

ORIGINAL ARTICLE

Comparison of Warfarin and Aspirin for Symptomatic Intracranial Arterial Stenosis

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ABSTRACT

BACKGROUND

Atherosclerotic intracranial arterial stenosis is an important cause of stroke. Warfarin is commonly used in preference to aspirin for this disorder, but these therapies have not been compared in a randomized trial.

METHODS

We randomly assigned patients with transient ischemic attack or stroke caused by angiographically verified 50 to 99 percent stenosis of a major intracranial artery to receive warfarin (target international normalized ratio, 2.0 to 3.0) or aspirin (1300 mg per day) in a double-blind, multicenter clinical trial. The primary end point was ischemic stroke, brain hemorrhage, or death from vascular causes other than stroke.

RESULTS

After 569 patients had undergone randomization, enrollment was stopped because of concerns about the safety of the patients who had been assigned to receive warfarin. During a mean follow-up period of 1.8 years, adverse events in the two groups included death (4.3 percent in the aspirin group vs. 9.7 percent in the warfarin group; hazard ratio for aspirin relative to warfarin, 0.46; 95 percent confidence interval, 0.23 to 0.90; $P=0.02$), major hemorrhage (3.2 percent vs. 8.3 percent, respectively; hazard ratio, 0.39; 95 percent confidence interval, 0.18 to 0.84; $P=0.01$), and myocardial infarction or sudden death (2.9 percent vs. 7.3 percent, respectively; hazard ratio, 0.40; 95 percent confidence interval, 0.18 to 0.91; $P=0.02$). The rate of death from vascular causes was 3.2 percent in the aspirin group and 5.9 percent in the warfarin group ($P=0.16$); the rate of death from nonvascular causes was 1.1 percent and 3.8 percent, respectively ($P=0.05$). The primary end point occurred in 22.1 percent of the patients in the aspirin group and 21.8 percent of those in the warfarin group (hazard ratio, 1.04; 95 percent confidence interval, 0.73 to 1.48; $P=0.83$).

CONCLUSIONS

Warfarin was associated with significantly higher rates of adverse events and provided no benefit over aspirin in this trial. Aspirin should be used in preference to warfarin for patients with intracranial arterial stenosis.

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N Engl J Med 2005;352:1305-16.

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ATHEROSCLEROTIC STENOSIS OF THE major intracranial arteries is an important cause of stroke, especially in blacks, Asians, and Hispanics.¹⁻³ Of the 900,000 strokes or transient ischemic attacks that occur each year in the United States,^{4,5} approximately 70,000 to 90,000 are caused by intracranial arterial stenosis.³ The risk of recurrent stroke in these patients may be as high as 15 percent per year.^{6,7}

Despite their high risk of stroke, there are no prospective studies comparing antithrombotic therapies in these patients. Anticoagulation was first used to treat intracranial arterial stenosis in 1955,⁸ and subsequent, retrospective studies suggested that warfarin may be more effective than aspirin.^{6,7,9} On the other hand, a more recent trial that compared aspirin with warfarin in patients with noncardioembolic stroke (most of whom had lacunar infarct) showed similar rates of recurrent stroke with the two treatments.¹⁰

Uncertainty about optimal antithrombotic therapy for intracranial arterial stenosis is illustrated by a recent survey showing that neurologists in the United States are evenly divided between those who prefer warfarin therapy and those who prefer antiplatelet therapy for this disease.¹¹ Given the importance of intracranial stenosis as a cause of stroke and the lack of evidence supporting a clear choice for treatment,¹² we conducted a clinical trial to compare aspirin with warfarin in patients with this disorder.

METHODS

STUDY DESIGN AND PATIENT ELIGIBILITY

Details of the study design have been published previously.^{13,14} The study was an investigator-initiated, randomized, double-blind, multicenter clinical trial conducted at 59 sites in North America. The National Institute of Neurological Disorders and Stroke (NINDS) sponsored the study. The study protocol was approved by the institutional review board at each site, and all patients gave written informed consent for participation. Patients who did not undergo angiography as part of routine care gave written informed consent for angiography as part of the study protocol. The operations committee was responsible for the design of the study, oversight of data collection, and data analysis. The steering committee was responsible for writing the manuscript.

Patients were enrolled between February 1999 and July 2003. Inclusion criteria included transient

ischemic attack or nondisabling stroke that occurred within 90 days before randomization and that was attributable to angiographically verified 50 to 99 percent stenosis of a major intracranial artery (carotid, middle cerebral, vertebral, or basilar), a modified Rankin score of 3 or less (indicating a nondisabling stroke), and an age of at least 40 years. Exclusion criteria included tandem 50 to 99 percent stenosis of the extracranial carotid artery, nonatherosclerotic stenosis of an intracranial artery, a cardiac source of embolism (e.g., atrial fibrillation), a contraindication to aspirin or warfarin therapy, an indication for heparin administration after randomization, and a coexisting condition that limited survival to less than five years.

RANDOMIZATION AND STUDY MEDICATIONS

Treatment assignments were stratified according to study site and were generated at the statistical coordinating center with the use of a pseudo-random-number generator with randomly permuted blocks. Patients were given two vials of medications, one marked "warfarin/placebo" and the other marked "aspirin/placebo." One vial contained active medication and the other contained placebo. The initially prescribed dose of warfarin (or its placebo) was 5 mg daily, and that of enteric-coated aspirin (or its placebo) was 650 mg twice daily. The dose of aspirin or its placebo could be lowered (minimum dose, 325 mg per day) if side effects, such as dyspepsia, developed.

At each site, there was a team blinded and one investigator not blinded to the study-group assignments. All patients underwent a blood test at least monthly to determine the international normalized ratio (INR); blood samples were sent overnight to the Quest Diagnostics Clinical Trials laboratory (Van Nuys, Calif.), where the sample was processed and the INR calculated. The result was then faxed to the nonblinded investigator, who made protocol-specified adjustments in the dose of active warfarin according to the INR (target range, 2.0 to 3.0) or the dose of placebo warfarin according to a predetermined dose-adjustment schedule based on real anticoagulation data.

FOLLOW-UP AND ASSESSMENT OF END POINTS

Patients were contacted monthly to determine whether any events had occurred. Every four months, patients were examined by a blinded neurologist who also managed the patient's vascular risk factors in association with the patient's primary

physician. If a stroke was suspected, patients underwent brain computed tomography (CT) or magnetic resonance imaging (MRI).

The components of the primary end point (ischemic stroke, brain hemorrhage, or death from vascular causes other than stroke) were adjudicated by independent panels of neurologists and cardiologists who were unaware of the patients' study-group assignments. Ischemic stroke was defined as a new focal neurologic deficit of sudden onset that lasted at least 24 hours and that was not associated with a hemorrhage on brain CT scanning or MRI. Brain hemorrhage was defined as evidence of parenchymal blood on CT scanning or MRI. Death from vascular causes other than stroke was defined as sudden death or death within 30 days after a myocardial infarction, pulmonary embolism, rupture of an aortic aneurysm, acute ischemia of a limb or internal organ, subdural or subarachnoid hemorrhage, or major systemic hemorrhage. Major hemorrhage was defined as any intracranial hemorrhage or systemic hemorrhage requiring hospitalization, blood transfusion, or surgery.

All patients were to be followed until any single component of the primary end point or death occurred or a common termination date (expected to be 17 months after the last patient was enrolled) was reached. The mean follow-up period was planned to be 36 months (range, 17 to 53).

STATISTICAL ANALYSIS

On the basis of previous studies,^{6,7,15} we proposed that the rates of the primary end point (ischemic stroke, brain hemorrhage, or death from vascular causes other than stroke) would be 33 percent over a three-year period with aspirin, as compared with 22 percent over a three-year period with warfarin. Given this effect size, a probability of a type I error of 0.05, a power of 0.80, a 24 percent rate of discontinuation of study medications, and 1 percent loss to follow-up, the required sample size based on a two-sided log-rank test was 403 patients per group.

The cumulative probability of an outcome over time was estimated by analyzing cumulative incidence, in which causes of death that were not part of the outcome were treated as competing risks.¹⁶ To estimate the probability of death from any cause over time, the product-limit method was used, and events other than death were censored. Data pertaining to patients lost to follow-up were censored on the last contact date. The two treatment groups were compared with the use of a log-rank test. A

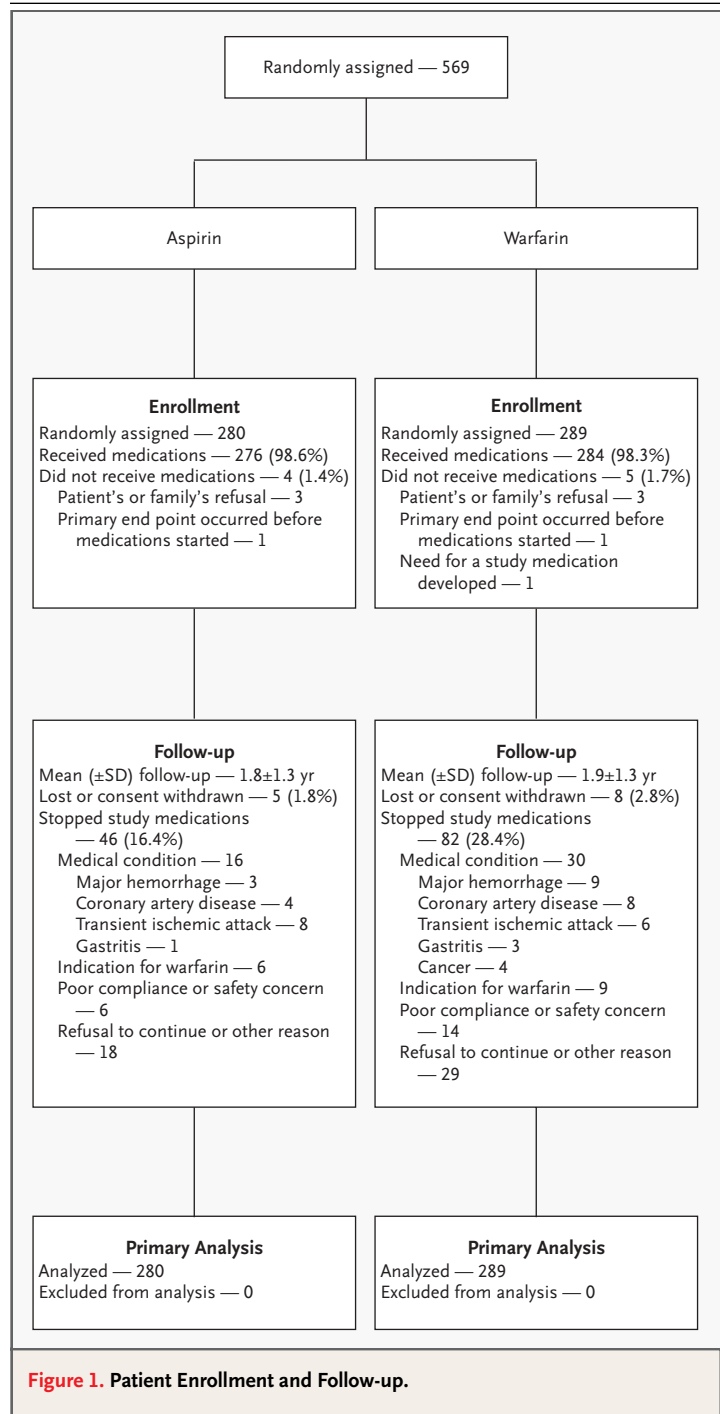


Figure 1. Patient Enrollment and Follow-up.

hazard ratio (for aspirin relative to warfarin) was calculated with the use of a Cox proportional-hazards regression model. Baseline features of the two groups were compared with the use of an independent group t-test (for means) or chi-square test (for percentages). All analyses were performed on an

Table 1. Baseline Characteristics of the Patients.*

| Characteristic | Aspirin (N=280) | Warfarin (N=289) |
|---|--------------------|---------------------|
| Age — yr | 62.8±11.3 | 64.3±11.5 |
| Male sex — no. (%) | 168/280 (60.0) | 182/289 (63.0) |
| Race — no. (%)† | | |
| Black | 83/280 (29.6) | 91/289 (31.5) |
| White | 162/280 (57.9) | 169/289 (58.5) |
| Other | 35/280 (12.5) | 29/289 (10.0) |
| History of hypertension — no. (%) | 230/280 (82.1) | 247/287 (86.1) |
| History of diabetes — no. (%) | 101/279 (36.2) | 115/289 (39.8) |
| History of a lipid disorder — no. (%) | 188/274 (68.6) | 203/278 (73.0) |
| Blood pressure — mm Hg | | |
| Systolic | 139.0±16.7 | 140.6±17.4 |
| Diastolic | 76.6±10.3 | 77.1±10.4 |
| Glycosylated hemoglobin — %‡ | 7.8±2.5 | 7.9±2.3 |
| Cholesterol — mg/dl | | |
| High-density lipoprotein | 43.6±13.1 | 43.4±12.1 |
| Low-density lipoprotein | 124.6±38.0 | 126.2±37.3 |
| Smoking status — no. (%) | | |
| Never | 96/280 (34.3) | 106/289 (36.7) |
| Previously | 115/280 (41.1) | 131/289 (45.3) |
| Currently | 69/280 (24.6) | 52/289 (18.0) |
| History of coronary artery disease — no. (%) | 68/273 (24.9) | 83/284 (29.2) |
| History of ischemic stroke — no. (%) | 58/271 (21.4) | 80/286 (28.0) |
| Qualifying event | | |
| Stroke | 164/280 (58.6) | 183/289 (63.3) |
| Transient ischemic attack | 116/280 (41.4) | 106/289 (36.7) |
| Use of antithrombotic therapy at time of qualifying event — no. (%) | 143/280 (51.1) | 156/288 (54.2) |
| Time from qualifying event to randomization — days | 18.0±14.0 | 16.0±12.0 |
| Concomitant medications at randomization — no. (%) | | |
| Statin | 163/280 (58.2) | 184/289 (63.7) |
| Diuretic | 64/280 (22.9) | 68/289 (23.5) |
| ACE inhibitor or angiotensin II receptor blocker | 113/280 (40.4) | 121/289 (41.9) |

intention-to-treat basis, unless specified otherwise. All reported P values are two-sided, without adjustment for multiple testing; P values of 0.05 or less were considered statistically significant.

PERFORMANCE AND SAFETY MONITORING

A performance and safety monitoring committee appointed by NINDS met every six months to review the progress of the study and accumulated data.

Early in the trial, three interim efficacy analyses of the primary end point — when approximately 25 percent, 50 percent, and 75 percent of the required end points had occurred — were planned.^{13,17} There were no prespecified stopping rules for safety. On the unanimous recommendation of the monitoring committee, NINDS stopped enrollment in the trial on July 18, 2003, because of concerns about the safety of patients assigned to warfarin. Patients

Table 1. (Continued.)*

| Characteristic | Aspirin (N=280) | Warfarin (N=289) |
|-------------------------------------|--------------------|---------------------|
| Stenotic artery | | |
| Internal carotid | 55/271 (20.3) | 64/280 (22.9) |
| Middle cerebral | 92/271 (33.9) | 87/280 (31.1) |
| Vertebral | 53/271 (19.6) | 54/280 (19.3) |
| Basilar | 55/271 (20.3) | 57/280 (20.4) |
| Multiple arteries [§] | 16/271 (5.9) | 18/280 (6.4) |
| Percent stenosis of affected artery | 64.1±16.5 | 63.3±16.0 |
| <50 — no. (%)¶ | 34/276 (12.3) | 36/285 (12.6) |
| 50–69 — no. (%) | 138/276 (50.0) | 142/285 (49.8) |
| 70–99 — no. (%) | 103/276 (37.3) | 105/285 (36.8) |
| 100 — no. (%)¶ | 1/276 (0.4) | 2/285 (0.7) |

* Plus-minus values are means ±SD, except for time from qualifying event to randomization, in which case the values are medians ± median absolute deviation. There were no significant differences between the groups at the P=0.05 level. ACE denotes angiotensin-converting enzyme.

† Race was determined by the investigators.

‡ The values reflect measurements in patients with diabetes only.

§ The affected arteries were a combination of the internal carotid and middle cerebral arteries, the vertebral and basilar arteries, or the left and right vertebral arteries.

¶ The data reflect the reading of the angiograms by the neuroradiologist at the clinical coordinating center. At the participating sites, these angiograms were interpreted as showing 50 to 99 percent stenosis.

were seen for close-out visits by September 1, 2003, and events occurring up to the time of the close-out visit were included in the analyses.

RESULTS

BASILINE CHARACTERISTICS, FOLLOW-UP, AND COMPLIANCE WITH TREATMENT GOALS

A total of 569 patients had been randomly assigned to a study group when enrollment in the trial was stopped (Fig. 1). None of the baseline characteristics differed significantly between the two treatment groups (Table 1). Multiple logistic-regression models did not identify any subset of baseline characteristics that was significantly different between the two groups.

The mean duration of follow-up was 1.8 years. Thirteen patients (2.3 percent) were lost to follow-up (six) or withdrew consent (seven) an average of six months after enrollment (Fig. 1). Study medications were permanently discontinued in 128 patients (22.5 percent) after an average period of 0.9 year, with a significantly higher rate of discontinuation among patients assigned to warfarin (28.4 percent) than among those assigned to aspirin (16.4 percent) (P<0.001).

During the maintenance phase of anticoagulation (i.e., the follow-up period after an INR of ≥2.0 was first achieved), the mean INR was 2.5. The percentages of maintenance time that patients spent at the prespecified INR ranges were as follows: 22.7 percent at an INR of less than 2.0, 63.1 percent at an INR of 2.0 to 3.0, 12.9 percent at an INR of 3.1 to 4.4, and 1.2 percent at an INR of 4.5 or greater. Among the patients randomly assigned to receive aspirin, the percentage of follow-up time at a dose of 1300 mg per day was 93.7 percent.

OUTCOMES

Efficacy

The primary end point occurred in 22.1 percent of the patients in the aspirin group and 21.8 percent of those in the warfarin group (hazard ratio, 1.04; 95 percent confidence interval, 0.73 to 1.48; P=0.83) (Table 2 and Fig. 2). An on-treatment analysis, in which data from patients who permanently stopped taking their study medications were censored at the time of withdrawal, showed virtually the same result (hazard ratio, 1.04; 95 percent confidence interval, 0.72 to 1.50; P=0.83). Prespecified secondary end points included ischemic stroke in any vascular territory; ischemic stroke in the territory of

Table 2. Primary and Secondary End Points.

| Event | Aspirin (N=280) | | | Warfarin (N=289) | | | Hazard Ratio (95% CI)* | P Value† |
|---|-----------------------------------|---------------------|---------------------|-----------------------------------|---------------------|---------------------|------------------------|----------|
| | Patients with an Event no. (%) | Probability at 1 Yr | Probability at 2 Yr | Patients with an Event no. (%) | Probability at 1 Yr | Probability at 2 Yr | | |
| Primary end point‡: | | | | | | | | |
| Ischemic stroke, brain hemorrhage, or death from vascular causes other than stroke | 62 (22.1) | 0.15 | 0.21 | 63 (21.8) | 0.17 | 0.22 | 1.04 (0.73–1.48) | 0.83 |
| Secondary end points | | | | | | | | |
| Ischemic stroke or brain hemorrhage | 58 (20.7) | 0.15 | 0.20 | 51 (17.6) | 0.15 | 0.18 | 1.20 (0.82–1.75) | 0.34 |
| Ischemic stroke | 57 (20.4) | 0.15 | 0.20 | 49 (17.0) | 0.14 | 0.17 | 1.23 (0.84–1.80) | 0.29 |
| Ischemic stroke in territory of stenotic artery | 42 (15.0) | 0.12 | 0.15 | 35 (12.1) | 0.11 | 0.13 | 1.26 (0.81–1.97) | 0.31 |
| Disabling or fatal ischemic stroke | 25 (8.9) | 0.08 | 0.09 | 18 (6.2) | 0.05 | 0.05 | 1.46 (0.80–2.68) | 0.22 |
| Ischemic stroke, myocardial infarction, or death from vascular causes other than stroke | 66 (23.6) | 0.16 | 0.23 | 71 (24.6) | 0.19 | 0.23 | 0.98 (0.70–1.37) | 0.90 |

* The hazard ratio in the aspirin group as compared with the warfarin group was determined with the use of a Cox proportional-hazards regression model, with treatment as the only covariate. CI denotes confidence interval.

† P values are for comparison between the aspirin group and the warfarin group and were calculated by the log-rank test.

‡ Given the number of patients recruited and the outcomes observed, if warfarin is in fact superior to aspirin by the degree hypothesized, the probability that the study, if completed, would have resulted in a statistically significant difference in favor of warfarin¹⁸ was 0.23.

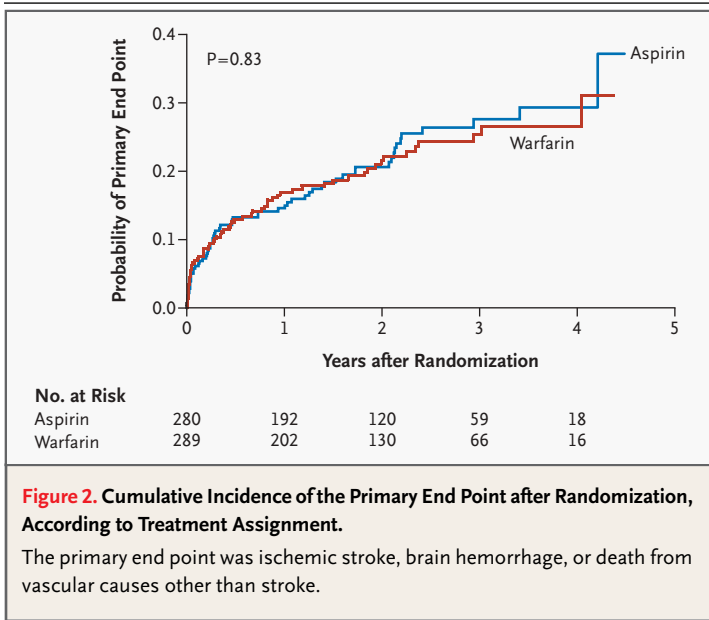


Figure 2. Cumulative Incidence of the Primary End Point after Randomization, According to Treatment Assignment.

The primary end point was ischemic stroke, brain hemorrhage, or death from vascular causes other than stroke.

the stenotic intracranial artery; and a composite of ischemic stroke, death from vascular causes other than stroke, or nonfatal myocardial infarction. There were no significant differences between the two treatment groups in the rates of any of these end points (Table 2). A major cardiac event (myocardial infarction or sudden death), which was not a pre-specified secondary end point, occurred significantly more frequently in the warfarin group than in the aspirin group (rate, 2.9 percent in the aspirin group vs. 7.3 percent in the warfarin group; hazard ratio, 0.40; 95 percent confidence interval, 0.18 to 0.91; P=0.02).

Adverse Events

The rate of death was significantly higher among patients assigned to warfarin (4.3 percent in the aspirin group vs. 9.7 percent in the warfarin group; hazard ratio, 0.46; 95 percent confidence interval, 0.23 to 0.90; P=0.02) (Table 3 and Fig. 3A). Patients

Table 3. Adverse Events.

| Event | Aspirin (N=280, 504.4 Patient-yr) | | Warfarin (N=289, 541.7 Patient-yr) | | Hazard Ratio (95% CI)* | P Value† |
|-------------------------------|--|---------------------------------|--|---------------------------------|---------------------------|----------|
| | Patients with an Event <i>no. (%)</i> | Events per 100 Patient-yr | Patients with an Event <i>no. (%)</i> | Events per 100 Patient-yr | | |
| | Death | 12 (4.3) | 2.4 | 28 (9.7) | | |
| Death from vascular causes | 9 (3.2) | 1.8 | 17 (5.9) | 3.1 | 0.56 (0.25–1.26) | 0.16 |
| Ischemic stroke | 5 | | 3 | | | |
| Brain hemorrhage | 0 | | 2 | | | |
| Other hemorrhage | 1 | | 0 | | | |
| Myocardial infarction | 0 | | 3 | | | |
| Sudden death | 2 | | 9 | | | |
| Aortic aneurysm | 1 | | 0 | | | |
| Death from nonvascular causes | 3 (1.1) | 0.6 | 11 (3.8) | 2.0 | 0.30 (0.08–1.07) | 0.05 |
| Cancer‡ | 3 | | 6 | | | |
| Congestive heart failure§ | 0 | | 2 | | | |
| Diabetes | 0 | | 1 | | | |
| Respiratory failure | 0 | | 1 | | | |
| Sepsis | 0 | | 1 | | | |
| Major hemorrhage | 9 (3.2) | 1.8 | 24 (8.3)¶ | 5.0 | 0.39 (0.18–0.84) | 0.01 |
| Brain hemorrhage | 1 | | 2 | | | |
| Subdural hematoma | 0 | | 1 | | | |
| Gastrointestinal hemorrhage | 6 | | 10 | | | |
| Ocular hemorrhage | 1 | | 4 | | | |
| Genitourinary hemorrhage | 0 | | 3 | | | |
| Aortic aneurysm | 1 | | 0 | | | |
| Other | 0 | | 4 | | | |
| Myocardial infarction | 7 (2.5)** | 1.6 | 12 (4.2) | 2.2 | 0.62 (0.24–1.58) | 0.31 |
| Fatal | 0 | | 3 | | | |
| Nonfatal | 7 | | 9 | | | |

* The hazard ratio in the aspirin group as compared with the warfarin group was determined with the use of a Cox proportional-hazards regression model, with treatment as the only covariate. CI denotes confidence interval.

† P values are for the comparison between the aspirin group and the warfarin group and were calculated by the log-rank test.

‡ In the aspirin group, two patients had lung cancer and one prostate cancer; in the warfarin group, three patients had lung cancer, one prostate cancer, one stomach cancer, and one cancer of the spine.

§ Death from congestive heart failure was prespecified as a type of death from nonvascular causes because congestive heart failure is usually a chronic condition.

¶ There were 27 hemorrhages among these 24 patients: 1 patient had 3 ocular hemorrhages, and 1 patient had 2 subdural hematomas.

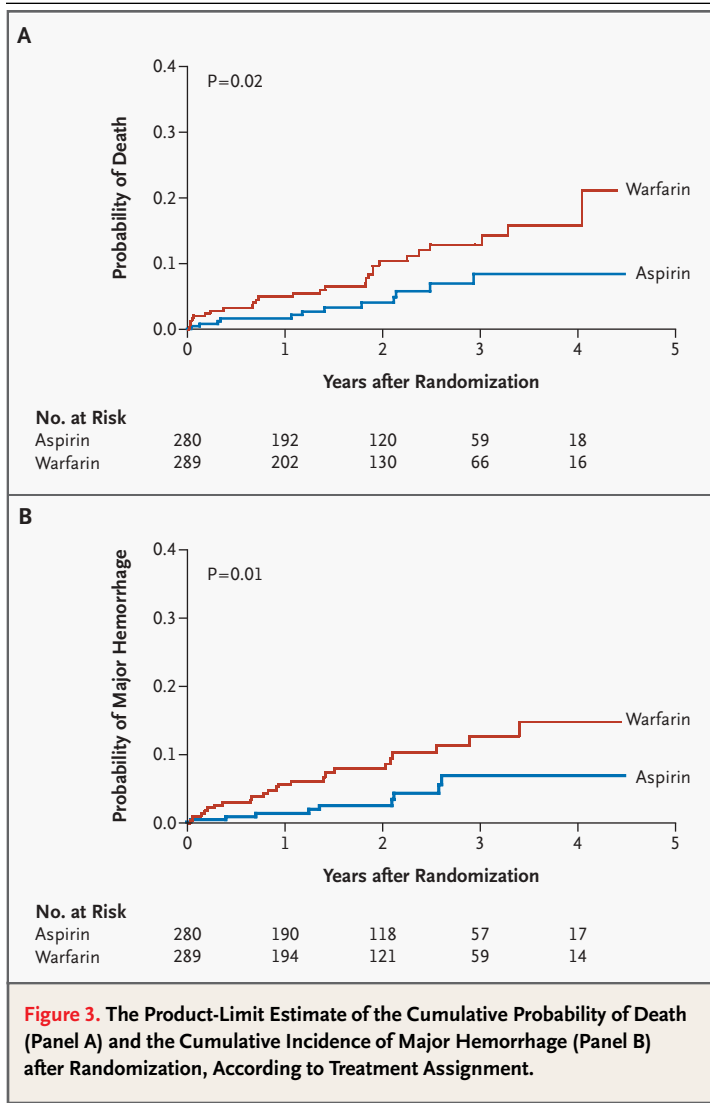
|| Of these four patients, three required transfusions: one because of severe anemia, one because of right-flank hematoma, and one because of oral bleeding after a tooth extraction; a fourth patient had bleeding from the nose and gums that led to hospitalization.

**There were eight myocardial infarctions among these seven patients.

assigned to warfarin had higher rates of death from vascular causes and from nonvascular causes, although only the latter reached statistical significance ($P=0.05$) (Table 3).

Major hemorrhages occurred significantly more often among patients assigned to warfarin (3.2 per-

cent in the aspirin group vs. 8.3 percent in the warfarin group; hazard ratio, 0.39; 95 percent confidence interval, 0.18 to 0.84; $P=0.01$) (Table 3 and Fig. 3B). Of the 147 patients enrolled who underwent angiography as part of the study protocol, none had a stroke related to angiography. (The other 422



study patients had undergone angiography as part of routine care before enrollment in the trial.)

Relationship of INR Values to Ischemic Stroke, Major Cardiac Events, and Major Hemorrhages

A post hoc on-treatment analysis of patients assigned to warfarin was performed to determine whether INRs below or above the target range were associated with an increased risk of ischemic or hemorrhagic events. INR-specific rates of these events were calculated on the basis of the INR closest to the date of the event, whether it was obtained before or as many as two days after the event (Table 4).¹⁹ INRs of less than 2.0 were associated with a significantly higher risk of ischemic stroke (P<0.001

by the exact test comparing Poisson means) and major cardiac events (P<0.001) than INRs of 2.0 or greater, whereas INRs greater than 3.0 were associated with a significantly higher risk of major hemorrhages (P<0.001) than INRs of 3.0 or less.

DISCUSSION

The common practice of administering warfarin rather than aspirin for symptomatic intracranial arterial stenosis is not supported by the results of this trial. Warfarin was associated with significantly higher rates of death and major hemorrhage and provided no advantage over aspirin in the prevention of ischemic stroke, brain hemorrhage, or death from vascular causes other than stroke. The rate of death from any cause was significantly higher in the warfarin group than in the aspirin group (P=0.02). Although the rates of death from vascular and non-vascular causes were higher in the warfarin group, only death from nonvascular causes reached statistical significance. The reason for the excess mortality from nonvascular causes (cancer, in most instances) in the warfarin group is unclear. It is not explained by the potential ability of aspirin to prevent colon cancer,²⁰ since none of the deaths in the warfarin group were from that disease. The low number of deaths from nonvascular causes in the trial (14 altogether) and the fact that warfarin has not been associated with an increased risk of death from nonvascular causes in previous anticoagulation trials raise the possibility that this finding was a chance occurrence.

The rate of major systemic hemorrhage during warfarin therapy was higher than projected on the basis of previous trials (observed rate, 4.6 per 100 patient-years, vs. a projected rate of less than 2 per 100 patient-years²¹), yet the rate of brain hemorrhage was lower than projected (observed rate, 0.4 per 100 patient-years, vs. a projected rate of 0.7 per 100 patient-years¹⁵). It is unlikely that these findings can be accounted for by the high burden of hypertension and other vascular risk factors in this population, since this characteristic does not explain why the risk of systemic hemorrhage was selectively increased. One possible explanation is that the definition of major systemic hemorrhage in this trial was broader than that in other stroke trials.^{10,22} In this trial, major systemic hemorrhage was defined as hemorrhage necessitating hospitalization, transfusion, or surgery, whereas other trials' definitions required transfusion,^{10,22} surgery,²² or bleeding

Table 4. Post Hoc Analysis of On-Treatment, INR-Specific Rates of Major Hemorrhage, Ischemic Stroke, and Major Cardiac Events among Patients Randomly Assigned to Receive Warfarin.*

| INR Category† | No. of Patient-yr‡ | Major Hemorrhage | | Ischemic Stroke | | Major Cardiac Event§ | |
|---------------|--------------------|------------------|---|-----------------|---|----------------------|---|
| | | No. of Events | No. of Events per 100 Patient-yr (95% CI) | No. of Events | No. of Events per 100 Patient-yr (95% CI) | No. of Events | No. of Events per 100 Patient-yr (95% CI) |
| <2.0 | 92.5 | 1 | 1.1 (0.03–6.0) | 23 | 24.9 (15.8–37.3) | 10 | 10.8 (5.2–19.9) |
| 2.0–3.0 | 256.9 | 9 | 3.5 (1.6–6.6) | 13 | 5.1 (2.7–8.7) | 1 | 0.4 (0.01–2.2) |
| 3.1–4.4 | 52.6 | 8 | 15.2 (6.6–30.0) | 3 | 5.7 (1.2–16.7) | 3 | 5.7 (1.2–16.7) |
| ≥4.5 | 4.9 | 6 | 123.3 (45.3–268.4) | 1 | 20.6 (0.5–114.5) | 0 | 0 (0–61.6) |

* The analysis did not include follow-up time or events while patients were not receiving study medication. The events not included were 3 of 27 major hemorrhages, 9 of 49 ischemic strokes, and 7 of 21 major cardiac events. INR denotes international normalized ratio, and CI confidence interval.

† The categories coincide with the prespecified target INR range (2.0 to 3.0) and critically high INR range (≥4.5).¹³

‡ The method assumed a linear interpolation to estimate INRs between consecutive INR tests. For example, if two consecutive INRs obtained a month apart were in the therapeutic range, the method assumed that the INR was in the therapeutic range for the entire month.

§ A major cardiac event was defined as myocardial infarction or sudden death.

that resulted in permanent impairment.²² If these more restrictive definitions¹⁰ had been used in this trial, the rates of major hemorrhage in both treatments groups would have been lower (1.2 per 100 patient-years in the aspirin group and 3.1 per 100 patient-years in the warfarin group), but the rate with warfarin would have remained significantly higher ($P=0.04$).

The rate of myocardial infarction or sudden death was also significantly higher with warfarin than with aspirin in this trial. This finding differs from the results of two recent trials comparing warfarin (target INR, 2.0 to 3.0) with low-dose aspirin (80 to 160 mg per day) in patients with acute coronary events; one trial showed that warfarin was more effective in preventing myocardial infarction,²³ and the other showed that it was equally effective.²⁴ These contrasting results are difficult to explain but may be related to the higher dose of aspirin used in this trial (1300 mg per day). This dose was chosen in part because higher doses of aspirin decrease platelet resistance,^{25,26} diminish shear-induced platelet aggregation,²⁷ and may decrease the inflammatory component of atherothrombosis.^{28,29}

Although a post hoc on-treatment analysis of the patients assigned to warfarin showed that ischemic stroke, major cardiac events, and major hemorrhages were less likely to occur when the INR was at least 2.0 but not more than 3.0, this narrow therapeutic range is difficult to achieve in clinical prac-

tice. INRs were within the target range for 63.1 percent of the maintenance period — a finding that is similar to the percentages observed in other anticoagulation trials, and one that exceeds the percentage typically achieved when patients are treated by their personal physicians.³⁰ Although it is possible that a protocol requiring more frequent INR tests could have achieved a higher percentage of time within the therapeutic range, patients' compliance with such a protocol and blinding of the trial would have been challenging. As other methods become available to improve the ability to maintain INRs within the therapeutic range (e.g., home monitoring³⁰) and as new anticoagulant drugs that do not require intensive monitoring are developed, a subsequent trial may be warranted to determine whether therapeutic anticoagulation has a role in the treatment of intracranial stenosis.

The burden of vascular risk factors in patients in this trial exceeds that observed in most other stroke-prevention trials.^{10,22,31–35} Moreover, the rates of ischemic stroke in this trial were substantially higher than in other trials of the secondary prevention of stroke in which aspirin or warfarin was evaluated. The two-year rates of ischemic stroke in this trial were 19.7 percent in the aspirin group and 17.2 percent in the warfarin group, as compared with 8 to 12 percent with aspirin^{10,31,35,36} and 8 to 14 percent with warfarin^{10,34,35} in trials of patients with other causes of stroke. These data indicate that intracranial stenosis is a high-risk disease for

which alternative therapies are needed. Other options include aggressive management of risk factors, alternative antiplatelet regimens,³⁷ and intracranial angioplasty or stenting.^{38,39} As yet, none of these treatments have been evaluated in a controlled clinical trial in patients with intracranial stenosis.

The results of this trial have important implications for clinical practice. First, aspirin, rather than warfarin, should be used to treat intracranial arterial stenosis. Although the optimal dose of aspirin for stroke prevention is uncertain, the only reliable outcome data in patients with intracranial stenosis are those pertaining to the dose used in this study: 1300 mg per day. Using aspirin rather than warfarin in these patients will substantially lower the risk of major hemorrhage and eliminate the inconvenience of using warfarin. In addition, considerable savings can be achieved by avoiding the costs of warfarin, INR testing, and treatment of warfarin-associated hemorrhages.⁴⁰ Second, the role of vascular imaging (magnetic resonance angiography, transcranial Doppler ultrasound, CT angiography, or catheter angiography) of the intracranial vessels as part of the initial evaluation of patients with transient ischemic attack or stroke needs to be reevaluated. Until therapy that is more effective than aspirin in combination with risk-factor management emerges, it could be argued that imaging of the intracranial vessels is unnecessary. On the other hand, identification of patients with intracranial stenosis has important prognostic implications, may influence treatment decisions (such as those regarding high-dose aspirin and aggressive risk-factor management), and may ultimately lead to more effective therapies for this high-risk disease.

Supported by a grant (R01 NS36643, to Dr. Chimowitz) from the National Institute of Neurological Disorders and Stroke, National Institutes of Health. In addition, the following General Clinical Research centers, funded by the National Institutes of Health, provided local support for the evaluation of patients in the trial: Emory University (M01 RR00039), Case Western University, MetroHealth Medical Center (5M01 RR00080), San Francisco General Hospital (M01 RR00083-42), Johns Hopkins University School of Medicine (M01 RR00052), Indiana University School of Medicine (5M01 RR000750-32), Cedars-Sinai Hospital (M01 RR00425), and the University of Maryland (M01 RR165001). Bristol-Myers Squibb (after the incorporation of DuPont Pharma) supplied the warfarin (Coumadin) and placebo warfarin tablets, and Bayer supplied the aspirin and placebo aspirin tablets for the trial; neither of these companies supplied direct funding for the trial.

Dr. Chimowitz reports having been paid fees by the Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership, AstraZeneca, and the Sankyo/Lilly partnership for consulting on antithrombotic agents that were not evaluated in this trial and by Guidant for consulting on a medical device (an intracranial stent) that was not evaluated in this trial. Dr. Stern reports having been paid fees by the Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership. Dr. Frankel reports having received lecture fees from Boehringer Ingelheim and Sanofi Pharmaceuticals. Dr. Levine reports having received grant support from Ono Pharmaceuticals and the Gaisman Frontiers of Biomedical Sciences; he also reports having received consulting fees from AstraZeneca, Medlink, Medscape, and the Discovery Institute of Medical Education and lecture fees from Boehringer Ingelheim and Inspire with regard to issues unrelated to this study. Dr. Chaturvedi reports having received grant support from Boehringer Ingelheim and having been paid lecture fees by Bristol-Myers Squibb, Sanofi Pharmaceuticals, and Boehringer Ingelheim. Dr. Kasner reports having received grant support from Boehringer Ingelheim, AstraZeneca, Ono Pharmaceuticals, Lilly, Novo Nordisk, and NMT Medical; consulting fees from Boehringer Ingelheim, AstraZeneca, Ono Pharmaceuticals, Novo Nordisk, Bristol-Myers Squibb, NMT Medical, Wyeth, and Novartis; and lecture fees from Boehringer Ingelheim, Bristol-Myers Squibb, AstraZeneca, Novo Nordisk, and Wyeth. Dr. Benesch reports having received grant support from Ono Pharmaceuticals. Dr. Sila reports having received lecture fees from Bristol-Myers Squibb. Dr. Romano reports having received lecture fees from Bristol-Myers Squibb and Boehringer Ingelheim and being on the scientific advisory board for NovaVision, which does not make products evaluated in this trial.

We are indebted to the patients who participated in this study; to H.J.M. Barnett, M.D., and R.G. Hart, M.D., for their advice and support beginning in 1995, when the study was initially planned; and to B. Tilley, Ph.D., for advice on statistical issues.

APPENDIX

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