JACC Vol. 18, No. 2
August 1991:349–55

Canadian Atrial Fibrillation Anticoagulation (CAFA) Study

STUART J. CONNOLLY, MD, FRCPC, ANDREAS LAUPACIS, MD, FRCPC, MICHAEL GENT, DSc, ROBIN S. ROBERTS, MSc, JOHN A. CAIRNS, MD, FRCPC, FACC, CAMPBELL JOYNER, MD, FRCPC FOR THE CAFA STUDY COINVESTIGATORS*

Hamilton, Ontario, Canada

The Canadian Atrial Fibrillation Anticoagulation Study was a randomized double-blind placebo-controlled trial to assess the potential of warfarin to reduce systemic thromboembolism and its inherent risk of hemorrhage. As a result of the publication of two other "positive" studies of similar design and objective, this study was stopped early before completion of its planned recruitment of 630 patients. There were 187 patients randomized to warfarin and 191 to placebo. Permanent discontinuation of study medication occurred in 26% of warfarin-treated and 23% of placebo-treated patients. The target range of the international normalized ratio was 2 to 3. For the warfarin-treated patients, the international normalized ratio was in the target range 43.7% of the study days, above it 16.6% of the study days and below it 39.6% of the study days. Fatal or major bleeding occurred at annual rates of 2.5% in warfarin-treated and 0.5% in placebo-treated patients. Minor bleeding occurred in 16% of patients receiving warfarin and 9% receiving placebo. The primary outcome event cluster was nonlacunar stroke, noncentral nervous systemic embolism and fatal or intracranial hemorrhage. Events were included in the primary analysis of efficacy if they occurred within 28 days of permanent discontinuation of the study medication. The annual rates of the primary outcome event cluster were 3.5% in warfarin-treated and 5.2% in placebo-treated patients, with a relative risk reduction of 37% (95% confidence limits, −63.5%, 75.5%, p = 0.17). This estimate of benefit of anticoagulant therapy in atrial fibrillation is consistent with the estimates from previous reports and supports the use of warfarin in patients with nonrheumatic valvular atrial fibrillation for the prevention of systemic thromboembolism.

(J Am Coll Cardiol 1991;18:349–55)

Atrial fibrillation is common, especially in the elderly. There is a well documented (1–3) association between atrial fibrillation and systemic embolism, although estimates of the absolute annual stroke risk in patients with atrial fibrillation vary from <1% to 8%. In the presence of mitral stenosis, the risk of stroke in patients with atrial fibrillation is sufficiently high that anticoagulation is usually recommended, even though there is little supporting evidence for this treatment from randomized studies (4). However, when mitral stenosis is not present, there is no consensus about the use of anticoagulant therapy in atrial fibrillation. The present study was a randomized double-blind placebo-controlled trial of warfarin in patients with nonrheumatic atrial fibrillation designed to assess both its potential to reduce systemic embolism and its inherent risk of hemorrhage. The protocol called for recruitment of 630 patients to be followed up on average for 2.5 years. Part way through recruitment for the study, the results of similar trials conducted in Denmark (the Copenhagen AFASAK study [5,6]) and the United States (preliminary reports from the Stroke Prevention Atrial Fibrillation [SPAF] study [3]) became available. With the publication of the second "positive" trial, the Steering Committee believed that the cumulative evidence of anticoagulant efficacy in this condition was sufficiently persuasive to warrant the early termination of the present study after randomizing only 383 patients.

Methods

Patient selection. This study was carried out between June 1987 and April 1990 in 11 Canadian centers. The study was approved by the Institutional Review Board of each center. Potentially eligible patients were identified by the screening of electrocardiograms (ECGs) in participating hospitals and associated outpatient laboratories, as well as by direct referral from physicians. Patients met the inclusion criteria of the study if they satisfied the following: 1) chronic atrial fibrillation documented to be present for ≥1 month or paroxysmal atrial fibrillation occurring at least three times in the previous 3 months (documented at least twice on the ECG); 2) age ≥19 years; 3) absence of any mitral valve prosthesis or mechanical aortic valve prosthesis; and 4) absence of mitral valve stenosis on two-dimensional echocardiography. Patients were excluded from the study for any of the following: 1) requirement for anticoagulation; 2) medical contraindication to anticoagulation; 3) stroke or transient ischemic attack within 1 year; 4) requirement for

*The investigators participating in this study are listed in the Appendix.

This study was supported by the Medical Research Council of Canada and Du Pont Canada Ltd., Mississauga, Ontario, Canada.

Manuscript received September 28, 1990; revised manuscript received January 21, 1991, accepted February 15, 1991.

Address for reprints: Stuart J. Connolly, MD, Hamilton General Hospital, 237 Barton Street East, Hamilton, Ontario L8L 2X2, Canada.

0735-1097/91/$3.50

antiplatelet drug therapy; 5) hyperthyroidism; 6) uncontrolled hypertension; and 7) myocardial infarction within 1 month.

Eligibility. Before randomization, a baseline evaluation was performed, consisting of a relevant medical history, cardiovascular and neurologic examination by an internist and laboratory evaluation including an ECG, two-dimensional echocardiogram, hemoglobin, platelet count, prothrombin and partial prothrombin times, serum thyroid and thyroglobulin binding and urinalysis. Randomization was effected by the strict sequential use of medication packages containing 5 mg tablets of warfarin (Coumadin) or matching placebo according to a predetermined random order.

Anticoagulation. All patients had periodic measurement of the prothrombin time to regulate the dose of the study medication. The study was carried out in a triple-blind manner (patients, investigators, coordinating center). In each clinical center, there was an unblinded anticoagulation supervisor who received the results of the prothrombin time measurements. This supervisor regulated the dose of the study medication for patients on active treatment to maintain an international normalized ratio in a range of 2 to 3. For patients receiving placebo, the results of the prothrombin time test were ignored and, instead, the dose of the study medication was modified according to a series of sequential "sham" prothrombin time results. Prothrombin time tests were done no less frequently than every 3 weeks. After each prothrombin time determination, the anticoagulation supervisor indicated what changes in study medication dose were required. The study nurse then informed the patient of the new dose; the anticoagulation supervisor never contacted the patient directly. In general, patients were free to choose the laboratory to be used for prothrombin tests.

Most laboratories used in the study did not report the prothrombin time result as an international normalized ratio. A nomogram based on the type of thromboplastin and the normal range of prothrombin time was used to determine for each laboratory the therapeutic range of prothrombin results corresponding to an international normalized ratio in the range of 2 to 3. To maintain blinding, patients admitted for elective surgery had administration of the study medication discontinued ≥6 days before admission and restarted at hospital discharge. At the discretion of the investigator, patients who were admitted to the hospital for other reasons often had the study medication discontinued temporarily during the hospital stay to reduce the risk of unblinding. In addition to regular telephone contact by the nurse to convey any change in the dose of study medication, patients were also seen at 6 weeks and at 3 months after randomization and then every 3 months thereafter. At these scheduled visits, blood pressure and an ECG were obtained and the patient was questioned as to the presence of any new symptoms indicative of systemic embolism or bleeding.

Bleeding events. Patients were requested to immediately report bleeding episodes of any type to the study nurse. Bleeding episodes were categorized as follows: 1) a life-threatening bleeding event was defined to be any intracranial or fatal bleeding; 2) a major bleeding event was defined as any bleeding episode associated with a ≥20 g/liter decrease in serum hemoglobin or requiring a blood transfusion or bleeding into a sensitive location such as the pericardium or retina; and 3) all other bleeding events were considered minor. In the event of life-threatening or major bleeding, the study medication was permanently discontinued. For minor bleeding, the study medication was stopped for ≥3 days and then resumed at a time and dose decided by the anticoagulation supervisor. For the purpose of analysis, bleeding was considered to have occurred during treatment with the study medication if it took place before or within 7 days of study medication discontinuation.

Outcome events. A primary outcome event was the first occurrence of any of the following: 1) any ischemic stroke except lacunar; 2) other systemic embolism to the gut, kidney, legs or arms; and 3) intracranial or fatal hemorrhage. Secondary outcome events were: 1) transient ischemic attack; 2) lacunar infarction; 3) major bleeding; 4) minor bleeding; and 5) death. Stroke was defined as the sudden onset of a new neurologic deficit lasting ≥24 h, including: 1) weakness or sensory impairment of the legs, arms or face; 2) speech impairment; 3) temporal spatial impairment; 4) visual loss; 5) two or more of a) incoordination, b) cranial nerve abnormality, and c) dysarthria; or 6) objective and persistent worsening of a previous deficit, with an appropriate new finding on computed tomography of the head. Lacunar infarction was considered to have occurred when all of the following were present: 1) arterial hypertension; 2) typical clinical findings (pure motor hemiplegia, pure sensory stroke, ataxia hemiparesis and dysarthria-clumsy hand syndrome); and 3) computed tomography of the head showing a small (<1 cm), deep infarction or no abnormality. Noncentral nervous system embolic events had to be documented by typical findings on angiography or at surgery. Transient ischemic attack was defined as abrupt onset of a focal neurologic deficit lasting >1 min and <24 h within the territory of a single major brain artery. A stroke was considered severe if 1 month after the event, the patient required assistance to eat, walk or communicate. A computed tomogram of the head was not required for the diagnosis of stroke and was not routinely performed.

Data analysis. The study plan was to enter 630 patients over 4 years, with follow-up evaluation to a common end point at 5 years. The sample size was calculated, assuming a one-sided alpha of 0.05 and an expected event rate of 5.6%/year in the placebo group to give 80% power to detect a risk reduction by treatment of 50%. Formal notification of permanent discontinuation of the study medication initiated a 28-day waiting period. The primary analysis of the study was planned to be an "efficacy" analysis in which events occurring >28 days after formal notification of permanent discontinuation would be excluded. When medication was temporarily discontinued, events occurring during that pe-

riod were included in the analysis of efficacy. When a temporary discontinuation progressed to a permanent discontinuation, the 28-day waiting period began not at the time of temporary discontinuation, but at the time of formal notification of permanent discontinuation. A comparison of the rates of primary outcome events using the "intention to treat" principle was planned as the most important secondary analysis. An interim analysis of efficacy by the External Safety and Efficacy Monitoring Committee was planned to occur once 50% of the total expected patient-years of follow-up had accumulated, but this point was never reached.

Standard analysis techniques for failure time data were used. The proportion of patients in each treatment group remaining event free over time was estimated using the Kaplan-Meier estimator (7) and compared using the Mantel-Haenszel tests (8). Confidence intervals for risk reduction were derived from the Cox proportional hazard model (9). To compare our results with those of other studies, observed hazard ratios were calculated from published results of the Stroke Prevention in Atrial Fibrillation Study (3), the Copenhagen AFASAK study (5,6) and Boston Area Anticoagulation Trial for Atrial Fibrillation (10). Approximate 95% confidence intervals were computed for the natural logarithm of hazard ratio as: log (observed hazard ratio) ± 1.96 $\sqrt{1/d_p + 1/d_w}$ (11), where d_p and d_w are the number of events observed in the placebo and warfarin groups, respectively. The conversion to the corresponding confidence interval for risk reduction was achieved by exponentiating and then subtracting 1. The degree of anticoagulation achieved in this trial was summarized by calculating the mean international normalized ratio and the proportion of international normalized ratios in the therapeutic range for each patient. Both were weighted by the time gap between successive determinations of the international normalized ratio and restricted to the period >90 days after randomization when initial stabilization should have occurred. Individual patient values of the mean international normalized ratio and percent of days in the therapeutic range were then averaged for all patients in the active treatment group to produce a summary statistic. Values are presented as mean values ± SD.

We performed detailed documentation of the reasons for exclusion for all patients who met the inclusion criteria between November 1987 and June 1988, during which time 1,430 patients were screened. After that time, detailed documentation of exclusions was done only for a selected sample. Of the 1,430 patients screened who met the study inclusion criteria, 17% had a contraindication to oral anticoagulation, 2% required anticoagulation, 17% required an antiplatelet drug, 4% had chronic alcoholism, 3.5% had a social-psychological reason for not participating and 12% were excluded for other reasons. Of the 13% who were eligible, 54% gave consent and were randomized. Six percent of patients meeting the inclusion criteria entered the study. A committee of blinded coinvestigators reviewed the eligibility of all patients and all reported outcome events.

Table 1. Baseline Patient Characteristics

	Warfarin Group (n = 187)	Placebo Group (n = 191)
Age (yr)*	68.0 ± 9.3	67.4 ± 9.6
Male (%)	75.9	73.3
Angina (%)	21.9	19.9
Prior myocardial infarction (%)	15.0	12.0
Heart failure (%)	23.5	20.4
Stroke or TIA (%)	3.2	4.2
Intermittent claudication (%)	10.2	4.7
Diabetes mellitus (%)	13.9	10.0
Cardiomyopathy (%)	6.4	5.8
History of hypertension (%)	45.3	34.0
LA dimension (mm)	45.8 ± 8.1	46.0 ± 8.3
LV end-diastolic dimension (mm)*	52.4 ± 7.8	51.6 ± 9.0
Arterial vascular bruit (%)	11.8	6.8
Years since diagnosis of AF (%)		
<1	19.8	18.3
1–3	24.6	25.7
4–6	17.1	17.3
>6	38.0	38.2
Unknown	0.5	0.5
Paroxysmal AF (%)	6.4	7.3

*Values are mean ± SD. AF = atrial fibrillation; LA = left atrial; LV = left ventricular; TIA = transient ischemic attack.

Results

Study patients and baseline characteristics. Three hundred eighty-three patients entered the study; five (two randomized to warfarin and three to placebo) did not have atrial fibrillation or had mitral stenosis and were judged by a blinded adjudication committee to be ineligible. Thirty-seven patients (24 randomized to warfarin and 13 to placebo) were judged to have atrial fibrillation but were technically ineligible as a result of a minimal violation of the entry criteria. All eligible and technically ineligible patients were included in the analysis; 187 were allocated to warfarin and 191 to placebo. No outcome events occurred in the five ineligible patients. The mean follow-up period was 15.2 months.

Table 1 summarizes the baseline characteristics of the patients randomized to warfarin or placebo. Although the randomization procedure provided reasonably comparable groups, there was a tendency for the warfarin group to contain more patients with diabetes mellitus, intermittent claudication, previous vascular surgery and arterial vascular bruit. Early permanent discontinuation of the study medication not due to a primary outcome event occurred in 49 warfarin-treated patients (26.2%) and 43 placebo-treated patients (22.5%). The causes of permanent discontinuation were patient or physician preference (30 in the warfarin and 22 in the placebo group), requirement for the contraindicated drug (9 in the warfarin and 10 in the placebo group), bleeding (4 in the warfarin and 2 in the placebo group) and other causes (6 in the warfarin and 9 in the placebo group). Temporary discontinuation of the study medication for >7 days occurred 58 times in 47 patients receiving warfarin and

Table 2. Outcome Events in the Two Treatment Groups

	Efficacy Analysis		Intention to Treat Analysis	
	Warfarin Group (n = 187)	Placebo Group (n = 191)	Warfarin Group (n = 187)	Placebo Group (n = 191)
Primary events				
Nonlacunar stroke	4	9	5	9
Non-CNS embolic event	1	2	1	2
Intracranial hemorrhage	1	0	1	0
Other fatal hemorrhage	1	0	1	0
Total	7	11	8	11
Secondary events				
TIA	1	2	2	2
Lacunar stroke	1	0	1	0
Vascular death	6	6	9	6
Other death	1	0	1	2
Total	9	8	13	10

CNS = central nervous system; TIA = transient ischemic attack.

78 times in 52 patients receiving placebo. The resultant proportion of days of study follow-up in which patients were not receiving the study medication because of temporary discontinuation was 5.8% for the warfarin group and 6.1% for the placebo group. The most common reason for an episode of temporary discontinuation of the study medication was a surgical procedure (44.8%).

Anticoagulation and bleeding. After an initial 90-day period of stabilization, the mean dose of the study medication was 4.6 ± 1.9 mg/day for warfarin and 5.6 ± 2.6 mg/day for placebo. The target range of the international normalized ratio was 2 to 3 and the mean international normalized ratio for warfarin-treated patients was 2.4 ± 0.4. The estimated percent of days during which the international normalized ratio was between 2 and 3 was 43.7%; the ratio was below the target range 39.6% of days and above it 16.6% of days. The effectiveness of blinding of therapy was assessed by having coinvestigators report all cases of unblinding. Unblinding of the patient, the family physician or study personnel was reported in 17 warfarin-treated patients and 12 placebo-treated patients. Patients were excluded from entry if they required aspirin or antiplatelet therapy and patients were advised not to take these agents during the study. Rarely, patients with an acute exacerbation of arthritis received a brief course of ibuprofen.

Life-threatening or major bleeding during receipt of the study medication occurred in five patients receiving warfarin and one patient receiving placebo; one other major bleeding episode occurred 524 days after permanent discontinuation of medication in a placebo-treated patient. The annual rate of fatal or major hemorrhage while patients were receiving study medication was 2.5% in those receiving warfarin and 0.5% in those receiving placebo. Two of the bleeding episodes during administration of warfarin and none during placebo administration were fatal. The international normalized ratio for the patient with a fatal intracranial hemorrhage was 3.5 2 days before the event and that of the patient with a fatal ruptured abdominal aorta was 2.6 1 day before the event; the ratios recorded immediately before the three other major bleeding episodes in the warfarin-treated patients were 2.7, 1.5 and 2.1. Minor bleeding occurred in 16% of warfarin-treated patients and 9.4% of placebo-treated patients.

Efficacy. Table 2 shows the primary and secondary outcome events occurring 1) up to 28 days after permanent discontinuation of the study medication (efficacy analysis), and 2) at any time during the study (intention to treat analysis). With the efficacy approach, the annual rate of the primary outcome event cluster in patients receiving warfarin or placebo was 3.5% and 5.2%, respectively. The relative risk reduction was 37% (95% confidence limits −63.5%, 75.5%; p = 0.17). One additional primary outcome event occurred in a patient randomized to warfarin 508 days after permanent medication discontinuation and was counted in the intention to treat analysis, yielding an annual event rate of the primary outcome event cluster for warfarin and placebo of 3.4% and 4.6%, respectively, with a relative risk reduction of 26% (95% confidence limits −83.0%, 70.4%; p = 0.25). When the efficacy analysis of the primary outcome event cluster was adjusted for differences in the distribution of baseline characteristics, the estimated risk reduction increased slightly to 45% (95% confidence limits −46%, 79.1%; p = 0.12). The annual rate of the event cluster of nonlacunar stroke or noncentral nervous system embolic events by the efficacy approach was 2.5% and 5.2% for warfarin and placebo, respectively, and the risk reduction was 55% (95% confidence limits −30.4%, 84.3%; p = 0.07). Figure 1 shows the cumulative risk of primary outcome event cluster and of the cluster of nonlacunar stroke or noncentral nervous system embolism using the efficacy approach.

Of the six nonhemorrhagic primary outcome events in the warfarin group, only one occurred in a patient whose international normalized ratio was in the target range. One

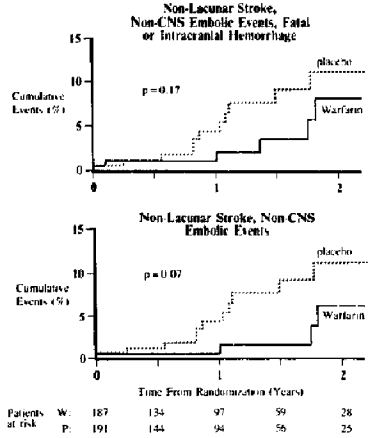

Figure 1. Cumulative rate of events for the two event clusters. CNS = central nervous system; P = placebo; W = warfarin.

event occurred 508 days after permanent discontinuation of the study medication and four occurred in patients without permanent discontinuation of the medication but with an international normalized ratio below the target range (international normalized ratio 1, 1.1, 1.1 and 1.4). One of these events occurred on the day of study entry and another occurred during temporary discontinuation of medication. Six of the nonlacunar strokes were judged to be severe (two in warfarin-treated and four in placebo-treated patients) and eight were mild (three in warfarin-treated and five in placebo-treated patients). One noncentral nervous system embolic event (in a warfarin-treated patient) required leg amputation and one (in a placebo-treated patient) required bowel resection. The only patient diagnosed to have a lacunar stroke subsequently had a nonlacunar stroke while taking the study medication.

Discussion

Reasons for early discontinuation of the trial. When the present study was initiated, it was uncertain whether anticoagulant therapy was effective in reducing the risk of systemic embolism and whether the balance between the risk and benefit of this treatment was favorable. After recruitment of 60% of the anticipated patients and before achieving 50% of the anticipated patient-years of follow-up, results of the Copenhagen AFASAK study (5) and the Stroke Prevention in Atrial Fibrillation study (3) were published, showing warfarin to significantly reduce the risk of systemic embolism. We considered these studies to be methodologically strong and reasonably similar to the present study in terms of the patient cohort studied and the hypothesis tested. We concluded that the previous uncertainty concerning the value of anticoagulation in patients with nonrheumatic atrial fibrillation had been greatly reduced and that it was no longer ethically possible to justify withholding anticoagulant therapy from our study patients. The decision to terminate the present study was made by its Steering Committee without knowledge of the study results. This decision was based on the argument that such knowledge would not alter the decision to stop the study because whether or not there was a trend in favor of warfarin, the confidence limits of the estimate would be wide and would almost certainly encompass those of the other published studies. Conversely, if the results showed a trend favoring placebo, continuation of the study to confirm a detrimental effect of therapy could not be justified. More recently, the Boston Area Anticoagulation Trial for Atrial Fibrillation (10) reported an 86% reduction in ischemic stroke and systemic embolism with warfarin compared with usual care.

Comparison with previous studies. Although the previously published studies (3,5,10) are similar to the present study in many respects, there are several differences. Only the present study was double-blind in design. Although logistically more complex, double-blind management of anticoagulation was successful in this study and provided a methodologically stronger approach through reduction of potential bias in the assessment of outcome events. The target range of the international normalized ratio for prothrombin time was 2.8 to 4.2 for the Copenhagen study (5), 2 to 3.5 for the Stroke Prevention in Atrial Fibrillation study (3), 2 to 3 for the present study and 1.5 to 2.7 for the Boston study (10).

Major hemorrhage was defined slightly differently in these studies, but the rates can be reasonably compared. The annual rates of intracranial and major bleeding in patients receiving placebo or warfarin, respectively, were 0.4% and 0.8% in the Copenhagen study (5), 0.9% and 1.7% in the Stroke Prevention in Atrial Fibrillation study (3) and 0.5% and 2.5% in the present study. Surprisingly, the rate of hemorrhage is somewhat lower in the Copenhagen AFASAK study (5) despite the higher target range for the international normalized ratio and higher mean age of the study patients.

It is obvious that the use of anticoagulant therapy in patients with atrial fibrillation implies a tradeoff between a reduction in systemic thromboembolism and an increase in serious hemorrhage. A study design that chooses to focus on the more biologic question of whether anticoagulation can reduce thromboembolism would exclude bleeding from the primary analysis and a study design more interested in the individual patient would include fatal or intracranial bleeding in the primary analysis. When comparing the results of the

JACC Vol. 18, No. 2
August 1991:349–55

Table 3. Comparison With Published Studies*

Study (reference)	Observed Events		Risk Reduction	
	Placebo	Warfarin	Observed	95% CI (approx)
SPAF (3)	18	3.5†	81.6%	42.1%, 94.1%
AFASAK (5,6)	22	9	60.0%	11%, 81%
BAATAF (10)	13†	2	86%	51%, 96%
Present study	11	6	44.8%	−49.9%, 79.5%

*This comparison uses the intention to treat approach, includes ischemic stroke and other systemic thromboembolism and excludes transient ischemic attack and hemorrhage. †Assumes that half of the seven events attributable during active treatment in group I of the Stroke Prevention in Atrial Fibrillation (SPAF) preliminary report are attributable to warfarin. ‡The control group in this study received "usual care." AFASAK = Copenhagen AFASAK study; BAATAF = Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA = Canadian Atrial Fibrillation Anticoagulation Study.

present study with those of other studies, one must consider the important differences in the composition of the primary outcome event clusters and type of analysis (efficacy or intention to treat). Whereas the Copenhagen AFASAK study (5) used an efficacy approach and included both transient ischemic attack and intracranial hemorrhage in the primary analysis, both the Stroke Prevention in Atrial Fibrillation study (3) and Boston Area Anticoagulation Trial for Atrial Fibrillation (10) used an intention to treat analysis and included neither event. The primary analysis of the present study used the efficacy approach and included fatal and intracranial hemorrhage.

Table 3 compares the present results with those of the Stroke Prevention in Atrial Fibrillation study (3), the Copenhagen AFASAK study (5,6) and the Boston Area Anticoagulation Trial for Atrial Fibrillation (10). To balance the comparison, the data of all of the studies are presented using the intention to treat principle. This comparison also excludes hemorrhage and transient ischemic attacks so as to examine the more purely biologic question of whether anticoagulation can reduce systemic thromboembolism. Because the Stroke Prevention in Atrial Fibrillation study preliminary report (3) combines the events occurring during administration of warfarin and aspirin (active treatment), the risk reduction for this study is estimated assuming that half of the seven events occurring during active treatment are attributable to warfarin. It is apparent from Table 3 that the confidence limits of the risk reduction for all the studies overlap to a great extent.

Implications. The consistency of the estimates of reduction in risk of systemic embolism and the relatively low rates of major hemorrhage in all of the published studies strongly support the use of warfarin in patients with atrial fibrillation. Although aspirin reduced thromboembolism in the Stroke Prevention in Atrial Fibrillation study (3), it was not beneficial in the Copenhagen AFASAK study (5). It has been suggested that the negative result of the Copenhagen AFASAK study may be due to the older patient age or the lower dose of aspirin used in that study. Although aspirin therapy may at present be preferred in patients at high risk of hemorrhage, the evidence supporting the use of warfarin in patients with atrial fibrillation is much stronger than that supporting aspirin.

Appendix

Canadian Atrial Fibrillation Anticoagulation Study Participants

McMaster University, Hamilton, Ontario: Stuart J. Connolly, MD, FRCPC, John A. Cairns, MD, FRCPC, FACC, Alexander G. G. Turpie, MD, FRCPC, John E. Paulseth, MD, FRCPC, Elaine P. Gordon, MD, FRCPC, Paul H. Tanser, MD, FACC, FRCPC, Brian J. Sealey, MD, FRCPC, Lorne S. Finkelstein, MD, FRCPC, Rolie Carron, RN, Gayle Stanborough, RN.

University of Western Ontario, London, Ontario: Andreas Laupacis, MD, FRCPC, Robert K. Stuart, MD, FRCPC, Vladimir C. Hachinski, MD, FRCPC, Libardo J. Melendez, MD, FRCPC, Larry M. Brownscombe, MD, FRCPC, Michele D. Goddard, MD, FRCPC, Helen Mackesy, RN.

University of Toronto, Toronto, Ontario: Campbell Joyner, MD, FRCPC, James D. Dubbin, MD, FRCPC, John A. Blakely, MD, FRCPC, John A. Norris, MD, FRCPC, Lyn Balleza, RN.

University of Ottawa, Ottawa, Ontario: Martin Green, MD, FRCPC, Donald S. Beanlands, MD, FRCPC, Nancy Simmons, RN.

University of British Columbia, Vancouver, British Columbia: Charles Kerr, MD, FRCPC, John Boone, MD, FRCPC, John Yeung, MD, FRCPC, William Martin, MD, FRCPC, Stephan Clarke, MD, FRCPC, Susan Mooney, RN.

University of Manitoba, Winnipeg, Manitoba: Andrew Morris, MD, FRCPC, Michael Frais, MD, FRCPC, A. Majid Shojania, MD, FRCPC, Joy MacKenzie, RN.

McGill University, Montreal, Quebec: Kenneth Fiegel, MD, FRCPC, Jaime Caro, MD, FRCPC, Antoine Hakim, MD, FRCPC, Patsy Tremblay-Marcoix, RN, Nathalie Hebert, RN.

Dalhousie University, Halifax, Nova Scotia: Elizabeth Mann, MD, FRCPC, K. Sue Robinson, MD, FRCPC, Stephan Phillips, MD, FRCPC, Barbara Grant, RN.

Queen's University, Kingston, Ontario: John Parker, MD, FRCPC, John Milliken, MD, FRCPC, Andrew Koval, MD, FRCPC, Lynda Reid, RN.

Memorial University, St. John's, Newfoundland: Bruce Sussex, MD, FRCPC, William Pryse-Phillips, MD, FRCPC, Lucinda Whitman, MD, FRCPC, Kathy Murphy, RN.

University of Montreal, Longueil, Quebec: Jacques Lenis, MD, FRCPC, Laurent Belanger, MD, FRCPC, Andre Rivard, MD, FRCPC, Colette Lemay, RN.

Safety Monitoring Committee, Hamilton, Ontario: George Carruthers, MD, FRCPC, Neville Bayer, MD, Wayne Taylor, MA.

Coordinating and Methods Centre, Hamilton, Ontario: Michael Gent, DSc, Robin Roberts, MSc, Annette (Seip) Mesquita, Harvey Nelson, Shelley Lee.

References

1. Kannel WB, Abbott RD, Savage DD, McNamara PM. Coronary heart disease and atrial fibrillation: the Framingham study. Am Heart J 1983; 106:389–96.
2. Kopecky SL, Gersh BJ, McGoon MD, et al. The natural history of lone atrial fibrillation. N Engl J Med 1987;317:669–74.
3. Special Report: preliminary report of the Stroke Prevention in Atrial Fibrillation study. N Engl J Med 1990;322:863–8.
4. Dunn M, Alexander J, De Silva R, Hildner F. Antithrombotic therapy in atrial fibrillation. Chest 1986;89(suppl):63S–74S.
5. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: the Copenhagen AFASAK study. Lancet 1989;1:175–9.
6. Petersen P, Boysen G. Prevention of stroke in atrial fibrillation (letter). N Engl J Med 1990;323:482.
7. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.
8. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 1966;50:163–70.
9. Cox DR. Regression models and life tables (with discussion). J R Stat Soc B 1972;34:187–220.
10. Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in non-rheumatic atrial fibrillation. N Engl J Med 1990;323:1505–11.
11. Kalbfleisch JD, Prentice RL. The Statistical Analysis of Failure Time Data. NY: John Wiley, 1980:48–50.