Annals of Internal Medicine | Review

Meta-analysis: Antithrombotic Therapy to Prevent Stroke in Patients Who Have Nonvalvular Atrial Fibrillation

Robert G. Hart, MD; Lesly A. Pearce, MS; and Maria I. Aguilar, MD

Background: Atrial fibrillation is a strong independent risk factor for stroke.

Purpose: To characterize the efficacy and safety of antithrombotic agents for stroke prevention in patients who have atrial fibrillation, adding 13 recent randomized trials to a previous meta-analysis.

Data Sources: Randomized trials identified by using the Cochrane Stroke Group search strategy, 1966 to March 2007, unrestricted by language.

Study Selection: All published randomized trials with a mean follow-up of 3 months or longer that tested antithrombotic agents in patients who have nonvalvular atrial fibrillation.

Data Extraction: Two coauthors independently extracted information regarding interventions; participants; and occurrences of ischemic and hemorrhagic stroke, major extracranial bleeding, and death.

Data Synthesis: Twenty-nine trials included 28 044 participants (mean age, 71 years; mean follow-up, 1.5 years). Compared with the control, adjusted-dose warfarin (6 trials, 2900 participants) and antiplatelet agents (8 trials, 4876 participants) reduced stroke by 64% (95% CI, 49% to 74%) and 22% (CI, 6% to 35%), respectively. Adjusted-dose warfarin was substantially more efficacious than antiplatelet therapy (relative risk reduction, 39% [CI, 22% to 52%]) (12 trials, 12 963 participants). Other randomized comparisons were inconclusive. Absolute increases in major extracranial hemorrhage were small (≤0.3% per year) on the basis of meta-analysis.

Limitation: Methodological features and quality varied substantially and often were incompletely reported.

Conclusions: Adjusted-dose warfarin and antiplatelet agents reduce stroke by approximately 60% and by approximately 20%, respectively, in patients who have atrial fibrillation. Warfarin is substantially more efficacious (by approximately 40%) than antiplatelet therapy. Absolute increases in major extracranial hemorrhage associated with antithrombotic therapy in participants from the trials included in this meta-analysis were less than the absolute reductions in stroke. Judicious use of antithrombotic therapy importantly reduces stroke for most patients who have atrial fibrillation.

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For author affiliations, see end of text.

Nonvalvular atrial fibrillation is an important cause of disabling stroke whose incidence can be reduced by using antithrombotic prophylaxis. Our meta-analysis of the initial 16 randomized clinical trials that tested antithrombotic therapies for stroke prevention included approximately 10 000 participants (1). Since then, 13 randomized trials that included 18 140 additional patients with atrial fibrillation have been reported (**Table 1** [2–31]). Results of single, relatively small trials are sometimes difficult to interpret and often conflict, and meta-analysis is useful to assess the totality of trial evidence. We present an updated meta-analysis of all currently available randomized trials that extends observations about the efficacy and safety of antithrombotic therapies for preventing stroke in patients who have atrial fibrillation.

Methods

Search and Selection Process

We identified unconfounded randomized trials that tested long-term (≥12 weeks) use of antithrombotic agents in patients who had nonvalvular atrial fibrillation. We did a computerized search of the OVID and MEDLINE databases (from 1966 to March 2007, unrestricted by language) and of the Cochrane Stroke Group Trials Register and queried investigators working in the field (1). Trials that included patients who have prosthetic cardiac valves or mitral stenosis were not considered; double-blind and open-label trial designs were eligible. Two physician-reviewers independently extracted data from published sources and determined whether the trials met the inclusion criteria. Disagreements were resolved by joint review and consensus. We included 29 of 41 randomized trials that tested antithrombotic therapies in patients who had atrial fibrillation (**Table 1**), including 2 trials that reported results for subgroups of patients with atrial fibrillation from a larger number of patients without atrial fibrillation (13, 18). We identified 4 randomized trials that are ongoing (32–34) or have not been published (**Appendix Table 1**, available at www.annals.org) and excluded 8 randomized trials: 5 in which the treatment duration averaged 3 to 8 weeks (35–39), 1 in which the results for the subset of patients who had atrial fibrillation were not reported separately (40), 1 that included patients who had mitral stenosis (41), and 1 because of potential confounding in

See also:

Print
Editors' Notes 858

Web-Only
Appendix Tables
CME quiz
Conversion of figure and tables into slides

Context

Thirteen new randomized, controlled trials are available since a 1999 meta-analysis of antithrombotic agents for stroke prevention in patients with atrial fibrillation.

Contribution

This updated meta-analysis shows that, compared with placebo, adjusted-dose warfarin reduces stroke risk by 64% (6 trials) and antiplatelet agents reduce stroke risk by 22% (8 trials). Meta-analysis of 12 trials shows that adjusted-dose warfarin is more effective than antiplatelet therapy, but it doubles the risk for major extracranial and intracranial hemorrhage. However, absolute rates of these adverse events were only 0.2% per year.

Implication

Additional trials are unlikely to substantially change current estimates of the effectiveness of vitamin K antagonists and antiplatelet agents in stroke prevention in patients with atrial fibrillation.

—The Editors

which 51% of randomly assigned participants were excluded from the reported analysis because of ill-defined nonadherence (42). The 5 short-term trials were considered only in the safety analyses (35–39).

Data Extraction

Two physician-reviewers independently extracted data from published sources regarding methodological features, the number of treated patients, total follow-up exposure, and the occurrence of the following 5 outcomes according to the intention-to-treat paradigm: all stroke (ischemic and hemorrhagic), ischemic stroke, intracranial hemorrhage, all-cause mortality, and major extracranial hemorrhage. Disagreements were resolved by joint review and consensus. The criteria for each outcome were those used by the individual trial. The fraction of participants with strokes who had neuroimaging or autopsy that reliably distinguished between ischemic or hemorrhagic stroke varied and was not consistently reported. Consequently, all stroke (ischemic and hemorrhagic) was chosen as the primary outcome. Undefined strokes in patients who did not have neuroimaging were considered ischemic. Intracranial hemorrhages included subdural hematomas and were considered with all strokes; transient ischemic attacks (TIAs) were not considered.

Data Synthesis

Two physician-reviewers abstracted key methodological features for each trial (**Appendix Table 2**, available at www.annals.org). Intention-to-treat results were used for the main analyses. Primary prevention refers to patients without previous stroke or TIA. Secondary prevention refers to patients with previous stroke or TIA. Three trials (11, 14, 23) that combined aspirin with very low, fixed doses of warfarin that did not substantially prolong international normalized ratios (INRs) were considered with those that tested aspirin alone because of the negligible effect of warfarin at these dosages (43–45).

Meta-analyses of the trial results are presented as relative risk reductions and absolute risk reductions for treatment groups compared with control groups. To estimate relative risk reduction, the combined odds ratio was computed by assuming a random-effects model (DerSimonian and Laird method) (46), and the estimate was then subtracted from 1. The absolute risk reduction is a weighted estimate of the difference in annualized event rates (46). Before estimating 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 or the Q_W statistic with unequal weights for the absolute risk scale (46). Lack of homogeneity across trials precluded estimation of the overall treatment effect as noted, and the exact *P* value was reported for all analyses in which the *P* value was less than 0.20. We computed estimates of relative risk reduction in individual trials by subtracting the estimated odds ratio from 1. A *P* value less than 0.05 was considered statistically significant; all tests and CIs were 2-sided. Calculations were done by using MedCalc for Windows, version 9.2.0.2 (MedCalc Software, Mariakerke, Belgium), and SPSS software (SPSS, Chicago, Illinois).

Role of the Funding Source

This study was not funded.

RESULTS

Twenty-nine published randomized trials included 28 044 patients with nonvalvular atrial fibrillation (**Table 1**). Methodological features varied; larger trials were more thoroughly reported and were of higher quality (**Appendix Table 2**, available at www.annals.org). Nine trials were double-blind designs to compare antiplatelet therapy (2, 5, 8, 13, 18, 20) and anticoagulation therapy (6, 7, 24) with control or with each other. Only outcomes during assigned treatment were published for 4 relatively small trials (13, 26, 30, 31).

Total follow-up exposure was approximately 42 450 patient-years (mean follow-up, 1.5 years per patient). The average age of the patients was 71 years, and 35% were women. Most trials were done in Europe (16 trials, 7390 patients) (2, 8, 9, 12–18, 20, 21, 23, 25, 27, 31) or North America (7 trials, 8349 patients) (4–7, 10, 11, 24), 2 were done in Japan (986 patients) (19, 26), 1 was done in China (704 patients) (30), and 3 were intercontinental (10 615 patients) (22, 28, 29). Eight studies enrolled more than 1000 patients; the average number of patients was 423 (range, 45 to 916 patients) in the remaining studies. Most trials studied oral vitamin K inhibitors or aspirin in varying dosages and intensities, but other anticoagulants (low-molec-

Table 1. **Randomized Trials of Antithrombotic Therapy for Patients with Nonvalvular Atrial Fibrillation***

Study, Year (Reference)	Participants, *n*	Interventions
AFASAK I, 1989 (2); 1990 (3)	1007	Warfarin†, aspirin, and placebo
BAATAF, 1990 (4)	420	Warfarin† and control
SPAF I, 1991 (5)	1330	Warfarin†, aspirin†, and placebo
CAFA, 1991 (6)	378	Warfarin and placebo
SPINAF, 1992 (7)	571	Warfarin† and placebo
EAFT, 1993 (8)‡	1007	Warfarin†, aspirin, and placebo
Harenberg et al., 1993 (9)	75	Low-molecular-weight heparin and control
SPAF II, 1994 (10)	1100	Warfarin and aspirin
SPAF III, 1996 (11)	1044	Warfarin† and low-dose warfarin plus aspirin
SIFA, 1997 (12)	916	Warfarin and indobufen
ESPS II, 1997 (13)	429	Aspirin, dipyridamole, aspirin plus dipyridamole, and placebo
AFASAK II, 1998 (14)	677	Warfarin, low-dose warfarin, aspirin, and low-dose warfarin plus aspirin
MWNAF, 1998 (15)	303	Warfarin and low-dose warfarin
PATAF, 1999 (16)‡	729	Warfarin, low-dose warfarin, and aspirin
LASAF, 1999 (17)	285	Aspirin daily, aspirin every other day, and control
UK-TIA, 1999 (18)	49	Aspirin (2 dosages) and placebo
JNAFESP, 2000 (19)	115	Warfarin (2 intensities)
FFAACS, 2001 (20)	157	Fluindione and fluindione plus aspirin
SPORTIF II, 2003 (21)	254	Ximelagatran (3 dosages) and warfarin
SPORTIF III, 2003 (22)	3407	Ximelagatran and warfarin
SAFT, 2003 (23)	668	Low-dose warfarin plus aspirin and control
NASPEAF, 2004 (25)	714§	Triflusal, acenocoumarol, or both
SPORTIF V, 2005 (24)	3922	Ximelagatran and warfarin
JAST, 2006 (26)	871	Aspirin and control
Vemmos et al., 2006 (27)	45	Warfarin, low-dose warfarin, and aspirin
ACTIVE-W, 2006 (28)	6706	Warfarin† and clopidogrel plus aspirin
PETRO, 2005 (29)	502	Dabigatran (3 dosages) with or without aspirin and warfarin
Chinese ATAFS, 2006 (30)	704	Warfarin and aspirin
WASPO, 2007 (31)	75	Warfarin and aspirin

* Published trials in order of year of major publication. ACTIVE-W = Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events; AFASAK = Atrial Fibrillation, ASpirin, AntiKoagulation; ATAFS = Antithrombotic Therapy in Atrial Fibrillation Study; BAATAF = Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA = Canadian Atrial Fibrillation Anticoagulation; EAFT = European Atrial Fibrillation Trial; ESPS = European Stroke Prevention Study; FFAACS = Fluindione Fibrillation Auriculaire Aspirin et Contraste Spontané; JAST = Japan Atrial fibrillation Stroke Trial; JNAFESP = Japanese Nonvalvular Atrial Fibrillation Embolism Secondary Prevention; LASAF = Low-dose Aspirin, Stroke, Atrial Fibrillation; MWNAF = Minidose Warfarin in Nonrheumatic Atrial Fibrillation; NASPEAF = NAtional Study for Prevention of Embolism in Atrial Fibrillation; PATAF = Prevention of Arterial Thromboembolism in Atrial Fibrillation; PETRO = Prevention of Embolic and ThROmbotic events; SAFT = Swedish Atrial Fibrillation Trial; SIFA = Studio Italiano Fibrillazione Atriale; SPAF = Stroke Prevention in Atrial Fibrillation; SPINAF = Stroke Prevention in Nonrheumatic Atrial Fibrillation; SPORTIF = Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation; UK-TIA = United Kingdom Transient Ischaemic Attack; WASPO = Warfarin vs. Aspirin for Stroke Prevention in Octogenarians.
† Indicates a statistically significant result reported for efficacy.
‡ Other oral vitamin K antagonists were used in addition to warfarin in a minority of participants.
§ High-risk patients are not included because most of them had mitral stenosis (that is, valvular atrial fibrillation) and the number of strokes for patients ($n = 184$) without mitral stenosis has not been reported separately.

ular-weight heparin, ximelagatran, and dabigatran) and other antiplatelet agents (clopidogrel, dipyridamole, indobufen, and triflusal) were also tested.

There were 3003 participants assigned to placebo or control groups in 12 trials. The average stroke rate for these untreated participants was 13% per year in trials that were restricted to those who had previous stroke or TIA (secondary prevention trials) and 4.1% per year for those in primary prevention trials.

Adjusted-Dose Warfarin Compared with Placebo or No Treatment

To our knowledge, no new trial data have been added since our 1999 meta-analysis (1), and abridged results are reported here. In 6 randomized trials, 2900 participants (mean age at study entry, 69 years; 29% were women; and 20% had previous stroke or TIA) were included who had had 186 strokes during a mean follow-up of 1.6 years per participant (**Table 2** [2, 4–8]). The mean achieved INR ranged from 2.0 to 2.6 among patients who were assigned warfarin in the 5 primary prevention trials (2 were double-blinded) and was 2.9 in the only secondary prevention trial. The average stroke rate was 4.5% per year for primary prevention and 12% per year for secondary prevention among patients assigned to the placebo or control groups.

According to meta-analysis, adjusted-dose warfarin was associated with a 64% (95% CI, 49% to 74%) reduction in stroke (**Table 2** and **Figure**, *top*). When we considered trials that stratified stroke severity, 60% of strokes were disabling and reductions in disabling (60%) and nondisabling (60%) strokes with anticoagulation therapy were similar. The absolute risk reduction in all strokes was 2.7% per year (number needed to treat [NNT_B] for 1 year to prevent 1 stroke was 37) for primary prevention and 8.4% per year (NNT_B, 12) for secondary prevention. When only ischemic strokes were considered, adjusted-dose warfarin

Table 2. **Adjusted-Dose Warfarin Compared with Placebo or No Treatment***

Study, Year (Reference)	Secondary Prevention, %†	Participants, *n*	Target INR	Strokes/Patients/Patient-Years; Warfarin vs. Placebo or Control, *n/n/n*	Relative Risk Reduction (95% CI), %‡	Absolute Risk Reduction, %/y‡
AFASAK I, 1989 (2); 1990 (3)	6	671	2.8–4.2	9/335/413 vs. 19/336/398	54	2.6
SPAF I, 1991 (5)	8	421	2.0–4.5§	8/210/263 vs. 19/211/245	60‖	4.7
BAATAF, 1990 (4)¶	3	420	1.5–2.7§	3/212/487 vs. 13/208/435	78‖	2.4
CAFA, 1991 (6)	4	378	2.0–3.0	6/187/237 vs. 9/191/241	33	1.2
SPINAF, 1992 (7)	8	571	1.4–2.8§	7/281/489 vs. 23/290/483	70‖	3.3
EAFT, 1993 (8)**	100	439	2.5–4.0	20/225/507 vs. 50/214/405	68‖	8.4
6 trials††	20	2900	–	53/1450/2396 vs. 133/1450/2207	64 (49 to 74)	Primary prevention, 2.7; secondary prevention, 8.4

* Please see footnote in Table 1 for definitions of study acronyms. INR = international normalized ratio.
† Proportion of patients who had previous stroke or transient ischemic attack.
‡ Risk reduction for combined ischemic and hemorrhagic strokes by intention-to-treat analysis.
§ Prothrombin time ratios were used with INR equivalents estimated by the investigators.
¶ A total of 46% of exposure in the control group was during self-selected use of various dosages of aspirin.
‖ $P < 0.05$, 2-sided.
** Several oral vitamin K antagonists were used (warfarin was not exclusively used).
†† Meta-analysis estimates of relative risk reductions ($P > 0.2$ for homogeneity) and absolute risk reductions ($P > 0.2$ for homogeneity) for trials of primary prevention (trials with ≤20% of participants with previous stroke) vs. secondary prevention; see Methods.

was associated with a 67% (CI, 54% to 77%) relative risk reduction.

Antiplatelet Therapy Compared with Placebo or No Treatment

Eight trials compared antiplatelet therapy with placebo in 4876 participants who had 488 strokes (**Table 3**). The mean age of the participants was 69 years, 37% were women, and 29% had previous stroke or TIA. In 5 trials (2, 5, 8, 13, 16), treatment was double-blinded. Seven trials that included 76% of follow-up exposure compared dosages of aspirin alone (range, 25 mg twice daily to 1300 mg/d) with placebo or control. During a mean follow-up of 1.7 years per participant, the average stroke rate was 4.0% per year for primary prevention trials (2, 5, 17, 23, 26) and 13% per year for secondary prevention trials (8, 13, 16) in participants who were assigned to the placebo or control groups.

When we compared aspirin alone with placebo or no treatment in 3990 participants in 7 trials, meta-analysis showed that aspirin was associated with a 19% (CI, −1% to 35%) reduced incidence of stroke. There was an absolute risk reduction of 0.8% per year (NNT_B, 125) for primary prevention trials (2, 5, 17, 26) and 2.5% per year (NNT_B, 40) for secondary prevention trials (8, 13, 18) (**Table 3** and **Figure**, *middle*). On the basis of available data from 4 trials (2, 5, 13, 17), 64% of strokes were deemed disabling. Aspirin was associated with a 13% (CI, −18% to 36%) reduction in disabling strokes and a 29% (CI, −6% to 53%) reduction in nondisabling strokes. When only strokes classified as ischemic were considered (5 trials [2, 5, 13, 17, 26]), aspirin resulted in a 21% (CI, −1% to 38%) reduction in strokes.

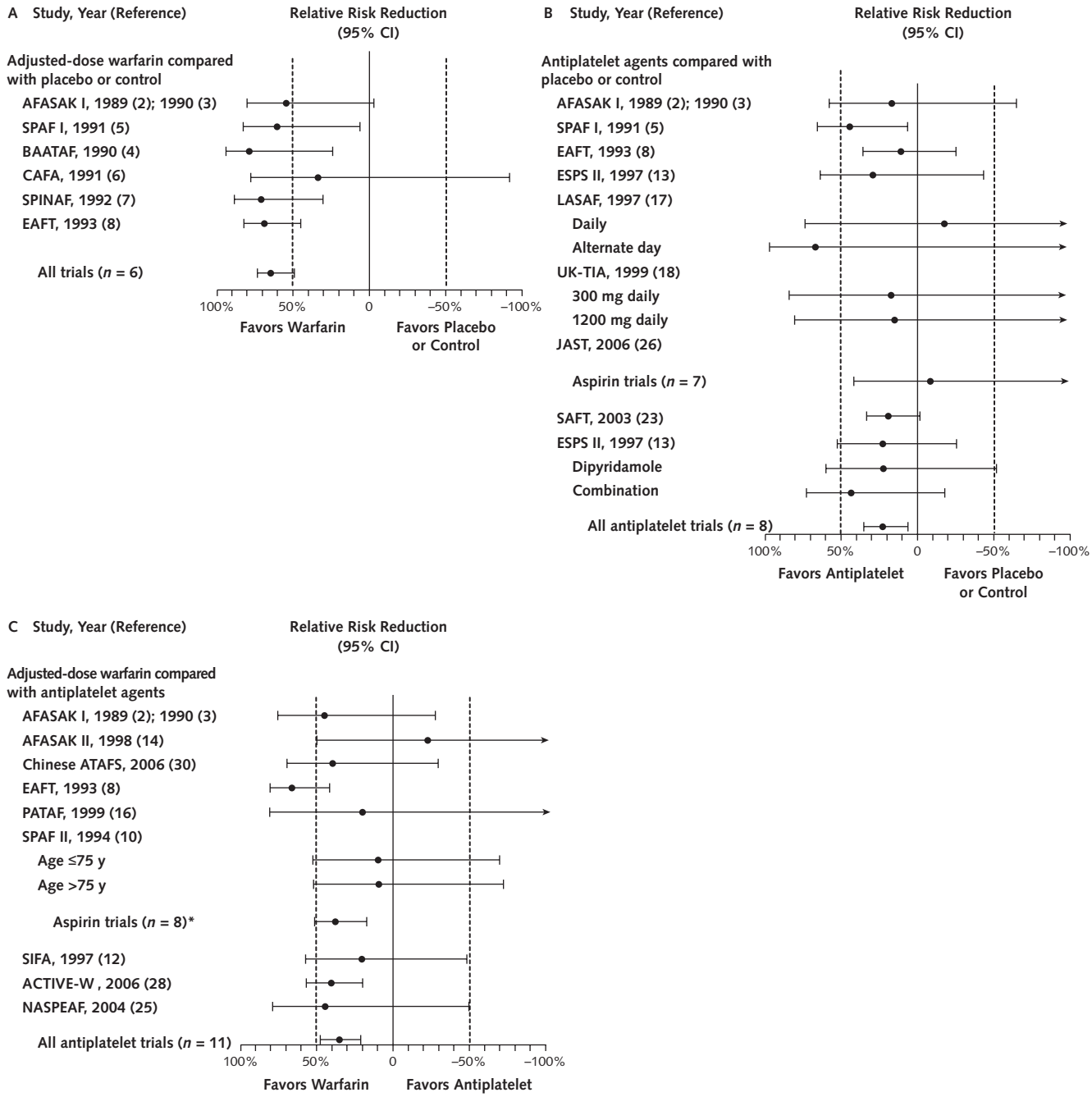
Two additional trials compared dipyridamole, dipyridamole plus aspirin, or aspirin plus very low-dose warfarin that did not prolong the INR to placebo or control groups, but the data were insufficient to be conclusive (13, 23) (**Table 3**). When we considered all randomized data from all comparisons of antiplatelet agents and placebo or control groups, antiplatelet therapy reduced stroke by 22% (CI, 6% to 35%).

Adjusted-Dose Warfarin Compared with Antiplatelet Therapy

Anticoagulation with warfarin and other oral vitamin K antagonists was compared with various dosages of aspirin in 9 randomized comparisons (3647 participants) (2, 8, 10, 14, 16, 27, 30, 31); with other antiplatelet agents in 3 trials (8101 participants) (12, 25, 28); and with aspirin combined with low, fixed (ineffective) dosages of warfarin in 2 comparisons (1385 participants) (11, 14) (**Table 4**). For the 12 trials that compared warfarin with antiplatelet agents alone, 11 748 participants had 462 strokes during a mean follow-up of 1.5 years per participant. The mean age of the participants was 70 years, 38% were women, and 23% had previous stroke or TIA. The average stroke rate was 2.6% per year among patients who were prescribed antiplatelet agents in 9 (mainly) primary prevention trials (2, 10, 14, 16, 25, 27, 28, 30, 31) and 8.0% per year in 2 secondary prevention trials (8, 10).

On the basis of 12 comparisons of adjusted-dose warfarin with antiplatelet therapy alone, warfarin was associated with a 37% (CI, 23% to 48%) reduction in strokes (**Figure**, *bottom*). The largest trial (ACTIVE-W [Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events]) studied 6706 participants who had 171 stroke events. In ACTIVE-W, anticoagulation therapy was superior to the combination of clopidogrel plus aspirin (relative risk reduction, 40% [CI, 18% to 56%]). Meta-analysis of antiplatelet trials with the 2 comparisons of aspirin combined with fixed,

Figure. **Relative effects of antithrombotic therapies on all stroke from randomized trials in patients with atrial fibrillation.**



Horizontal lines represent 95% CIs around point estimates. Please see footnote in Table 1 for definitions of study acronyms. **A.** Adjusted-dose warfarin compared with placebo or no treatment in 6 randomized trials. **B.** Antiplatelet agents compared with placebo or no treatment in 8 randomized trials. In SAFT (23), aspirin was combined with low, inefficacious dosages of warfarin. In ESPS II (13), *combination* refers to aspirin plus dipyridamole. **C.** Adjusted-dose warfarin compared with antiplatelet agents in 11 randomized trials. Nonaspirin antiplatelet agents were indobufen (SIFA [12]), clopidogrel plus aspirin (ACTIVE-W [28]), and triflusal (NASPEAF [25]). *The Vemmos et al. (27) and WASPO (31) trials are not shown; however, the information is shown in Table 4.

low-dose warfarin yielded a 39% (CI, 22% to 52%) relative risk reduction in all strokes and adjusted-dose warfarin yielded a 52% (CI, 41% to 62%) relative risk reduction in ischemic stroke among all 12 963 patients (**Table 4**).

Other Randomized Comparisons

In the 3 randomized SPORTIF (Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation) trials, ximelagatran (36 mg twice daily) was compared with adjusted-dose warfarin in 7458 patients who had atrial fi-

Table 3. **Antiplatelet Agents Compared with Placebo or No Treatment***

Study, Year (Reference)	Secondary Prevention, %†	Participants, *n*	Dosage	Strokes/Patients/Patient-Years; Antiplatelet vs. Placebo or No Treatment, *n/n/n*‡	Relative Risk Reduction (95% CI), %§	Absolute Risk Reduction, %/*y*
Aspirin vs. placebo						
AFASAK I, 1989 (2); 1990 (3)	6	672	75 mg/d	16/336/409 vs. 19/336/398	17	0.9
SPAF I, 1991 (5)	7	1120	325 mg/d	25/552/723 vs. 44/568/734	44‖	2.5
EAFT, 1993 (8)	100	782	300 mg/d	88/404/853 vs. 90/378/734	11	1.9
ESPS II, 1997 (13)	100	211	50 mg/d	17/104/123 vs. 23/107/111	29¶	6.9
UK-TIA, 1999 (18)**	100	28	300 mg/d	3/13/52 vs. 4/15/60	17	0.9
	100	36	1200 mg/d	5/21/84 vs. 4/15/60	14	0.7
5 aspirin–placebo trials††	41	2834	–	154/1430/2244 vs. 184/1419/2097	22 (2 to 39)	Primary prevention, 1.9; secondary prevention, 2.5
Aspirin vs. no treatment						
LASAF, 1997 (17)	0	195	125 mg/d	4/104/145 vs. 3/91/135	−17	−0.5
	0	181	125 mg qod	1/90/148 vs. 3/91/135	67	1.5
JAST, 2006 (26)	3	871	150 mg/d	20/426/895 vs. 19/445/935	−10	−0.2
7 aspirin trials††	30	3990	–	179/2050/3432 vs. 209/2046/3302	19 (−1 to 35)	Primary prevention, 0.8; secondary prevention, 2.5
Aspirin plus low-dose warfarin vs. control						
SAFT, 2003 (23)**	0	668	75 mg/d‡‡	32/334/919 vs. 41/334/919	24	1.0
Dipyridamole vs. placebo						
ESPS II, 1997 (13)	100	221	200 mg bid	20/114/133 vs. 23/107/111	22¶	5.7
Dipyridamole plus aspirin vs. placebo						
ESPS II, 1997 (13)	100	211	§ §	14/104/127 vs. 23/107/111	43¶	9.7
10 antiplatelet trials††	29	4876	–	245/2602/4611 vs. 296/2594/4443	22 (6 to 35)	Primary prevention, 0.8; secondary prevention, 3.8

* Please see footnote in Table 1 for definitions of study acronyms. bid = twice daily; qod = every other day.
† Proportion of patients who had previous stroke or transient ischemic attack.
‡ Data for the control patients in LASAF, ESPS II, and UK-TIA were counted twice for the meta-analysis.
§ Risk reduction for combined ischemic and hemorrhagic strokes by intention-to-treat analysis, unless otherwise specified.
‖ $P < 0.05$, 2-sided.
¶ Only efficacy (that is, "on-therapy") results were reported.
** Total patient-years of exposure was estimated from the mean follow-up because total exposure was not published.
†† Meta-analysis estimates of relative risk reductions ($P > 0.2$ for homogeneity for 3 meta-analyses) and absolute risk reductions ($P > 0.2$ for homogeneity for all 6 meta-analyses) for primary prevention trials (with ≤20% of participants who had previous stroke) compared with secondary prevention; see Methods.
‡‡ Aspirin (75 mg/d) plus warfarin (1.25 mg/d) did not prolong the international normalized ratio beyond the control range in 91% of measurements and therefore did not provide substantial clinical antithrombotic effect (40, 41).
§ § Extended-release dipyridamole (200 mg bid) plus aspirin (25 mg bid).

brillation and at least 1 additional stroke risk factor for stroke (21, 22, 24). Meta-analysis showed an 8% (CI, −38% to 38%) reduction in stroke with ximelagatran (94 strokes) over adjusted-dose warfarin (102 strokes) (**Appendix Table 3**, available at www.annals.org). Nineteen additional randomized comparisons of antithrombotic regimens have been published (**Appendix Table 3**, available at www.annals.org). Individually and after meta-analysis, no comparisons included sufficient numbers of strokes or major hemorrhages to allow for meaningful assessment of efficacy or safety.

Major Bleeding Events and Mortality

Major extracranial bleeding events and intracranial hemorrhage were less frequent than ischemic strokes; therefore, meta-analysis estimates of the effects of antithrombotic therapies are less precise (**Table 5**). Of note, intracranial hemorrhage was included with ischemic stroke as all strokes; therefore, this most serious consequence of antithrombotic therapy is considered in the primary analysis. Two results of pooled data were statistically significant: The risk for intracranial hemorrhage was doubled with adjusted-dose warfarin compared with aspirin, although the absolute risk increase was small (0.2% per

year), and all-cause mortality was substantially reduced (26% [CI, 3% to 43%]) by adjusted-dose warfarin versus control (**Table 5**).

Because early discontinuation of treatment due to safety concerns could potentially bias overall estimates of major bleeding events, the 5 short-duration (<12 weeks) trials excluded from other analyses were considered in the analyses of major bleeding events and mortality (35–39) (**Appendix Table 4**, available at www.annals.org). No trials were terminated early because of safety concerns, and no trials included comparisons relevant to those analyzed in **Table 5**. One additional trial (33) that compared idraparinux (a factor Xa inhibitor) with adjusted-dose warfarin was terminated early because of excessive bleeding episodes among patients who were assigned to idraparinux, but results have not been reported (**Appendix Table 1**, available at www.annals.org).

DISCUSSION

The randomized clinical trials in our meta-analysis included more than 28 000 patients and have established a solid evidence base that supports antithrombotic therapy for most patients who have atrial fibrillation. Results of single trials can be difficult to generalize, but meta-analyses of all randomized trials lead to firm conclusions. We have confirmed the main findings of our previous meta-analysis of the initial 16 randomized trials (1), but we have improved the precision of the estimates of benefits and risks because of the addition of 13 trials and the more than doubling of the total number of participants and strokes. Major new evidence includes comparisons of adjusted-dose warfarin with the combination of clopidogrel plus aspirin (1 trial with 6706 participants) and a more precise estimate of anticoagulation therapy compared with all antiplatelet therapies (6 additional trials with 8911 participants).

Table 4. **Adjusted-Dose Warfarin Compared with Antiplatelet Therapy***

Study, Year (Reference)	Secondary Prevention, %†	Participants, *n*	Target INR	Strokes/Patients/Patient-Years; Adjusted-Dose Warfarin vs. Antiplatelet, *n/n/n*	Relative Risk Reduction (95% CI), %‡	Absolute Risk Reduction, *%/y*
Adjusted-dose warfarin vs. aspirin						
AFASAK I, 1989 (2); 1990 (3)	6	671	2.8–4.2	9/335/413 vs. 16/336/409	45	1.7
SPAF II, 1994 (10) (patients age ≤75 y)	6	715	2–4.5	19/358/1099 vs. 21/357/1083	10	0.2
SPAF II, 1994 (10) (patients age >75 y)	9	385	2–4.5	20/197/394 vs. 21/188/377	10	0.5
EAFT, 1993 (8)§	100	455	2.5–4	20/225/507 vs. 52/230/477	67‖	7.0
AFASAK II, 1998 (14)	8	339	2–3	11/170/355 vs. 9/169/365	−23	−0.6
PATAF, 1999 (16)	0	272	2.5–3.5	3/131/401 vs. 4/141/392	20	0.3
Vemmos et al., 2006 (27)	0	31	1.6–2.5	0/16/5 vs. 2/15/5	100	40
Chinese ATAFS, 2006 (30)§	19	704	2–3	9/335/530 vs. 17/369/583	43	1.2
WASPO, 2007 (31)	0	75	2–3	0/36/36 vs. 0/39/39	NC	NC
8 aspirin trials¶	21	3647	–	91/1803/3740 vs. 142/1844/3730	38 (18 to 52)	Primary prevention, 0.7; secondary prevention, 7.0
Adjusted-dose warfarin vs. nonaspirin antiplatelet agents						
SIFA, 1997 (12)§	100	916	2–3.5	18/454/450 vs. 23/462/460	21	1.0
NASPEAF, 2004 (25)	0	479	2–3	6/237/556 vs. 11/242/576	45	0.8
ACTIVE-W, 2006 (28)§	15	6706	2–3	65/3371/4200 vs. 106/3335/4180	40	1.0
11 antiplatelet trials¶	22	11748	–	180/5865/8946 vs. 282/5883/8946	37 (23 to 48)	Primary prevention, 0.9; secondary prevention, NC
Adjusted-dose warfarin vs. low- and fixed-dose warfarin plus aspirin**						
SPAF III, 1996 (11)	38	1044	2–3	14/523/581 vs. 48/521/558	73‖	6.2
AFASAK II, 1998 (14)	10	341	2–3	11/170/355 vs. 11/171/377	−1	−0.2
12 antiplatelet trials¶	24	12963	–	205/6558/9982 vs. 341/6575/9881	39 (22 to 52)	Primary prevention, 0.9; secondary prevention, NC

* Warfarin was used in most trials, various coumarins were used in EAFT (8) and PATAF (16), and only acenocoumarol was used in NASPEAF (25). Please see footnote in Table 1 for definitions of study acronyms. NC = not computed.
† Proportion of patients who had previous stroke or transient ischemic attack.
‡ Risk reduction for combined ischemic and hemorrhagic strokes by intention-to-treat analysis, unless otherwise specified.
§ Total patient-years of exposure was estimated from the mean follow-up because total exposure was not published.
‖ $P < 0.05$, 2-sided.
¶ Meta-analysis estimates of relative risk reductions ($P > 0.2$, $P > 0.2$, and $P = 0.11$ for the 8, 11, and 12 antiplatelet trials, respectively) and absolute risk reductions ($P = 0.08$, $P = 0.18$, and $P = 0.15$ for the 8, 11, and 12 antiplatelet trials' primary prevention analyses, respectively; heterogeneity for secondary prevention trials precluded meta-analytic estimates: $P = 0.03$ for 11 antiplatelet trials and $P = 0.01$ for 12 antiplatelet trials); see Methods.
** Meta-analysis of trials comparing adjusted-dose warfarin with aspirin alone and with aspirin plus low- and fixed-dose warfarin is supported by the lack of efficacy of these dosages of warfarin (43, 44).

Table 5. **Safety Outcomes for Major Antithrombotic Comparisons***

Variable	Adjusted-Dose Warfarin vs. Control or Placebo	Aspirin vs. Control or No Treatment†	Adjusted-Dose Warfarin vs. Aspirin
Trials (references), *n*	6 (3–8)	5 (3, 5, 8, 17, 26)	8 (3, 8, 10, 14, 16, 27, 30, 31)
Patients, *n*	2900	3762	3647
Intracranial hemorrhage‡			
Events, *n*	6 vs. 3	8 vs. 4	20 vs. 7
Relative risk reduction (95% CI), %	NC	NC	−128 (−399 to −4)
Absolute risk reduction, %/*y*	NC	NC	−0.2
Major extracranial hemorrhage			
Events, *n*	31 vs. 17§	16 vs. 15	40 vs. 22
Relative risk reduction (95% CI), %	−66 (−235 to 18)	2 (−98 to 52)	−70 (−234 to 14)
Absolute risk reduction, %/*y*	−0.3	−0.2	−0.2
All-cause mortality			
Deaths, *n*	110 vs. 143	184 vs. 204	117 vs. 128‖
Relative risk reduction (95% CI), %	26 (3 to 43)	14 (−7 to 31)	9 (−19 to 30)
Absolute risk reduction, %/*y*	1.6	0.5	0.5

* NC = not calculated because of the large proportion of empty cells in several individual trials.
† Results are not available from 2 additional small trials that included patients who have atrial fibrillation as a subgroup of larger randomized trials (13, 18).
‡ Intracranial hemorrhages were intracerebral hemorrhages and subdural hematomas and are included as part of the primary outcome of all stroke considered in Tables 2 to 4 and Figure 1.
§ 46% of exposure in the control group of the Boston Area Anticoagulation Trial for Atrial Fibrillation (4) was during participant self-selected aspirin therapy in varying dosages. When this trial was excluded, the relative risk reduction was −130% (CI, −389% to −8%) and absolute risk reduction was −0.3% per year.
‖ Mortality data were not available from the European Atrial Fibrillation Trial (8).

The substantial relative risk reduction in stroke with adjusted-dose warfarin is consistent for all patient subgroups over a wide range of absolute stroke risks (47, 48). Achieved INRs in randomized trials ranged from 2.0 to 2.9 (4, 7, 8). Direct randomized comparisons of different intensities of adjusted-dose warfarin are limited (16, 19) (**Appendix Table 3**, available at www.annals.org). Achieved INRs between 2.0 and 2.5 offer large relative risk reductions for primary stroke prevention (4, 7, 49, 50), whereas the absolute increase in intracerebral hemorrhage during anticoagulation therapy remains relatively small if the INR is 3.5 or less in elderly patients who have atrial fibrillation (44, 51).

The best overall estimate of the reduction in stroke by antiplatelet therapy for patients who have atrial fibrillation is approximately 20%, but this number is less consistent among trials than that seen with adjusted-dose warfarin (**Figure**, *middle*). A recent analysis that used a novel mixed-treatment comparison method and included 19 trials reported a larger estimate of the efficacy of aspirin (risk reduction, 36% [95% credible interval, 12% to 56%]) (50). Aspirin seems to have a larger effect on nondisabling, noncardioembolic strokes than on cardioembolic infarctions (52). It is unclear from the available data whether specific antiplatelet agents and their combinations are more efficacious or less efficacious in patients who have atrial fibrillation. No evidence favors 1 dosage of aspirin over another. The point estimate of the relative risk reduction with adjusted-dose warfarin was similar when compared with clopidogrel plus aspirin (40%) (28) and with pooled results from 8 trials of aspirin alone (38%) (**Table 4**). This suggests that there is no major benefit of adding clopidogrel to aspirin in patients who have atrial fibrillation, but these antiplatelet agents are being directly compared in the ongoing ACTIVE-A trial (34).

In recent surveys, 10% to 20% of patients who have

Table 6. **Meta-analysis of the Efficacy of Antithrombotic Therapies for Stroke Prevention in Patients Who Have Atrial Fibrillation***

Comparison	Trials, *n*	Patients, *n*	Strokes, *n*	Relative Risk Reduction, %	Hypothetical NNT: Primary Prevention†	Hypothetical NNT: Secondary Prevention†
Adjusted-dose warfarin versus control	6	2900	186	64	40	14
Antiplatelet agents versus control	8	4876	488	22	111	34
Adjusted-dose warfarin versus antiplatelet agents	12	12 963	546	39	81	24

* NNT = number needed to treat.
† Calculated on the basis of relative risk reduction derived from meta-analysis of clinical trials applied to the following hypothetical rates to yield the NNT for 1 year to prevent 1 stroke: control patients, 4% per year and 13% per year, and patients who received antiplatelet therapy, 3% per year and 10% per year, for primary (no prior stroke or transient ischemic attack) and secondary prevention, respectively.

atrial fibrillation and are receiving adjusted-dose warfarin also receive antiplatelet therapy, mainly low-dose aspirin (51, 53, 54). The 2 available randomized trials (20, 25) that added antiplatelet therapy to full-dose anticoagulant therapy were too small and had too few events to adequately characterize the efficacy and safety of such therapy (**Appendix Table 3**, available at www.annals.org). On the basis of observational data, intracerebral hemorrhage was increased when aspirin was combined with anticoagulant therapy in 1 large study (53) but not in another study (51). Currently, benefits versus risks for combining antiplatelet therapy with adjusted-dose warfarin are inadequately defined and require additional study before their routine use in elderly patients who have atrial fibrillation.

The finding of only small increases in major extracranial hemorrhage during anticoagulation are reassuring (**Table 5**), but several caveats may be relevant. In recent clinical trials involving anticoagulants, as part of the clinical care, most patients received warfarin for varying lengths of time without major bleeding events before study participation (that is, not as a planned trial "run-in"). This probably biases toward reporting lower rates of hemorrhage than those seen in warfarin-naive patients who subsequently receive anticoagulant therapy (28). Trials in which most participants were taking warfarin before study entry tended to have lower rates of withdrawal, which also biases results to an uncertain degree in favor of warfarin. Age is an independent risk factor for serious bleeding events during anticoagulant therapy (55). The relative benefits of such therapy have been defined in clinical trials in which the average age of the participants was approximately 70 years; the benefits and risks for octogenarians who have atrial fibrillation may not be identical (47). Although internally valid, the design of recent randomized trials may result in more favorable estimates of the effects on bleeding than those that can be anticipated in clinical practice for warfarin-naive patients and for older patients. However, recent, large, practice- and population-based studies report reassuringly similar results (55–57).

The impressive relative risk reduction in stroke with adjusted-dose warfarin does not imply clinically important benefits for all patients who have atrial fibrillation. The intrinsic risk for stroke among such patients varies 20-fold. Many low-risk patients do not benefit substantially from warfarin, and low-risk patients who have atrial fibrillation can be reliably identified (56, 58–60). High-risk patients (particularly those with previous stroke or TIA) have large absolute reductions in stroke rate with anticoagulation therapy (**Table 6**). The choice of antithrombotic prophylaxis is best individualized and should consider the patient's inherent stroke risk and the best estimate of the absolute benefits, as well as bleeding risk, access to high-quality anticoagulation monitoring, and patient preferences.

For patients who have atrial fibrillation, adjusted-dose warfarin reduces stroke by approximately 60% and death by approximately 25% compared with no antithrombotic treatment. Antiplatelet therapy reduces stroke by approximately 20%. Compared with antiplatelet therapy, adjusted-dose warfarin reduces stroke by approximately 40%. Accentuation of major hemorrhage by antithrombotic therapies did not offset benefits for selected patients who have atrial fibrillation and were participating in randomized trials. These results reaffirm recommendations for adjusted-dose warfarin for patients with atrial fibrillation who are deemed to be at high risk for stroke, with antiplatelet therapy for low-risk patients and for those who cannot safely receive warfarin. Substantial unmet need remains for antithrombotic agents that are more efficacious than aspirin and that are safer or more easily administered than adjusted-dose warfarin.

From the University of Texas Health Science Center, San Antonio, Texas, and Mayo Clinic Scottsdale, Scottsdale, Arizona.

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Requests for Single Reprints: Robert G. Hart, MD, Department of Medicine (Neurology), University of Texas Health Science Center, 7703 Floyd Curl Drive, MC# 7883, San Antonio, TX 78229-3900; e-mail, hartr@uthscsa.edu.

Current author addresses are available at www.annals.org.

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Current Author Addresses: Dr. Hart: Department of Medicine (Neurology), University of Texas Health Science Center, 7703 Floyd Curl Drive, MC# 7883, San Antonio, TX 78229-3900.
Ms. Pearce: 2509 Bel Air Court, Minot, ND 58703.
Dr. Aguilar: Department of Neurology, Division of Cerebrovascular Disease, Mayo Clinic, 5777 East Mayo Boulevard, Phoenix, AZ 85054.

61. Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) With Dabigatran Etexilate. Accessed at www.clinicaltrials.gov/ct/show/NCT00262600?order=1 on 20 March 2007.

Appendix Table 1. **Unpublished or Ongoing Randomized Trials of Antithrombotic Therapies for Nonvalvular Atrial Fibrillation***

Study, Year (Reference)	Participants, *n*	Intervention	Sponsor	Expected Year of Publication
BAFTA, 2003 (32)	973	Warfarin and aspirin	Medical Research Council (London, United Kingdom)	2007
ACTIVE-A, 2006 (34)†	7500	Clopidogrel plus aspirin and aspirin	Sanofi-Aventis (Paris, France) and Bristol-Myers Squibb (Princeton, New Jersey)	2008
AMADEUS, 2005 (33)‡	Unknown	Idraparinux and warfarin	Organon (Roseland, New Jersey)	2007
RE-LY (61)†	15 000	Warfarin and dabigatran (2 dosages)	Boehringer Ingelheim (Ingelheim, Germany)	2010

* ACTIVE-A = Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events; AF = atrial fibrillation; AMADEUS = Atrial fibrillation trial of Monitored Adjusted Dose vitamin K antagonists comparing Efficacy and safety with Unadjusted SanOrg 34006; BAFTA = Birmingham Atrial Fibrillation Trial in the Aged; RE-LY = Randomized Evaluation of Long term anticoagulant therapY.
† Trial is ongoing.
‡ The AMADEUS trial was terminated at an interim analysis in July 2005 because of excessive bleeding events among patients who were assigned to idraparinux. No data have yet been published.

Appendix Table 2. **Key Methodological Features of the 29 Included Randomized Trials***

Study, Year (Reference)	Participants, *n*	Mean Age, *y*	Mean Follow-up, *y*	Men, %	Methodological Criteria Adapted from the CONSORT Statement										
					Participants Taking Anticoagulants before Trial Entry, %	Detailed Inclusion and Exclusion Criteria Reported	Participant Features Reported in Detail and Balanced between Assigned Treatments	Randomization Methods Reported	Randomization Sequence Blocked from Previewing	Masked (Blinded) Treatment Assignment	Intention-to-Treat Results Reported	Adherence to Assigned Treatments Described	Rate of Loss Follow-up, %	Fraction of Patients with CNS Events Undergoing Neuroimaging or Autopsy, %	Blinded Central Events Adjudication†
AFASAK I, 1989 (2); 1990 (3)	1007	74	1.2‡	54	0	Yes	Yes	Yes	NR	Partly	Yes	Yes	NR	78	NR
BAATAF, 1990 (4)	420	68	2.2	72	NR	Yes	Yes	Yes	NR	No	Yes	Yes	NR	100	Yes
SPAF I, 1991 (5)	1330	67	1.3	71	NR	Yes	Yes	Yes	NR	Partly	Yes	Yes	0	99	Yes
CAFA, 1991 (6)	378	68	1.3	75	NR	Yes	Yes	Yes	NR	Yes	Yes	Yes	NR	NR	NA
SPINAF, 1992 (7)	571	67	1.7	100	NR	Yes	Yes	Yes	NR	Yes	Yes	Yes	3	NR	NA
EAFT, 1993 (8)	1007	73	2.3	56	0	Yes	Yes	No	NR	Partly	Yes	Yes	<1	~80	Yes
Harenberg et al., 1993 (9)	75	82	0.4	71	NR	Yes	Yes	No	NR	No	Yes	No	NR	0	No
SPAF II, 1994 (10)	1100	70	2.8	59	NR	Yes	Yes	Yes	Yes	No	Yes	Yes	<1	98	Yes
SPAF III, 1996 (11)	1044	72	1.1	61	56	Yes	Yes	Yes	Yes	No	Yes	Yes	0	92	Yes
SIFA, 1997 (12)	916	73	1.0‡	48	NR	Yes	Yes	Yes	NR	No	Yes	Yes	1	80	Yes
ESPS II, 1997 (13)	429	NR	1.2	NR	NR	Yes	NR	Yes	NR	Yes	No	No	NR	73	NA
AFASAK II, 1998 (14)	677	73	2.2	60	0	Yes	Yes	Yes	NR	No	Yes	Yes	0	97	Yes
MWNAF, 1998 (15)	303	74	1.2	45	NR	Yes	Yes	Yes	NR	No	Yes	Yes	1	100	Yes
PATAF, 1999 (16)	729	75	2.7	45	0	Yes	Yes	Yes	Yes	No	Yes	Yes	0	NR	Yes
LASAF, 1999 (17)	285	66	1.5	51	NR	Yes	Yes	No	NR	No	Yes	Yes	NR	NR	No
UK-TIA, 1999 (18)	49	69	4.0	76	NR	Yes	NR	Yes	NR	Yes	Yes	No	NR	NR	NA
JNAFESP, 2000 (19)	115	67	1.8	72	NR	Yes	Yes	No	NR	No	Yes	Yes	NR	100	No
FFAACS, 2001 (20)	157	74	0.8	52	85	Yes	Yes	Yes	NR	Yes	Yes	Yes	0	NR	NA
SPORTIF II, 2003 (21)	254	70	0.2‡	61	61	Yes	Yes	Yes	NR	Partly	Yes	Yes	NR	100	Yes
SPORTIF III, 2003 (22)	3407	70	1.4	69	74	Yes	Yes	Yes	Yes	No	Yes	Yes	NR	NR	Yes
SAFT, 2003 (23)	668	73	2.8	63	NR	Yes	Yes	Yes	NR	No	Yes	No	<1	NR	NR
SPORTIF V, 2005 (24)	3922	72	1.6	69	84	Yes	Yes	Yes	NR	Yes	Yes	Yes	NR	NR	Yes
NASPEAF, 2004 (25)	714	70	2.3	57	NR	Yes	Yes	Yes	Yes	No	Yes	No	4	NR	Yes
JAST, 2006 (26)	871	65	2.1	70	8	Yes	Yes	Yes	Yes	No	No	No	NR	100	Yes
Vemmos et al., 2006 (27)	45	80	0.3	51	NR	Yes	Yes	Yes	NR	No	Yes	No	NR	NR	NR
ACTIVE-W, 2006 (28)	6706	70	1.3	66	77	Yes	Yes	Yes	NR	No	Yes	Yes	<1	NR	Yes
PETRO, 2005 (29)	502	70	0.2‡	82	NR	NR	NR	No	NR	Partly	No	No	NR	NR	NR
Chinese ATAFS, 2006 (30)	704	63	1.6	60	NR	Yes	NR	No	NR	No	No	No	NR	NR	No
WASPO, 2007 (31)	75	84	1.0‡	47	0	Yes	Yes	Yes	Yes	No	No	Yes	NR	NA	No

* Please see footnote in Table 1 for definitions of study acronyms. CNS = central nervous system; CONSORT = Consolidated Standards for Reporting Trials; NA = not applicable; NR = not reported.
† For trials that were not double-blind.
‡ Estimated from available data.

Appendix Table 3. **Additional Randomized Comparisons of Antithrombotic Agents***

Study, Year (Reference)	Secondary Prevention, %†	Participants, *n*	Mean Achieved INRs	Strokes/Patients/Patient-Years, *n/n/n*	Relative Risk Reduction (95% CI), %‡
Ximelagatran vs. adjusted-dose warfarin§					
SPORTIF II, 2003 (21)‖	NR	129	NR	0/62/14 vs. 0/67/15	–
SPORTIF III, 2003 (22)	24	3407	2.5	42/1704/2446 vs. 58/1703/2440	28
SPORTIF V, 2005 (24)	19	3922	2.4	52/1960/3193 vs. 44/1962/3212	−19
3 trials¶	21	7458	–	94/3726/5653 vs. 102/3732/5667	8 (−38 to 38)
Adjusted-dose anticoagulation plus aspirin or triflusal vs. adjusted-dose anticoagulation					
FFAACS, 2001 (20)	65	157	~2.4 (aspirin group) vs. ~2.4	1/76/63 vs. 0/81/70	–
NASPEAF, 2004 (25)	0	472	1.9 (triflusal group) vs 2.5	3/235/541 vs. 6/237/556	50
2 trials¶	24	629	–	4/311/604 vs. 6/318/626	29 (−201 to 83)
Adjusted-dose warfarin vs. low-dose, fixed-dose warfarin					
AFASAK II, 1998 (14)	7	337	2.2 vs. <1.2	11/170/355 vs. 14/167/363	24
MWNAF, 1998 (15)**	0	303	2.4 vs. <1.2	1/153/182 vs. 5/150/183	81
Vemmos et al., 2006 (27)	0	30	2.0 vs. 1.8	0/16/5 vs. 1/14/4	100
3 trials‖	4	670	–	12/339/537 vs. 20/331/550	39 (−28 to 71)
Adjusted-dose warfarin vs. low-intensity, adjusted-dose warfarin					
PATAF, 1999 (16)	0	253	3.1 vs. 1.4	3/131/401 vs. 4/122/361	31
JNAFESP, 2000 (19)**	100	115	2.3 vs. 1.9	2/55/91 vs. 2/60/116	−9
2 trials¶	31	368	–	5/186/492 vs. 6/182/477	18 (−174 to 76)
Aspirin vs. low- or fixed-dose anticoagulation					
AFASAK II, 1998 (14)	7	336	<1.2	9/169/365 vs. 14/167/363	39
PATAF, 1999 (16)	0	598	1.4	21/319/803 vs. 18/279/735	−2
Vemmos et al., 2006 (27)	0	29	1.8	2/15/5 vs. 1/14/4	−100
3 trials¶	2	963	–	32/503/1173 vs. 33/460/1102	12 (−47 to 47)
Aspirin or triflusal plus low- or fixed-dose anticoagulation vs. aspirin or triflusal					
AFASAK II, 1998 (14)	10	340	<1.2	11/171/377 vs. 9/169/365	−22
NASPEAF, 2004 (25)	0	477	1.9	2/235/541 vs. 9/242/576	78
2 trials¶	4	817	–	13/406/918 vs. 18/411/941	41 (−211 to 89)¶
Aspirin (300 mg/d) plus low-dose, fixed-dose warfarin vs. low-dose, fixed-dose warfarin					
AFASAK II, 1998 (14)	9	338	<1.2 vs. <1.2	11/171/377 vs. 14/167/363	25 (−82 to 69)
Aspirin (25 mg twice daily) vs. dipyridamole (200 mg twice daily)					
ESPS II, 1997 (13)††	100	218	–	17/104/123 vs. 20/114/133	8 (−97 to 57)
Aspirin (25 mg twice daily) plus dipyridamole (200 mg twice daily) vs. aspirin					
ESPS II, 1997 (13)††	100	208	–	14/104/127 vs. 17/104/123	20 (−83 to 65)
Aspirin (25 mg twice daily) plus dipyridamole (200 mg twice daily) vs. dipyridamole					
ESPS II, 1997 (13)††	100	218	–	14/104/127 vs. 20/114/133	27 (−63 to 67)
Aspirin (125 mg on alternate days) vs. aspirin (125 mg/d)					
LASAF, 1999 (17)	0	194	–	1/90/149 vs. 4/104/146	72 (−92 to 99)
Low-molecular-weight heparin (7500 anti–factor Xa U/d) vs. control					
Harenberg et al., 1993 (9)	29	75	–	2/35/12 vs. 6/40/16	66 (−83 to 94)
Aspirin (300 mg/d) vs. aspirin (1200 mg/d)					
UK-TIA, 1999 (18)**	100	34	–	3/13/52 vs. 5/21/84	4 (−530 to 88)

* Three dosages of dabigatran etexilate (50 mg, 150 mg, and 300 mg, each administered twice daily) combined with 2 aspirin dosages (81 mg and 325 mg daily) and no aspirin (that is, 9 treatment cells) were compared with adjusted-dose warfarin (target INR, 2 to 3) in the PETRO pilot trial (29). Among the 502 randomly assigned patients who were followed up for approximately 113 patient-years, only 2 thromboembolic events occurred, both in the dabigatran, 50 mg twice daily, group (1 with concomitant aspirin and 1 without concomitant aspirin). Two thromboembolic events among 10 treatment cells precludes meaningful comparison. Warfarin was the oral anticoagulant used exclusively in most trials, various coumarins were used in PATAF, and acenocoumerol was used in NASPEAF and fluindione in FFAACS. Please see footnote in Table 1 for definitions of study acronyms. INR = international normalized ratio; NR = not reported.

† Proportion of patients with previous stroke or transient ischemic attack.

‡ Risk reduction for combined ischemic and hemorrhagic strokes by intention-to-treat analysis, unless otherwise specified.

§ Subdural hematomas ($n = 22$) are considered hemorrhagic strokes. Low-dose aspirin was used by 2% of participants in SPORTIF II, 12% in SPORTIF III, and 15% in SPORTIF V. The dosage of ximelagatran was 36 mg to 40 mg twice daily. Additional SPORTIF II participants who were assigned to ximelagatran, 20 mg twice per day ($n = 66$) or 60 mg twice per day ($n = 59$), are not included because of the differences in dosage.

‖ In addition to the comparison included in this table (ximelagatran, 40 mg twice daily, in 62 patients vs. adjusted-dose warfarin in 67 patients), the SPORTIF II pilot trial randomly assigned participants to 2 additional dosages of ximelagatran (20 mg twice daily in 66 patients and 60 mg twice daily in 59 patients) (21). Only 1 stroke (in the 60 mg twice daily group) and 1 death (in the 20 mg twice daily group) occurred during the 12-week follow-up. These 5 additional direct randomized comparisons included too few events for meaningful analysis, and they are not listed individually.

¶ Weighted estimates of relative risk reductions ($P > 0.2$ for homogeneity for all comparisons except for aspirin or triflusal plus low-dose warfarin vs. aspirin or triflusal alone; $P = 0.06$); see Methods.

** Total patient-years of exposure was estimated from the mean follow-up because total exposure was not published.

†† Only "on-therapy" results are published.

Appendix Table 4. **Summary of 5 Short-Duration Randomized Trials of Antithrombotic Therapy in Patients Who Have Atrial Fibrillation***

Study, Year (Reference)	Setting	Antithrombotic Comparison	Patients, *n*	Mean Follow-up, *d*	Central Nervous System Bleeding Event	Major Extracranial Bleeding Event
ACUTE II, 2006 (36)†	TEE-guided cardioversion	Enoxaparin vs. UFH	155	9	None	None
ACE, 2004 (37)‡	Elective cardioversion	Enoxaparin vs. UFH plus phenprocoumon	496	49	None	2 enoxaparin recipients and 6 UFH recipients
Kamath et al., 2002 (35)§	Effects on hemostatic markers	Warfarin vs. aspirin plus clopidogrel	70	42	No clinical outcomes reported	No clinical outcomes reported
Li-Saw-Hee et al., 2000 (39)‖	Effects on hemostatic markers	Warfarin (2 mg) vs. warfarin (2 mg) plus aspirin vs. warfarin (1 mg) plus aspirin	61	56	No clinical outcomes reported	No clinical outcomes reported
CLAAF, 2004 (38)¶	Effects on hemostatic markers	Warfarin vs. aspirin plus clopidogrel	30	21	None	None

* ACE = Anticoagulation in Cardioversion using Enoxaparin; ACUTE II = Assessment of Cardioversion Using Transesophageal Echocardiography; CLAAF = CLopidogrel-Aspirin Atrial Fibrillation; TEE = transesophageal echocardiography; UFH = unfractionated heparin.
† Enoxaparin ($n = 76$) was compared with UFH ($n = 79$) for 7 to 10 days before TEE-guided cardioversion. The mean patient age was 63 years, and most patients had recent-onset atrial fibrillation. No patients died.
‡ Enoxaparin ($n = 248$) was compared with UFH followed by phenprocoumon ($n = 248$) for 28 days in 431 patients and for 49 days in 65 patients before planned cardioversion. The mean age of the patients was 65.5 years, and most had recent-onset atrial fibrillation. Eight patients died (3 enoxaparin recipients and 5 UFH plus phenprocoumon recipients).
§ Patients who had nonvalvular atrial fibrillation were randomly assigned to warfarin ($n = 35$) or aspirin plus clopidogrel ($n = 35$) and followed for 6 weeks to assess the relative effects of antithrombotic therapy on D-dimer, β-thromboglobulin, and soluble P-selectin levels.
‖ Patients with nonvalvular atrial fibrillation (mean age, 64 years) were randomly assigned to warfarin (2 mg/d) ($n = 23$), warfarin (1 mg/d) plus aspirin (300 mg/d) ($n = 21$), or warfarin (2 mg/d) plus aspirin (300 mg/d) ($n = 17$) and followed for 8 weeks to assess the relative effects on D-dimer, type 1 plasminogen activator inhibitor, fibrinogen, and soluble von Willebrand factor.
¶ Thirty patients, including 18 who were awaiting cardioversion, were randomly assigned to adjusted-dose warfarin versus aspirin plus clopidogrel and were followed for 21 days to assess the effects on hemostatic markers.