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## HIGH-DOSE ATORVASTATIN AFTER STROKE OR TRANSIENT ISCHEMIC ATTACK

Statins reduce the incidence of strokes among patients at increased risk for cardiovascular disease; whether they reduce the risk of stroke after a recent stroke or transient ischemic attack (TIA) remains to be established. This study randomly assigned 4731 patients who had a stroke or TIA within one to six months before study entry, had low-density lipoprotein (LDL) cholesterol levels of 100 to 190 mg per deciliter (2.6 to 4.9 mmol per liter), and had no known coronary heart disease to doubleblind treatment with 80 mg of atorvastatin per day or placebo. The primary end point was a first nonfatal or fatal stroke.

The mean LDL cholesterol level during the trial was 73 mg per deciliter (1.9 mmol per liter) among patients receiving atorvastatin and 129 mg per deciliter (3.3 mmol per liter) among patients receiving placebo. During a median follow-up of 4.9 years, 265 patients (11.2 percent) receiving atorvastatin and 311 patients (13.1 percent) receiving placebo had a fatal or nonfatal stroke (5-year absolute reduction in risk, 2.2 percent). The atorvastatin group had 218 ischemic strokes and 55 hemorrhagic strokes, whereas the placebo group had 274 ischemic strokes and 33 hemorrhagic strokes. The five-year absolute reduction in the risk of major cardiovascular events was 3.5 percent. The overall mortality rate was similar, with 216 deaths in the atorvastatin group and 211 deaths in the placebo group ( $P=0.98$ ), as were the rates of serious adverse events. Elevated liver enzyme values were more common in patients taking atorvastatin.

In patients with recent stroke or TIA and without known coronary heart disease, 80 mg of atorvastatin per day reduced the overall incidence of strokes and of cardiovascular

events, despite a small increase in the incidence of hemorrhagic stroke.

*Amarenco P, Bogousslavsky J, Callahan A 3rd, Goldstein LB, Hennerici M, Rudolph AE, Silleesen H. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med. 2006 Aug 10;355(6):549-59.*

### Comment:

It has been shown that using statins in patients with known or suspected CAD can reduce the risk of CVA/TIA. What has not been known is whether aggressive statin use in patients with recent CVA/TIA can decrease further events. This study demonstrated quite convincingly that aggressive statin use can decrease further events. Despite a small increase in the frequency of hemorrhagic CVA, the use of 80mg of atorvastatin decreased the overall incidence of CVA/TIA by 20%. Clearly, this patient population, just like every other group with atherosclerotic vascular disease receives significant benefit from aggressive statin therapy. Again, the question is not "Who benefits?" but rather "Who doesn't?"—**M. Nicholas Burke, MD**, Senior Consulting Cardiologist, Minneapolis Heart Institute.

## MIGRAINE AND RISK OF CARDIOVASCULAR DISEASE IN WOMEN

Migraine with aura has been associated with an adverse cardiovascular risk profile and prothrombotic factors that, along with migraine-specific physiology, may increase the risk of vascular events. Although migraine with aura has been associated with increased risk of ischemic stroke, an association with cardiovascular disease (CVD) and, specifically, coronary events remains unclear.

The study's objective was to evaluate the association between migraine with and without aura and subsequent risk of overall and specific CVD. A prospective cohort study of 27,840 US women aged 45 years or older who were participating in the Women's Health Study, were free of CVD and angina at study entry (1992-1995), and who had information on self-reported migraine and aura status, and lipid measurements. This report is based on follow-up data through March 31, 2004.

The primary outcome measure was the combined end point of major CVD (first instance of nonfatal ischemic stroke, nonfatal myocardial infarction, or death due to ischemic CVD); other measures were first ischemic stroke, myocardial infarction, coronary revascularization, angina, and death due to ischemic CVD.

At baseline, 5125 women (18.4%) reported any history of migraine; of the 3610 with active migraine (migraine in the prior year), 1434 (39.7%) indicated aura symptoms. During a mean of 10 years of follow-up, 580 major CVD events occurred. Compared with women with no migraine history, women who reported active migraine with aura had multivariable-adjusted hazard ratios of 2.15 (95% confidence interval [CI], 1.58-2.92;  $P < .001$ ) for major CVD, 1.91 (95% CI, 1.17-3.10;  $P = .01$ ) for ischemic stroke, 2.08 (95% CI, 1.30-3.31;  $P = .002$ ) for myocardial infarction, 1.74 (95% CI, 1.23-2.46;  $P = .002$ ) for coronary revascularization, 1.71 (95% CI, 1.16- 2.53;  $P = .007$ ) for angina, and 2.33 (95% CI, 1.21-4.51;  $P = .01$ ) for ischemic CVD death. After adjusting for age, there were 18 additional major CVD events attributable to migraine with aura per 10 000 women per year. Women who reported active migraine without aura did not have increased risk of any vascular events or angina.

In this large, prospective cohort of women, active migraine with aura was associated with increased risk of major CVD, myocardial infarction, ischemic stroke, and death due to ischemic CVD, as well as with coronary revascularization and angina. Active migraine

without aura was not associated with increased risk of any CVD event.

*Kurth T, Gaziano JM, Cook NR, Logroscino G, Diener HC, Buring JE. Migraine and risk of cardiovascular disease in women. JAMA. 2006 Jul 19;296(3):283-91.*

### **Comment:**

In this large prospective study, migraine with aura was associated with a two-fold risk of major cardiovascular disease, myocardial infarction, ischemic stroke and death due to MI. Migraine with aura was also associated with a 1.7-fold increased risk of coronary revascularization. These risks remained significant after adjusting for the major cardiovascular risk factors. Interestingly, these associations did not hold for the "common migraine" (migraine without aura).

The reason for the association between migraines with aura and cardiovascular disease is unclear. The study did not detail use of triptans and ergot alkaloids—vasoactive medications which could potentially increase the risk of cardiovascular disease. These medications, however, are used equally for migraines with and without aura, which makes vasoactive medications a less likely explanation. A possible explanation of the association between aura and cardiovascular disease may be a polymorphism in the methyltetrahydrofolate reductase gene (C677T) which is associated with moderate elevation of homocysteine, as well as increased risk of cardiovascular disease. This same gene is overexpressed in migraine with aura, but not in migraine without aura. Whether or not anti-platelet or statin treatment or homocysteine lowering therapy is indicated for patients who have migraine with aura merits further study.—  
**E. Grey, MD**, Senior Consulting Cardiologist, Minneapolis Heart Institute.

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<b>EDITOR-IN-CHIEF</b>	<b>MANAGING EDITOR</b>	<b>CONTRIBUTING EDITOR</b>
M. Nicholas Burke, MD	Michelle Croteau	E. Grey, MD
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