

## Does combining aspirin and warfarin decrease the risk of stroke for patients with nonvalvular atrial fibrillation?

### ■ EVIDENCE-BASED ANSWER

Adjusted-dose warfarin (international normalized ratio [INR]=2.0–3.0) remains the most efficacious antithrombotic regimen for the primary and secondary prevention of cardioembolic stroke in high-risk patients with nonvalvular atrial fibrillation (NVAF) (strength of recommendation [SOR]: **A**, based on randomized controlled trials).

Aspirin therapy at a dose of 75 to 325 mg reduces the risk of stroke to a lesser degree and may be useful for low-risk patients with NVAF or patients at high risk for bleeding (SOR: **A**, based on randomized controlled trials).

Combination therapy with low, fixed-dose warfarin (1–2 mg) and aspirin has not been shown to be superior to aspirin therapy alone. Moreover, this combination appears to be inferior to adjusted-dose warfarin (SOR: **A**, based on randomized controlled trials). To date, no clinical trials have investigated the efficacy and safety of combining adjusted-dose warfarin and aspirin for the prevention of stroke from NVAF.

### ■ EVIDENCE SUMMARY

Thromboprophylaxis with warfarin for patients with NVAF has been studied in 5 major clinical trials.<sup>1–5</sup> Pooled analysis with more than 2900 patients revealed an annual stroke risk of 4.5% for control patients and 1.4% for patients receiving adjusted-dose warfarin (number needed to treat [NNT] for 1 year=32).<sup>6</sup> Studies comparing aspirin with placebo for treatment of NVAF are less robust and have heterogeneous results. Combined data from the Atrial Fibrillation Aspirin Anticoagulation Study (AFASAK-1),<sup>1</sup> the European Atrial Fibrillation

Trial,<sup>7</sup> and the Stroke Prevention in Atrial Fibrillation (SPAF) I studies<sup>2</sup> revealed a small but statistically significant reduction in stroke rates (relative risk reduction [RRR]=21%; 8.1% vs 6.3% annual stroke rate; NNT=55), with no increase in major bleeding risk.<sup>8</sup>

The SPAF III investigators further compared adjusted-dose warfarin with low-intensity, fixed-dose warfarin plus aspirin in high-risk patients with NVAF.<sup>9</sup> An interim analysis at 1.1 years revealed superiority in the reduction of ischemic strokes and systemic embolisms with adjusted-dose warfarin (7.9% vs 1.9% per year, respectively; NNT=16), which led to the trial's termination. Rates of major hemorrhage did not differ between treatment groups (2.4% per year with combination vs 2.1% per year with warfarin).

Two similar studies published in 1998 were terminated early, in light of the SPAF III results. The Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study<sup>10</sup> (AFASAK-2) completed 3 of the scheduled 6 years; it compared warfarin 1.25 mg/d, warfarin 1.25 mg/d plus aspirin 300 mg, aspirin 300 mg alone, and adjusted-dose warfarin (INR=2.0–3.0) to treat NVAF for patients with a median age of 74 years (range, 44–89). The cumulative stroke event rate after 1 year was 5.8% on fixed-dose warfarin, 7.2% on combination, 3.6% on aspirin, and 2.8% on adjusted-dose warfarin. The researchers concluded that while the difference was not statistically significant, adjusted-dose warfarin seemed superior to other treatments after 1 year.

In a similar fashion, Pengo et al<sup>11</sup> randomized patients with NVAF aged >60 years to fixed-dose (1.25 mg/d) or adjusted-dose warfarin (INR=2.0–3.0) to evaluate ischemic stroke rates and major bleeding. This trial enrolled 303 patients who were followed up for 14.5 months before discontinuation of the trial. The rate of ischemic stroke was significantly higher in the fixed-dose warfarin group compared with the adjusted warfarin group (3.7%

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TABLE

## ACCP Stroke Prevention Guidelines 2001

Atrial fibrillation stroke profile	Risk factors	Treatment guidelines
<b>High risk</b>	<i>One or more of the following:</i> Age 75 years History of hypertension Cerebrovascular accident/ transient ischemic attack Arterial thromboembolism Poor left ventricular systolic dysfunction (ejection fraction <40%) Rheumatic mitral valve disease or prosthetic heart valve 2 or more moderate risk factors	Warfarin (INR=2.5; range, 2–3)
<b>Moderate risk</b>	<i>No high risk factors and 1 of the following:</i> Age 65–74 years Diabetes Coronary artery disease	Warfarin (INR=2.5, range, 2–3) or Aspirin 325 mg/d
<b>Low risk</b>	<i>No high or moderate risk factors and:</i> Age <65 years	Aspirin 325 mg/d

INR, international normalized ratio

vs 0% per year; NNT=27). Major bleeds were more frequent in the adjusted warfarin group (2.6% vs 1% per year, number needed to harm=63). While the combined primary end-point did not show a significant benefit for adjusted-dose warfarin, this study suggests that fixed-dose warfarin does not protect against ischemic stroke in NVAf patients.

The intensity of warfarin therapy and stroke severity has recently been studied for patients with NVAf.<sup>12</sup> A subtherapeutic INR (<2.0) on the day of admission was independently associated with severe stroke (odds ratio=1.9; 95% confidence interval [CI], 1.1–3.4), and risk of death at 30 days (hazard ratio, 3.4; 95% CI, 1.1–10.1) compared with an INR of 2.0 or greater. Furthermore, an admission INR of 1.5–1.9 had a similar mortality rate (18%) as an INR of <1.5 (15%), and for those patients on aspirin (15%).

These findings further support the importance of achieving therapeutic INR goals for patients with NVAf.

#### ■ RECOMMENDATIONS FROM OTHERS

The American Heart Association, the American College of Cardiology,<sup>13</sup> and the American College of Chest Physicians (ACCP)<sup>14</sup> recommend adjusted-dose warfarin for nonvalvular atrial fibrillation patients at high risk for ischemic stroke. Risk stratification is a key component in order to maximize efficacy while minimizing bleeding risk.

The **Table** summarizes the ACCP guidelines for prevention of ischemic stroke based on patient risk factors.

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## ■ 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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