shown that intense LDL-C lowering reduced the risk of major cardiovascular events better than standard therapy [10, 17-19]. PROVE-IT randomized patients with recently symptomatic coronary artery disease (n=4,162) to either pravastatin 40 mg/day or atorvastatin 80 mg/day, with an achieved average on-treatment LDL-C of 95 and 62 mg/dL, respectively [17]. TNT (n=10,001) randomized patients with stabilized coronary heart disease between atorvastatin 80 mg/day vs. atorvastatin 10 mg/day, achieving an average on-treatment LDL-C of 77 and 101 mg/dL, respectively [10]. IDEAL randomized patients with coronary heart disease between simvastatin 20-40 mg/dL and atorvastatin 80 mg/day, achieving an average on-treatment LDL-C of 100 and 80 mg/dL,

respectively [18]. Finally, ALLIANCE (n=2,442) randomized CAD patients between atorvastatin titrated to a LDL-C target of <70 mg/dL (median dose of atorvastatin 41 mg/day) vs. "usual care" achieving an average on-treatment LDL-C of 95 and 110 mg/dL, respectively [19]. The crude meta-analysis of these trials (n=25,409 patients) shows that, compared to standard statin therapy, intense statin therapy reduced the risk of stroke by 17% (95% CI, 3.0-28.0) with no heterogeneity between trials (Figure 2): 713 patients had a stroke, and the incidence of stroke in the intensive arm was 2.54% (n=324/12,750) compared to 3.04% (n=387/12,743) in the conventional arm [OR=0.83 (95% CI, 0.72-0.97, p=0.02)]. For major cardiovascular events (stroke, myocardial infarction and vascular death), the same crude meta-analysis found a relative risk reduction of 21% with no heterogeneity between trials (Figure 3): 2857 patients had a MCE, and the incidence of MCE in the intensive arm was 10.05% (n=1282/12750) compared to 12.36% (n=1575/12743) in the conventional arm [OR=0.79 (95% CI, 0.73-0.86) p<0.0001].
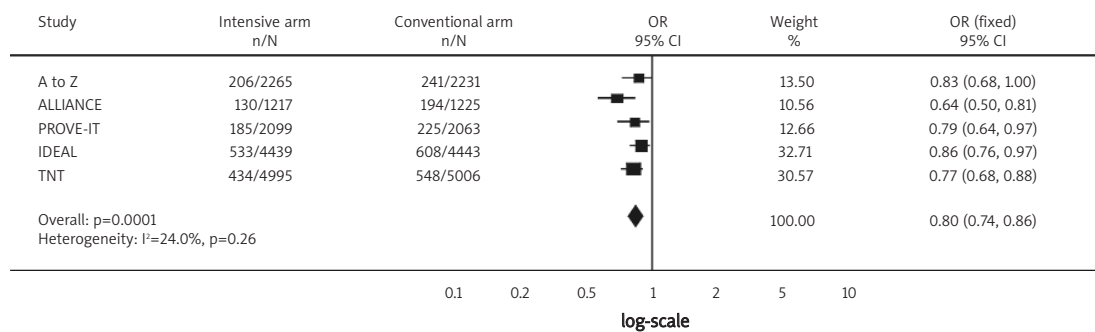
The results of this meta-analysis, together with the post-hoc analysis of the SPARCL trial mentioned above, reinforce the case for an evaluation of two LDL-C lowering strategies (achieved LDL-C <70 mg/dL vs. standard dose of statin) in secondary prevention of stroke.

## Future perspective

Current recommendations use target LDL-C levels, together with associated risk factors or disease (e.g., diabetes, carotid stenosis) or clinical events (e.g., myocardial infarction) to drive the prescription of statins. In the following years, results obtained in SPARCL should be implemented and included in guidelines and recommendations to spread the prescription of statin following stroke or TIA and to improve adherence of patients. SPARCL secondary analyses showing that LDL-C levels less than 70 mg/dL may be associated with 2 times more risk reduction than that observed in the intention to treat analysis may help develop recommendation. However, target
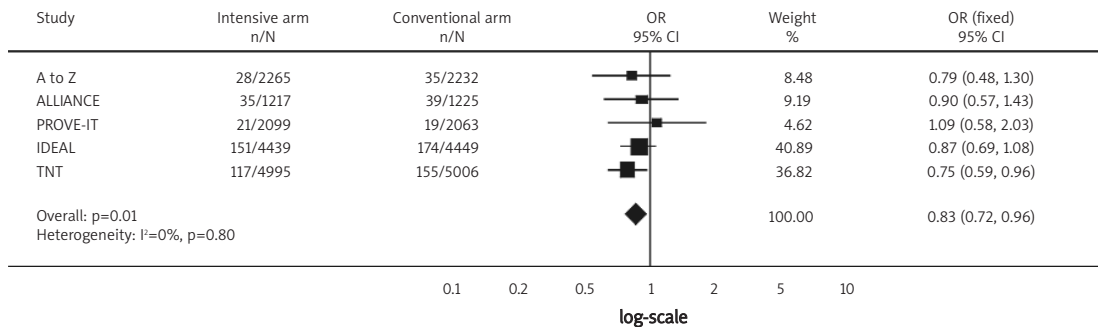


**Figure 3.** Meta-analysis of four statin trials that evaluated the effect of intensive lipid-lowering therapy versus standard statin therapy: fatal and nonfatal stroke incidence

| Study | Intensive arm n/N | Conventional arm n/N | OR 95% CI | Weight % | OR (fixed) 95% CI |
|-------|-------------------|----------------------|-----------|----------|-------------------|
| A to Z | 206/2265 | 241/2231 | | 13.50 | 0.83 (0.68, 1.00) |
| ALLIANCE | 130/1217 | 194/1225 | | 10.56 | 0.64 (0.50, 0.81) |
| PROVE-IT | 185/2099 | 225/2063 | | 12.66 | 0.79 (0.64, 0.97) |
| IDEAL | 533/4439 | 608/4443 | | 32.71 | 0.86 (0.76, 0.97) |
| TNT | 434/4995 | 548/5006 | | 30.57 | 0.77 (0.68, 0.88) |
| Overall: p=0.0001 Heterogeneity: $I^2$=24.0%, p=0.26 | | | | 100.00 | 0.80 (0.74, 0.86) |

0.1   0.2   0.5   1   2   5   10

**log-scale**

**Figure 4.** Meta-analysis of four statin trial that evaluated the effect of intensive lipid-lowering therapy versus standard statin therapy: major cardiovascular events (including stroke, myocardial infarction and vascular death)

LDL-C levels in secondary stroke prevention currently are hypothesis generating from post hoc analysis rather than evidence based. To me the recommendation after a stroke or a TIA can only be "just prescribe a statin", particularly atorvastatin 80 mg/day.

A randomized controlled trial should evaluate whether achieving a LDL-C less than 70 mg/dL is better than a standard dose of statin (LDL around 100-110 mg/dL) in the secondary prevention of stroke. Other directions include evaluation of combination therapy (statin and ezetimide, statin and HDL-raising drugs), primary prevention of stroke and TIA as well as other cardiovascular events in patients at intermediate risk, and to evaluate the benefit/risk of PPAR agonist such as fibrate, alone or in combination with statins.

In conclusions statins are among the most effective drugs in reducing the risk of stroke in population of patients at high vascular risk, as well as the risk of major coronary events. In secondary prevention of stroke, statins clearly reduced the risk of major coronary event and, in the SPARCL trial, atorvastatin reduced the risk of recurrent stroke.

## Disclosure

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