

THERAPEUTICS

# Cholesterol lowering with simvastatin reduced stroke in patients with, or at risk for, vascular disease

Collins R, Armitage J, Parish S, Sleight P, Peto R. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20 536 people with cerebrovascular disease or other high-risk conditions. *Lancet*. 2004;363:757-67.

**QUESTION**

Does cholesterol lowering with simvastatin reduce the incidence of stroke in patients with, or at high risk for, vascular disease?

**METHODS**

**Design:** Randomized controlled trial (Heart Protection Study).

**Allocation:** {Concealed}†.\*

**Blinding:** Blinded {patients, clinicians, and data monitoring committee}†.\*

**Follow-up period:** 5 years.

**Setting:** {69 hospitals in the United Kingdom}†.

**Patients:** 20 536 patients (mean age 64 y, 75% men) who had nonfasting total cholesterol levels  $\geq 3.5$  mmol/L (135 mg/dL) and a medical history of cerebrovascular disease, coronary disease, other occlusive arterial disease, or diabetes or were men  $\geq 65$  years of age treated for hypertension. Exclusion criteria were clear indication or contraindication for statin therapy; stroke, myocardial infarction, or admission for angina in the previous 6 months; chronic liver disease; severe renal disease; inflammatory muscle disease; concurrent treatment with cyclosporin, fibrates, or high-dose niacin; child-bearing potential; severe heart failure; or

life-threatening conditions.

**Intervention:** Simvastatin, 40 mg daily ( $n = 10 269$ ), or matching placebo ( $n = 10 267$ ) for 5 years.

**Outcomes:** First major vascular events (i.e., nonfatal myocardial infarction or coronary death, stroke, or revascularization procedure). Secondary outcomes included total (nonfatal and fatal) stroke, presumed ischemic stroke, and hemorrhagic stroke.

**Patient follow-up:** {99.7% of patients had complete follow-up over 5 years}† (intention-to-treat analysis).

**MAIN RESULTS**

At 5 years, patients in the simvastatin group had greater reductions in first occurrence of major vascular events and stroke than did

patients in the placebo group (Table). The groups did not differ for hemorrhagic stroke (0.5% vs 0.5%).

**CONCLUSION**

Cholesterol lowering with simvastatin reduced stroke in patients with, or at high risk for, vascular disease.

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\*See Glossary.

†Heart Protection Study Collaborative Group. *Lancet*. 2002;360:7-22.

**Simvastatin vs placebo in patients at high risk for vascular disease†**

Outcomes at 5 years	Simvastatin	Placebo	RRR (95% CI)	NNT (CI)
$\geq 1$ major vascular event <sup>§</sup>	20%	25%	24% (19 to 28)	17 (15 to 21)
$\geq 1$ stroke	4.3%	5.7%	25% (15 to 34)	71 (52 to 117)
$\geq 1$ ischemic stroke	2.8%	4.0%	30% (19 to 40)	84 (63 to 133)

†Abbreviations defined in Glossary; NNT and CI calculated from control event rate and rate ratio in article.

<sup>§</sup>Nonfatal myocardial infarction or coronary death, stroke, or revascularization procedure.

**COMMENTARY**

The primary results of the impressive Heart Protection Study were published in 2002 and showed that simvastatin reduced the risk for major vascular events in patients at high risk (1). In the current subgroup analysis, more complete data are provided on the effect of therapy on risk for stroke in the overall cohort and on major vascular events in the subgroup with cerebrovascular disease at study entry. Subgroup analyses have rightly earned a bad reputation for producing findings of questionable significance; however, this analysis confirms the findings of the overall study and is less susceptible to bias. The investigators are asking the question, "Do results really apply to the specific diseases that were clustered together in the primary analysis?"

Other recent trials have also shown benefits of statins in reduction of stroke and cardiovascular events, independent of baseline cholesterol levels and with various other statins (2). Although this trial did not include patients with vascular events occurring within 6 months before randomization, statin initiation during hospitalization for ischemic stroke or transient ischemic attack of atherosclerotic origin is probably justified and may increase rates of long-term use. Results of the ongoing Stroke Prevention by Aggressive Reduction in Cholesterol Levels

(SPARCL) trial (3) may provide confirmation of the role of statins in the minority of patients with previous stroke but no history of cardiovascular disease, other occlusive arterial disease, or diabetes. In the meantime, we will be initiating statins in all patients who can tolerate them after atherothrombotic stroke or transient ischemic attack.

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**References**

- Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7-22.
- Corvol JC, Bouzamondo A, Sirol M, et al. Differential effects of lipid-lowering therapies on stroke prevention: a meta-analysis of randomized trials. *Arch Intern Med*. 2003;163:669-76.
- Sillescu H, Callahan AS. Design of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Study. The American Stroke Association 28th International Stroke Conference. February 13 to 15, 2003. [http://216.185.112.6/sc\\_includes/pdfs/CTP21.pdf](http://216.185.112.6/sc_includes/pdfs/CTP21.pdf).