CME

Antithrombotic therapy in atrial fibrillation

ALEXANDER G.G. TURPIE, MD
STUART J. CONNOLLY, MD

OBJECTIVE To review the evidence for antithrombotic therapy in patients with nonrheumatic atrial fibrillation.

QUALITY OF EVIDENCE Five primary prevention trials and one secondary prevention trial compare antithrombotic therapy with placebo or no treatment. Two trials also determine the efficacy and safety of acetylsalicylic acid.

MAIN FINDINGS Warfarin reduces the risk of stroke by 68%. The effect is consistent in all identifiable groups of patients with nonrheumatic atrial fibrillation, except patients at serious risk of hemorrhage. The absolute benefit of anticoagulants varies among patients because of markedly different inherent risk of stroke among patient subgroups.

CONCLUSIONS Anticoagulant therapy should be considered for all patients with atrial fibrillation. Oral anticoagulant therapy is more effective than ASA in reducing the risk of stroke among patients with nonrheumatic atrial fibrillation.

OBJECTIF Passer en revue les preuves à l'appui de la thérapie antithrombotique chez les patients porteurs d'une fibrillation auriculaire non rhumatismale.

QUALITÉ DES PREUVES Cinq essais de prévention primaire et un essai de prévention secondaire comparent la thérapie antithrombotique au placebo ou à l'absence de traitement. De plus, deux essais déterminent l'efficacité et l'innocuité de l'acide acétylsalicylique (AAS).

PRINCIPAUX RÉSULTATS La warfarine réduit de 68 % le risque d'accident vasculaire cérébral. Cet effet est demeuré constant dans tous les groupes identifiables de patients porteurs d'une fibrillation auriculaire non rhumatismale, sauf chez les patients à risque sérieux d'hémorragie. L'avantage absolu des anticoagulants est variable selon les sous-groupes de patients puisque ceux-ci présentent des différences marquées en termes de risque inhérent d'accident vasculaire cérébral.

CONCLUSIONS On devrait considérer l'anticoagulothérapie chez tous les patients porteurs d'une fibrillation auriculaire. L'anticoagulothérapie orale est plus efficace que l'AAS pour réduire le risque d'accident vasculaire cérébral chez les patients porteurs d'une fibrillation auriculaire.

Can Fam Physician 1996;42:1341-1345.

Dr Turpie *is a Professor of Medicine and* **Dr Connolly** *is a Professor in the Faculty of Health Sciences at McMaster University in Hamilton, Ont.* **Dr Turpie** *is an Internist and* **Dr Connolly** *is in Cardiology at Hamilton Civic Hospitals, General Division.*

THE ROLE OF ANTITHROMBOTIC therapy in preventing stroke in patients with atrial fibrillation (AF) has been addressed in several recent, randomized, clinical trials.[1-7] All the studies evaluated oral anticoagulant therapy, and several evaluated acetylsalicylic acid. These trials provide considerable information on the efficacy of these two treatments for preventing stroke, systemic embolism, myocardial infarction, and vascular death; give a reliable estimate of the risk of hemorrhage; and allow assessment of the relative benefits of anticoagulation and ASA therapy.

Primary prevention trials

Five randomized, primary prevention trials compared antithrombotic therapy with placebo or no treatment in patients with nonrheumatic AF. These include the Atrial Fibrillation, Aspirin, Anticoagulation Study from Copenhagen (AFASAK),[1] the Stroke Prevention in Atrial Fibrillation (SPAF) study,[2] the Boston Area Anticoagulation Trial in Atrial Fibrillation (BAATAF),[3] the Canadian Atrial Fibrillation Anticoagulation (CAFA) trial,[4] and the Veteran Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation study (SPINAF).[5] Patients with AF secondary to

← FOR PRESCRIBING INFORMATION SEE PAGE 1382

rheumatic heart disease were excluded from these trials because data from the Framingham study,[6] indicating a very high relative risk of stroke in such patients, which was reduced with anticoagulants, was generally accepted. A few patients (6%) in the primary prevention trials had had strokes or transient ischemic attacks (TIA).

All trials evaluated the safety and efficacy of warfarin, which was administered double-blind in two of the studies[4,5] and open-label in three.[1-3] Two trials used the International Normalized Ratio (INR) (target range 2.5:4.0 and 2.0:3.0) and three used the prothrombin time ratio (PT) (target range 1.3:1.8 and 1.2:1.5) to regulate anticoagulant therapy. Two compared ASA to placebo using two different doses of ASA (75 mg/d[1] and 325 mg/d[2]). Patients in the five trials were similar. Patients at high risk of bleeding were excluded from the anticoagulation comparison in all studies. Stroke was the primary outcome measure in all of the trials. Patient enrolment per study ranged from 378 to 671 for the anticoagulant therapy comparisons and from 672 to 1120 for the ASA comparisons.

Secondary prevention trial

The European Atrial Fibrillation Trial (EAFT)[7] was a secondary prevention, placebo-controlled trial of oral anticoagulation or ASA in AF patients with prior TIA or minor ischemic stroke. Patients at low risk of hemorrhage were randomized to open-label anticoagulant (INR 2.5:4.0) or to double-blind ASA (300 mg/d) or placebo. Patients at high risk for bleeding were randomized to double-blind ASA (300 mg/d) or placebo.

Comparative trial

The Stroke Prevention in Atrial Fibrillation (SPAF II) trial[8] was designed specifically to compare the relative efficacy and safety of oral anticoagulation (PT ratio 1.3:1.8) and ASA (325 mg/d) in nonrheumatic AF patients. The SPAF II, a continuation of SPAF, studied 416 patients originally randomized in SPAF and 419 additional patients. Patients were stratified according to age, 75 years or younger (715 patients) and older than 75 years (385), to determine the relative safety and efficacy of the two treatments for the elderly.

Efficacy of antithrombotic therapy

Warfarin. All five primary prevention trials and the secondary prevention trial compared anticoagulation to placebo and showed a reduction in the incidence of stroke and systemic embolism with warfarin. *Table 1* shows results of a meta-analysis of the five primary prevention trials.[9] Overall, anticoagulation resulted in a 68% reduction (from 4.5% to 1.4%) in all strokes per year ($P < 0.001$), an absolute reduction of three strokes per 100 patients in each treatment year. Major strokes with residual deficit were also reduced by 68% with anticoagulants, but because they accounted for less than half of all strokes, the absolute reduction of severe strokes was only 1.4 events per 100 patients during each treatment year. Mortality from any cause was reduced by 33% with anticoagulants (from 5.4% to 3.6% per year, $P < 0.01$), and the frequency of the combined adverse outcome of stroke, systemic embolism, or death was reduced from 9.8% to 5.0% per year ($P = 0.001$), an absolute reduction of 4.8 events per 100 patients during each treatment year.

The EAFT included patients who had had TIAs or minor strokes and reported a 12% per year risk of stroke with placebo. This rate was reduced by 66% to 4% per year with oral anticoagulants ($P < 0.001$), an absolute reduction of eight strokes per 100 patients for each treatment year. The composite outcome of stroke, systemic embolism, myocardial infarction, or vascular death was reduced in the EAFT from 17% to 8% per year ($P = 0.001$) with warfarin, a relative risk reduction of 47%.

In the primary prevention trials, 6% of the patients had had strokes or TIAs, identified as the most potent risk factor for subsequent stroke in the meta-analysis.[9] The annual stroke rate in patients with prior stroke or TIA in the primary prevention trials was 11.7% with placebo and 5.1% with warfarin, a reduction of 6.6% events per year, consistent with the results of the EAFT. Several other independent risk factors for stroke were identified in the meta-analysis: age, diabetes, hypertension, and ischemic heart disease.[9] The relative benefit of warfarin was quantitatively similar in all subgroups compared in the meta-analysis, but the absolute

benefit of anticoagulation for low-risk patients, such as those younger than 65 without risk factors for stroke, was small.[9]

Warfarin benefited a select population of AF patients; most primary prevention trials carefully excluded patients identified as high risk for hemorrhage, including the elderly and patients with a history of bleeding, uncontrolled hypertension, use of nonsteroidal anti-inflammatory drugs, low hemoglobin count, or alcoholism. The studies used different levels of anticoagulation so the exact intensity is not known precisely because some used the PT ratio rather than the INR to monitor anticoagulant response. However, the target INR range estimated from the PT ratios reported was most likely from a low of 1.4:2.7 to a high of 2.5:4.0. The studies all showed similar efficacy for warfarin.

We conclude that warfarin reduces the risk of stroke by 68% and that the effect is consistent across all identifiable groups of patients with nonrheumatic AF, except patients at serious risk of hemorrhage. The absolute benefit of anticoagulants varies among patients due to markedly different inherent risk of stroke among patient subgroups.

Acetylsalicylic acid. Two of the primary prevention trials, AFASAK and SPAF, and the EAFT evaluated ASA against placebo, each using a different dose (AFASAK 75 mg/d, EAFT 300 mg/d, and SPAF 325 mg/d). All three studies showed ASA reduced the risk of stroke compared with placebo, but the difference between ASA and placebo was statistically significant only in SPAF.[2] An intention-to-treat analysis showed that ASA resulted in a decrease in stroke of 18% ($P = 0.57$) in AFASAK and of 44% ($P = 0.02$) in SPAF.

When data were combined in the meta-analysis,[9] ASA was shown to decrease the risk of stroke by 36% ($P = 0.03$) and the combined rate of stroke, systemic embolism, or death by 28% ($P = 0.02$). In the EAFT,[7] ASA reduced the risk of stroke from 12% to 10% per year (a non-significant 14% reduction) and the combined outcome of stroke, systemic embolism, myocardial infarction,

Table 1. **Overview of primary prevention trials: outcomes of patients receiving warfarin were compared with those of controls.**

OUTCOME	CONTROL PATIENTS (N = 1236) N (%/Y)	PATIENTS RECEIVING WARFARIN (N = 1225) N (%/Y)	REDUCTION (%)	95% CI (P)
Stroke	81 (4.5)	27 (1.4)	68	50-79 (<001)
Stroke with residual deficit*	36 (2.0)	12 (0.6)	68	39-83 (<001)
Systemic embolism	10 (0.5)	5 (0.3)		
Stroke or systemic embolism	89 (5.0)	32 (1.7)	65	48-77 (<001)
Death	99 (5.4)	69 (3.6)	33	9-51 (.01)
Stroke, systemic embolism, or death	176 (9.8)	95 (5.0)	48	34-60 (<001)
Transient ischemic attack	23 (1.3)	13 (0.7)		
Major hemorrhage†	18 (1.0)	24 (1.3)		
Intracranial bleed	2 (0.1)	6 (0.3)		
Intracerebral bleed	0 (0.0)	4 (0.2)		

Reprinted with permission from the Atrial Fibrillation investigators.[9]
**Functional deficit persists 1 to 3 months after event.*
†*Bleeding requires 2 U of blood or hospital admission.*

or death from 19% to 15% per year (a non-significant reduction of 17%). The 20% to 25% reduction in stroke among nonrheumatic AF patients was similar to the reduction in stroke with ASA reported by the Antiplatelet Trialists' Collaboration in an overview of randomized trials of ASA in vascular disease.[10]

Comparison of anticoagulation and ASA. Three comparisons allow an estimate of the relative efficacy of anticoagulant and ASA therapy in AF: a comparison of ASA with placebo and warfarin with placebo in the primary prevention trials; the direct ASA-to-warfarin comparisons reported in SPAF II; and the direct ASA-to- anticoagulation comparison reported in EAFT.

The overall 68% reduction in embolic events seen with warfarin in six trials, compared with the 17%, 19%, and 44% reductions observed with ASA, suggest that warfarin is more effective than ASA. In SPAF II, warfarin reduced the risk of stroke by 44% (from 1.9% to 1.3% per year) in patients 75 years or older when compared with ASA ($P = 0.22$). In patients older than 75 years, risk of stroke was non-significantly reduced by 25% (from 4.8% to 3.0% per year) by warfarin ($P = 0.41$). The statistical power of SPAF II was relatively low due to the small number of events observed. In EAFT, compared with ASA, warfarin reduced the risk of stroke by 62% ($P < 0.001$) and the risk of the combined outcomes of stroke, systemic embolism, myocardial infarction, or death by 40% ($P = 0.008$).[7]

Thus, these three comparisons yield relatively consistent information. The main reason for the difference in the results of SPAF II and EAFT is that absolute event rates were high in EAFT due to inclusion of a high-risk AF population and low in SPAF II due to inclusion of a more general AF population. The reductions in risk of stroke with warfarin compared with ASA are thus consistent and suggest that warfarin reduces risk overall about 50% more than ASA.

Hemorrhage

The overall clinical benefit of antithrombotic therapy depends on both the efficacy of the intervention and its safety. Therefore, the decision to use antithrombotic therapy for patients with nonrheumatic AF should take into account the composite outcome of hemorrhagic as well as ischemic stroke and major non-intracranial, intracranial, or fatal hemorrhage.

Hemorrhage is the most common complication of oral anticoagulant therapy and limits the effectiveness of long-term treatment. Several studies have been carried out to determine the safety and efficacy of long-term anticoagulants for managing thromboembolic disorders. Descriptive studies have identified risk factors for hemorrhage among anticoagulant-treated patients, but the most definitive data are derived from prospective, randomized clinical trials comparing different intensities of anticoagulant therapy. Specific data on the rate of hemorrhage are also available from randomized trials of patients with AF. Data from the AF trials are somewhat difficult to interpret due to the widely differing definitions of bleeding and target anticoagulant levels used in the studies.

The most important risk factor for hemorrhage with long-term oral anticoagulants is the intensity of the anticoagulant regimen,[11-13] with significantly lower rates of bleeding reported with an INR of 2.0:3.0 compared with an INR of 3.0:4.5. Descriptive studies have correlated several characteristics with increased risk of bleeding, including age older than 65 years, history of stroke, previous gastrointestinal hemorrhage, and serious comorbid conditions (eg, recent myocardial infarction, renal insufficiency, or severe anemia).[14-16] In addition, clinical disorders leading to use of anticoagulant therapy contribute to bleeding risk; ischemic cerebral vascular disease, venous thromboembolism, and atrial fibrillation have been shown to be independent risk factors for bleeding in anticoagulated patients. Also, when long-term therapy is being considered, the cumulative risk of bleeding is directly related to the duration of therapy.[14]

Atrial fibrillation trials

Bleeding rates in randomized trials of anticoagulant therapy in patients with nonrheumatic AF are reasonably consistent, and the frequency was low in all studies.[1-4] Meta-analysis indicates a

slight increase in the rate of major hemorrhage in anticoagulant-treated patients (1.3%/y) compared with control patients (1.0%/y). Anticoagulated patients had a slight increase in the rate of intracranial hemorrhage (0.3% vs 0.1%) and intracerebral hemorrhage (0.2% vs 0.0%) compared with controls.

The EAFT trial showed rates of serious bleeding greater in the anticoagulant group (2.9%/y) than the primary prevention trials, but there were no intracranial bleeds. In SPAF II, the occurrence of hemorrhage was age-dependent. In anticoagulated patients, the rates of major hemorrhage were 1.7%/y in patients 75 years old and younger and 4.2%/y in patients older than 75 years. The rates in anticoagulated patients were higher than in ASA-treated patients, whose corresponding rates were 0.9%/y and 1.6%/y. In addition, annual rates of intracranial hemorrhage were considerably higher among patients older than 75 compared with younger patients (1.8% and 0.5%, respectively.)

Thus, the risk of major hemorrhage is greater with anticoagulant therapy than with either ASA or placebo. The risk of hemorrhage with warfarin varies among patients according to their risk profiles. The most important risk factors are intensity of anticoagulation, advanced age, prior gastrointestinal bleeding, prior stroke, and severe comorbid disease. ■

Correspondence to: *Dr A.G.G. Turpie, HGH McMaster Clinic, Hamilton General Hospital, 237 Barton St E, Hamilton, ON L8L 2X2*

References

1. Peterson P, Boysen G, Godtfredsen J, Andersen E, Andersen B. Placebo-controlled randomized trial of warfarin for prevention of thromboembolic complications in chronic atrial fibrillation: the Copenhagen AFASAK study. *Lancet* 1989;1:175-8.
2. Stroke Prevention in Atrial Fibrillation investigators. Stroke Prevention in Atrial Fibrillation study. Final results. *Circulation* 1991;84:527-39.
3. The Boston Area Anticoagulation Trial for Atrial Fibrillation investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. *N Engl J Med* 1990;323:1505-11.
4. Connolly SJ, Laupacis A, Gent M, Roberts RS, Cairns JA, Joyner C, for the CAFA study co-investigators. Canadian Atrial Fibrillation Anticoagulation (CAFA) study. *J Am Coll Cardiol* 1991;18:349-55.
5. Ezekowitz MD, Bridgers SL, James KE, Carliner NH, Colling CL, Gornick CC, et al. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. *N Engl J Med* 1992;327:1406-12.
6. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke. *Stroke* 1991;22:983-8.
7. EAFT (European Atrial Fibrillation Trial) study group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischemic attack or minor stroke. *Lancet* 1993; 342:1255-62.
8. Stroke Prevention in Atrial Fibrillation investigators. A comparison of warfarin with aspirin for prevention of thromboembolism in atrial fibrillation: the Stroke Prevention in Atrial Fibrillation II study. *Lancet* 1994;343:687-97.
9. Atrial fibrillation investigators. Risk factors for stroke and efficacy of anti-thrombotic therapy in atrial fibrillation: analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994;154:1449-57.
10. Antiplatelet Trialists' Collaboration. Secondary prevention of vascular disease by prolonged antiplatelet treatment. *BMJ* 1988;296:320-31.
11. Hull R, Hirsh J, Jay R, Carter C, England C, Gent M, et al. Different intensities of oral anticoagulant therapy in the treatment of proximal-vein thrombosis. *N Engl J Med* 1982;307:1676-81.
12. Turpie AG, Gunstensen J, Hirsh J, Nelson H, Gent M. Randomised comparison of two intensities of oral anticoagulant therapy after tissue heart valve replacement. *Lancet* 1988;1:1242-5.
13. Altman R, Rouvier J, Gurfinkel E, D'Ortencio O, Manzanel R, de La Fuente L, et al. Comparison of two levels of anticoagulant therapy in patients with substitute heart valves. *J Thorac Cardiovasc Surg* 1991;101(3):427-31.
14. Levine MN, Raskob G, Landefeld S, Hirsh J. Hemorrhagic complications of anticoagulant treatment. *Chest* 1995;108(4 Suppl):276S-290S.
15. Landefeld CS, Goldman I. Major bleeding in outpatients treated with warfarin: incidence and prediction by factors known at the start of outpatient therapy. *Am J Med* 1989; 87(2):144-52.
16. Landefeld CS, Beyth RJ. Anticoagulant-related bleeding: clinical epidemiology, prediction, and prevention. *Am J Med* 1993;95(3):315-28.