Adjusted-dose warfarin for atrial fibrillation reduced stroke risk better than low-dose warfarin plus aspirin

Stroke Prevention in Atrial Fibrillation Investigators. **Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial.** Lancet. 1996 Sep 7;348:633-8.

Objective
To compare the effectiveness of low-intensity, fixed-dose warfarin plus aspirin with conventional adjusted-dose warfarin in patients with atrial fibrillation who were at high risk for stroke.

Design
Randomized controlled trial (Stroke Prevention in Atrial Fibrillation [SPAF] III) that was stopped after a mean follow-up of 1.1 years.

Setting
20 clinical centers in North America.

Patients
1044 patients (mean age 72 y; 61% men) with current or recurrent nonvalvular atrial fibrillation and ≥ 1 thromboembolic risk factor. Exclusion criteria were prosthetic heart valves; mitral stenosis; other conditions that required anticoagulation therapy; or contraindication to aspirin or warfarin. No patients were lost to follow-up.

Intervention
521 patients were allocated to low-intensity, fixed-dose warfarin, 0.5 to 3.0 mg/d (to raise the international normalized ratio [INR] to between 1.2 and 1.5), plus aspirin, 325 mg/d. The fixed dose of warfarin was not adjusted unless the patient's INR exceeded 3.0 or bleeding occurred. 523 patients were allocated to adjusted-dose warfarin; the initial dose was based on the patient's age and then adjusted to stabilize the INR between 2.0 and 3.0.

Main outcome measures
Ischemic stroke, systemic embolism, transient ischemic attack, myocardial infarction, major hemorrhage, and death.

Main results
The mean INR in patients receiving combination therapy was 1.3 compared with 2.4 for those receiving adjusted-dose warfarin. 44 patients (7.9%) receiving combination therapy had an ischemic stroke or systemic embolism compared with 11 patients (1.9%) receiving adjusted-dose warfarin ($P < 0.001$). [This absolute risk difference of 6% means that for a mean of 1.1 years, 1 additional ischemic stroke or systemic embolism occurred for every 17 patients who received combination therapy (rather than adjusted-dose warfarin), 95% CI 11 to 27; the relative risk increase was 301%, CI 113% to 661%.]* Combination therapy also led to higher rates of disabling and fatal strokes than did therapy with adjusted-dose warfarin (5.6% vs 1.7%, $P < 0.001$). No difference existed between the treatment groups for rates of major hemorrhage (2% for each group) or vascular death.

Conclusion
Therapy with low-intensity, fixed-dose warfarin plus aspirin led to higher rates of ischemic stroke in patients with nonvalvular atrial fibrillation who were at high risk for thromboembolism than did therapy with adjusted-dose warfarin.

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*Numbers calculated from data in article.

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Commentary

Good evidence exists that adjusted-dose warfarin reduces the risk for stroke in patients with nonvalvular atrial fibrillation (1). However, because regular monitoring of the INR is required and because of the risk for hemorrhage, a safer alternative is desirable. Aspirin is safer and more convenient but less effective than warfarin (2, 3). This study was restricted to patients who had at least 1 risk factor for stroke in addition to atrial fibrillation. In these patients, the effects of low-intensity, fixed-dose warfarin plus aspirin were disappointing; the risk for stroke increased, and the risk for major hemorrhage was not reduced.

Patients who are at high risk for stroke stand to gain more from treatment than patients at low risk for stroke, and the SPAF III study confirms the benefit of adjusted-dose warfarin for these patients. Increasing evidence supports a target range of 2.0 to 3.0 for the INR. The risk for stroke rises steeply if the INR is < 2, and the risk for hemorrhage rises if it is > 4 (4). The SPAF III study shows that adding aspirin does not compensate for the reduced anticoagulation effect associated with a target INR < 1.5.

For patients who are at high risk for hemorrhage, the decision remains problematic. The rate of major hemorrhage in patients in the SPAF III study was low, and higher rates may occur in clinical practice. The relative ineffectiveness of combination therapy is likely to give clinicians a lower threshold for prescribing warfarin in these circumstances and a higher threshold for using aspirin.

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References

1. **Atrial Fibrillation Investigators.** Arch Intern Med. 1994;154:1449-57.
2. **Stroke Prevention in Atrial Fibrillation Investigators.** Lancet. 1994;343:687-91.
3. **European Atrial Fibrillation Trial Study Group.** Lancet. 1993;342:1255-62.
4. **Hylek EM, Skates SJ, Shechan MA, Singer DE.** N Engl J Med. 1996;335:540-6.