

A COMPARISON OF WARFARIN AND ASPIRIN FOR THE PREVENTION OF RECURRENT ISCHEMIC STROKE

J.P. MOHR, M.D., J.L.P. THOMPSON, PH.D., R.M. LAZAR, PH.D., B. LEVIN, M.D., R.L. SACCO, M.D., K.L. FURIE, M.D., J.P. KISTLER, M.D., G.W. ALBERS, M.D., L.C. PETTIGREW, M.D., H.P. ADAMS, JR., M.D., C.M. JACKSON, M.D., AND P. PULLICINO, M.D., FOR THE WARFARIN-ASPIRIN RECURRENT STROKE STUDY GROUP*

ABSTRACT

Background Despite the use of antiplatelet agents, usually aspirin, in patients who have had an ischemic stroke, there is still a substantial rate of recurrence. Therefore, we investigated whether warfarin, which is effective and superior to aspirin in the prevention of cardiogenic embolism, would also prove superior in the prevention of recurrent ischemic stroke in patients with a prior noncardioembolic ischemic stroke.

Methods In a multicenter, double-blind, randomized trial, we compared the effect of warfarin (at a dose adjusted to produce an international normalized ratio of 1.4 to 2.8) and that of aspirin (325 mg per day) on the combined primary end point of recurrent ischemic stroke or death from any cause within two years.

Results The two randomized study groups were similar with respect to base-line risk factors. In the intention-to-treat analysis, no significant differences were found between the treatment groups in any of the outcomes measured. The primary end point of death or recurrent ischemic stroke was reached by 196 of 1103 patients assigned to warfarin (17.8 percent) and 176 of 1103 assigned to aspirin (16.0 percent; $P=0.25$; hazard ratio comparing warfarin with aspirin, 1.13; 95 percent confidence interval, 0.92 to 1.38). The rates of major hemorrhage were low (2.22 per 100 patient-years in the warfarin group and 1.49 per 100 patient-years in the aspirin group). Also, there were no significant treatment-related differences in the frequency of or time to the primary end point or major hemorrhage according to the cause of the initial stroke.

Conclusions Over a two-year period, we found no difference between aspirin and warfarin in the prevention of recurrent ischemic stroke or death or in the rate of major hemorrhage. Consequently, we regard both warfarin and aspirin as reasonable therapeutic alternatives. (N Engl J Med 2001;345:1444-51.)

Copyright © 2001 Massachusetts Medical Society.

LONG-STANDING doubts, expressed as late as the 1980s, about the efficacy of warfarin for the prevention of stroke¹ were mitigated by the results of more recent clinical trials. Recurrence rates were lower with warfarin than with placebo in patients who had stroke after myocardial infarction.² The rates of first stroke in patients with atrial fibrillation were lower with warfarin than with

a range of other therapies,³ placebo,⁴ or aspirin.⁵ Also, in open-label studies, the rates of recurrent stroke were lower with warfarin than with placebo or aspirin.⁶ Rates of adverse events with warfarin were acceptably low at the ranges of the international normalized ratio (INR) used in the studies (1.5 to 3.0).^{5,7}

Most previous clinical trials of drugs to prevent recurrent ischemic stroke after a noncardiogenic ischemic stroke studied one or more of a wide variety of platelet-antiaggregant drugs, particularly aspirin, with which the recurrence rate approximates 8 percent.⁸⁻¹¹ The organizers of the current trial believed that a trial comparing warfarin and aspirin in the prevention of recurrent ischemic stroke was justified. This belief was based on the success of warfarin in the prevention of strokes among patients with atrial fibrillation and the inference that some ischemic strokes are due to embolism.¹² Furthermore, no trial had determined whether anticoagulant agents were superior to platelet-antiaggregant drugs in preventing other, noncardioembolic forms of ischemic stroke.

METHODS

Study Design

The Warfarin-Aspirin Recurrent Stroke Study (WARSS) was an investigator-initiated, randomized, double-blind, multicenter clinical trial conducted in 48 academic medical centers in the United States and sponsored by the National Institute of Neurological Disorders and Stroke. It also served as the basis for four parallel stroke studies.¹³ The trial was formulated and designed by the stroke research staff at the Neurological Institute of Columbia Presbyterian Medical Center. Clinical data were collected and monitored by the data-management center in the Stroke Unit at the Neurological Institute. Management of data on anticoagulant therapy, double-blinding procedures, and statistical analysis were conducted by the statistical-analysis center of the Department of Biostatistics, Mailman School of Public Health, Columbia University. Study medications were bottled, packaged, and distributed by Quintiles (Mount Laurel, N.J.). To eliminate variations between laboratories,¹⁴ blood samples for determination of the INR were processed centrally by Quest Diagnostics (Teterboro, N.J.). The study protocol was approved by the institutional review board at each participating center. Written informed consent was obtained from

From the Neurological Institute (J.P.M., R.M.L., R.L.S.) and the Department of Biostatistics (J.L.P.T., B.L.), Columbia Presbyterian Medical Center, New York; Massachusetts General Hospital, Boston (K.L.F., J.P.K.); Stanford University Medical Center, Palo Alto, Calif. (G.W.A.); the University of Kentucky Medical Center, Louisville (L.C.P.); University of Iowa Health Care, Iowa City (H.P.A.); the University of California at San Diego, San Diego (C.M.J.); and the State University of New York at Buffalo, Buffalo (P.P.). Address reprint requests to Dr. Mohr at the Neurological Institute, 710 W. 168th St., New York, NY 10032, or at jpm10@columbia.edu.

*Participants in the study group are listed in the Appendix.

each patient. Patient recruitment began in June 1993, and follow-up ended, as scheduled, in June 2000.

Eligibility

Eligible patients were 30 to 85 years old, were considered acceptable candidates for warfarin therapy, had had an ischemic stroke within the previous 30 days, and had scores of 3 or more on the Glasgow Outcome Scale. On this scale a score of 3 indicates severe disability, a score of 4 moderate disability, and a score of 5 minimal or no disability. Patients were ineligible if they had a base-line INR above the normal range (more than 1.4), stroke that was due to a procedure or that was attributed to high-grade carotid stenosis for which surgery was planned, or stroke associated with an inferred cardioembolic source; most of the last group had atrial fibrillation at the time of stroke. Eligibility was verified before randomization by telephone contact with the data-management center, in which each criterion for eligibility or ineligibility, the dates of stroke and randomization, magnetic resonance imaging or computed tomography of the brain, and signing of the consent form were confirmed.

Medications and Blinding

The medications evaluated were aspirin (Bayer, Morristown, N.J.), one 325-mg tablet daily, and warfarin (Dupont, Wilmington, Del.), one 2-mg scored tablet daily. The warfarin doses were adjusted to achieve and maintain an INR in the range of 1.4 to 2.8. The patients were randomly assigned to receive active aspirin and warfarin placebo or active warfarin and aspirin placebo. Randomization was stratified according to site. No patients received two placebos or two active treatments. All centers and patients were informed as to the double-blind design and the plan for the use of false INR values in the group receiving active aspirin and warfarin placebo. All centers followed the same schedule of visits to the clinic for drawing of blood to measure the INR, monitoring of medication, and adjustment of the dose of warfarin or warfarin placebo.

Blood samples for determination of the INR were sent to Quest Diagnostics on the same day or by overnight courier service. Before a center was admitted as a study site, we confirmed that blood samples sent to Quest Diagnostics were viable and yielded reliable INR determinations. All INR results were transferred electronically to the statistical-analysis center, which sent the results to the local centers by facsimile transmission. According to prior agreement among the center clinicians and with the use of a method validated early in the trial,¹⁵ the INR results sent to local centers were unmodified for the patients receiving active warfarin, but for patients receiving active aspirin and warfarin placebo, they were replaced by the statistical-analysis center with fabricated values that were plausible for the dose and duration of warfarin therapy. No INR results were available directly to the local centers from Quest Diagnostics. According to the guidelines of the Food and Drug Administration, high INR values (4.5 or more) were forwarded to the data-management center and transmitted immediately to local centers by cellular telephone. To preserve blinding, some emergency notifications for falsely elevated values in patients receiving warfarin placebo were also sent by the statistical-analysis center. The principal clinical investigator reviewed all outgoing INR reports, writing a personal cautionary note to the local investigator in the case of reports showing trends for values below or above the desired ranges. All participants other than the principal statistical investigator at the statistical-analysis center were blinded to the patients' study-group assignments. During the course of the trial, unblinding was required for 15 patients, in most cases because of the need for an invasive surgical procedure. All 15 patients stopped treatment with study drugs, but their data were included in the intention-to-treat analysis.

Follow-up

Patients were followed for 2 years \pm 1 month, up to a maximum of 761 days. Follow-up was conducted monthly by telephone or

in person at the time of drawing of blood for the determination of the INR to assess compliance and to regulate INR values, quarterly in person for clinical evaluation, and annually for detailed examination; the occurrence of end points was also ascertained at each contact. Personnel at the data-management center also conducted site visits to audit the records of all patients at each center for end points and adverse events.

Assessment of End Points and Major Adverse Events

The primary end point was death from any cause or recurrent ischemic stroke, whichever occurred first. Recurrent ischemic stroke was defined as a new lesion detected by computed tomography or magnetic resonance imaging or, in the absence of a new lesion, clinical findings consistent with the occurrence of stroke that lasted for more than 24 hours. Local centers reported potential outcome events to the events coordinator at the data-management center and submitted clinical summaries, study forms documenting clinical details, and brain imaging studies. An independent, treatment-blinded neuroradiologist reviewed the images. Five treatment-blinded neurologists adjudicated all clinical events using a majority verdict for decisions about outcomes.

Major hemorrhage was defined as intracranial, intraspinal, intracerebral, subarachnoid, subdural, or epidural hemorrhage or any other bleeding event requiring transfusion. Minor hemorrhage, which did not require transfusion, included gastrointestinal, genitourinary, retroperitoneal, joint, subcutaneous or muscular, gingival or oral, and conjunctival hemorrhage; epistaxis; hemoptysis; ecchymoses; and hemorrhage after trauma or from multiple sites. A treatment-blinded adjudicator classified hemorrhagic events as major or minor, reviewed data on death due to any reported hemorrhage, and determined the relation of the hemorrhage to treatment.

Statistical Analysis

The primary null hypothesis was that there would be no difference between patients receiving warfarin and those receiving aspirin in the time to or rate of death from any cause or recurrent ischemic stroke. Secondary null hypotheses of major clinical interest were that there would be no differences in the time to either component of the primary end point or to major hemorrhage according to sex, race or ethnic group, or cause of prior stroke.

The original target sample size was 1920 patients, which provided the study with 80 percent power and a 5 percent two-sided probability of a type I error for a test of the primary null hypothesis according to the intention to treat, allowing for a 30 percent reduction in the event rate for one therapy from a 16 percent event rate over two years for the other, and an overall dropout and discontinuation rate of 20 percent at two years for both therapies combined. In 1995, while still blinded to event rates according to treatment group, the performance and safety monitoring board appointed by the National Institute of Neurological Disorders and Stroke increased the target sample size to 2200 to adjust for the possible effects of interruption of therapy. In 1996, they revised the original stopping rule based on a single interim analysis by adopting a modified repeated significance test¹⁶ procedure that called for three scheduled interim analyses and allowed for additional interim analyses. The trial proceeded to its planned completion and final analysis without crossing the efficacy or safety boundaries.

All the major study hypotheses were prespecified and tested on an intention-to-treat basis with a two-tailed alpha of 0.05. The Kaplan-Meier method¹⁷ was used to estimate curves for the length of time to the event, and the log-rank test¹⁸ was used to compare the cumulative incidence curves in the treatment groups. The primary analysis was adjusted for loss to follow-up by a prespecified stratified imputation procedure that distinguishes different types of loss to follow-up and incorporates assumptions appropriate to each. The reported P values and confidence intervals have not been adjusted for interim analyses.

RESULTS

A total of 2206 patients were randomly assigned to treatment groups at a steady rate during the re-

cruitment phase. Their clinical and demographic features are shown in Table 1. Of these, 1302 (59 percent) were over the age of 60 years, 1309 (59 percent) were male, 1499 (68 percent) had hypertension, 705 (32 percent) had diabetes, 504 (23 percent) had cardiac disease, 390 (18 percent) had angina or prior myocardial infarction, and 629 (29 percent) had prior amaurosis fugax, transient ischemic attack, or stroke. The end-point status at two years was established for 2173 (98.5 percent). An additional 33 (1.5 percent) withdrew consent or were lost to follow-up for other reasons, at a mean of 10.2 ± 7.5 months after randomization. Figure 1 illustrates follow-up and imputation of events according to treatment.

Laboratory Testing

Quest Diagnostics determined 48,931 INR values. The mean interval between the dates of blood sampling was 27.9 ± 12.6 days. The mean daily INR for patients taking warfarin was 2.1 (median, 1.9). Overall, 70.7 percent of daily INR values determined 28 or more days after randomization were within the target range (1.4 to 2.8), 13.0 percent were above the range, and 16.3 percent were below the range. There were no significant differences in INR values among patients with different types of prior stroke (cryptogenic; small-vessel or lacunar; severe stenosis, or occlusion of a large artery; other, determined cause; and conflicting mechanism [there was more than one di-

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	WARFARIN (N=1103)	ASPIRIN (N=1103)	CHARACTERISTIC	WARFARIN (N=1103)	ASPIRIN (N=1103)
Clinical and demographic characteristics			Characteristics of initial stroke		
Age — yr	63.3±11.2	62.6±11.4	Duration of symptoms — no. (%)		
Female sex — no. (%)	447 (40.5)	450 (40.8)	≤24 hr, with clinically relevant infarct on CT or MRI	74 (6.7)	66 (6.0)
Race or ethnic group — no. (%)			>24 hr, with clinically relevant infarct on CT or MRI	729 (66.1)	769 (69.7)
White	627 (56.8)	626 (56.8)	>24 hr, without clinically relevant infarct on CT or MRI	300 (27.2)	268 (24.3)
Black	338 (30.6)	325 (29.5)	Presumed cause of prior stroke — no. (%)		
Hispanic	105 (9.5)	118 (10.7)	Cryptogenic	281 (25.5)	295 (26.7)
Other	33 (3.0)	34 (3.1)	Small-vessel or lacunar	612 (55.5)	625 (56.7)
Education — no. (%)			Large-artery, severe stenosis, or occlusion	144 (13.1)	115 (10.4)
High school or less	805 (73.0)	796 (72.2)	Other determined cause	30 (2.7)	33 (3.0)
After high school	287 (26.0)	295 (26.7)	Conflicting mechanism	36 (3.3)	35 (3.2)
Unknown	11 (1.0)	12 (1.1)	Lesion found on brain imaging — no. (%)		
Hypertension — no. (%)			Superficial, cortical, or cerebellar	143 (13.0)	137 (12.4)
Yes	746 (67.6)	753 (68.3)	Large deep (basal ganglia and other)	77 (7.0)	102 (9.2)
No	343 (31.1)	338 (30.6)	Superficial and deep combined	126 (11.4)	110 (10.0)
Unknown	14 (1.3)	12 (1.1)	Small deep	315 (28.6)	333 (30.2)
Diabetes mellitus — no. (%)			Brain stem	110 (10.0)	134 (12.1)
Yes	367 (33.3)	338 (30.6)	No primary lesion visible on scan	304 (27.6)	264 (23.9)
No	733 (66.5)	763 (69.2)	Unknown	28 (2.5)	23 (2.1)
Unknown	3 (0.3)	2 (0.2)	Glasgow score — no. (%)‡		
Any cardiac disease — no. (%)†			2	0	0
Yes	250 (22.7)	254 (23.0)	3	78 (7.1)	90 (8.2)
No	822 (74.5)	824 (74.7)	4	327 (29.6)	319 (28.9)
Unknown	31 (2.8)	25 (2.3)	5	698 (63.3)	694 (62.9)
History of transient ischemic attack, amaurosis fugax, or stroke — no. (%)			Barthel Index§		
Yes	321 (29.1)	308 (27.9)	95 to 100 — no. (%)	806 (73.1)	765 (69.4)
No	731 (66.3)	740 (67.1)	65 to 90 — no. (%)	214 (19.4)	246 (22.3)
Unknown	51 (4.6)	55 (5.0)	0 to 60 — no. (%)	83 (7.5)	92 (8.3)
Current smoking — no. (%)			Mean score	91.8±15.3	90.8±16.4
Yes	306 (27.7)	337 (30.6)			
No	792 (71.8)	761 (69.0)			
Unknown	5 (0.5)	5 (0.5)			
Heavy alcohol intake (≥4 drinks/day) — no. (%)					
Yes	40 (3.6)	34 (3.1)			
No	1060 (96.1)	1060 (96.1)			
Unknown	3 (0.3)	9 (0.8)			

*The treatment groups did not differ significantly in any characteristic. Percentages may not sum to 100 because of rounding. Plus-minus values are means ±SD. CT denotes computed tomography, and MRI magnetic resonance imaging.

†Cardiac disease was defined as myocardial infarction, congestive heart failure, angina, atrial fibrillation, arrhythmia, or valvular heart disease. Unknown means data were missing on all of these cardiac conditions, or any combination of missing data and “No.”

‡Scores on the Glasgow Outcome Scale range from 1 to 5; 1 indicates death, 2 a persistent vegetative state, 3 severe disability (with the patient conscious but disabled), 4 moderate disability (with the patient disabled but independent), and 5 minimal or no disability.

§Scores on the Barthel Index range from 0 to 100, with scores of 0 to 60 indicating dependence, scores of 65 to 90 moderate independence, and scores of 95 to 100 complete independence.

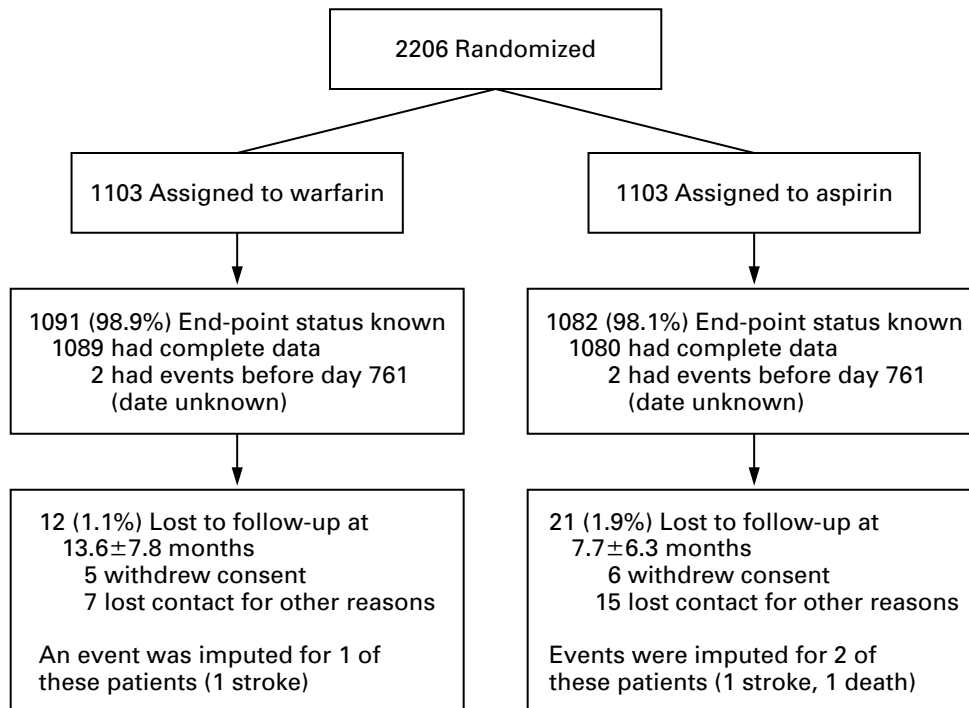


Figure 1. Follow-up of Patients and Imputation of Events.

Events for which exact dates were unknown were considered to have occurred at the midpoints of the calendar periods during which they occurred. Plus-minus values are means \pm SE.

agnostic possibility]) ($P=0.24$ by F test with log-transformed INR values).

Outcomes

The overall rate of the primary end point of death or recurrent ischemic stroke of 16.9 percent (372 of 2206 patients) slightly exceeded the 16 percent rate assumed in the trial design. In the primary intention-to-treat analysis, there were no significant differences between the warfarin and aspirin groups in the time to the primary end point ($P=0.25$ by two-tailed log-rank test; hazard ratio for warfarin as compared with aspirin, 1.13; 95 percent confidence interval, 0.92 to 1.38; two-year probability of an event, 17.8 percent with warfarin and 16.0 percent with aspirin) (Table 2 and Fig. 2). Censoring data from subjects whose data were incomplete at the time of loss to follow-up did not materially affect the outcome of the primary analysis, and incorporating the interruption of study medication as a time-dependent covariate showed that the effects of warfarin and aspirin therapy did not differ.

The rates of major hemorrhage were low, with no significant differences between treatment groups; the annual rates were 2.22 per 100 patient-years for warfarin and 1.49 per 100 patient-years for aspirin (rate

ratio, 1.48; $P=0.10$). Patients in the warfarin group had significantly more minor hemorrhages than did those in the aspirin group (Table 3). There was no significant difference between groups in the time to the first occurrence of major hemorrhage or the primary end point ($P=0.16$; hazard ratio with warfarin as compared with aspirin, 1.15; 95 percent confidence interval, 0.95 to 1.39) (Table 2).

There were also no significant differences in the time to a primary end point between patients of different sexes, of different racial or ethnic groups, or with different types of prior stroke (Table 2). Figure 3 shows INR-specific rates of primary events plotted by the method of Rosendaal et al.,¹⁹ with use of the last INR value before the event. The rates decline for INR values until the INR interval of 1.5 to less than 2.0, but change little thereafter.

DISCUSSION

We observed no significant difference between treatment with warfarin and treatment with aspirin in the prevention of recurrent ischemic stroke or death or in the occurrence of serious adverse events in this large cohort of patients with inferred noncardioembolic ischemic stroke. Not only did the use of warfarin not lead to a 30 percent reduction in the risk of re-

TABLE 2. RESULTS OF PRIMARY AND SECONDARY ANALYSES.

ANALYSIS	EVENTS		PROBABILITY OF EVENT AT 2 Yr*		HAZARD RATIO (95% CI)†	P VALUE‡
	WARFARIN	ASPIRIN	WARFARIN	ASPIRIN		
	no. with events/total no.					
Primary and secondary analyses						
Recurrent ischemic stroke or death	196/1103	176/1103	17.8	16.0	1.13 (0.92–1.38)	0.25
Recurrent ischemic stroke or death or major hemorrhage	222/1103	196/1103	20.0	17.8	1.15 (0.95–1.39)	0.16
Recurrent ischemic stroke or death, with data from patients lost to follow-up censored	195/1103	174/1103	17.6	15.9	1.13 (0.92–1.39)	0.24
Recurrent ischemic stroke or death (model including interaction of treatment assignment and interruption of treatment)	196/1103	176/1103				
Subgroup analyses for primary end point						
Sex						
Male	122/656	101/653	18.5	15.4	1.23 (0.95–1.61)	0.12
Female	74/447	75/450	16.2	16.8	0.98 (0.71–1.36)	0.92
Race or ethnic group						
Black	70/338	59/325	20.2	18.4	1.14 (0.81–1.62)	0.45
White	98/627	90/626	15.5	14.3	1.10 (0.83–1.47)	0.50
Hispanic	21/105	21/118	20.1	17.9	1.14 (0.62–2.09)	0.66
Other	7/33	6/34	21.2	17.6	1.18 (0.40–3.50)	0.77
Cause of prior stroke						
Cryptogenic	42/281	48/295	15.0	16.5	0.92 (0.61–1.39)	0.68
Small vessel or lacunar	107/612	95/625	17.1	15.2	1.15 (0.88–1.52)	0.31
Large artery, severe stenosis, or occlusion	27/144	18/115	18.8	15.7	1.22 (0.67–2.22)	0.51
Other determined cause	11/30	7/33	36.7	21.2	1.99 (0.77–5.15)	0.15
Conflicting mechanism	9/36	8/35	25.0	23.0	1.14 (0.44–2.96)	0.79

*Probabilities of events were derived from Kaplan–Meier curves.

†Hazard ratios were calculated by the discrete-time Cox model. CI denotes confidence interval.

‡P values were calculated with the log-rank test, except for those for the interruption-of-therapy model, which were calculated by the Wald test.

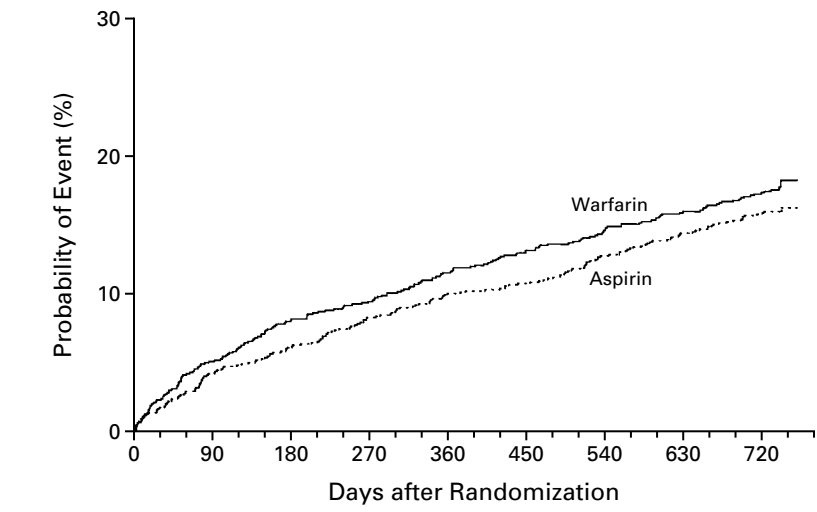
current stroke — the reduction used to estimate the sample size — but it was also associated with a non-significant, 13 percent higher increase in risk over that with aspirin. Treatment with warfarin did not result in excess event rates during the first 30 days or in a significant increase in the rates of hemorrhage; these potential outcomes affected the trial design because of concern that either of these outcomes would offset any benefit of warfarin.

Two observations suggest that the demographic characteristics of the study population and outcomes compare favorably with those of other trials of aspirin or warfarin. First, the event rate among patients assigned to aspirin was similar to that in other trials of aspirin for the prevention of recurrent ischemic stroke.^{10–12,14} Furthermore, the low rates of hemorrhage with warfarin were similar to those in warfarin-treated patients with stroke associated with atrial fibrillation whose INR values were similar to those of our patients.^{5,7} Our finding that the rate of recurrent stroke with warfarin was similar to the rate with aspirin suggests that warfarin is an effective therapy in patients

with a prior ischemic stroke. However, in our trial, warfarin was not superior to aspirin. If anything, the reverse was true; warfarin did not decrease the rate of severe recurrent stroke, as it does in patients with prior stroke associated with atrial fibrillation.^{5–7} Moreover, warfarin costs more than aspirin and requires close monitoring.

It is unlikely that the range of INR values chosen was too low to show the superiority of warfarin. Treatment targeted to the same range of values was successful for the prevention of first strokes in patients with atrial fibrillation. Published graphs showing the effect of the INR on the risk of stroke showed curves similar in shape to those in our results, flattening for INR values of 1.5 to 2.0 and remaining relatively stable for higher values up to 3.0. However, the event rates in relation to the same range of INR values (1.5 to 3.0) among patients with atrial fibrillation were well below that in our study.^{5–7}

We considered using higher INR values than those used in studies of patients with atrial fibrillation, but observations from other studies published during the



No. AT RISK	0	90	180	270	360	450	540	630	720
Warfarin	1103	1047	1013	998	972	956	939	924	885
Aspirin	1103	1057	1032	1004	984	974	951	932	900

Figure 2. Kaplan–Meier Analyses of the Time to Recurrent Ischemic Stroke or Death According to Treatment Assignment.

TABLE 3. ADVERSE EVENTS ACCORDING TO TREATMENT ASSIGNMENT.*

EVENT	WARFARIN (N=1103)	ASPIRIN (N=1103)	ODDS RATIO (95% CI)	P VALUE†
	no. (%)			
Death	47 (4.3)	53 (4.8)	0.88 (0.58–1.32)	0.61
Related to hemorrhage	7 (0.6)	5 (0.4)	1.40 (0.42–5.13)	0.77
First hemorrhage‡				
Major	38 (3.4)	30 (2.7)	1.28 (0.78–2.10)	0.39
Minor	261 (23.7)	188 (17.0)	1.51 (1.22–1.87)	<0.001
			RATE RATIO (95% CI)	P VALUE§
	no. of events (rate/100 patient-yr)			
All hemorrhages¶				
Major	44 (2.2)	30 (1.5)	1.48 (0.93–2.44)	0.10
Minor	413 (20.8)	259 (12.9)	1.61 (1.38–1.89)	<0.001

*Maximal follow-up was 25 months. Hemorrhages occurring on the day of the primary event (death or recurrent ischemic stroke) are included. CI denotes confidence interval.
 †P values were calculated by the exact test of two independent proportions.
 ‡The first hemorrhage is the first or only hemorrhage for each patient.
 §P values were calculated by the exact conditional binomial test for two independent Poisson processes.
 ¶All hemorrhages include all hemorrhages in any patient.

course of our study supported our concern about safety.²⁰⁻²⁴ Higher rates of major hemorrhage could have stopped the trial before efficacy could be validly tested, as happened for the Stroke Prevention in Reversible Ischemia Trial, an open-label comparison of warfarin with lower-dose aspirin after transient ische-

mic attacks and stroke that used an INR range of 3.0 to 4.5 (mean, 3.5).²⁵ Higher INR ranges than those we used in other, nonstroke settings have had mixed results with respect to safety as compared with studies of warfarin alone²⁶ or in combination with aspirin.²⁷

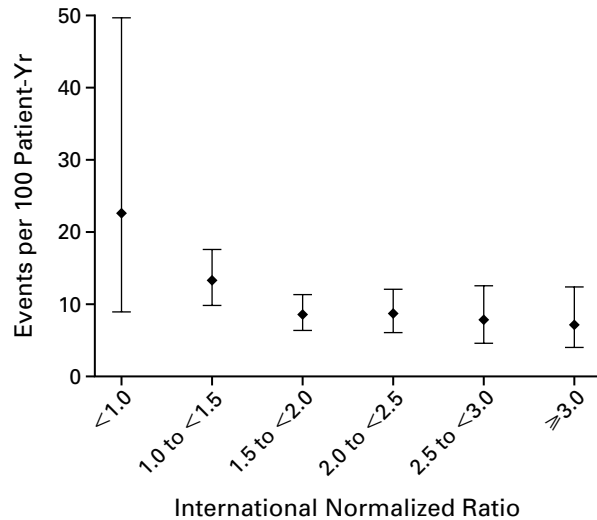


Figure 3. Incidence of Recurrent Ischemic Stroke or Death among Patients Assigned to Warfarin, According to the International Normalized Ratio.

The I bars indicate 95 percent confidence intervals. The international normalized ratio was the last measured before the event.

The overall percentages of patients with INR values in, above, or below the target range in our study also compare favorably with the percentages in other trials. These findings argue against the possibility that warfarin's lack of superiority to aspirin was due to high percentages of patients with low INR values. Because reports of studies showing the success of warfarin in patients with atrial fibrillation did not present data on the time course of INR values during the trials in graphic form, no direct time-based comparisons with our data are possible.

As a direct test of warfarin versus aspirin for the prevention of recurrent ischemic stroke in a broad clinical setting (excluding patients with stroke due to embolism), our study necessarily included patients with a variety of types of prior ischemic stroke. Because it is not always easy to separate different types of stroke, regardless of the classification scheme used,²⁸⁻³⁰ some patients with cardiogenic embolism may have been included. If so, they did not favorably affect the findings with regard to the effect of warfarin. The recurrence rates in patients with different types of prior ischemic stroke are similar to those found in the Stroke Data Bank of the National Institute of Neurological Disorders and Stroke²⁸ and the Northern Manhattan Stroke Study³¹ but differ somewhat from those in other studies.³²

Like the studies of tissue plasminogen activator for acute stroke,³³ our study did not find significant differences in the effects of treatment among patients

with different clinically identifiable types of prior ischemic stroke. Despite our study's lack of sufficient power to show such differences, our data nonetheless suggest some possible selective treatment effects. Aspirin was slightly, but not significantly, superior to warfarin in patients with large-vessel and lacunar infarcts. Patients with large-vessel strokes are currently under study.³⁴ If aspirin is superior to warfarin in lacunar stroke, that finding will support the idea that there is a mechanistic link between lacunar disease and large-intracranial-artery atheroma.^{35,36} Cryptogenic stroke, in which the prevalence of superficial brain convexity infarcts and lack of evidence of large-artery disease have made clinically occult embolism¹⁵ or coagulopathy³⁷ the leading presumed causes, was the only clinically identified stroke type for which a possible benefit of warfarin was suggested by our data; but the reduction in risk was small (8 percent) and not statistically significant.

Warfarin offered no additional benefit over aspirin in preventing recurrent ischemic stroke in the population we studied. Patients with other, established reasons for warfarin use may take comfort in the evidence of safety and lack of significant difference overall, as compared with aspirin. However, aspirin, either alone or in combination with some other antiplatelet agents,³⁸ appears to be a well-justified choice for the prevention of recurrent ischemic stroke.

Supported by a grant (RO1-NS-28371) from the National Institute of Neurological Disorders and Stroke. Medications and placebos were supplied by Dupont Pharmaceuticals and Bayer.

APPENDIX

The following participated in the WARSS: *Executive committee*: J.P. Mohr, R.L. Sacco, R.M. Lazar, J.L.P. Thompson, B. Levin, J.P. Kistler, G.W. Albers, L.C. Pettigrew, H.P. Adams, Jr., and C.M. Jackson; *National Institute of Neurological Disorders and Stroke*: J.R. Marler, program director; B. Radziszewka, clinical research project manager; *Data Management Center*: R.M. Lazar, D.E. Gohs, M. Clavijo, K. Slane, D. Balbuena, D. Martino, C. Inguanzo, J. Pittman, R. Sciacca, K. Evans, K. Lord, B. Jaffe, J. Kim, L. Lynn, J. Ruzicka, P. Chugh, A. Zidel, B. Fields, M. Coleman, R. King, J.G. Mohr, I. Carretero, O. Mendoza, and A. Barlow; *Statistical Analysis Center*: J.L.P. Thompson, B. Levin, W. Ma, T. Costigan, A. Murphy, X. Chen, E. Etienne, R. Hilbawi, K. Sridharan, D. Burroughs, G. Kanu, R. Okunieff, D. Xu, and K. Chin; *Consultants*: P.A. Wolf, B.C. Tilley, and B. Rosner; *Performance and Safety Monitoring Board*: D.G. Sherman (chair), M.L. Dyken, A. Lowe, I. Meissner, D.W. Taylor; *Adjudication Committee*: H.J.M. Barnett, C.M. Fisher, J.C. Gautier, P. Sandercock, and J.P. Whisnant; *Neuroradiologist adjudicators*: S.K. Hilal (deceased) and J. Pile-Spellman; *Hemorrhage adjudicator*: A.G.G. Turpie; *Myocardial-infarction adjudicator*: E.-G.V. Giardina. The following institutions, local principal investigators, and local coordinators also participated; numbers of patients enrolled are shown in parentheses: *Columbia Presbyterian Medical Center (153)*: R. Sacco, R. Marshall, M. Elkind, C. Stapf, H. Mast, M. Clavijo, and A. Cruz; *Massachusetts General Hospital (105)*: J. Kistler, K.L. Furie, F. Buonanno, and L. Oertel; *Stanford Stroke Center (105)*: G.W. Albers, S. Kemp, and N. Hock; *University of Kentucky Medical Center (103)*: R. Dempsey, L. Pettigrew, B. Stidham, and I. Lamb; *University of Iowa Hospitals and Clinics (92)*: H.P. Adams, Jr., A. Tanna, and L. Vining; *University of California at San Diego Medical Center (89)*: C. Jackson, N. Kelly, and J. Werner; *Buffalo General Hospital (87)*: P. Pullicino, M. Hens, N. Meiler, and A. Martinez; *Lankenau Medical Research Center (84)*: M. Alter, G. Friday, M. Lloyd, T. Listner, and A. Smith; *Syracuse Veterans Affairs Medical Center (75)*: A. Culebras, M. Benedict, D. Pastor, and T. Dean; *Georgetown University (71)*: M. Yaseen, J. Burfoot, and E. Green; *Long Island Jewish Medical Center (70)*: R. Libman and R. Gonzaga-Camfield;

University of Tennessee at Memphis (67): K. Gaines, B. O'Brien, C. Bonds, J. Shaw, and A. Payne; *University of Texas Medical School* (64): J. Grotta and D. Vital; *Vanderbilt Medical Center* (64): H. Kirschner, A. Nelson, S. O'Connell, K. Heyden, and D. Klein; *Johns Hopkins Bayview Medical Center* (63): C. Johnson, C. Early, and J. Alt; *University of Illinois Medical Center* (60): C. Helgason, J. Hoff, and T. Gnutek; *Henry Ford Hospital* (60): P. Mitsias, K. Sawaya, P. Marchese, and J. Reuther; *Marshfield Clinic* (56): P. Karanjia, S. Lobner, and L. Stephani; *Mount Sinai School of Medicine* (47): S. Tuhim and S. Augustine; *Metrohealth Medical Center* (46): J. Schmidley, M. Winkelman, and A. Liskay; *Medical College of Wisconsin at Froedtert* (43): J. Binder and H. Patrick; *Hennepin County Medical Center* (41): D. Anderson, D. Brauer, and D. Radtke; *Wayne State University* (41): S. Chaturvedi, L. Femino, E. St. Pierre, L. Quinones, and F. Mada; *Rochester General Hospital* (38): J. Hollander, G.W. Honch, and C. Weber; *Montefiore Medical Center* (36): D.M. Rosenbaum, E. Klonowski, S. Rybak, and J.P. Noonan; *Indiana University Medical Center* (36): J. Biller and L. Chadwick; *Medical College of Georgia* (35): F. Nichols and M. Sahm; *Cleveland Clinic Foundation* (33): C. Sila, B. Dyko, and N. Rudd; *Barrow Neurological Institute* (32): J. Frey, C. Darbonne, L. Marlor, J. Minor, and J. Snyder; *Yale University School of Medicine* (29): L. Brass, A. Lovejoy, and B. Kennedy; *University of South Alabama* (28): J. Rothrock, R. Zweifler, S. Cunningham, and R. Yunker; *Boston University Medical Center* (27): C. Kase, E. Licata-Gehr, and N. Allen; *New England Medical Center* (26): M. Pessin (deceased), L. Caplan, and L. Barron; *Maimonides Medical Center* (25): A. Miller, L.R. Caplan, T. Morgante, K. Chin, and T. LaRocca; *University of Miami School of Medicine* (25): R. Kelley, A. Forteza, and J. Arias; *Albert Einstein Medical Center* (21): S. Silliman, J. Dissin, and C. Borschell; *Beth Israel Deaconess Hospital, Boston* (18): C. Mayman (deceased), S. Warach, L.R. Caplan, M. Tijerina, A. Connor, S. Connors, and L. Barron; *New York University-Veterans Affairs* (15): H. Weinreb, K. Siller, L. Chin, and G. Allen; *Helen Hayes Hospital* (15): L. Lennihan and L. Tenteromano; *University of Southern California* (14): M. Fisher, G. Fischberg, A. Scicli, and A. Mohammadi; *Pennsylvania Hospital* (14): D. Jamieson, C. Gonnella, and M. Hellstern; *Cleveland Clinic Florida* (11): B. Dandapani, V. Salinga, P. Parks, and M. Piccirillo; *Little Rock Veterans Affairs Medical Center* (10): M. Chesser, B. Boop, S. Nazarian, L. Kennedy, and D. Hollis-Holderfield; *Bassett Healthcare* (9): L. Hamilton, A. Nafziger, J. Zeller, and L. Cabelus; *University of Michigan Medical Center* (8): M. Chimowitz and Z. Noorani; *St. Paul-Ramsey Medical Center* (7): M. Ramirez-Lassepas and C. Espinosa; *University of Vermont* (5): J. Dissin, R. Hamill, P. Krusinski, and M. Fitzpatrick; *University of Virginia* (3): E. Haley and G. Kongable.

REFERENCES

1. Sandercock P, Warlow C, Bamford J, Peto R, Starkey I. Is a controlled trial of long-term oral anticoagulants in patients with stroke and non-rheumatic atrial fibrillation worthwhile? *Lancet* 1986;1:788-92.
2. A double-blind trial to assess long-term oral anticoagulant therapy in elderly patients after myocardial infarction: report of the Sixty Plus Reinfarction Study Research Group. *Lancet* 1980;2:989-94.
3. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. *N Engl J Med* 1990;323:1505-11.
4. Ezekowitz MD, Bridgers SL, James KE, et al. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. *N Engl J Med* 1992;327:1406-12. [Erratum, *N Engl J Med* 1993;328:148.]
5. Stroke Prevention in Atrial Fibrillation Investigators. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. *Lancet* 1994;343:687-91.
6. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: the Copenhagen AFASAK study. *Lancet* 1989;1:175-9.
7. Goldstein LB, Adams R, Becker K, et al. Primary prevention of ischemic stroke: a statement for healthcare professionals from the Stroke Council of the American Heart Association. *Stroke* 2001;32:280-99.
8. Bousser MG, Eschwege E, Hageunau M, et al. "AICLA" controlled trial of aspirin and dipyridamole in the secondary prevention of atherothrombotic cerebral ischemia. *Stroke* 1983;14:5-14.
9. Hass WK, Easton JD, Adams HP Jr, et al. A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. *N Engl J Med* 1989;321:501-7.
10. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;348:1329-39.
11. European Stroke Prevention Study 2: efficacy and safety data. *J Neurol Sci* 1997;151:Suppl:S1-S77.
12. Mohr JP. Cryptogenic stroke. *N Engl J Med* 1988;318:1197-8.
13. The WARSS, APASS, PICSS, HAS, and GENESIS Study Groups. The

feasibility of a collaborative double-blind study using an anticoagulant. *Cerebrovasc Dis* 1997;7:100-12.

14. Lind SE, Pearce LA, Feinberg WM, Bowill EG. Clinically significant differences in the International Normalized Ratio measured with reagents of different sensitivities. *Blood Coagul Fibrinolysis* 1999;10:215-27.
15. Thompson JLP, Fleiss JL, James K, et al. Test of an algorithm for simulating prothrombin times in a double-blind anticoagulation drug trial. *Ann Neurol* 1994;36:305-6. abstract.
16. Modified repeated significance tests. In: Siegmund D. *Sequential analysis: tests and confidence intervals*. New York: Springer-Verlag, 1985: 86-9.
17. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
18. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966;50:163-70.
19. Rosendaal FR, Cannegieter SC, van der Meer FJM, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost* 1993;69:236-9.
20. Gullov AL, Koefoed BG, Petersen P. Bleeding during warfarin and aspirin therapy in patients with atrial fibrillation: the AFASAK 2 study. *Arch Intern Med* 1999;159:1322-8.
21. Yamaguchi T. Optimal intensity of warfarin therapy for secondary prevention of stroke in patients with nonvalvular atrial fibrillation: a multicenter, prospective, randomized trial. *Stroke* 2000;31:817-21.
22. Pengo V, Legnani C, Noventa F, Palareti G. Oral anticoagulant therapy in patients with nonrheumatic atrial fibrillation and risk of bleeding: a Multicenter Inception Cohort study. *Thromb Haemost* 2001;85:418-22.
23. Liu M, Counsell C, Sandercock P. Anticoagulants for preventing recurrence following ischaemic stroke or transient ischaemic attack (Cochrane review). *Cochrane Library*, issue 3. Oxford, England: Update Software, 2001. (Accessed September 18, 2001, at <http://www.update-software.com/abstracts/ab000248.htm>.)
24. Go AS, Hylek EM, Phillips KA, et al. Implications of stroke risk criteria on the anticoagulation decision in nonvalvular atrial fibrillation: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. *Circulation* 2000;102:11-3.
25. Gorter JW. Major bleeding during anticoagulation after cerebral ischemia: patterns and risk factors: Stroke Prevention in Reversible Ischemia Trial (SPIRIT). *Neurology* 1999;53:1319-27.
26. Witte K, Thackray S, Clark AL, Cooklin M, Cleland JG. Clinical trials update: IMPROVEMENT-HF, COPERNICUS, MUSTIC, ASPECT-II, APRICOT and HEART. *Eur J Heart Fail* 2000;2:455-60.
27. Huynh T, Thérout P, Bogaty P, Nasmith J, Solymoss S. Aspirin, warfarin, or the combination for secondary prevention of coronary events in patients with acute coronary syndromes and prior coronary artery bypass surgery. *Circulation* 2001;103:3069-74.
28. Foulkes MA, Wolf PA, Price TR, Mohr JP, Hier DB. The Stroke Data Bank: design, methods, and baseline characteristics. *Stroke* 1988;19:547-54.
29. Anderson CS, Taylor BV, Hankey GJ, Stewart-Wynne EG, Jamrozik KD. Validation of a clinical classification for subtypes of acute cerebral infarction. *J Neurol Neurosurg Psychiatry* 1994;57:1173-9.
30. Madden KP, Karanjia PN, Adams HP Jr, Clarke WR. Accuracy of initial stroke subtype diagnosis in the TOAST study: Trial of ORG 10172 in Acute Stroke Treatment. *Neurology* 1995;45:1975-9.
31. Sacco RL, Shi T, Zamanillo MC, Kargman DE. Predictors of mortality and recurrence after hospitalized cerebral infarction in an urban community: the Northern Manhattan Stroke Study. *Neurology* 1994;44:626-34.
32. Petty GW, Brown RD Jr, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Ischemic stroke subtypes: a population-based study of functional outcome, survival, and recurrence. *Stroke* 2000;31:1062-8.
33. Kwiatkowski TG, Libman RB, Frankel M, et al. Effects of tissue plasminogen activator for acute ischemic stroke at one year. *N Engl J Med* 1999;340:1781-7.
34. The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) Study Group. Prognosis of patients with symptomatic vertebral or basilar artery stenosis. *Stroke* 1998;29:1389-92.
35. Fisher CM. The arterial lesions underlying lacunes. *Acta Neuropathol (Berl)* 1968;12:1-15.
36. Kappelle LJ, van Latum JC, van Swieten JCA, Algra A, Koudstaal PJ, van Gijn J. Recurrent stroke after transient ischemic attack or minor ischaemic stroke: does the distinction between small and large vessel disease remain true to type? *J Neurol Neurosurg Psychiatry* 1995;59:127-31.
37. Bushnell CD, Goldstein LB. Diagnostic testing for coagulopathies in patients with ischemic stroke. *Stroke* 2000;31:3067-78.
38. Albers GW, Amarenco P, Easton JD, Sacco RL, Teal P. Antithrombotic and thrombolytic therapy for ischemic stroke. *Chest* 2001;119:Suppl:300S-320S.

Copyright © 2001 Massachusetts Medical Society.