This Weeks Question:

For which of the following conditions has cholesterol-lowering been shown to possibly raise risk?

1. Myocardial infarction
2. Myocardial infarction in patients with moderate cholesterol levels
3. Ischemic stroke
4. Hemorrhagic stroke

Clinical Context

Elevated cholesterol levels can play an important role in cardiovascular disease, and lowering these levels has been proven to reduce cardiovascular morbidity and mortality, even among patients with moderate levels of hypercholesterolemia. Although data regarding the relationship between hypercholesterolemia and stroke are less robust, there is some suggestion that reducing cholesterol can reduce ischemic stroke. However, the authors of the current study note that this possible benefit must be weighed against some evidence suggesting that lowering cholesterol levels may increase the risk of hemorrhagic stroke, particularly among patients with elevated blood pressure.

Evidence from studies examining atherosclerotic disease outcomes has supported the use of statin drugs in the prevention of stroke. In a prospective trial by White and colleagues of 9,014 patients with coronary artery disease, pravastatin reduced the risk of ischemic stroke by 23%. The study, published in the August 2000 issue of the *New England Journal of Medicine*, also demonstrated that the risk of hemorrhagic stroke was low overall and not altered with pravastatin treatment.

The authors of the current study used a large community-based population sample to further elaborate the efficacy of statins in reducing the risk of cerebrovascular disease.

Study Highlights

- Patients were involved in the Heart Protection Study. All were between 40 and 80 years old and had cholesterol levels of at least 135 mg/dL. They also had a history of cerebrovascular disease, coronary artery disease, other arterial disease, diabetes, or hypertension. Patients were excluded from participation if they had a history of vascular event within 6 months of enrollment, chronic renal or liver disease, or severe congestive heart failure.

- Participants were randomized to receive either simvastatin 40 mg daily or matching placebo. They were followed for 5 years at several clinic visits during the first year, and then semi-annually.

- The main study outcome was the combined outcome of nonfatal myocardial infarction or coronary death, stroke, or any revascularization procedure. The authors of the current study paid particular attention to stroke, which was defined as a neurologic event lasting more than 24 hours. Subjects were also followed for transient ischemic attack, carotid events, cognitive function, and neuropathy.

- 20,536 high-risk patients were recruited to participate in the study, of whom 3,280 had a history of cerebrovascular disease. Of the subgroup with cerebrovascular disease, 63% had a history of stroke, and 46% had a history of transient ischemic attack.

- Compliance with simvastatin treatment was 85%. 17% of the placebo group started statin therapy during the intervention period.

- Simvastatin produced a 24% relative reduction in the first occurrence of nonfatal myocardial infarction or coronary death. The reduction of cardiovascular events was similar between study subgroups of patients with a history of cerebrovascular disease or other high-risk conditions (20% and 25%, respectively).

- The simvastatin group also had a 25% reduced overall rate of stroke compared with the placebo group. This effect on stroke was statistically significant by year 2 of the study. The positive effect of simvastatin

on stroke risk was limited to ischemic strokes; hemorrhagic strokes were rare and occurred at similar frequencies in both treatment groups.

- Of subjects with a previous history of stroke, simvastatin was not protective in preventing another stroke compared with placebo.

- A 39 mg/dL reduction in cholesterol level with simvastatin protected 14 of 1,000 subjects from stroke.

- The reduction in stroke was similar among patients with various atherosclerotic risk factors, including coronary disease and diabetes. The results were also significant for subjects with cholesterol levels as low as 100 mg/dL.

- Rates of carotid endarterectomy or angioplasty were twice as high in the placebo group compared with the simvastatin group. Simvastatin was particularly protective regarding these outcomes in subjects with a previous history of cerebrovascular disease.

- Episodes of transient cerebral ischemia were reduced by 17% in the simvastatin group compared with placebo.

- There was no difference between the placebo and simvastatin groups in cognitive function or neuropathy complications.

- Given that compliance with the study protocol was not 100% in either the simvastatin or placebo groups, the authors estimate that the relative risk reduction for stroke with simvastatin may be underestimated in the current study. They state that the relative risk reduction could be up to one third in subjects with perfect compliance.

Pearls for Practice

- Research has established cholesterol's effects in promoting cardiovascular disease, but its role in cerebrovascular disease, especially whether statins can improve cerebrovascular outcomes, is less clear.

- Simvastatin seems effective in reducing cerebrovascular outcomes in high-risk individuals. However, it may not be as effective in this regard in patients with a prior history of stroke.

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