

Antithrombotic Therapy To Prevent Stroke in Patients with Atrial Fibrillation: A Meta-Analysis

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Purpose: To characterize the efficacy and safety of anticoagulants and antiplatelet agents for prevention of stroke in patients with atrial fibrillation.

Data Sources: Randomized trials identified by using the search strategy developed by the Cochrane Collaboration Stroke Review Group.

Study Selection: All published randomized trials testing antithrombotic agents to prevent stroke in patients with atrial fibrillation.

Data Extraction: Data on interventions, number of participants, duration of exposure and occurrence of all stroke (ischemic and hemorrhagic), major extracranial bleeding, and death were extracted independently by two investigators.

Data Synthesis: Sixteen trials included a total of 9874 participants (mean follow-up, 1.7 years). Adjusted-dose warfarin (six trials, 2900 participants) reduced stroke by 62% (95% CI, 48% to 72%); absolute risk reductions were 2.7% per year for primary prevention and 8.4% per year for secondary prevention. Major extracranial bleeding was increased by warfarin therapy (absolute risk increase, 0.3% per year). Aspirin (six trials, 3119 participants) reduced stroke by 22% (CI, 2% to 38%); absolute risk reductions were 1.5% per year for primary prevention and 2.5% per year for secondary prevention. Adjusted-dose warfarin (five trials, 2837 participants) was more efficacious than aspirin (relative risk reduction, 36% [CI, 14% to 52%]). Other randomized comparisons yielded inconclusive results.

Conclusions: Adjusted-dose warfarin and aspirin reduce stroke in patients with atrial fibrillation, and warfarin is substantially more efficacious than aspirin. The benefit of antithrombotic therapy was not offset by the occurrence of major hemorrhage among participants in randomized trials. Judicious use of antithrombotic therapy, tailored according to the inherent risk for stroke, importantly reduces stroke in patients with atrial fibrillation.

Nonvalvular atrial fibrillation is an important independent risk factor for stroke. Since 1989, 16 published clinical trials have conducted 36 separate randomized comparisons of antithrombotic agents in approximately 10 000 participants with atrial fibrillation (1–17). Previously published meta-analyses and pooled analyses of individual patient data (18–20) have considered, in various combinations, the first 6 clinical trials to be published. We present a meta-analysis of all currently available trials to further characterize the comparative efficacy and safety of antithrombotic therapy for the prevention of stroke in patients with atrial fibrillation.

Methods

Randomized trials testing long-term (>3 months) use of antithrombotic agents in patients with atrial fibrillation were sought by a computerized search of the OVID/MEDLINE databases (from 1966 to 1999, not restricted by language) and by inquiries to the Cochrane Collaboration Stroke Review Group and Antithrombotic Trialists Collaboration. Studies of atrial fibrillation associated with prosthetic cardiac valves or mitral stenosis were not considered; trials reporting results for subgroups of participants with atrial fibrillation among other participants without atrial fibrillation were included (14, 16). Double-blind and nonblinded trials were included, and sensitivity analysis was used to compare pooled results, as appropriate. We excluded one randomized trial in which results for participants with atrial fibrillation (approximately half of all participants) were not reported separately (21). We have anecdotal knowledge of two additional trials that are ongoing or have not been published (Table 1).

Two reviewers independently extracted data from published sources on the number of patients treated, total follow-up exposure, and the occurrence of five outcomes by intention-to-treat analysis: all stroke (hemorrhagic and ischemic), ischemic stroke, intracranial hemorrhage, all-cause mortality, and major extracranial bleeding. The criteria for each of these

Table 1. Randomized Clinical Trials for Nonvalvular Atrial Fibrillation*

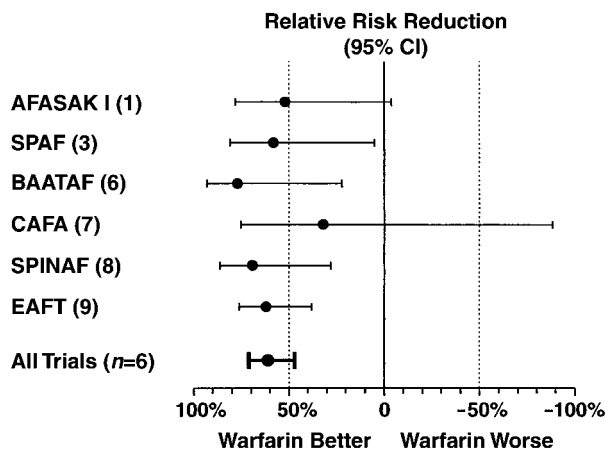
Study (Reference)	Year Published	Participants, n
Large published trials		
AFASAK (1)	1989	1007
AFASAK II (2)	1998	677
SPAF (3)	1991	1330
SPAF II (4)	1994	1100
SPAF III (5)	1996	1044
BAATAF (6)	1990	420
CAFA (7)	1991	378
SPINAF (8)	1992	571
EAFI (9, 17)	1993	1007
SIFA (10)	1997	916
MWNAF (11)	1998	303
PATAF (15)	1997	729
Small trials or pilot trials		
Harenberg et al. (12)	1993	75
LASAF (13)	1999	285
Trials that included subgroups of patients with atrial fibrillation		
ESPS II (14)	1997	429
UK-TIA (16)	1999	49
Ongoing or unpublished trials		
FACCS	-	-
SAFT	-	-

* AFASAK = Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study; BAATAF = Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA = Canadian Atrial Fibrillation Anticoagulation Study; EAFI = European Atrial Fibrillation Trial; ESPS II = European Stroke Prevention Study II; FACCS = French Aspirin Coumarin Collaborative Study; LASAF = Low-Dose Aspirin, Stroke, and Atrial Fibrillation Pilot Study; MWNAF = Minidose Warfarin in Nonrheumatic Atrial Fibrillation; PATAF = Prevention of Arterial Thromboembolism in Atrial Fibrillation; SAFT = Stroke in Atrial Fibrillation Study; SPAF = Stroke Prevention in Atrial Fibrillation Study; SPINAF = Stroke Prevention in Nonrheumatic Atrial Fibrillation; UK-TIA = United Kingdom TIA Study.

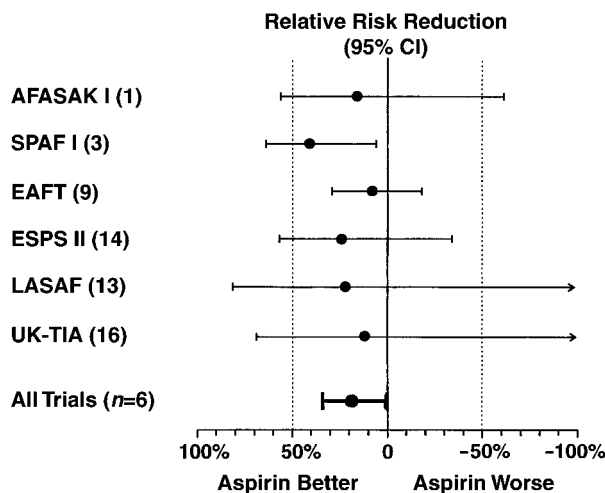
outcomes were those used in each individual trial; major deviations are noted in footnotes to the tables. Intracranial hemorrhage included spontaneous and traumatic subdural hematomas. Transient ischemic attacks (TIAs) were not considered. The percentage of participants who underwent neuroimaging or autopsy to reliably distinguish between ischemic or hemorrhagic stroke varied, and this percentage was not always reported. Therefore, all stroke (hemorrhagic and ischemic) was chosen as the primary outcome. Effects of antithrombotic therapy on combinations of events (for example, stroke, myocardial infarction, or vascular death) and effects of age and sex were not consistently reported and are not considered here. Intention-to-treat results were used for the main analyses, but only results noted during treatment were available for one small trial that tested antiplatelet agents (14). Primary prevention refers to patients without previous stroke or TIA; secondary prevention refers to patients with previous stroke or TIA.

Detailed consideration of the design and execution of individual trials can be found in our systematic reviews prepared for the Cochrane Collaboration Stroke Review Group (16, 22). The authors participated in the Stroke Prevention in Atrial Fibrillation (SPAF) I, II, and III clinical trials (1987

Adjusted-Dose Warfarin Compared with Placebo



Aspirin Compared with Placebo



Warfarin Compared with Aspirin

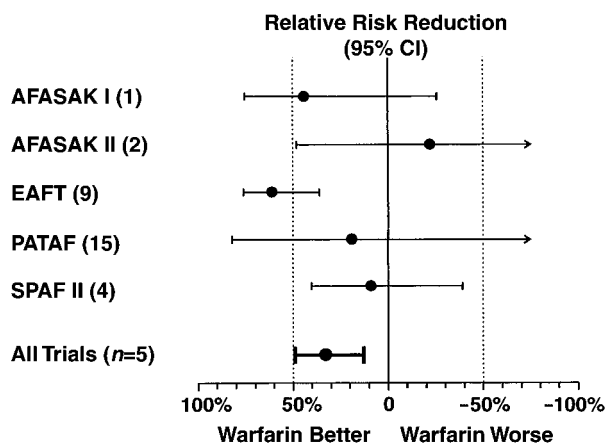


Figure. Effects on all stroke (ischemic and hemorrhagic) of therapies for patients with atrial fibrillation. **Top.** Adjusted-dose warfarin compared with placebo (six randomized trials). **Middle.** Aspirin compared with placebo (six randomized trials). **Bottom.** Adjusted-dose warfarin compared with aspirin (five randomized trials). Horizontal lines are 95% CIs around the point estimates. AFASAK = Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study; BAATAF = Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA = Canadian Atrial Fibrillation Anticoagulation Study; EAFI = European Atrial Fibrillation Trial; ESPS II = European Stroke Prevention Study II; LASAF = Low-Dose Aspirin, Stroke, and Atrial Fibrillation Pilot Study; PATAF = Prevention of Arterial Thromboembolism in Atrial Fibrillation; SPAF = Stroke Prevention in Atrial Fibrillation Study; SPINAF = Stroke Prevention in Nonrheumatic Atrial Fibrillation; UK-TIA = United Kingdom TIA Study.

Table 2. Adjusted-Dose Warfarin Compared with Placebo*

Study (Reference)	Year	Type of Prevention	Total Participants	Target International Normalized Ratio	Warfarin Group			Placebo Group			Relative Risk Reduction (95% CI)†	Absolute Risk Reduction per Year
					Strokes	Participants	Person-Years	Strokes	Participants	Person-Years		
					<i>n</i>	<i>n</i>		<i>n</i>			%	
AFASAK (1)	1989	Primary	671	2.8–4.2	9	335	413	19	336	398	54	2.6
SPAF (3)	1991	Primary	421	2.0–4.5‡	8	210	263	19	211	245	60§	4.7
BAATAF (6)	1990	Primary	420	1.5–2.7‡	3	212	487	13	208	435	78§	2.4
CAFA (7)	1991	Primary	378	2.0–3.0	6	187	237	9	191	241	33	1.2
SPINAF (8)	1992	Primary	571	1.4–2.8‡	7	281	489	23	290	483	70§	3.3
EAFI (9)¶	1993	Secondary	439	2.5–4.0	20	225	507	50	214	405	68§	8.4
All trials**	–	–	2900	–	53	1450	2396	133	1450	2207	62 (48–72)	3.1

* AFASAK = Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study; BAATAF = Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA = Canadian Atrial Fibrillation Anticoagulation Study; EAFI = European Atrial Fibrillation Trial; SPAF = Stroke Prevention in Atrial Fibrillation Study; SPINAF = Stroke Prevention in Nonrheumatic Atrial Fibrillation.

† For combined ischemic and hemorrhagic stroke by intention-to-treat analysis; trials of primary prevention included 3%–8% of participants with previous stroke or transient ischemic attack. In EAFI, a variety of coumarins were used, not only warfarin.

‡ Prothrombin time ratios were used; international normalized ratios were estimated by the investigators.

§ $P < 0.05$, two-sided.

|| 46% of exposure in the control group occurred during self-selected use of varying doses of aspirin.

¶ Various types of coumarin were used.

** Weighted estimates of relative risk reduction ($P > 0.2$ for homogeneity) and absolute risk reduction ($P > 0.2$ for homogeneity); see the Methods section.

to 1999), which were funded by the National Institute of Neurological Disorders and Stroke.

Meta-analyses of the results of the trials are presented as relative risk reductions and absolute risk reductions for treatment groups compared with control groups. To estimate the relative risk reduction, the combined odds ratio was computed by using the modified Mantel–Haenszel (Peto) method (23), and the estimate was then subtracted from 1. For a study in which no events were observed for a spe-

cific outcome and treatment, 0.5 was added to the empty cell. The absolute risk reduction is a weighted estimate of the difference in annualized event rates (24). Before we estimated risk reduction, we tested the assumption of the statistical homogeneity of the treatment effect (across trials and within a specific scenario) by using the Q_L statistic for the relative odds scale (24) or the Q_W statistic with unequal weights for the absolute risk scale (24). Lack of homogeneity across trials precluded estima-

Table 3. Antiplatelet Agents Compared with Placebo*

Study (Reference)	Year	Type of Prevention†	Total Participants	Dosage	Antiplatelet Treatment Group		
					Strokes	Participants	Person-Years
					<i>n</i>	<i>n</i>	
Aspirin compared with placebo							
AFASAK (1)	1989	Primary	672	75 mg/d	16	336	409
SPAF (3)	1991	Primary	1120	325 mg/d	25	552	723
EAFI (9)	1993	Secondary	782	300 mg/d	88	404	853
ESPS II (14)	1997	Secondary	211	25 mg twice per day	17	104	123
LASAF (13)	1996	Primary	195	125 mg/d	4	104	145
			181	125 mg every other day	1	90	148
UK-TIA (16)	1999	Secondary	28	300 mg/d	3	13	52
			36	1200 mg/d	5	21	84
All aspirin trials	–	–	3119	–	159	1624	2539
Dipyridamole compared with placebo							
ESPS II (14)	1997	Secondary	221	200 mg twice per day	20	114	133
Dipyridamole and aspirin compared with placebo							
ESPS II (14)	1997	Secondary	211	Dipyridamole, 200 mg twice per day, plus aspirin, 25 mg twice per day	14	104	127
All antiplatelet trials¶	–	–	3337	–	193	1842	2799

* AFASAK = Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study; ESPS II = European Stroke Prevention Study II; LASAF = Low-Dose Aspirin, Stroke, and Atrial Fibrillation Pilot Study; SPAF = Stroke Prevention in Atrial Fibrillation Study; UK-TIA = United Kingdom TIA Study.

† In trials of primary prevention, 6%–8% of participants had previous stroke or transient ischemic attack.

‡ For combined ischemic and hemorrhagic stroke by intention-to-treat analysis unless otherwise specified.

§ Only results of efficacy (that is, results of participants receiving therapy) were reported.

|| Total patient-years of exposure were estimated from mean duration of follow-up because total exposure was not published.

¶ Weighted estimates of relative risk reductions ($P > 0.2$ for homogeneity for all aspirin trials and for all antiplatelet trials) and absolute risk reductions ($P > 0.2$ for homogeneity for all aspirin trials and $P > 0.2$ for all antiplatelet trials).

tion of the treatment effect, as noted. Homogeneity was assessed for all meta-analyses of relative risk reduction and absolute risk reduction; the exact *P* value was reported for all main analyses and for analyses in which the *P* value was less than 0.2. Estimates of relative risk reduction in individual trials were computed by subtracting the estimated odds ratio from 1. We estimated absolute risk reductions in individual trials by calculating the absolute difference in annualized event rates (events per person-years of observation). A *P* value less than 0.05 was considered statistically significant; all tests and CIs are two-sided. Calculations were done by using SPSS software (SPSS, Inc., Chicago, Illinois) and EGRET software (Cytel Software Corp., Cambridge, Massachusetts).

Results

Sixteen randomized trials published between 1989 and 1999 included 9874 participants with nonvalvular atrial fibrillation, with 2239 participants assigned to placebo (Table 1) (1–16). Total reported exposure was about 16 400 person-years (mean follow-up, 1.7 years). Fourteen trials included only participants with atrial fibrillation (1–13, 15); 2 trials included participants with atrial fibrillation in larger trials of secondary stroke prevention (14, 16). Warfarin was used exclusively in 10 trials testing oral anticoagu-

lant agents; other derivatives of coumarin were also used in 2 additional trials (9, 15).

Adjusted-Dose Warfarin Compared with Placebo

In six trials involving 2900 patients with a total of 186 strokes, anticoagulation with oral vitamin K antagonists was compared with placebo (in five trials [1, 3, 7–9]) or control (in one trial [6]) (Table 2). The mean age of participants at study entry was 69 years (approximately 20% of participants were >75 years of age). Twenty-nine percent of participants were women, 45% had hypertension, and 20% had previous stroke or TIA. The target range for the international normalized ratio (INR) varied (Table 2); the mean achieved INR ranged from 2.0 to 2.6 in the five primary prevention trials and was 2.9 in the single secondary prevention trial. Mean duration of follow-up ranged from 1.2 to 2.3 years (overall average, 1.6 years per participant). The rate of stroke among participants who were not assigned to receive anticoagulation averaged 4.6% per year for primary prevention and 12.3% per year for secondary prevention. Four of these six trials were stopped at an interim analysis because of treatment efficacy (1, 3, 6, 8).

Meta-analysis showed that therapy with adjusted-dose warfarin reduced the relative risk for stroke by 62% (95% CI, 48% to 72%). This effect was statistically significant in four individual trials (3, 6, 8, 9) (Figure). The pooled result of primary prevention trials (59% reduction) was similar to that from the secondary prevention trial (68% reduction); results from the two double-blind trials (58% reduction) (7, 8) and the four open-label trials (63% reduction) (1, 3, 6, 9) were also similar. Warfarin was associated with similar relative risk reductions in disabling stroke (59%) and nondisabling stroke (61%). The absolute risk reduction for all stroke was 2.7% per year (number needed to treat [NNT] for 1 year to prevent one stroke, 37) for primary prevention and 8.4% per year (NNT, 12) for secondary prevention.

When only ischemic strokes were considered, treatment with adjusted-dose warfarin was associated with a 65% (CI, 52% to 74%) relative risk reduction. Twice as many intracranial hemorrhages were identified in participants who were assigned to receive warfarin (six compared with three), but the difference was not statistically significant. The rate of intracranial hemorrhage averaged 0.3% per year during anticoagulation and was 0.1% per year with placebo. The rate of major extracranial hemorrhage averaged 0.6% per year in patients who received placebo. The relative risk for major extracranial hemorrhage was 2.4 (CI, 1.2 to 4.6; absolute risk increase, 0.3% per year) for participants who received warfarin (excluding one trial in which almost half of the control group took aspirin [6]). All-cause

Table 3—Continued

Strokes	Placebo Group		Relative Risk Reduction (95% CI)†	Absolute Risk Reduction per Year
	Participants	Person-Years		
	<i>n</i>		%	
19	336	398	17	0.9
44	568	734	44	2.5
90	378	734	11	1.9
23	107	111	29§	6.9
3	91	135	–17	–0.5
3	91	135	67	1.6
4	15	60	17	0.9
4	15	60	14	0.7
190	1601	2363	22 (2 to 38)	1.7
23	107	111	22 (–60 to 62)§	5.7
23	107	111	43 (–24 to 74)§	9.7
236	1815	2585	24 (7 to 39)	1.9

Table 4. Adjusted-Dose Warfarin Compared with Other Antithrombotic Regimens*

Study (Reference)	Year	Type of Prevention	Total Participants	Target International Normalized Ratio	Target Dosage
			<i>n</i>		<i>mg/d</i>
Adjusted-dose warfarin compared with aspirin					
AFASAK (1)	1989	Primary	671	2 to 3	75
SPAF II (4)	1994	Primary	—	2.0 to 4.5	325
		Age ≤75	715	—	
		Age >75	385	—	
EAFI (9)‡	1993	Secondary	455	2.5 to 4.0	300
AFASAK II (2)	1998	Primary	339	2 to 3	300
PATAF (15)‡	1997	Primary	272	2.5 to 3.5	150
All trials		—	2837		
Adjusted-dose warfarin compared with low- or fixed-dose warfarin plus aspirin					
SPAF III (5)	1996	Primary and Secondary	1044††	2 to 3	1 to 3 plus 325
AFASAK II (2)	1998	Primary	341	2 to 3	1.25 plus 300
Adjusted-dose warfarin compared with indobufen					
SIFA (10)	1997	Secondary	916	2.0 to 3.5	400
Adjusted-dose warfarin compared with low- or fixed-dose warfarin					
AFASAK II (2)	1998	Primary	337	2 to 3	1.25
MWNAF (11)	1998	Primary	303	2 to 3	1.25
PATAF (15)	1997	Primary	253	2.5 to 3.5	1.1 to 1.6‡‡
All trials			893		

* AFASAK = Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study; EAFI = European Atrial Fibrillation Trial; MWNAF = Minidose Warfarin in Nonrheumatic Atrial Fibrillation; PATAF = Prevention of Arterial Thromboembolism in Atrial Fibrillation; SIFA = Studio Italiano Fibrillazione Atriale; SPAF = Stroke Prevention in Atrial Fibrillation.

† For combined ischemic and hemorrhagic strokes by intention-to-treat analysis.

‡ Various types of coumarin were used.

§ Total patient-years of exposure were estimated from mean duration of follow-up because total exposure was not published.

|| $P < 0.05$, two-sided.

¶ Weighted estimates ($P = 0.09$ for homogeneity for comparisons with aspirin and $P > 0.2$ for comparisons with low-dose warfarin).

** Weighted estimates ($P = 0.2$ for homogeneity for comparisons with aspirin and $P > 0.2$ for comparisons with low-dose warfarin).

†† Preselected as those with high rates of stroke during aspirin therapy.

‡‡ International normalized ratio.

mortality decreased in participants who received warfarin (relative risk reduction, 26% [CI, 4% to 43%]; $P > 0.2$ for homogeneity; absolute risk reduction, 1.6% per year).

Antiplatelet Therapy Compared with Placebo

Six trials compared antiplatelet therapy with placebo (1, 3, 9, 13, 14, 16). In these trials, 3337 participants experienced a total of 376 strokes while being randomly assigned to receive antiplatelet therapy or placebo (Table 3). In five trials (1, 3, 9, 14, 16), assignment was double-blind. Approximately 90% of total follow-up exposure during antiplatelet therapy was with aspirin alone. Aspirin dosage ranged from 25 mg twice daily to 1300 mg/d. On the basis of available data from the three largest trials (1, 3, 9), the mean age of participants was 70 years (about 33% of participants were > age 75 years). Thirty-eight percent of participants were women, 46% had hypertension, and 40% had previous stroke or TIA. Mean duration of follow-up in these trials ranged from 1.2 to 4 years (overall average, 1.5 years per participant). The average rate of stroke among participants as-

signed to placebo was 5.2% per year for primary prevention and 12.9% per year for secondary prevention.

Meta-analysis of all six trials showed that aspirin reduced the incidence of stroke by 22% (CI, 2% to 38%). On the basis of these six trials, the absolute risk reduction was 1.5% per year (NNT, 67) for primary prevention and 2.5% per year (NNT, 40) for secondary prevention.

Although all six trials showed trends toward reduced stroke that were associated with aspirin (Figure), this result was statistically significant only in the SPAF Study (3), which was stopped at an interim analysis because of aspirin's efficacy. This trial had the highest proportion of nondisabling stroke (52%); the effect of aspirin was qualitatively different for nondisabling stroke (relative risk reduction, 62%; $P = 0.008$) than for disabling stroke (relative risk reduction, 17%; $P > 0.2$). When disabling stroke from the three largest trials that reported stroke severity was considered (1, 3, 9), aspirin use was associated with a relative risk reduction of 13% (CI, -19% to 36%).

When only strokes classified as ischemic in the three largest trials were considered (1, 3, 9), aspirin

Table 4—Continued

Warfarin Group			Other Treatment Groups			Relative Risk Reduction (95% CI)†	Absolute Risk Reduction per Year
Strokes	Participants	Patient-Years	Strokes	Participants	Patient-Years		
<i>n</i>			<i>n</i>			%	
9	335	413	16	336	409	45	1.7
19	358	1099	21	357	1083	10	0.2
20	197	394	21	188	377	10	0.5
20	225	507	52	230	477§	67	7.0
11	170	355	9	169	365	-23	-0.6
3	131	401	4	141	392	20	0.3
82	1416	3169	123	1421	3103	36 (14 to 52)¶	0.8**
14	523	581	48	521	558	73	6.2
11	170	355	11	171	377	-1	-0.2
18	454	450§	23	462	460§	21 (-54 to 60)	1.0
11	170	355	14	167	363	24	0.8
1	153	182§	5	150	183§	81	2.2
3	131	401	4	122	361	31	0.4
15	454	938	23	439	907	38 (-20 to 68)¶	1.0**

resulted in a 23% reduction (CI, 0% to 40%). Only 7 cases of intracranial bleeding (4 aspirin recipients and 3 placebo recipients; rate for aspirin, 0.2% per year) and 28 major extracranial hemorrhages (13 aspirin recipients and 15 placebo recipients) occurred in the six trials. According to data from four trials (1, 3, 9, 13), all-cause mortality was not significantly reduced by aspirin (relative risk reduction, 16% [CI, -5% to 33%]).

One small randomized trial (14) compared dipyridamole and dipyridamole plus aspirin with placebo (Table 3); however, the data are insufficient to allow assessment of the individual efficacy of dipyridamole. When all randomized data from all antiplatelet comparisons were considered, antiplatelet therapy reduced stroke by 24% (CI, 7% to 39%) compared with placebo (Table 3) (absolute risk reduction, 1.9% per year; NNT, 53).

Adjusted-Dose Warfarin Compared with Aspirin

Anticoagulation was compared with aspirin alone in five nonblinded randomized trials involving 2837 participants who had a total of 205 strokes during a mean follow-up of 2.2 years per participant (1, 2, 4,

9, 15). The mean age of participants at study entry was 71 years. Thirty-eight percent of participants were women, 45% had hypertension, and 21% had previous stroke or TIA. The mean achieved INR ranged from 2.2 to 3.1 in the four primary prevention trials and was 2.9 in the single secondary prevention trial. The average rate of all strokes among aspirin recipients was 2.7% per year in the primary prevention trials and 10.9% per year in the secondary prevention trial.

The effect of warfarin on stroke compared with that of aspirin varied widely among these five trials (Table 4, Figure). No statistically significant heterogeneity was seen ($P = 0.09$), and meta-analysis showed that adjusted-dose warfarin reduced overall relative risk for all stroke by 36% (CI, 14% to 52%) compared with aspirin. When only ischemic strokes were considered, adjusted-dose warfarin was associated with a 46% (CI, 27% to 60%) relative risk reduction compared with aspirin. This difference in relative risk reduction—all strokes compared with only ischemic strokes—was mostly caused by the higher absolute risk for intracranial hemorrhage during warfarin therapy in the SPAF II Study (4)

Table 5. Randomized Comparisons of Other Antithrombotic Agents*

Study	Year	Type of Prevention	Total Participants	First Treatment Group			Second Treatment Group			Relative Risk Reduction (95% CI)†
				Strokes	Participants	Person-Years	Strokes	Participants	Person-Years	
				<i>n</i>	<i>n</i>		<i>n</i>			
Aspirin compared with low- or fixed-dose warfarin										
AFASAK II (2)	1998	Primary	336	9	169	365	14	167	363	39
PATAF (15)‡	1999	Primary	598	21	319	803	18	279	735	-2
Aggregate		-	934	30	488	1168	32	446	1098	15 (-42 to 49)
Aspirin (30 mg/d) compared with low-, fixed-dose warfarin (1.25 mg/d) plus aspirin										
AFASAK II (2)	1998	Primary	340	9	169	365	11	171	377	18 (-112 to 70)
Aspirin (300 mg/d) plus low-, fixed-dose warfarin (1.25 mg/d) compared with low-, fixed-dose warfarin alone										
AFASAK II (2)	1998	Primary	338	11	171	377	14	167	363	25 (-82 to 69)
Aspirin (25 mg twice per day) compared with dipyridamole (200 mg twice per day)										
ESPS II (14)	1997	Secondary	218	17	104	123	20	114	133	8 (-97 to 57)
Aspirin (25 mg twice per day) plus dipyridamole (200 mg twice per day) compared with aspirin alone										
ESPS II (14)	1997	Secondary	208	14	104	127	17	104	123	20 (-83 to 65)§
Dipyridamole (200 mg twice per day) plus aspirin (25 mg twice per day) compared with dipyridamole alone										
ESPS II (14)	1997	Secondary	218	14	104	127	20	114	133	27 (-63 to 67)§
Aspirin (125 mg/d every other day) compared with aspirin (125 mg/d)										
LASAF (13)	1999	Primary	194	1	90	148	4	104	145	72 (-192 to 99)§
Low-molecular-weight heparin (7500 antiXa U/d) compared with control										
Harenberg et al. (12)	1993	Primary and Secondary	75	3	35	12	8	40	16	62 (-77 to 94)
Aspirin (300 mg/d) compared with aspirin (1200 mg/d)										
UK-TIA (16)	1999	Secondary	34	3	13	52	5	21	84	4 (-530 to 88)

* AFASAK = Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study; ESPS II = European Stroke Prevention Study II; LASAF = Low-Dose Aspirin, Stroke, and Atrial Fibrillation Pilot Study; PATAF = Prevention of Arterial Thromboembolism in Atrial Fibrillation; UK-TIA = United Kingdom TIA Study.

† Weighted risk reduction for combined ischemic and hemorrhagic stroke by intention-to-treat analysis unless otherwise specified.

‡ Various types of coumarin were used.

§ Only results of efficacy (that is, results of patients while they received therapy) were reported.

|| Total person-years of exposure were estimated from mean duration of follow-up.

(0.9% per year). Risk for intracranial hemorrhage was more than three times higher in this trial than in the other trials (1, 2, 9, 15) and can probably be explained by use of prothrombin time monitoring and a relatively high target intensity of anticoagulation in a very elderly cohort (4). When the results of the SPAF II Study (4) were excluded, the relative risk reduction in all stroke for adjusted-dose warfarin compared with aspirin was 49% (CI, 26% to 65%) and the absolute risk reduction in all stroke for warfarin compared with aspirin was 0.6% per year (NNT, 167) for primary prevention and 7.0% per year (NNT, 14) for secondary prevention.

Persons who received warfarin had more than twice as many intracranial hemorrhages than those who received aspirin (17 compared with 7) (relative risk, 2.1 [CI, 1.0 to 4.6]). Major extracranial hem-

orrhage increased in persons who received warfarin compared with those who received aspirin (relative risk, 2.0 [CI, 1.2 to 3.4]; absolute risk increase, 0.2% per year). On the basis of available data from four trials (1, 2, 4, 15), all-cause mortality was similar in persons who received adjusted-dose warfarin and those who received aspirin (relative risk reduction, 8% [CI, -21% to 30%]).

Adjusted-Dose Warfarin Compared with Other Antithrombotic Regimens

Two additional randomized trials compared adjusted-dose warfarin with aspirin plus low, fixed doses of warfarin (2, 5) (Table 4). The larger trial (5), which included only participants at high risk for stroke and was terminated at an interim analysis

because of efficacy, reported large reductions in relative and absolute risk for adjusted-dose warfarin. The second trial (2), which involved participants at lower risk, was terminated in response to the first trial; results at termination showed no difference between therapies. Tests for homogeneity were significant ($P < 0.001$ for relative risk; $P = 0.004$ for absolute risk), precluding meta-analysis.

Three trials compared adjusted-dose warfarin (target INRs, 2 to 3.5) with low or fixed doses of warfarin (mean achieved INR, 1.1 to 1.4). Pooled analysis showed a 38% reduction for adjusted-dose warfarin that was not statistically significant (Table 4) (2, 11, 15).

A single trial compared adjusted-dose warfarin and indobufen, an antiplatelet agent, in participants with atrial fibrillation who had had recent TIA or ischemic stroke (10). Fewer strokes occurred among persons who received warfarin than among those who received indobufen (18 compared with 23, respectively). The CI for the relative risk reduction overlapped that derived from comparisons of warfarin and aspirin (Table 4) but not that derived from comparisons of warfarin and placebo (Table 2).

Other Randomized Comparisons

Ten additional randomized comparisons of antithrombotic regimens have been published (Table 5), but none include enough events to allow meaningful definitions of relative efficacy or safety.

Discussion

Antithrombotic therapy has unequivocal efficacy for reducing stroke in patients with atrial fibrillation. For most patients, the increased risk for major hemorrhage associated with antithrombotic agents does not offset this benefit. The occurrence of all stroke (ischemic and hemorrhagic) is reduced approximately 60% by adjusted-dose warfarin compared with no treatment, about 20% by aspirin

compared with no treatment, and about 40% by warfarin compared with aspirin. Our analysis of these 16 randomized trials confirmed the remarkable efficacy of adjusted-dose warfarin and the modest, less consistent effects of aspirin.

Meta-analysis of the intention-to-treat results of six randomized trials showed that adjusted-dose warfarin reduced *ischemic* stroke by 65%. This impressive result occurred despite the substantial number of participants who stopped anticoagulation in these trials (an average of 20% over the initial 1.5 years of follow-up). However, the mean duration of follow-up in these clinical trials generally averaged between 1 and 2 years, and warfarin may not be as effective in long-term use because anticoagulant therapy is difficult to sustain in many elderly persons. In addition, the efficacy and safety of hard-to-administer therapies, such as adjusted-dose warfarin, may be different in clinical practice than in clinical trials. Nevertheless, the efficacy of adjusted-dose warfarin for prevention of ischemic stroke in patients with atrial fibrillation is pronounced.

The optimal target intensity of anticoagulation that would balance benefits with risks remains controversial for patients with atrial fibrillation, most of whom are elderly (25, 26). Target INRs between 2 and 3 are highly efficacious for stroke reduction and are often recommended (26). An INR of 1.5 or less offers minimal efficacy (25). The largest reductions in stroke were seen in two trials with estimated target INRs between 1.4 and 2.8 (6, 8).

The largest amount of data on antithrombotic therapy from randomized clinical trials involves the comparison of aspirin and placebo; however, many important aspects of aspirin's efficacy remain unclear (19). Overall, aspirin reduces stroke by approximately 20% in patients with atrial fibrillation but seems to primarily affect nondisabling, noncardioembolic stroke (27). The relative risk reduction achieved by aspirin in disabling strokes may be lower. Aspirin did not increase major hemorrhage in clinical trials involving patients with atrial fibril-

Table 6. Estimated Size of Treatment Effects according to Risk Status in Patients with Nonvalvular Atrial Fibrillation*

Variable	Primary Prevention for All Stroke			Secondary Prevention for All Stroke	Major Extracranial Hemorrhage†
	Low	Moderate	High		
Intrinsic rate per year (no therapy), %	1	3.5	6	12	0.6
Events per year per 1000 persons treated, <i>n</i>					
Adjusted-dose warfarin compared with no therapy‡§	↓ 6	↓ 21	↓ 36	↓ 72	↑ ±3
Aspirin compared with no therapy§	↓ 2	↓ 7	↓ 12	↓ 24	↑ ±1
Warfarin compared with aspirin¶§	↓ 4	↓ 14	↓ 24	↓ 48	↑ ±2

* General estimates to illustrate the effect of risk stratification on the magnitude of treatment effects. Assumes the same rate of major extracranial hemorrhage for all stroke risk groups.
 † Based on weighted estimates for increases associated with antithrombotic therapies in clinical trials. Rates are probably higher in patients who are not in clinical trials and patients older than 75 years of age.

‡ Relative risk reduction, 60%.

§ Arrows indicate increase or decrease in the number of events.

|| Relative risk reduction, 20%.

¶ Relative risk reduction, 40%.

lation, but risk for major bleeding increased after even low doses of aspirin in larger trials of patients without atrial fibrillation (28). The value of other antiplatelet agents, used alone or in combination, in patients with atrial fibrillation is uncertain.

Although adjusted-dose warfarin is clearly superior to aspirin for stroke prevention in patients with atrial fibrillation, the best estimate of the magnitude of difference is unclear. A 36% relative risk reduction (Table 4) is probably a low estimate because it is influenced by a large number of intracranial hemorrhages from one trial (4). On the other hand, the 73% relative risk reduction observed in the SPAF III Study may be exaggerated because the trial was terminated at an interim analysis because of treatment efficacy (5). When available data are considered, a 40% to 50% relative risk reduction in all stroke from warfarin compared with aspirin is probably applicable to most patients with atrial fibrillation. However, the relative risk reduction for adjusted-dose warfarin compared with aspirin may be related to the absolute stroke rates; persons at higher risk may have larger relative reductions ($P = 0.09$, Spearman rank correlation) (Table 4) as well as larger absolute reductions. This finding may be explained by the fact that a greater proportion of cardioembolic strokes occur in patients who are at higher risk for strokes that are particularly prevented by warfarin (27).

We included several studies that were terminated before planned completion because of treatment efficacy, which can bias results toward overestimates of treatment effect. Studies that were terminated early included four of six trials comparing warfarin with placebo and the only trial comparing aspirin with placebo that claimed a statistically significant benefit. Therefore, the overall estimates of efficacy may be inflated to an uncertain degree.

The magnitude of benefit (that is, the absolute risk reduction) conferred by adjusted-dose warfarin varies with the inherent risk for stroke (Table 6). Patients with atrial fibrillation who are at high risk, particularly those with previous stroke or TIA, potentially have the most to gain from treatment with warfarin instead of aspirin. For example, anticoagulation instead of aspirin for 1000 patients with atrial fibrillation who had previous stroke or TIA is estimated to prevent 48 strokes per year, with an excess of 2 major extracranial hemorrhages (Table 6). In contrast, for low-risk patients with atrial fibrillation, only 4 strokes would be avoided annually per 1000 patients who received warfarin instead of aspirin. Risk stratification schemes have been proposed to identify patients with atrial fibrillation who are at low, moderate, and high risk for stroke (18, 29–31); however, additional studies are needed to validate these schemes in clinical practice (32).

During the past decade, results of randomized clinical trials conducted by investigators around the world have provided solid evidence on which to base strategies of stroke prevention for persons with nonvalvular atrial fibrillation. Atrial fibrillation is a powerful risk factor for stroke, but its threat can be substantially diminished by judicious use of anti-thrombotic agents.

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