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High dose atorvastatin after stroke or transient ischaemic attack (SPARCL)--does every stroke patient in Pakistan deserve a statin

Maria Khan
Aga Khan University

Ayeesha Kamran Kamal
Aga Khan University

Evidence Based Medicine

High dose Atorvastatin after stroke or Transient Ischaemic Attack (SPARCL) — Does every stroke patient in Pakistan deserve a statin?

Maria Khan, Ayeesha Kamran Kamal
Stroke Service and Vascular Fellowship Program, Aga Khan University Hospital, Karachi, Pakistan.

Why is this study important?

It was well established from previous studies that therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) reduces the risk of stroke among patients with coronary heart disease and those at increased risk for cardiovascular disease. But prior to this study no data existed regarding the benefits of statins in patients with history of stroke or transient ischemic attacks.

The aim of Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial was to determine the impact of 80 mg of Atorvastatin per day on stroke prevention in patients with history of stroke or TIA within the past six months and with no known history of coronary artery disease.

Who were the participants?

Patients were eligible if they had a stroke or TIA one to six months before randomization. Haemorrhagic strokes were also included if the physicians felt that these patients were at risk of ischaemic events. Patients with cardioembolic strokes, subarachnoid haemorrhage, LDL<100 and modified Rankin score greater than 3 were excluded. A patient with a Modified Rankin Score of 3 is a patient with Moderate disability; requiring some help, but able to walk without assistance

These patients were selected from twenty seven countries across five continents. Majority of the patients were from Europe. The contribution from the Middle East was limited to just 61 patients from Israel. There were no South Asian patients in this landmark trial.

What was the intervention?

A total of 6670 patients were screened, 4731 were deemed eligible and were randomly assigned to double-blind therapy with either 80 mg of Atorvastatin per day or placebo. 2365 were randomized to active arm and 2366 to the placebo arm.

Follow-up visits were scheduled one, three, and six months after enrollment and every six months thereafter. Patients were followed up for a median of 4.9 years. Efficacy and safety analyses were both on intention to treat basis.

The two groups were well matched in terms of age, gender, blood pressure, entry event, other risk factors and concomitant medication use. They were also well matched with respect to their baseline lipid values.

What was the outcome?

The mean values for LDL, total cholesterol and triglycerides were significantly lower in the Atorvastatin arm compared to the placebo arm. Hence treatment was adhered to. LDL cholesterol was 72.9±0.5 mg per deciliter in the Atorvastatin group, as compared with 128.5±0.5 mg per deciliter in the placebo group (P<0.001); total cholesterol, 147.2±0.6 as compared with 208.4±0.6 mg per deciliter (P<0.001); and triglycerides, 111.5±1.3 as compared with 145.0±1.3 mg per deciliter, respectively (P<0.001).); high-density lipoprotein (HDL) cholesterol was 52.1±0.3 in the active arm as compared with 51.0±0.3 mg per deciliter in the placebo arm (P = 0.006).

A primary end point (any nonfatal or fatal stroke) occurred in 265 patients in the Atorvastatin group and 311 in the placebo group (unadjusted P = 0.05). After prespecified adjustment for baseline factors, Atorvastatin was associated with a 16.0 percent relative reduction in the risk of nonfatal or fatal stroke (hazard ratio, 0.84; 95 percent confidence interval, 0.71 to 0.99; P = 0.03).

Analysis of secondary end points showed reductions in the combined risk of stroke and TIA. The risk of cardiovascular events, including major coronary events and revascularization procedures, was reduced substantially. There was however, no significant difference between treatment groups in overall mortality.

There were significant differences in the treatment effects based on the type of stroke. The risk was decreased for ischaemic and unclassified strokes but it was increased for haemorrhagic strokes with a hazard ratio of 1.66 (95% CI 1.08-2.55).Persistent elevation of alanine or aspartate aminotransferase (>3 times the upper limit of the normal group on two consecutive occasions) was more frequent in the atorvastatin group (51 patients, or 2.2%) than in the placebo group (11 patients or 0.5%). There were no cases of liver failure.

Safety analysis revealed no significant differences in the two arms in terms of serious adverse events.

What were the author's conclusions?

The authors concluded that aggressive lowering of cholesterol in patients with history of prior stroke or TIA significantly decreases the risk of recurrent non fatal stroke, major cardiovascular events and need for revascularization.

On the basis of this data, 46 patients (95 percent confidence interval, 24 to 243) would need to be treated for five years to prevent one stroke, 29 patients (95 percent confidence interval, 18 to 75) to prevent one major cardiovascular event, and 32 patients (95 percent confidence interval, 22 to 59) to avoid one revascularization procedure.

So how important are statins in Pakistani stroke patients?

After Diabetes and Hypertension, the third important modifiable risk factor for stroke is dyslipidaemia. This trial clearly shows that aggressive lowering of cholesterol in patients 1-6 months from their stroke or TIA, reduces the risk of recurrent strokes and other cardiovascular events as well. Until this study, most of us did not consider a stroke or a TIA an independent vascular indication for statin administration. It is important for us to consider the cost, risk and benefits of statin therapy in every South Asian patient with ischaemic stroke - at the very least.

Although the study was not powered to detect impact in various stroke subtypes, there was an increase in the risk of haemorrhages overall. This effect may be magnified in South Asian setting as there is a relatively higher proportion of patients (30 % vs. 17%) who present with intracerebral haemorrhage. Additionally, the liver enzymes must be carefully monitored in areas where Hepatitis is endemic. The potential risk of recurrent haemorrhage should be considered when one is deciding whether to administer a statin to patients who have had a haemorrhagic stroke and the enzymes must be monitored judiciously.

Although the numbers needed to treat for prevention are significant, this does not undermine the importance of the intervention. It does however, put statin therapy lower down in the priority list where cost is a major limitation to treatment. We should encourage local, cheaper generic statins to assuage some of the cost issues with therapy.

Recommended Reading:

1. SPARCL Amarenco P, Bogousslavsky J, Callahan A 3rd, Goldstein LB, et al. High dose Atorvastatin after stroke or transient ischemic attack. N Engl J Med 2006; 355: 549-59.