

RAPID APPRAISAL

Name of Trial: High-dose atorvastatin after stroke or transient ischemic attack

Reference: The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. *New England Journal of Medicine* 2006;355:549-59

Question: Does atorvastatin 80 mg once daily reduce the risk of stroke in patients with no known coronary heart disease and a history of stroke or transient ischaemic attack?

Summary: In this well designed study, atorvastatin 80 mg once daily reduced the absolute risk of stroke in patients with no known CHD and with a recent history of a stroke or TIA by 2.2%, corresponding to a relative risk reduction of 16%. This difference was statistically significant only after adjustment for differences in baseline demographics between the two groups. However the outcome depends on the nature of the event; for an ischaemic stroke the relative risk reduction is 22% but for haemorrhagic stroke there is an increased relative risk of 66%. The cost effectiveness of this intervention has not been assessed but 46 patients would need to be treated with atorvastatin 80 mg once daily for five years to prevent one stroke at a cost of £84,350. Currently, most patients with previous ischaemic stroke should be treated with a generic statin. This trial does not provide evidence on which to base a change in this practice.

Did the study ask a clearly focussed question?

Yes. The study had a clear focus from inception and was designed to evaluate the effects of atorvastatin 80mg daily in patients with a recent history of a stroke or a transient ischaemic attack (TIA) but with no known coronary heart disease (CHD). The study inclusion and exclusion criteria were numerous but fair; patients had no prior history of CHD, a positive history of a stroke or TIA within the preceding 1 to 6 months, an LDL cholesterol level between 2.6 and 4.9 mmol/L (i.e. relatively low), and no history of atrial fibrillation, peripheral vascular disease, uncontrolled hypertension, and other factors. Additionally patients were defined as at least 'functionally independent' according to independent criteria. If patients had used any drugs known to affect lipid levels a 30-day washout period was required.^{1,2}

Patients (n = 4,371) were randomised to treatment with atorvastatin 80 mg (n = 2,365) or placebo (n = 2,366) once daily. All patients received dietary advice. The primary outcome measure was time to first occurrence of a stroke.¹ Secondary endpoints included total number of strokes or TIA, major coronary event defined as any death from cardiac causes, nonfatal myocardial infarction or resuscitation after cardiac arrest, and major cardiovascular event defined as any major coronary event or stroke.²

Was the study design appropriate?

Yes. The trial was a randomized, multi-centre, prospective, placebo-controlled, international trial. The trial was supported by Pfizer, manufacturers of atorvastatin (Lipitor® in the UK).^{1,2}

Were participants appropriately allocated to intervention and control groups?

Yes. Patients were randomly assigned to one of two treatments.^{1,2} The two groups were well matched with respect to several demographic and relevant clinical parameters.¹ The main trial results reported are calculated with adjustments made for baseline differences in geographic region, entry event (stroke or TIA), time since entry event, sex, and age.

Were participants, staff and study personnel 'blind' to participants study group?

Yes. Patients and investigators were blind to the allocated treatment. Furthermore, as un-blinding of treatment group was possible through knowledge of patient serum lipid levels, measures were put in place to ensure that this did not occur. Two independent endpoint committees adjudicated all potential endpoints without knowledge of the patients' treatment status or cholesterol levels. Open-label non-study statin use was permitted and this resulted in 25.4% of placebo and 11.4% of atorvastatin patients receiving such treatment. The overall difference in statin use between the two groups was 78.1%. A small number of patients (n = 9) were unblinded to their physician during the study.¹

Were all of the participants who entered into the trial accounted for at its conclusion?

Yes. Results are reported on an intention-to-treat basis and include all randomised patients. There is no significant difference in the number of patients in each treatment group lost to follow up. More patients in the placebo group withdrew consent, discontinued treatment, and commenced open-label non-study statin therapy. In total 2,272 (96%) in the atorvastatin group and 2,253 (95%) in the placebo group were followed for endpoints throughout the study or until death.¹

Were the participants in all groups followed up and data collected in the same way?

Yes. At the end of the study the median period of follow-up was 4.9 years, range 4.0 to 6.6. Both groups were treated in exactly the same way with follow-up visits at one, three, and six months after enrolment and every six months thereafter. Recruitment was complete within two and a half years.¹

Was the study large enough?

Yes. The design of the study required a minimum of 4,200 patients to provide 90% power to detect an absolute 25% reduction in the 5-year cumulative primary outcome measure between treatment groups, with a two-sided 5% level of significance. This correlates to a total of 540 study endpoints within the five years; in fact there were 576. Due to planned annual interim analyses the p value has to be less than 0.048 to indicate a significant difference. Certain other assumptions were made and these are supported by the trial results.^{1,2} As all of these conditions were met the study was sufficiently powered to make reliable conclusions.

How are the results presented and what is the main result?

The results are presented as the proportion of patients experiencing each event with censorship occurring at the time of occurrence of the primary outcome measure (i.e. stroke). Kaplan-Meier survival curves are also provided for the primary and many of the secondary outcome measures. Unadjusted probability values are presented alongside an adjusted value with associated hazard ratio and 95% confidence interval (CI). Adjustments were made to compensate for geographic region, entry event (stroke or TIA), time since entry event, sex, and age at baseline.¹

The primary outcome measure is reported as the total number of strokes; 265 (11.2%) in the atorvastatin group and 311 (13.1%) in the placebo group, $p = 0.03$ (hazard ratio [HR] 0.74, 95% CI 0.71 to 0.99), unadjusted $p = 0.05$. Significant reductions were observed for fatal (24 vs. 41, $p = 0.03$) but not nonfatal strokes (247 vs. 280, $p = 0.11$). The HR for the risk of a major coronary event was 0.65 (95% CI 0.49 to 0.87), $p = 0.006$, and the HR for the risk of a major cardiovascular event was 0.80 (95% CI 0.69 to 0.92), $p = 0.005$. There was no reduction in overall mortality (9.1% vs. 8.9%, $p = 0.98$) despite the reduced risk in fatal stroke.¹

The effect of atorvastatin on stroke depended on the type; for ischaemic strokes the hazard ratio (HR) is 0.78 (95% CI 0.66 to 0.94), but for haemorrhagic stroke the HR is 1.66 (95% CI 1.08 to 2.55). Thus the risk reduction in ischaemic strokes is to the detriment of an increased risk of haemorrhagic stroke. Overall, because ischaemic strokes were a more frequent event, the 5-year stroke risk is reduced by an absolute value of 2.2%

(95% CI 0.2 to 4.2%), or relatively by 16% (95% CI 1 to 29%). This corresponds to a number needed to treat (NNT) of 46 (95% CI 24 to 500)^{1,3} to prevent one stroke over five years in this patient population.

How safe were the regimens?

There were no significant differences between groups in the incidence of serious adverse events. There were five cases of rhabdomyolysis, two in the atorvastatin group. The rate of discontinuation of study treatment due to any adverse event was 17.5% in the atorvastatin group and 14.5% in the placebo group.¹

How precise are the results?

The primary outcome measure is only statistically significant when pre-planned adjustments are made to the data set to allow for differences in the treatment group populations. Probability values for the outcomes are stated with 95% confidence intervals. For the primary outcome measure the HR 95% CI is 0.71 to 0.99.¹ This means that with 95% certainty the true value lies within this range, i.e. the true effect may be as much as a 29% or as little as a 1% relative risk reduction. Given the large numbers involved in the study the results can be considered to have a high degree of precision.

Can the results be applied to the local population?

Yes. There were several UK-based investigators involved in the study, and many from Europe but the majority were American. The randomized population consisted of less than 1% of patients of Asian origin and this may be less than can be expected from a UK derived population.¹

Does atorvastatin 80 mg once daily reduce the risk of stroke in patients with no known coronary heart disease and a history of stroke or transient ischaemic attack?

Yes. This is the first trial of a statin with proven outcomes in a population of recent stroke or TIA patients with no CHD history. The absolute stroke risk reduction benefit for atorvastatin 80 mg once daily is small with no reduction in mortality. The cost effectiveness of this intervention has not been assessed but assuming a NNT of 46 and using current drug prices,³ the cost to prevent one stroke in this patient population over five years is £84,350. From the results of this study there are strong suggestions that certain sub-groups of stroke or TIA patients may benefit more than others, for example those with ischaemic cerebrovascular events. It would be prudent not to alter practice until well designed, randomised, large studies have been performed specifically in such populations. Currently, many patients with previous ischaemic stroke are already treated with less intensive generic statin regimens (e.g. simvastatin 40 mg daily). There is currently inadequate evidence on which to base a change in this practice.

REFERENCES

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3. Altman DG. Confidence intervals for the number needed to treat. *British Medical Journal* 1998;317:1309-12

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KEY: RCT - randomised controlled trial

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