

CLINICAL INQUIRIES

■ CLINICAL COMMENTARY:

When warfarin is started, aspirin should be stopped

The lack of evidence to support the combined use of aspirin and warfarin creates an excellent opportunity to remove an unnecessary drug from a patient's medication list. Patients who were taking aspirin for thrombosis prophylaxis occasionally develop atrial fibrillation. Many patients who take aspirin for prophylaxis do so because they are already at moderate to high risk for embolic stroke. The onset of atrial fibrillation in these patients appropriately leads to the initiation of warfarin. At the time of warfarin initiation, the aspirin should be stopped. By stopping the aspirin at the initiation of the warfarin, one can reduce the number of medications that the patient must take, avoid the interactions of aspirin and warfarin, and eliminate the side effects of the aspirin.

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Do statins reduce the risk of stroke?

■ EVIDENCE-BASED ANSWER

HMG Co-A reductase inhibitors (statins) are effective for primary prevention of ischemic stroke in people who have a history of occlusive artery disease, coronary artery disease, or diabetes without history of cerebrovascular disease (strength of recommendation [SOR]: **A**, based on 1 randomized controlled trial [RCT]).

Statins reduce the risk of ischemic stroke in hypertensive patients with multiple cardiovascular risk factors and nonfasting total cholesterol <250 mg/dL (SOR: **A**, based on RCT). Statins also reduce the risk of ischemic stroke for patients with coronary disease or equivalents (such as diabetes or peripheral artery disease), including patients who have a normal fasting lipid profile (SOR: **A**, based on RCT). For patients with ischemic stroke who have coronary disease, statins prevent recurrent ischemic stroke; evidence is conflicting about whether this benefit is proportional to initial cholesterol levels (SOR: **A**, systematic review). Statins do not prevent hemorrhagic stroke (SOR: **A**, based on RCTs).

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Statins reduce the risk of ischemic stroke for patients with coronary disease or equivalents

■ EVIDENCE SUMMARY

We found no studies evaluating statins for the primary prevention of stroke. An observational study of 433 patients with ischemic stroke found that patients who were taking statins before hospital admission more often had better outcomes (51%) than those who were not taking statins (38%). However, the groups differed in many respects.¹ Many coronary event prevention and treatment trials using statins include the risk of primary and recurrent ischemic stroke as secondary endpoints for patients with high cardiac risk.

Primary prevention of stroke in vascular disease. The Heart Protection Study followed 20,536 patients in the United Kingdom (aged 40–80 years), 3280 with a history of cerebrovascular disease (defined as nondisabling stroke, transient cerebral ischemic attack, or carotid endarterectomy or angioplasty) and 17,256 with other occlusive arterial disease, coronary artery disease, or diabetes. Patients were randomized to receive either simvastatin 40 mg or placebo for an average of 5 years. The endpoint was major vascular events: myocardial infarction, stroke of any type, and revascularization procedure.

Simvastatin reduced the combined risk of nonfatal or fatal ischemic stroke for patients with no history of cerebrovascular disease (3.2% for simvastatin vs 4.8% with placebo; relative risk reduction=33%, number needed to treat [NNT]=63; $P=.0001$).² As noted in other well-done studies, the Heart Protection Study showed no difference in the number of hemorrhagic strokes between treatment and placebo groups. There were 3500 subjects with pretreatment low-density lipoprotein (LDL) cholesterol <100 mg/dL; lowering LDL to 65 mg/dL reduced major vascular event risk by about 25%.³

Hypertension with multiple cardiovascular risk factors and cholesterol <250 mg/dL. The ASCOT-LLA study compared atorvastatin with

placebo in 10,305 hypertensive Caucasian patients with multiple cardiovascular risk factors and a total nonfasting cholesterol of 250 mg/dL (6.5 mmol/L) or less. Patients were aged 40 to 79 years and had at least 3 other cardiovascular risk factors (left ventricular hypertrophy, abnormal electrocardiogram, type 2 diabetes, peripheral artery disease, stroke or transient ischemic attack, male sex, age >55 years, proteinuria or microalbuminuria, smoking, family history of premature coronary heart disease). The study was stopped early at a median of 3.3 years because atorvastatin significantly reduced cardiac events. Atorvastatin also significantly reduced ischemic strokes when compared with placebo (relative risk [RR]=0.73, 95% confidence interval [CI], 0.56–0.96; $P=.024$). This study did not differentiate between first or second stroke. The NNT was 155.⁴

Ischemic stroke and coronary disease. The LIPID trial randomized 9014 patients with a history of acute coronary syndromes and total cholesterol of 150 to 270 mg/dL (4 to 7 mmol/L) to either pravastatin or placebo and followed them for 6 years. Among the 350 patients with prior ischemic stroke, there were 388 new ischemic strokes over the course of the study. When adjusted for risk factors (atrial fibrillation, history of cerebrovascular accident, diabetes, hypertension, cigarette smoking, body mass index, and male sex), pravastatin reduced recurrent ischemic stroke by 21% relative to placebo ($P=.024$). The reduction was not modified by baseline lipid level.⁵

A meta-analysis of 15 randomized placebo-controlled trials using various statins (32,684 participants) assessed the risk of strokes for patients with a history of coronary disease. Among patients who had cerebrovascular disease, statins significantly reduced recurrent ischemic stroke (RR=0.74; 95% CI, 0.64–0.86). One recurrence of ischemic stroke would be prevented for every 110 coronary disease patients treated with a statin. Achieving final total cholesterol <232 mg/dL correlated with reduced

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risk of recurrent stroke.⁶ Three of the studies evaluated primary prevention of stroke and did not show a significant risk reduction (RR=0.85; $P=.4$). Statins did not reduce the rate of hemorrhagic stroke or fatal strokes.

Risks of statins. In 1 study involving 35,000 participants and 158,000 person-years of observation, there were 8 cases of rhabdomyolysis in the treatment groups vs 5 in the placebo groups.⁷ Forty-three deaths attributed to statin therapy have been reported to the Food and Drug Administration from 1987 to 2001, or 1 per million person-years of use. The Heart Protection Study found simvastatin and placebo users reported myopathy or muscle pain at the same annual rate of 0.01%.

■ RECOMMENDATIONS FROM OTHERS

We found no recommendations specifically regarding the use of statins to prevent stroke. However, the *Third Report of the National Cholesterol Education Program, Adult Treatment Panel III* (NCEP-ATP III) describes symptomatic carotid artery disease as a coronary heart disease risk equivalent and recommends therapy to reduce the LDL below 100 mg/dL.⁸

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■ CLINICAL COMMENTARY:

Statins prevent cerebrovascular accidents and have low adverse event rates

Statins are effective for primary and tertiary cardiovascular disease prevention. For those with vascular disease or significant risks, statins prevent cerebrovascular accidents and have low adverse event rates.

While no evidence is available about primary prevention of cerebrovascular accidents for those at lower risk, in practice statins are often appropriately initiated. NCEP-ATP III,⁸ the key guideline on when to start statins, is based more on cardiac benefits. Most studies evaluating statins use a triple outcome of mortality, myocardial infarction, or cerebrovascular accident. Since myocardial infarction is more common than the other adverse endpoints, there is a greater demonstrated cardioprotective effect (prevention of myocardial infarction: NNT=95; prevention of cerebrovascular accidents: NNT=735).⁹ However, regardless of whether the benefits are cardiac or cerebrovascular, statins will prevent disease for many patients.

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