

Review: Antithrombotic agents prevent stroke in nonvalvular atrial fibrillation

Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med.* 1999 Oct 5;131:492-501.

QUESTION

How efficacious and safe are anticoagulants and antiplatelet agents for preventing stroke in patients with nonvalvular atrial fibrillation (AF)?

DATA SOURCES

Randomized controlled trials were identified by searching MEDLINE (1966 to 1999), making contact with the Cochrane Collaboration Stroke Review Group and Antithrombotic Trialists Collaboration, and contacting experts.

STUDY SELECTION

Trials were included if they evaluated long-term (> 3 mo) use of antithrombotic agents in patients with nonvalvular AF. The exclusion criterion was AF associated with prosthetic cardiac valves or mitral stenosis.

DATA EXTRACTION

Data were extracted on patient numbers, follow-up duration, agents studied, type of prevention (primary or secondary), and outcomes (all-cause mortality, stroke, ischemic stroke, intracranial hemorrhage, and major extracranial hemorrhage).

MAIN RESULTS

16 trials (9874 patients) met the inclusion criteria. 10 studies evaluated warfarin. On

average, the 1-year risk for stroke in the placebo group was approximately 5% in the primary prevention studies and 12% in the secondary prevention studies. All agents were more effective than placebo at reducing the incidence of stroke: adjusted-dose warfarin (6 trials, 2900 patients, relative risk reduction [RRR] 62%, 95% CI 48% to 72%), aspirin (6 trials, 3119 patients, dose range 50 to 1300 mg/d, RRR 22%, CI 2% to 38%), and all antiplatelet agents (6 trials, 3337 patients, most of whom were taking aspirin; RRR 24%; CI 7% to 39%). Adjusted-dose warfarin was more effective than aspirin for reducing stroke (RRR 36%, CI 14% to 52%). Warfarin was associated with more intracranial (0.3% vs 0.1%/y) and major extracranial hemorrhages than placebo (0.6%/y vs 0.3%/y). Similar increases in the rate of hemorrhage were seen when warfarin was compared with aspirin but not when aspirin was compared with placebo. Comparisons of other agents (10 studies) show few outcome events or adverse effects and inconclusive results. The absolute benefit of each intervention depends on the baseline risk of certain groups (e.g., primary vs secondary prevention, individual patients). Estimates of the number needed to treat (NNT) to prevent 1 additional stroke at 1 year for

warfarin compared with placebo were 37 for primary prevention and 12 for secondary prevention. For aspirin compared with placebo, estimated NNTs were 67 for primary prevention and 40 for secondary prevention; for warfarin compared with aspirin, estimated NNTs were between 42 and 250 for primary prevention, depending on the underlying risk for stroke, and 21 for secondary prevention.

CONCLUSIONS

Antithrombotic agents are more effective at preventing stroke in patients with atrial fibrillation than is placebo. Warfarin is more effective than aspirin. The balance of benefit and risk between warfarin and aspirin depends on the underlying risk for stroke and hemorrhage in each patient.

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COMMENTARY

The excellent meta-analysis by Hart and colleagues is the largest to date and provides us with clear data on the size of the risk reduction with warfarin and aspirin in primary and secondary prevention of stroke in AF. It reassures us that intracranial and major extracranial bleeding rates are low and do not offset the benefits of warfarin. Warfarin reduced mortality (RRR 26%, CI 4% to 43%) more than did placebo, even though 20% of patients discontinued the drug.

This study underscores the need for tailoring antithrombotic therapy to a patient's risk for stroke. Because aspirin had no effect on disabling stroke, it is important clinically to temper use of aspirin in patients with high risk for stroke. Stroke subtype may also be important when deciding on treatment: Approximately 65% of strokes associated with AF are cardioembolic, and aspirin is less effective than warfarin in reducing cardioembolic stroke (1). Greater risk reductions are possible with warfarin in patients who have had a stroke, in women (2), and if cardioembolic stroke risk is high (e.g., presence of echocardiographic left ventricular systolic dysfunction) (3).

Elderly patients with hypertension should receive warfarin if they have atrial fibrillation. Clinicians fear hemorrhage in this group,

despite the low rates found in this meta-analysis. These patients are at great risk for stroke and hemorrhage. Target international normalized ratio (INR) ranges in the studies analyzed were often wide and reached 4.5. Because approximately 30% of the INRs are typically outside the target range, use of tighter INR ranges or a single-point INR target, such as 2.5, and wider use of computerized dosing algorithms should improve anticoagulation control and safety.

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3. Echocardiographic predictors of stroke in patients with atrial fibrillation: a prospective study of 1066 patients from 3 clinical trials. *Arch Intern Med.* 1998;158:1316-20.