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


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 baseline 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 (2.2 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.)

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LONG-STANDING doubts, expressed as late as the 1980s, about the efficacy of warfarin for the prevention of stroke 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. The rates of first stroke in patients with atrial fibrillation were lower with warfarin than with a range of other therapies, placebo, or aspirin. Also, in open-label studies, the rates of recurrent stroke were lower with warfarin than with placebo or aspirin. 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). Most previous clinical trials of drugs to prevent recurrent ischemic stroke after a noncardioembolic ischemic stroke studied one or more of a wide variety of platelet-antiaggregant drugs, particularly aspirin, with which the recurrence rate approximates 8 percent. 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. 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. 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, 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 participants in the study group as listed in the Appendix.

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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 ac-
ceptable 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 se-
vere disability, a score of 4 moderate disability, and a score of
5 minimal or no disability. Patients were ineligible if they had a
baseline 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 be-
fore randomization by telephone contact with the data-manage-
ment center, in which each criterion for eligibility or ineligibility,
the dates of stroke and randomization, medianation of surgery,
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 ad-
justed to achieve and maintain an INR in the range of 1.4 to 2.0.
The patients were randomly assigned to receive active aspirin and
warfarin placebo or active warfarin and aspirin placebo. Random-
ization 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 war-
farin 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 elec-
tronically 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 meth-
od validated early in the trial,36 the INR results sent to local cen-
ters 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 val-
ues that were plausible for the dose and duration of warfarin ther-
apy. 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 for-
warded to the data-management center and transmitted immedi-
ately 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 in-
vestigator in the case of reports showing trends for values below
or above the desired ranges. All participants other than the prin-
cipal 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 they required an invasive surgical procedure. All 15 pa-
ients stopped treatment with study drugs, but their data were in-
cluded in the intention-to-treat analysis.

Follow-up
Patients were followed for 2 years ±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, quar-
terly 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 con-
ducted 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 de-
tails, and brain imaging studies. An independent, treatment-blinded
neuroradiologist reviewed the images. Five treatment-blinded neu-
rologists adjudicated all clinical events using a majority verdict for
decisions about outcomes.

Major hemorrhage was defined as intracranial, intraspinal, intra-
cerebral, subarachnoid, subdural, or epidural hemorrhage or any
other bleeding event requiring transfusion. Minor hemorrhage,
which did not require transfusion, included gastrointestinal, geni-
tourinary, retroperitoneal, joint, subcutaneous or muscular, gingival
or oral, and conjunctival hemorrhage; epistaxis; hemothorax; ecle-
theses, and hemorrhage after trauma or from multiple sites. A treat-
ment-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 differ-
ce between patients receiving warfarin and those receiving aspi-
rin in the time to or rate of death from any cause or recurrent
ischemic stroke. Secondary null hypotheses of major clinical inter-
est were that there would be no differences in the time to either
component of the primary end point or to major hemorrhage ac-
cording to sex, race or ethnic group, or cause of prior stroke.

The original target sample size was 1920 patients, which pro-
vided 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 hypoth-
esis 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 dis-
continuation rate of 20 percent at two years for both therapies com-
bined. 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 test37 procedure that called for three
scheduled interim analyses and allowed for additional interim analy-
ses. 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 Kap-
lan–Meier method37 was used to estimate curves for the length of
time to the event, and the log-rank test38 was used to compare
the cumulative incidence curves in the treatment groups. The pri-
mary analysis was adjusted for loss to follow-up by a prespecified
stratified imputation procedure that distinguishes different types of
losses to follow-up and incorporates assumptions appropriate to each
reported P values and confidence intervals have not been ad-
justed for interim analyses.

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


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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.*

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>WARFARIN (N=1103)</th>
<th>ASPIRIN (N=1103)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical and demographic characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age — yr</td>
<td>63.3±11.2</td>
<td>62.6±11.4</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>447 (40.5)</td>
<td>450 (40.8)</td>
</tr>
<tr>
<td>Race or ethnic group — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>627 (56.8)</td>
<td>626 (56.8)</td>
</tr>
<tr>
<td>Black</td>
<td>538 (30.6)</td>
<td>525 (29.5)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>105 (9.5)</td>
<td>118 (10.7)</td>
</tr>
<tr>
<td>Other</td>
<td>33 (3.0)</td>
<td>34 (3.1)</td>
</tr>
<tr>
<td>Education — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school or less</td>
<td>805 (73.0)</td>
<td>796 (72.2)</td>
</tr>
<tr>
<td>After high school</td>
<td>287 (26.0)</td>
<td>295 (26.7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>11 (1.0)</td>
<td>12 (1.1)</td>
</tr>
<tr>
<td><strong>Hypertension — no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>746 (67.6)</td>
<td>753 (68.3)</td>
</tr>
<tr>
<td>No</td>
<td>343 (31.1)</td>
<td>338 (30.6)</td>
</tr>
<tr>
<td>Unknown</td>
<td>14 (1.3)</td>
<td>12 (1.1)</td>
</tr>
<tr>
<td><strong>Diabetes mellitus — no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>287 (26.0)</td>
<td>285 (25.6)</td>
</tr>
<tr>
<td>No</td>
<td>792 (71.8)</td>
<td>761 (69.2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (0.3)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td><strong>Any cardiac disease — no. (%)†</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>321 (29.1)</td>
<td>304 (27.6)</td>
</tr>
<tr>
<td>No</td>
<td>822 (74.5)</td>
<td>824 (74.7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>31 (2.8)</td>
<td>25 (2.3)</td>
</tr>
<tr>
<td><strong>History of transient ischemic attack, amaurosis fugax, or stroke — no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>321 (29.1)</td>
<td>304 (27.6)</td>
</tr>
<tr>
<td>No</td>
<td>822 (74.5)</td>
<td>824 (74.7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>31 (2.8)</td>
<td>25 (2.3)</td>
</tr>
<tr>
<td><strong>Current smoking — no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>306 (27.7)</td>
<td>307 (26.7)</td>
</tr>
<tr>
<td>No</td>
<td>792 (71.8)</td>
<td>761 (69.0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>5 (0.5)</td>
<td>5 (0.5)</td>
</tr>
<tr>
<td><strong>Heavy alcohol intake (≥4 drinks/day) — no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>40 (3.6)</td>
<td>34 (3.1)</td>
</tr>
<tr>
<td>No</td>
<td>1060 (96.1)</td>
<td>1060 (96.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (0.3)</td>
<td>9 (0.8)</td>
</tr>
</tbody>
</table>

**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.
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-
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

<table>
<thead>
<tr>
<th>TABLE 2. RESULTS OF PRIMARY AND SECONDARY ANALYSES.</th>
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<tr>
<td><strong>ANALYSIS</strong></td>
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<tr>
<td>Recurrent ischemic stroke or death</td>
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<tr>
<td>Reccurent ischemic stroke or death or major hemorrhage</td>
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<tr>
<td>Recurrent ischemic stroke or death, with data from patients lost to follow-up censored</td>
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<tr>
<td>Recurrent ischemic stroke or death (model including interaction of treatment assignment and interruption of treatment)</td>
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<tr>
<td>Subgroup analyses for primary end point</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Male</td>
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<tr>
<td>Female</td>
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<td>Race or ethnic group</td>
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<td>Black</td>
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<td>White</td>
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<tr>
<td>Hispanic</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Cause of prior stroke</td>
</tr>
<tr>
<td>Cryptogenic</td>
</tr>
<tr>
<td>Small vessel or lacunar</td>
</tr>
<tr>
<td>Large artery, severe stenosis, occlusion</td>
</tr>
<tr>
<td>Other determined cause</td>
</tr>
<tr>
<td>Conflicting mechanism</td>
</tr>
</tbody>
</table>

*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.
course of our study supported our concern about safety.\textsuperscript{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 ischemic attacks and stroke that used an INR range of 3.0 to 4.5 (mean, 3.5).\textsuperscript{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 alone\textsuperscript{26} or in combination with aspirin.\textsuperscript{27}
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, 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 Stroke and the Northern Manhattan Stroke Study but differ somewhat from those in other studies.

Like the studies of tissue plasminogen activator for acute stroke, 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. 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. Cryptogenic stroke, in which the prevalence of superficial brain convexity infarcts and lack of evidence of large-artery disease have made clinically occult embolism or coagulopathy 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, 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


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


REFERENCES


