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

METHODS

Design: randomised 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 UK]*

Patients: 20,536 patients (mean age 64 y, 75% men) who had non-fasting total cholesterol concentrations ≥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 ≥65 years of age treated for hypertension. Exclusion criteria: clear indication or contraindication for statin therapy; stroke, myocardial infarction, or admission for angiography 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 = 10,267), or matching placebo (n = 10,267) for 5 years.

Outcomes: first major vascular events (ie, non-fatal myocardial infarction or coronary death, stroke, or revascularisation procedure). Secondary outcomes included total (non-fatal and fatal) stroke, presumed ischaemic stroke, and haemorrhagic stroke.

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

*See glossary.

MAIN RESULTS

At 5 years, patients in the simvastatin group had greater reductions in first occurrence of major vascular events and stroke than patients in the placebo group (table). The groups did not differ for haemorrhagic stroke (0.5% v 0.5%).

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CONCLUSION

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

Abstract and commentary also appear in ACP Journal Club.

Commentary

The primary results of the impressive Heart Protection Study were published in 2002 and showed that simvastatin reduced the risk of major vascular events in patients at high risk. In the current subgroup analysis, more complete data are provided on the effect of therapy on risk of 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 concentrations and with various other statins. Although this trial did not include patients with vascular events occurring within 6 months before randomisation, statin initiation during hospitalisation for ischaemic stroke or transient ischaemic 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 (SPARC) trial 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 ischaemic attack.

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| Simvastatin (Sim) v placebo in patients at high risk of vascular disease* |
|------------------------|--------|------------------|------------------|----------|
| Outcomes at 5 years    | Sim    | Placebo RRR (95% CI) | NNT (CI) |
|                       |        |                   |                 |
| ≥1 major vascular event| 20%    | 25%               | 24% (19 to 28)  | 17 (15 to 21)|
| ≥1 stroke              | 4.3%   | 5.7%              | 25% (15 to 34)  | 71 (52 to 117)|
| ≥1 ischaemic 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.
†Non-fatal myocardial infarction or coronary death, stroke, or revascularisation procedure.