Fixed Minidose Warfarin and Aspirin Alone and in Combination vs Adjusted-Dose Warfarin for Stroke Prevention in Atrial Fibrillation

Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study

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Background: Despite the efficacy of warfarin sodium therapy for stroke prevention in atrial fibrillation, many physicians hesitate to prescribe it to elderly patients because of the risk for bleeding complications and because of inconvenience for the patients.

Methods: The Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study was a randomized, controlled trial examining the following therapies: warfarin sodium, 1.25 mg/d; warfarin sodium, 1.25 mg/d, plus aspirin, 300 mg/d; and aspirin, 300 mg/d. These were compared with adjusted-dose warfarin therapy (international normalized ratio of prothrombin time [INR], 2.0-3.0). Stroke or a systemic thromboembolic event was the primary outcome event. Transient ischemic attack, acute myocardial infarction, and death were secondary events. Data were handled as survival data, and risk factors were identified using the Cox proportional hazards model. The trial was scheduled for 6 years from May 1, 1993, but due to scientific evidence of inefficiency of low-intensity warfarin plus aspirin therapy from another study, our trial was prematurely terminated on October 2, 1996.

Results: We included 677 patients (median age, 74 years). The cumulative primary event rate after 1 year was 5.8% in patients receiving minidose warfarin; 7.2%, warfarin plus aspirin; 3.6%, aspirin; and 2.8%, adjusted-dose warfarin ($P = .67$). After 3 years, no difference among the groups was seen. Major bleeding events were rare.

Conclusions: Although the difference was insignificant, adjusted-dose warfarin seemed superior to minidose warfarin and to warfarin plus aspirin after 1 year of treatment. The results do not justify a change in the current recommendation of adjusted-dose warfarin (INR, 2.0-3.0) for stroke prevention in atrial fibrillation.

Arch Intern Med. 1998;158:1513-1521

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ATRIAL FIBRILLATION is associated with an overall risk for ischemic stroke of 4.5% per year, which is about 6 times the risk with sinus rhythm.[1,2] Seven randomized studies have shown that adjusted-dose oral anticoagulant therapy is effective for primary and secondary prevention of thromboembolic events in patients with nonvalvular atrial fibrillation.[3-9] Therefore, anticoagulant therapy with the intensity of the international normalized ratio of prothrombin time (INR) of 2.0 to 3.0 is recommended.[10] Antiplatelet therapy seems less effective.

Despite the efficacy of warfarin therapy, many physicians hesitate to prescribe the anticoagulant to patients with atrial fibrillation, probably because of the risk for bleeding complications, inconvenience for the patients, and expected poor compliance in elderly patients.[11-15] The safety and tolerability of long-term oral anticoagulation therapy is not entirely clear in elderly patients, who have the highest risk for stroke[11] and may have an increased risk for bleeding complications.[16]

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Studies on antiplatelet therapy and less intense oral anticoagulation strategies have been conducted to diminish the risk for bleeding and to make frequent

PATIENTS AND METHODS

The AFASAK 2 Study was a randomized, controlled trial conducted from a single center recruiting outpatients with chronic atrial fibrillation. The design and methods have been described elsewhere.[17]

ELIGIBILITY

Patients 18 years or older with nonvalvular chronic atrial fibrillation were eligible. Before randomization, atrial fibrillation had to be documented twice using electrocardiography (ECG), with an interval of at least 1 month.

Patients younger than 60 years with lone atrial fibrillation (ie, with no underlying ischemic or hypertensive heart disease, congestive heart failure, hyperthyroidism, or chronic obstructive pulmonary disease) were excluded, along with patients with systolic or diastolic blood pressure above 180/100 mm Hg, stroke, or a transient ischemic attack (TIA) within 6 months; risk factors for bleeding; or contraindications for warfarin or aspirin therapy. Patients already receiving adjusted-dose warfarin were also ineligible.

Participants were recruited from general practices in Copenhagen, Denmark, and the surrounding areas. Before randomization, patients were interviewed and examined by 1 of 3 investigators. Baseline characteristics were recorded in standardized case record forms.[17]

RANDOMIZATION AND STUDY TREATMENTS

According to computer-generated randomization, eligible patients were assigned to daily treatment with warfarin sodium, 1.25 mg/d; warfarin sodium, 1.25 mg/d, plus aspirin, 300 mg/d; aspirin, 300 mg/d; or adjusted-dose warfarin with an INR of 2.0 to 3.0. Warfarin (Marevan tablets of 2.5 and 1.25 mg) and aspirin (Hjertemagnyl, nonenteric coated tablets of 150 mg) were supplied by Nycomed DAK A/S, Roskilde, Denmark. The treatment was not blinded to the patients and the investigators. Discontinuation of study treatment was allowed for a maximum of 4 weeks per year.

THERAPY MONITORING

Treatment with adjusted-dose warfarin sodium was generally initiated with a loading dose of 10 mg. During the first week of therapy, the intensity of anticoagulation therapy was monitored using INR on 5 consecutive days, and dose adjustments were made to achieve INR of 2.0 to 3.0. For the following 3 weeks, INR was monitored once a week. When stable anticoagulant therapy was achieved, INR determinations were performed with a maximum interval of 4 weeks.

Until December 31, 1995, the level of anticoagulation in patients assigned to minidose warfarin and combined minidose warfarin and aspirin therapies was monitored twice during the first week, once a week for the following 3 weeks, and then once every 4 weeks. From January 1, 1996, the INRs in patients receiving warfarin sodium, 1.25 mg/d, were monitored only once every 3 months after an introduction of 3 months. Aspirin therapy was not monitored using blood tests.

The patients were free to choose among 12 laboratories, including the AFASAK 2 Study center. Blood samples were analyzed using 1 of several commercially available automatic coagulation analyzers (Nycomatic, Nycomed Pharma A/S; Thrombolyser, Behringwerke AG, Marburg, Germany; and ACL 200, Instrumentation Laboratory, Milan, Italy). Two commercially available thromboplastins were used (Nycotest PT, Nycomed Pharma A/S, with an international sensitivity index of 0.97; SPA, Diagnostica Stago, Asnieres sur-Seine, France, with an international sensitivity index of 1.04).

FOLLOW-UP

Patients receiving treatment also underwent physical examinations 3 and 6 months after inclusion, and then at 6-month intervals until termination of the trial. By the end of the trial, all randomized patients were contacted to obtain information on outcome events that might have occurred since the last visit at the laboratory technician's or physician's office in the study center or after discontinuation of the study treatment.

OUTCOME EVENTS

The primary event was a stroke (ischemic or hemorrhagic) or a systemic thromboembolic event. Stroke was defined as acute onset of a focal neurological deficit of presumed vascular genesis lasting for 24 hours or more. Traumatic intracranial hemorrhage was considered an adverse event and not a primary outcome. To grade the severity of stroke, all events were reassessed after 1 month. The events were graded as minor, nondisabling, disabling, or fatal.

Systemic thromboembolic events in extremities, kidneys, mesenteric arteries, lungs, spleen, retina, or grafts were also primary outcome events and had to be verified using angiography, surgery, scintigraphy, or autopsy.

monitoring unnecessary.[17-21] The Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation (AFASAK 2) Study was designed in 1992 to investigate the effect of minidose warfarin alone and in combination with aspirin in patients with chronic nonvalvular atrial fibrillation.[17] On October 2, 1996, the trial was stopped prematurely due to the results of another randomized clinical trial[18] indicating that low-intensity warfarin plus aspirin therapy was significantly less effective than adjusted-dose warfarin therapy, and due to other studies indicating that anticoagulation therapy below the INR of 2.0 is inefficient for stroke prevention in atrial fibrillation.[19,20]

RESULTS

PATIENTS

Throughout the study, the recruitment was almost linear, with an intake of approximately 20 patients per

The secondary events of the trial were acute myocardial infarction (AMI), TIA, and death not due to other end points. The diagnosis of AMI required any 2 of the following criteria: history of typical chest pain, serial creatine kinase-MB changes typical of AMI, or ECG changes typical of AMI. A TIA was defined as acute onset of focal neurological deficit of presumed vascular genesis lasting less than 24 hours, regardless of computed tomographic or magnetic resonance imaging findings. Death was classified as vascular, nonvascular, or unknown (ie, unexpected death without subsequent autopsy).

All endpoints were evaluated by an end-point committee unaware of treatment status. The committee consisted of 2 neurologists and 2 cardiologists.

ADVERSE EVENTS

Hemorrhagic events were classified as minor or major. A major bleeding event was fatal, life-threatening, or potentially life-threatening, requiring surgical treatment or blood transfusion. All reports of major bleeding events were confirmed by hospital records. Minor bleeding events included overt or occult gastrointestinal tract bleeding, hemoptysis, gross hematuria, nose bleeding, bruising, symptomatic anemia ascribed to bleeding, and chronic bleeding with moderate loss of blood.

ETHICS

The study protocol was approved by the regional ethics committees and the Danish National Board of Health, and the trial was performed according to the Second Declaration of Helsinki. All patients received oral and written information about the background and procedures of the trial, and signed informed consent was obtained.

SAMPLE SIZE CALCULATION AND STOPPING RULES

For initial sample size calculations, the following assumptions were made: The risk for thromboembolic complications in atrial fibrillation was set to 1.67% per year during adjusted-dose warfarin therapy and to 3.33% per year during aspirin therapy. The risk due to minidose warfarin therapy was unknown but was expected to be lower than that due to aspirin therapy and higher than that due to adjusted-dose warfarin therapy. Provided there was uniform recruitment and distribution of patients among the 4 groups throughout the study, the null hypothesis could be tested with 80% power at a 5% significance level using 1-sided, 2-sample χ^2 test with an intake of 20 patients per month (ie, 1500 patients during 6 years). Using this sample size, a significant difference between the effects of aspirin and adjusted-dose warfarin was expected. The effect of minidose warfarin alone and in combination with aspirin should be compared with that of aspirin and adjusted-dose warfarin.

A group sequential analysis was scheduled after inclusion of 1200 patients, and the trial was to be terminated if 1 of the minidose warfarin regimens was significantly more effective than aspirin therapy or if both minidose warfarin regimens were significantly less effective than adjusted-dose warfarin therapy.

ANALYSES AND STATISTICS

Baseline comparisons among the 4 groups were performed using χ^2 test for categorical data and analysis of variance for continuous data.

The total number of patient-years at observation was calculated from the day of randomization to time of a primary or secondary outcome event or to the end of the trial. The number of thromboembolic events in patients who actually received the study medication are reported, along with the number of events that occurred after discontinuation of study therapy.

The primary analysis of the study was a calculation of the cumulative rate of outcome events in patients receiving treatment. For the 4 groups, the cumulative rates of total primary events and death were calculated using the Kaplan-Meier method,[22] and the log-rank statistics were used for comparison of the event rates.

Intention-to-treat analysis was performed to facilitate comparison of the rate of thromboembolic events in this and other studies. The rate is expressed as the number of events per patient-year (ie, from randomization to termination of the trial).

Times until dropout, withdrawal, primary event, bleeding event, and death were analyzed using the Cox regression model.[23] Backward selection was used to identify significant risk factors. Dropout and withdrawal were regarded as censoring for all outcome variables. Secondary events were treated as censoring in the analysis of primary events and vice versa. Bleeding and other adverse events were included as time-dependent covariates in the analysis of primary events. For the calculation of bleeding rates, the time to the first hemorrhagic event was used. The INRs were calculated using linear interpolation for days where INR was not observed and consequently included as time-dependent covariates in the analysis of primary events and bleeding.

month. To estimate the recruitment fraction, all ECGs showing atrial fibrillation during 9 months in 1993 were collected from the laboratory referring patients to the study. During this period, 560 patients with atrial fibrillation were registered. Of these patients, 193 (34.5%) accepted an examination by the investigators, 260 (46.4%) refused to participate, and 107 (19.1%) were excluded because of their medical history. Major reasons for exclusion in this subgroup were ongoing oral anticoagulant therapy in 45 patients (42.1%) and presumed increased risk for adverse events due to antithrombotic therapy in 33 patients (30.8%). Six patients (5.6%) did not fulfill the inclusion criterion, 4 (3.7%) had a concomitant disease, and 18 (16.8%) were excluded for other reasons. Finally, 133 patients were included, corresponding to 24% of the 560 invited patients or to 69% of the 193 patients accepting the health examination.

During the 42-month study, 887 patients were examined by the investigators, and 677 (76.3%) were in-

cluded. Reasons for ineligibility in 210 patients are listed in the following tabulation:

	No. of Patients
Inclusion criteria not fullfilled	
Nonchronic atrial fibrillation	72
Atrial flutter	6
Mitral valve stenosis	5
Refused	29
Lone atrial fibrillation	7
Increased risk for stroke	
Recent stroke or TIA	5
Myxoma	1
Increased risk for adverse events	
Previous intracerebral hemorrhage	6
Previous adverse effects of aspirin or warfarin	2
Arterial hypertension	5
Predictable poor compliance (eg, dementia, alcoholism)	16
Permanent use of nonsteroidal anti-inflammatory drugs	6
Comcomitant diseases	
Liver disorder	4
Kidney disorder or hematuria	2
Gastritis or rectal bleeding	3
Thrombocytopenia	2
Malignant disease	4
Anemia	5
Hemorrhagic retinopathy	1
Recurrent syncopes	2
Ongoing or planned oral anticoagulant therapy	
Direct current cardioversion scheduled	17
Pacemaker	1
Other	4
Death before inclusion	2
Other	3
Total	**210**

Of the 677 eligible patients, 167 were allocated to minidose warfarin therapy; 171, to combined warfarin and aspirin therapy; 169, to aspirin therapy; and 170, to adjusted-dose warfarin therapy. During the trial, 58 patients (8.6%) dropped out, 112 (16.5%) were withdrawn, 39 (5.8%) had a primary adverse event, and 47 (6.9%) had a secondary adverse event. By the end of the trial, 421 (62.2%) of the randomized patients were receiving treatment and free of adverse events. All patients were available for follow-up.

BASELINE CHARACTERISTICS

Baseline data of the study population according to assigned treatment are listed in **Table 1**. Approximately one third of the patients had atrial fibrillation of recent onset (ie, within 1 year). At randomization, there was no statistical difference in the distribution of baseline data among the 4 groups except in respect to left ventricle fractional shortening, which was better in patients receiving aspirin ($P = .01$).

LEVEL OF ANTICOAGULATION

The median baseline INR of all randomized patients was 1.05 (range, 0.80-1.48), with no difference among the 4 groups ($P = .31$). After 1 month of treatment, the INR had increased significantly in all patients receiving warfarin in any dose and combination. In patients receiving minidose warfarin, median INR increased from 1.05 to 1.10 (range, 0.90-2.63; mean, 1.14 [SD = 0.20]) ($P<.001$); in patients receiving combined warfarin and aspirin, from 1.04 to 1.11 (range, 0.99-2.33; mean, 1.12 [SD = 0.22]) ($P = .002$); and in patients receiving adjusted-dose warfarin, from 1.11 to 2.20 (range, 1.11-4.60; mean, 2.33 [SD = 0.66]) ($P = .001$).

The INRs of patients receiving adjusted-dose warfarin were within the range of 2.0 to 3.0 for 73% of the

Table 1. Baseline Characteristics*

	Study Groups			
	Minidose Warfarin (n = 167)	Warfarin Plus Aspirin (n = 171)	Aspirin (n = 169)	Adjusted-Dose Warfarin (n = 170)
Female, %	41	41	35	43
Age, y				
Mean (SD)	74.2 (7.7)	72.7 (8.2)	73.1 (7.2)	73.2 (7.0)
Median (range)	76 (46-87)	74 (44-87)	74 (51-89)	74 (50-87)
History of hypertension, %	41	39	43	47
Previous AMI, %	7	11	7	8
Heart failure, %†	69	74	70	70
Previous TIA, %	1	4	3	3
Previous stroke, %	4	9	5	5
Diabetes, %	14	15	10	14
Cigarette smoking, %‡	29	33	38	31
Mean (SD) blood pressure, mm Hg				
Systolic	147.7 (19.5)	150.1 (18.6)	147.2 (20.3)	149.2 (18.3)
Diastolic	86.5 (8.7)	87.3 (8.4)	87.7 (9.1)	87.2 (9.1)
Results of echocardiography				
Mean left atrial diameter, mm/m^2 (SD)	27.6 (4.8)	23.4 (4.9)	23.9 (4.6)	23.7 (5.3)
Mean (SD) fractional shortening, %, §	27.3 (9.6)	27.8 (10.5)	30.1 (9.2)	27.0 (9.1)

**For study groups, patients received warfarin sodium, 1.25 mg (minidose warfarin group); warfarin sodium, 1.25 mg, plus aspirin, 300 mg (warfarin plus aspirin group); aspirin, 300 mg (aspirin group); or warfarin with the dose adjusted to the international normalized ratio of prothrombin time of 2.0 to 3.0 (adjusted-dose warfarin group). AMI indicates acute myocardial infarction; TIA, transient ischemic attack.*

†Indicates patients with New York Heart Association classification of heart failure (NYHA) criteria 2 to 3; no patients fulfilled the criteria of NYHA 4.

‡Indicates current or within 2 years.

§P = .01.

Table 2. Primary and Secondary Adverse Events*

Patients (n)	Study Groups: Minidose Warfarin (n = 167)	Warfarin Plus Aspirin (n = 171)	Aspirin (n = 169)	Adjusted-Dose Warfarin (n = 170)	Total (N = 677)
Patient-years	363	377	365	355	1460
Primary adverse events	**14**	**12**	**10**	**12**	**48**
	12 (2)	12 (0)	8 (2)	7 (5)	39 (9)
Strokes	**13**	**11**	**9**	**10**	**43**
Ischemic†	5 (1)	8 (0)	5 (0)	3 (1)	21 (2)
Hemorrhagic†	0 (0)	0 (0)	1 (0)	1 (0)	2 (0)
No infarct†	6‡ (1)	3 (0)	2 (1)	3 (2)	14 (4)
Minor	3 (0)	4 (0)	0 (0)	0 (0)	7 (0)
Nondisabling	4 (2)	3 (0)	2 (1)	4 (3)	13 (6)
Disabling	2 (0)	4 (0)	4 (0)	3 (0)	13 (0)
Fatal	2 (0)	0 (0)	2 (0)	0 (0)	4 (0)
Other TE	**1**	**1**	**1**	**2**	**5**
	1 (0)	1 (0)	0 (1)	0 (2)	2 (3)
Fatal	1 (0)	1 (0)	0 (1)	0 (0)	2 (1)
Secondary adverse events	**16**	**11**	**20**	**22**	**69**
	12 (4)	8 (3)	13 (7)	14 (8)	47 (22)
AMI	**6**	**0**	**4**	**4**	**14**
	5 (1)	0 (0)	2 (2)	3 (1)	10 (4)
Fatal	1 (1)	0 (0)	0 (1)	1 (0)	2 (2)
TIA	**4**	**2**	**2**	**1**	**9**
	3 (1)	2 (0)	1 (1)	1 (0)	7 (2)
Death	**6**	**9**	**14**	**17**	**46**
Vascular cause	2 (1)	3 (1)	4 (0)	5 (0)	14 (2)
Nonvascular cause	0 (1)	1 (1)	3 (3)	2 (4)	6 (9)
Unknown cause	2 (0)	2 (1)	3 (1)	3 (3)	10 (5)

*Study groups are described in the first footnote to Table 1. Boldface indicates total numbers of events; lightface, number of events while receiving treatment; and numbers in parentheses, numbers of events while not receiving treatment. Abbreviations are described in the first footnote to Table 1. TE indicates thromboembolic event.

†Confirmed using computed tomographic scan.

‡One patient did not undergo computed tomographic scan.

total time of treatment, above for 9%, and below for 18%. For 89% of the time, INRs were within the range of 1.8 to 3.2.

OUTCOME EVENTS

Primary Adverse Events

Thirty-nine primary thromboembolic events occurred in patients receiving treatment and 9 in patients not receiving treatment. The mean age of the patients was 76.5 (SD, 6.9) years. The events occurred from 3 to 983 (median, 291) days after randomization. In patients receiving any warfarin dose, no thromboembolic events occurred within the 2 weeks after randomization. The distribution of events in patients receiving treatment and after withdrawal is presented in **Table 2**.

Stroke. Thirty-seven patients suffered a stroke while receiving treatment. Seven strokes were categorized as minor, 13 as nondisabling, 13 as disabling, and 4 as fatal. Fatal stroke occurred in 2 patients receiving minidose warfarin and in 2 receiving aspirin. Patients with stroke underwent computed tomography, which showed ischemic infarction in 21, intracerebral hemorrhage in 2, and no lesion in 13. One patient did not undergo computed tomography.

Systemic Embolism. Two patients receiving treatment had a systemic thromboembolic event, and both events were fatal. One had an acute arterial occlusion in a lower extremity, and one had mesenteric thrombosis (Table 2).

The number of patients at risk and the cumulative primary event rates after 1, 2, and 3 years are given in **Table 3**. There were no significant differences among the 4 groups ($P = .67$), but after 1 year of treatment, there was a trend toward a lower stroke rate in patients receiving adjusted-dose warfarin (2.8%; 95% confidence intervals [CI], 0.1%-5.4%) than in those receiving combined therapy (7.2%; 95% CI, 2.6%-11.8%). Odds ratios with 95% CI for primary events are presented in **Figure 1**, and plots of survival without a primary event are presented in **Figure 2**.

Using intention-to-treat analysis, the annual risk for a primary thromboembolic event was 3.9% (95% CI, 2.3%-6.6%) in patients receiving warfarin sodium, 1.25 mg/d; 3.2% (95% CI, 1.8%-5.6%), warfarin sodium, 1.25 mg/d, plus aspirin, 300 mg/d; 2.7% (95% CI, 1.5%-5.0%), aspirin, 300 mg/d; and 3.4% (95% CI, 1.9%-6.0%), adjusted-dose warfarin.

Risk factor analysis revealed that increasing age ($P = .001$), adverse reactions to the study treatments ($P = .01$), and previous MI ($P = .04$) were independent risk factors for stroke and systemic thromboembolism. Thus, sex; study medication; and history of stroke, diabetes,

Table 3. Cumulative Rate of Primary Adverse Events*

Study Groups	Time, y 1	2	3
Minidose warfarin (n = 167)			
Rate (95% CI), %	5.8 (1.9-9.7)	8.0 (3.1-12.9)	11.9 (4.8-19.0)
No. of patients at risk	106	56	12
No. of cumulated events	8	10	12
Warfarin plus aspirin (n = 171)			
Rate (95% CI), %	7.2 (2.6-11.8)	9.4 (4.0-14.8)	12.8 (4.5-21.1)
No. of patients at risk	96	51	15
No. of cumulated events	9	11	12
Aspirin (n = 169)			
Rate (95% CI), %	3.6 (0.4-6.8)	6.0 (1.5-10.5)	8.4 (1.9-14.9)
No. of patients at risk	100	45	15
No. of cumulated events	5	7	8
Adjusted-dose warfarin (n=170)			
Rate (95% CI), %	2.8 (0.1-5.4)	5.5 (1.0-10.0)	8.3 (1.3-15.3)
No. of patients at risk	87	41	10
No. of cumulated events	4	6	7

*Study groups are described in the first footnote to Table 1. Differences between groups were not significant (P = .67). CI indicates confidence interval.

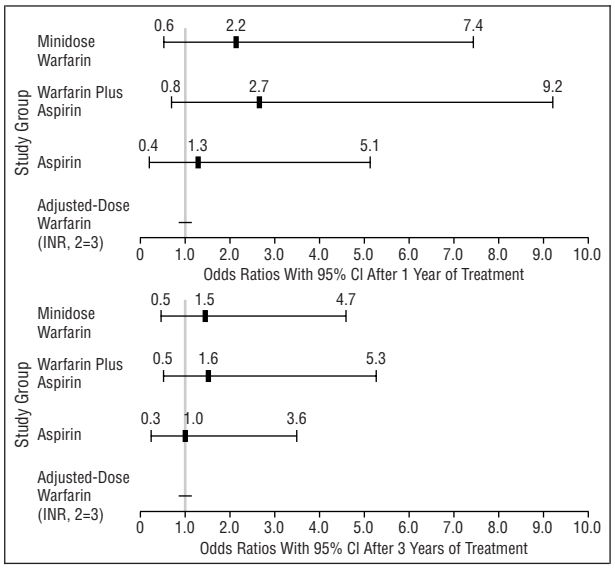

Figure 1. *Odds ratios for primary adverse events. INR indicates international normalized ratio of prothromin time; CI, confidence interval. Study groups are described in the first footnote to Table 1.*

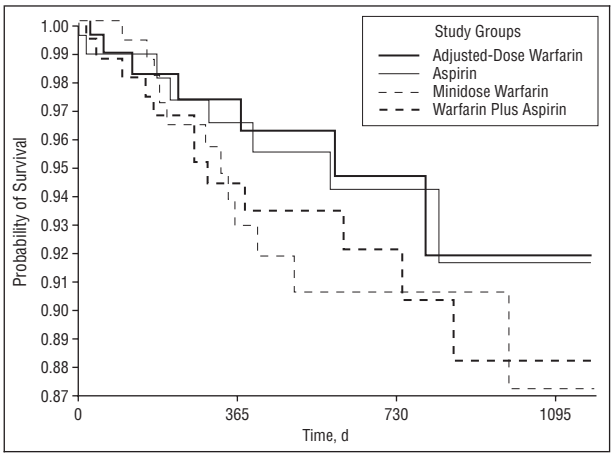

Figure 2. *Survival without primary adverse event while receiving treatment (P = .67). INR indicates international normalized ratio of prothrombin time. Study groups are described in the first footnote to Table 1.*

smoking, heart failure, and hypertension had no significant impact on the occurrence of primary outcome events. The significantly better fractional shortening in patients receiving aspirin may, however, have been a confounding factor for the relatively small number of thromboembolic events in these patients.

A total of 194 patients were younger than 75 years and had no history of hypertension, stroke, TIA, or diabetes. Three of the 38 low-risk patients receiving warfarin sodium, 1.25 mg; 1 of 54 receiving warfarin plus aspirin; none of 55 receiving aspirin; and 2 receiving adjusted-dose warfarin suffered a primary adverse event. The corresponding cumulative rates after 3 years were 9.7% (95% CI, 3.1%-29.9%), 2.6% (95% CI, 0.4%-18.2%), 0%, and 11.4% (95% CI, 2.9%-46.1%), respectively. Without respect to assigned treatment, the cumulative risk after 3 years was 5.3% (95% CI, 2.4%-11.9%) in low-risk patients.

Secondary Adverse Events

Forty-seven patients receiving treatment and 22 not receiving treatment had a secondary adverse event. The distribution of events according to assigned treatment appears in Table 2.

Myocardial Infarction. Five patients receiving minidose warfarin, 2 receiving aspirin, and 3 receiving adjusted-dose warfarin had an MI. One patient receiving minidose warfarin and 1 receiving adjusted-dose warfarin died.

Transient Ischemic Attack. Seven patients had a TIA. The distribution for the 4 groups is shown in Table 2.

Table 4. Adverse Effects of Study Treatments*

Adverse Effects	Study Groups			
	Minidose Warfarin	Warfarin Plus Aspirin	Aspirin	Adjusted-Dose Warfarin
Minor bleeding	21	28	26	42
Major bleeding	3	1	5	4
Intracerebral	1	0	1†	1 + 1†
Cumulative rate (95% confidence interval) of bleeding after 3 y, %	24.7 (14.0-35.4)	24.4 (15.3-33.5)	30.0 (15.0-45.0)	41.1 (29.4-52.8)‡
Rash	0	4	1	0
Dyspepsia	0	2	7	0
Diarrhea	0	1	0	0
Constipation	0	1	1	0
Tinnitus	0	0	1	0

*Study groups are described in the first footnote to Table 1. Unless otherwise indicated, data are given as number of patients.
†Indicates fatal bleeding.
‡P=.003.

Mortality. Thirty patients receiving treatment died of causes other than thromboembolic events or AMI (Table 2).

In patients receiving treatment, vascular events accounted for 22 deaths (57.9%). Of these, 2 were due to MI, 4 to stroke, and 2 to systemic thromboembolism. Of 14 deaths unrelated to other primary and secondary adverse events, 4 were ascribed to congestive heart failure, 1 to a traumatic intracerebral hemorrhage, and 9 to sudden death. Nonvascular causes accounted for 6 secondary adverse events (15.8%). Of these, 4 events were ascribed to a malignant disease, 1 event to pneumonia, and 1 event to pulmonary insufficiency. In 10 patients (26.3%) who unexpectedly died at home, autopsy was not performed, and the cause of death remained unknown.

In patients receiving minidose warfarin, cumulative mortality after 1, 2, and 3 years was 2.9%, 3.9%, and 3.9% (95% CI, 0.5%-7.3%), respectively; in patients receiving combined warfarin and aspirin, 1.3%, 3.6%, and 5.9% (95% CI, 0.3%-11.5%), respectively; in patients receiving aspirin, 3.2%, 11.1%, and 13.4% (95% CI, 5.4%-21.4%), respectively; and in patients receiving adjusted-dose warfarin, 5.6%, 8.0%, and 10.3% (95% CI, 3.5%-17.1%), respectively ($P = .27$). Increasing age was the only independent risk factor for death ($P = .003$).

ADVERSE EVENTS AND DISCONTINUATION OF THERAPY

Hemorrhagic Events

A total of 130 patients experienced bleeding (**Table 4**). Thirteen major and 139 minor bleeding events were noted. In 3 patients, a major hemorrhagic event was proceeded by a minor event, and 16 patients had more than 1 minor bleeding event.

Traumatic intracerebral bleeding occurred in 1 patient receiving minidose warfarin and in 1 receiving adjusted-dose warfarin. Furthermore, 1 patient receiving aspirin and 1 receiving adjusted-dose warfarin each had a spontaneous intracerebral hemorrhage.

The cumulative incidence of bleeding events after 3 years of treatment was 24.7% in patients receiving minidose warfarin; 24.4%, warfarin plus aspirin; 30.0%, aspirin; and 41.1%, adjusted-dose warfarin. The rate of bleeding was significantly higher in patients receiving adjusted-dose warfarin than in any of the other groups ($P = .003$), but the difference was ascribed only to a higher rate of minor bleeding. Adding ulcer dyspepsia and allergic reactions to the calculation, the cumulated rate of adverse events in patients receiving aspirin alone increased to 46.2% after 3 years (Table 4). Thus, adverse events occurred with the same rate in patients receiving adjusted-dose warfarin and those receiving aspirin, 300 mg/d. Adverse events occurred less frequently in patients receiving minidose warfarin alone and in combination with aspirin.

Risk factors for bleeding were previous MI ($P = .001$) and treatment with adjusted-dose warfarin ($P = .001$), with risk increasing proportionately with INR. Thus, arterial hypertension, previous stroke or TIA, smoking, and high age had no impact on this outcome.

INR Before Ischemic Stroke or Major Bleeding Event With Adjusted-Dose Warfarin

Of patients randomized to adjusted-dose warfarin therapy, 6 had an ischemic stroke and 4 had a major bleeding event while receiving the medication. For each patient, the last 3 INRs obtained in the study laboratory before the events are presented in **Table 5**. All patients with stroke had the last INR within the therapeutic range, and no major variations in the anticoagulation level were seen. Major bleeding events also occurred during stable anticoagulant therapy within or below the therapeutic level.

Discontinuation of the Study Treatments

In 170 patients (25.1%), the study treatment was permanently discontinued for reasons other than primary and secondary adverse events. Of these, 58 (8.6%) dropped out, and 112 (16.5%) were withdrawn by the investiga-

Table 5. INR Before Stroke or Major Bleeding Events in Patients Receiving Adjusted-Dose Warfarin*

Patient Subgroup	Recent INRs, Month 1	2	3
6 Patients with ischemic stroke†			
Patient with nondisabling stroke	2.0	2.5	2.3
Patient with disabling stroke	2.5	2.3	2.7
Patient with disabling stroke	2.7	2.3	2.2
Patient with nondisabling stroke	3.9	1.8	2.1
Patient with disabling stroke‡	1.8	2.1	2.1
Patient with nondisabling stroke	2.3	2.1	3.0
4 Patients with major bleeding events			
Patient with subretinal hemorrhage	2.2	2.0	2.8
Patient with nondisabling intracerebral hemorrhage§	2.0	1.8	1.3
Patient with traumatic intracranial bleeding (fatal)	2.6	2.4	2.3
Patient with bleeding from rectal tumor	3.1	3.3	2.1

*Study group is described in the first footnote to Table 1. INR indicates international normalized ratio of prothrombin time. INRs were obtained at the 3 last visits in the laboratory (once every 4 weeks).

†For patients with ischemic stroke, disabling and nondisabling indicate the severity of stroke.

‡ Indicates weekly monitoring.

§Indicates weekly monitoring succeeded by monthly monitoring.

tors. The reasons for withdrawal were adverse effects to the study treatment in 42, poor compliance in 18, prescription of adjusted-dose warfarin by other physicians in 17, permanent need of a nonsteroidal antiinflammatory drug in 14, and miscellaneous in 19. The median age of all excluded patients was 76 years (range, 46-88 years), and the median time of participation to dropout or withdrawal was 171 days (range, 2-1134 days). Increasing age was an independent risk factor for dropout ($P<.001$), and high heart rate ($P=.03$), enlargement of the left atrium ($P=.02$), and low fractional shortening ($P=.05$) were independent risk factors for withdrawal.

COMMENT

As a relatively large number of patients were expected to drop out or to be withdrawn from the study with subsequent varying use of antithrombotics, the data of the AFASAK 2 Study were handled as survival data focusing on the cumulative rates of primary and secondary events in patients actually receiving the study medication.

In our study, there was no significant difference in the frequency of stroke, systemic thromboembolic events, AMI, TIA, or death among groups. However, the AFASAK 2 Study was underpowered due to the early termination after inclusion of only 45% of the estimated sample size, and, accordingly, the results should be interpreted with caution.

The rates of primary events of 7.2% for patients receiving combined warfarin and aspirin and 2.8% for those receiving adjusted-dose warfarin after 1 year in the AFASAK 2 Study are comparable to the annual rates of ischemic stroke and systemic embolism in the recent Stroke Prevention in Atrial Fibrillation III (SPAF III) randomized trial, where the effects of low-intensity warfarin therapy (INR, 1.2-1.5) plus aspirin, 325 mg/d, and adjusted-dose warfarin therapy (INR, 2.0-3.0) were investigated in high-risk patients with nonvalvular atrial fibrillation.[18] In the SPAF III trial, the annual rate of ischemic stroke and systemic embolism was 1.9% among patients receiving adjusted-dose warfarin and 7.9% among patients receiving combined therapy. After 3 years of treatment, however, the difference between patients receiving adjusted-dose warfarin and those receiving warfarin plus aspirin was less pronounced in our study than in the SPAF III trial.[18] Due to the early termination of the AFASAK 2 Study, the significance of this finding will remain unknown.

The somewhat lower mean incidence of stroke and systemic embolism during combined warfarin and aspirin therapy in the AFASAK 2 Study than in the SPAF III trial[18] is interesting, as the mean INR during combined warfarin and aspirin therapy was lower in our study than in the SPAF III trial (1.1 vs 1.3, after 1 month of therapy) and as 71.0% of the participants in the AFASAK 2 Study had at least 1 of the high-risk factors for stroke required for inclusion in the SPAF III high-risk group. The difference may be that the AFASAK 2 Study patients were outpatients recruited from general practice, whereas many SPAF III patients were recruited from hospitals.

In the recently published Studio Italiano Fibrillazione Atriale (SIFA) of indobufen vs warfarin therapy for secondary prevention of major vascular events in nonrheumatic atrial fibrillation, the combined incidence of nonfatal stroke, systemic embolism, MI, and death due to vascular events (after 1 year of follow-up) was 10.6% in the indobufen group and 9.0% in the warfarin group (probability of equivalence, $P<.025$).[19] Because of the small absolute difference between the groups, these investigators suggested indobufen as an alternative antithrombotic treatment for patients with contraindications for warfarin therapy.

Like the SPAF III trial,[9] the AFASAK 2 Study suggests aspirin as an alternative treatment for primary stroke prevention in patients with atrial fibrillation for whom adjusted-dose warfarin therapy is inappropriate. Due to the significant superiority of adjusted-dose warfarin therapy compared with low-intensity, fixed-dose warfarin plus aspirin therapy in the SPAF III trial and the insignificant outcome of the AFASAK II Study, very-low-intensity warfarin plus aspirin therapy should not be used in patients with atrial fibrillation.

The antithrombotic treatments in the AFASAK 2 Study were safe in regard to bleeding and other adverse effects, and major bleeding events were equally distributed among the 4 groups. Neither combined warfarin-aspirin therapy nor adjusted-dose warfarin therapy caused more severe hemorrhages than minidose warfarin and aspirin given separately. Minor bleeding events, however, were significantly more frequent in patients assigned to adjusted-dose warfarin therapy than in any of the other groups.

In the AFASAK 2 Study, high age was a risk factor for stroke but not for bleeding events or withdrawal. Accordingly, we do not suggest that high age per se should

contraindicate oral anticoagulant therapy in patients with atrial fibrillation.

Several trials have convincingly shown that oral anticoagulant therapy with warfarin is effective for primary and secondary stroke prevention in patients with atrial fibrillation. Concerning the optimal intensity of warfarin, more trials now indicate that warfarin given at an INR of less than 2.0 is not effective and that the optimal INR is from 2.0 to 3.0.[18,19] The results of the AFASAK 2 Study do not justify a change in the present recommendations.

We suggest that future attempts to reduce the risk for stroke in patients with atrial fibrillation should focus on the arrhythmia per se to control the heart rate and to improve the left ventricular function and on optimizing the organization of oral anticoagulant therapy.

Accepted for publication January 15, 1998.

This study was supported by grants from The Danish Heart Foundation, Copenhagen; Nycomed DAK A/S Roskilde, Denmark; Du Pont Pharma, Wilmington, Del; The Danish Foundation for Medical Research for the Region of Copenhagen, the Faroe Islands, and Greenland, Copenhagen; The Danish General Practitioners Foundation for the Municipalities of Copenhagen, Frederiksburg, and Dragør, Copenhagen; The Danish Medical Research Foundation, Copenhagen; the Sophus and Astrid Jacobsen Foundation, Virum, Denmark; The Jacob and Olga Madsen Foundation, Copenhagen; The Katherine and Vigo Skovgård Foundation, Roskilde, Denmark; The Danish National Stroke and Aphasis Foundation, Copenhagen; The Beckett Foundation, Copenhagen; The Leo Pharmaceuticals Research Foundation, Ballerup, Denmark; The Hede Nielsen Family Foundation, Copenhagen; The Director E. Danielsen Foundation, Lyngby, Denmark; The Therese Maria Hansen Grant, Bagsvaerd, Denmark; The Michael Hermann Nielsen Grant, Copenhagen; and The Mimi and Victor Larsen Foundation, Birkerod, Denmark.

We thank secretary Helle Vilhelmsen and laboratory technicians Käthe Rasmussen and Isabella Frederiksen for their enthusiastic work during the trial; the general practitioners in Copenhagen, Frederiksberg, Denmark, and the counties of Roskilde and Copenhagen for their cooperation; the staff and the laboratory technicians of Copenhagen General Practitioners Laboratory for accommodation and support; Sissel Vorstrup, MD, DMSc; Per Sidenius, MD, DMSc; Jan Kyst Madsen, MD, DMSc; and Jens Kastrup, MD, DMSc, for serving on the end-point committee; and Jørgen Hilden, MD; Kai Jensen, MD, DMSc; and Knud Skagen, MD, DMSc, for serving on the safety committee.

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