

# American Family Physician

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### FPIN's Clinical Inquiries

#### Warfarin for Prevention of Ischemic Stroke Recurrence?

##### Clinical Question

Does anticoagulation with warfarin (Coumadin) prevent stroke recurrence in a patient with a history of noncardioembolic ischemic stroke?

##### Evidence-Based Answer

There is no evidence that anticoagulation with warfarin, initiated after a noncardioembolic ischemic stroke, significantly reduces stroke recurrence. Furthermore, anticoagulation significantly increases the risk of fatal and nonfatal hemorrhagic stroke and extracranial hemorrhage in these patients.<sup>1-3</sup> However, warfarin clearly is indicated for patients who have embolic strokes caused by underlying conditions such as atrial fibrillation or myxoma. (Strength of recommendation: A)

##### Evidence Summary

Evidence-based guidelines recommend antiplatelet agents (e.g., aspirin) for most patients with noncardioembolic stroke and recommend warfarin for those with cardioembolic stroke. Researchers have wondered whether more aggressive anticoagulation also would benefit patients with noncardioembolic stroke.

A Cochrane systematic review<sup>1</sup> identified 11 randomized controlled trials (RCTs) with a combined 2,487 patients randomly assigned to receive anticoagulation (with warfarin or one of its analogues) or placebo after a presumed noncardioembolic ischemic stroke or transient ischemic attack. Nine of these trials were small and occurred before 1980 when computed tomography was not used routinely. Therefore, some initial hemorrhagic strokes possibly were included in the studies, and the lack of International Normalization Ratio (INR) monitoring of anticoagulation therapy in some studies may have contributed to an increased incidence of hemorrhage. The authors concluded that anticoagulation did not prevent recurrent ischemic stroke but that there was a significant increase in fatal intracranial hemorrhage (odds ratio [OR], 2.54; 95% confidence interval [CI], 1.19 to 5.45; number needed to harm [NNH] = 50) and major fatal and nonfatal extracranial hemorrhage (OR, 3.43; 95% CI, 1.94 to 6.08; NNH = 20).

Two studies not included in the above review have addressed some of these methodologic shortcomings. A large double-blinded RCT<sup>2</sup> compared warfarin with aspirin for the prevention

of recurrent ischemic stroke in 2,206 patients with a previous noncardioembolic stroke. The warfarin dosage was adjusted to produce an INR of 1.4 to 2.8, and aspirin was given at a fixed dosage of 325 mg per day. After two years there was no difference between warfarin and aspirin in the prevention of recurrent ischemic stroke or death or in the rate of major hemorrhage. The rate of recurrent stroke was 17.8 percent in patients receiving warfarin and 16.0 percent in those receiving aspirin. However, in the warfarin group, the median daily INR was 1.9, and 16.3 percent of the daily INR values were less than 1.4. It is possible that any favorable or unfavorable treatment effects of warfarin were underestimated.

A well-designed, double-blinded, multicenter RCT<sup>3</sup> compared warfarin with aspirin in 569 patients with symptomatic intracranial arterial stenosis. In this study, patients older than 40 years with transient ischemic attack or stroke caused by a moderate to severe stenosis (50 to 99 percent obstruction) of a major intracranial artery were randomly assigned to receive warfarin (with a target INR of 2 to 3) or 1,300 mg of aspirin per day. The primary end point was recurrent ischemic stroke, brain hemorrhage, or death from vascular causes other than stroke. With a mean follow-up period of 1.8 years, there was no difference in the likelihood of recurrent ischemic stroke, brain hemorrhage, or death from vascular causes other than stroke (21.1 percent in the aspirin group and 21.8 percent in the warfarin group). There also was no difference in the likelihood of recurrent ischemic stroke, ischemic stroke in the territory of the stenotic artery, and disabling or fatal ischemic stroke. However, compared with aspirin, warfarin significantly increased the risk of death (9.7 versus 4.3 percent;  $P = .02$ ; NNH = 19) and major bleeding (8.3 versus 3.2 percent;  $P = .01$ ; NNH = 20). Therefore, warfarin is no more effective than aspirin in preventing recurrent stroke but causes a significantly higher number of adverse events.

table 1

Common Cardiac and Noncardiac Conditions  
Associated with Increased Risk of Embolism  
Cardiac

Acute and subacute bacterial endocarditis

Chronic atrial fibrillation

Congenital heart defect (patent foramen ovale)

Complication of cardiac surgery

Myxoma

Recent myocardial infarction with mural  
thrombus

Valve prosthesis

Valvular diseases (mitral stenosis, prolapsed

## Recommendations from Others

The guideline for medical treatment for stroke prevention from the American College of Physicians<sup>4</sup>; the report of the Joint Stroke Guideline Development Committee of the American Academy of Neurology and the American Stroke Association<sup>5</sup>; the Seventh American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy<sup>6</sup>; and the guideline for prevention of stroke in patients with ischemic stroke or transient ischemic attack from the American Heart Association, American Stroke Association, and the American Academy of Neurology<sup>7</sup> all recommend aspirin rather than warfarin to prevent recurrent stroke after a presumed noncardioembolic ischemic stroke. The latter guideline<sup>7</sup> suggests that warfarin is an option in patients with a prothrombotic disorder, however.

mitral valve)

Noncardiac

Atherosclerosis of aorta and carotid arteries

Dissections and fibromuscular dysplasia of carotid and vertebral arteries

Fat, tumor, or air embolism

Thrombosis of the pulmonary veins

## Clinical Commentary

Making a clinical distinction between cardioembolic and noncardioembolic ischemic stroke can be difficult when no obvious risks or sources of embolism can be identified. The symptoms and signs of stroke are similar with embolic and thrombotic causes. However, the onset and progression of an embolic stroke generally are more rapid and without warning episodes. Therefore, it is imperative that physicians identify the presence of conditions that may increase the risk of embolism (Table 1) and initiate oral anticoagulation when cardioembolic stroke is suspected. For other noncardioembolic ischemic strokes, antiplatelet agents are recommended.

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Clinical Inquiries provides answers to questions submitted by practicing family physicians to the Family Physicians Inquiries Network (FPIN). Members of the network select questions based on their relevance to family medicine. Answers are drawn from an approved set of evidence-based resources and undergo peer review. The strength of recommendations and the level of evidence for individual studies are rated using criteria developed by the Evidence-Based Medicine Working Group ([http://www.cebm.net/levels\\_of\\_evidence.asp](http://www.cebm.net/levels_of_evidence.asp)).

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