A Randomized Trial of Anticoagulants Versus Aspirin after Cerebral Ischemia of Presumed Arterial Origin

The Stroke Prevention In Reversible Ischemia Trial (SPIRIT) Study Group*

Aspirin is only modestly effective in the secondary prevention after cerebral ischemia. Studies in other vascular disorders suggest that anticoagulant drugs in patients with cerebral ischemia of presumed arterial (noncardiac) origin might be more effective. The aim of the Stroke Prevention in Reversible Ischemia Trial (SPIRIT) therefore was to compare the efficacy and safety of 30 mg aspirin daily and oral anticoagulation (international normalized ratio [INR] 3.0–4.5). Patients referred to a neurologist in one of 58 collaborating centers because of a transient ischemic attack or minor ischemic stroke (Rankin grade ≤3) were eligible. Randomization was concealed, treatment assignment was open, and assessment of outcome events was masked. The primary measure of outcome was the composite event "death from all vascular causes, nonfatal stroke, nonfatal myocardial infarction, or nonfatal major bleeding complication." The trial was stopped at the first interim analysis. A total of 1,316 patients participated; their mean follow-up was 14 months. There was an excess of the primary outcome event in the anticoagulated group (81 of 651) versus 36 of 665 in the aspirin group (hazard ratio, 2.3; 95% confidence interval [CI], 1.6–3.5). This excess could be attributed to 53 major bleeding complications (27 intracranial; 17 fatal) during anticoagulant therapy versus 6 on aspirin (3 intracranial; 1 fatal). The bleeding incidence increased by a factor of 1.43 (95% CI, 0.96–2.13) for each 0.5 unit increase of the achieved INR. Anticoagulant therapy with an INR range of 3.0 to 4.5 in patients after cerebral ischemia of presumed arterial origin is not safe. The efficacy of a lower intensity anticoagulation regimen remains to be determined.

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Patients who have had a transient ischemic attack (TIA) or nondisabling ischemic stroke have an annual risk of important vascular events (death from all vascular causes, nonfatal stroke, or nonfatal myocardial infarction) ranging between 4% and 16% in clinical trials [1, 2]. The corresponding estimate for population-based studies is 9% per year [3]. Aspirin, in any daily dose from 30 mg on, offers only modest protection after cerebral ischemia; it reduces the incidence of major vascular events by 20% at most [1, 2, 4]. Oral anticoagulant drugs might be more effective in preventing vascular complications after cerebral ischemia. Secondary prevention trials after myocardial infarction indicate that treatment with oral anticoagulant drugs is associated with a risk reduction approximately twice that of treatment with aspirin or other antiplatelet drugs [1, 5–8]. Both treatment with aspirin and anticoagulants increases the risk of bleeding complications [2, 9]. Few data are available on the efficacy and safety of oral anticoagulant treatment in patients with cerebral ischemia [10], except in those with atrial fibrillation [11].

The Stroke Prevention In Reversible Ischemia Trial (SPIRIT) was an open, randomized, multicenter, controlled clinical trial testing full-dose anticoagulation (international normalized ratio [INR], 3.0–4.5) versus low-dose aspirin (30 mg/day) in patients with a TIA or nondisabling ischemic stroke of presumed arterial (noncardiac) origin. The current target range of anticoagulation for the prevention of arterial disease in The Netherlands, as recommended by the Federation of Dutch Thrombosis Centers, was an INR range of 3.0 to 4.5 [12]. Similar intensities had been used in the secondary prevention trials after myocardial infarction; 2.7 to 4.5 in the Sixty Plus Study [5], 2.8 to 4.8 in (WARIS) [6], and 2.8 to 4.8 also in the Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) study [7]. In several other countries comparable levels of intensity are used to prevent arterial complications [13]. To use the full therapeutic potential of anticoagulation, we used the INR range of 3.0 to 4.5.

*Participating investigators are listed in the Appendix on page 864.

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Patients and Methods

Eligible Patients

Patients referred to a neurologist or general physician at one of the collaborating centers (see Appendix) were eligible for the trial if they had had a TIA or minor ischemic stroke (grade ≤ 3 on the modified Rankin scale [14, 15]) within the preceding 6 months. Patients were excluded if they had cerebral ischemia due to high-grade carotid stenosis requiring surgery or by embolism secondary to atrial fibrillation, cardiac valve disease, or a recent myocardial infarction. Patients with disorders of blood coagulation or those with a (contra) indication for oral anticoagulation or aspirin were also excluded. The study protocol was reviewed and approved by the institutional review boards of the participating hospitals. All patients were informed about the background and procedures of the trial and gave their explicit consent.

Baseline Characteristics

At the time of randomization, data were collected on the nature of the longest episode of focal neurological deficits during the last 6 months as well as on duration, mode of onset, and number of attacks. Demographic data, the grade on the modified Rankin scale, vascular risk factors, and vascular history were recorded. Computed tomography (CT) of the brain was required in all patients except those with transient monocular blindness. Chest radiography and electrocardiography (ECG) were mandatory; duplex scanning of the carotid arteries was optional.

Treatment

Patients eligible for the trial were randomly assigned to open treatment with either aspirin or oral anticoagulant treatment. Balance between treatment assignments within hospitals was achieved with the use of random permuted blocks. Randomization codes were centrally stored in a computer and communicated by telephone to the neurologists on enrollment of a new patient. A computer file containing all randomization codes was submitted to the Data Monitoring Committee at the start of the study. Aspirin was prescribed as pulverized carbasalate calcium (Ascal) in a dose of 38 mg (equivalent to 30 mg aspirin) daily. If a participating center preferred this, regular aspirin could be prescribed in higher doses, up to 100 mg daily. The patients were advised to take only acetaminophen as an analgesic agent.

The preferred anticoagulant drug was phenprocoumon (Marcoumar) because more stable anticoagulation is expected with this drug than with short-acting preparations, but acenocoumarol (Sintrom mitis) and warfarin (Australian, Italian, and UK centers) were also used. In The Netherlands the dose of the anticoagulant drug was adjusted by local thrombosis centers and in the other countries by hospital-based physicians. At each visit the prothrombin time was measured and converted to an INR; the target value was 3.5 and the target range was an INR value of 3.0 to 4.5.

Follow-Up

Every 6 months all patients were seen by their neurologist, or, if this was not possible, follow-up information was obtained from the general practitioner or by telephone contact with the patient or caregiver. After premature termination of the trial (see below), follow-up data of all patients were completed up to May 15, 1996, including auditing of all outcome events not yet reported at the time of the first interim analysis. At each contact the occurrence of any potential outcome event, hospital admissions, and possible adverse effects were recorded as well as current handicap (by means of the modified Rankin scale) and changes in trial medication. Follow-up was complete in all patients.

Outcome Events

The primary outcome measure was the composite event "death from all vascular causes, nonfatal stroke, nonfatal myocardial infarction, or nonfatal major bleeding complication," whichever occurred first. Secondary outcome events were death from all causes, death from vascular causes, and death from vascular causes or nonfatal stroke. After the premature termination of the trial, we defined post hoc a tertiary outcome event for explanatory purposes, ie, any major ischemic event, namely, nonhemorrhagic death from vascular causes, nonfatal ischemic stroke, or nonfatal myocardial infarction. Death from vascular disease included sudden death (reliable observation of the time between onset of symptoms and death, or the patient being found dead), or death from stroke, myocardial infarction, congestive heart failure, any bleed, peripheral vascular disease, pulmonary embolism, or other vascular causes. The diagnosis of nonfatal stroke required a focal neurological deficit of sudden onset persisting for more than 24 hours, with an increase in handicap of at least one grade on the Rankin scale. CT scanning was encouraged after each possible stroke; these scans were audited by physicians blinded to treatment allocation. Myocardial infarction was defined by at least two of the following: history of chest discomfort for at least half an hour, specific cardiac enzymes more than twice the upper limit of normal, or the development of new Q waves on the standard 12-lead ECG. The definition of major bleeding complication included intracranial bleeding, fatal bleeding, and any bleeding requiring hospitalization irrespective of interventions.

All events were independently classified by three members of the auditing committee for outcome events. The reviewers were blinded to the assigned treatment; in case of differences of opinion, the outcome event was discussed in the Executive Committee and decided by majority vote.

Calculation of INR-Specific Event Rates

Intensity-specific incidence rates were calculated as the ratio of the number of events that took place at a certain achieved intensity of INR (subdivided according to intervals of 0.5 INR units) and the number of patient-years that this INR level had been achieved by the patient population. This method has been described in detail by Rosendaal and colleagues [16]. The INR at the time of an outcome event was obtained from the hospital records. If this measurement had not been performed or could not be retrieved, we used the last INR measurement at the anticoagulation clinic within 8 days before the event. If this information was not available, the event was disregarded for this purpose.

Size of the Study and Interim Analysis

We calculated that 3,000 patients should be followed for a mean period of 2.9 years to detect a relative decrease of 24%

in the incidence of the primary outcome event in the anticoagulated group, assuming a type I error of 5%, a type II error of 20%, and an incidence of the primary outcome event of 6 per 100 patient-years in the aspirin group [4].

During the trial, none of the investigators had knowledge of event rates or complication rates according to treatment allocation. An independent Data Monitoring Committee (a neurologist, a hematologist, and an epidemiologist/statistician) monitored the study results. Five interim analyses were planned, each after an additional 1,500 patient-years had been accrued; an asymmetrical stopping rule was agreed on [17]. This asymmetry was chosen because we considered the amount of evidence needed to rule out a positive effect of anticoagulant therapy to be smaller than that to prove its superiority above aspirin. At the end of April 1996, unblinded data on approximately 1,200 person-years for the first interim analysis were submitted to the Data Monitoring Committee. On the basis of that analysis (primary outcome event, as far as known by that time, had occurred in 54 of the 616 patients allocated to anticoagulant treatment and in 26 of the 627 patients in the aspirin group; relative risk, 2.1; 95% confidence interval [CI], 1.3–3.3) the Data Monitoring Committee advised the Steering Committee on May 6 to stop the trial in its original design. Soon thereafter all participating neurologists and thrombosis centers were informed that the trial was stopped for all patients; patients on anticoagulant treatment were switched to low-dose aspirin.

Data Analysis

The principal aim of the data analysis was to compare the incidence of the primary outcome event between the anticoagulation and aspirin treatment strategies. The analysis was based on the intention-to-treat principle; that is, whether medication was taken or not, the patients were analyzed according to their originally assigned treatment. The occurrence of the primary outcome event in the two groups was compared in terms of the hazard ratio (HR), which may be interpreted as a relative risk. HRs were obtained by means of the Cox proportional hazard model [18]. The precision of the HR estimates was described with the 95% CIs obtained from the Cox model. A Poisson model was fitted to determine the relationship between the intensity of anticoagulation (in 0.5 INR units) and the incidence of major bleeding complications. Cox and Poisson models were set up by means of the EGRET statistical package [19].

Results

Between April 23, 1993, and May 15, 1996, 1,316 patients were enrolled at 58 centers. Most (1,277) patients originated from 52 Dutch centers whereas 39 patients were randomized from other countries (see Appendix). The mean length of follow-up was 14 months, with a range of 0 to 37 months. One randomization number was allocated to a person whose existence could not be subsequently confirmed. Seven patients, of whom 2 were allocated to aspirin, were, in retrospect, inappropriately enrolled in the trial; ie, 3 had a brain tumor, 1 amyotrophic lateral sclerosis, 1 cervical myelopathy, and 2 atrial fibrillation; these 7 patients, however, were included in the intention-to-treat analysis. Table 1 shows the characteristics of the patients at baseline. Approximately two-thirds of the patients were males and the mean age was 63.3 (±10.5) years. The longest episode of cerebral ischemia had occurred within the previous month in about half the patients; approximately 40% had had a TIA. Baseline CT scans of the brain were available in all but 46 patients; in 25 patients with transient monocular blindness it was not required and in 21 patients with cerebral ischemia the scan was missing. All but three qualifying events with any relevant infarct on the baseline CT scan were classified as ischemic; two ischemic lesions were rated as moderately hemorrhagic and one as severely hemorrhagic; no outcome event occurred in these 3 patients. Most CT scans were done within 2 weeks after onset of symptoms of the qualifying event (65%), another 13% was done between 2 and 4 weeks. There were no major differences between the groups with regard to prognostic variables at baseline.

Patients randomized to aspirin and anticoagulant drugs equally often visited their randomizing physician. Almost all patients allocated to aspirin used 30 mg aspirin daily (95%), whereas 3% used 75 mg and 2% had 100 mg aspirin daily. Patients allocated to anticoagulant drugs visited the thrombosis centers with a mean interval of 2.6 (±1.8) weeks and somewhat more often during the first 6 months after randomization (mean interval, 1.9 [±1.2] weeks). During the trial 143 patients who took anticoagulant drugs discontinued their trial medication; 44 did so in the group allocated to aspirin (Table 2). Most patients who stopped using anticoagulants did so within 6 months after randomization. Figure 1 shows the number of patient-years spent in each class of 0.5 INR unit during the time that patients allocated to anticoagulants used their study drugs.

In the 60 patients with stroke, on follow-up, CT scanning was performed in 53 patients (88%); in 2 patients the diagnosis was based on autopsy and in 5 on clinical history. In 4 of these 5 patients no certain distinction could be made between hemorrhage and infarction; 1 patient had a history of a sudden focal brain lesion rapidly evolving into herniation, which was classified as intracranial hemorrhage. Most CT scans were done within 2 weeks after onset of symptoms (83%) and another 6% was done between 2 and 4 weeks.

Table 3 shows an excess of the primary outcome event in the 651 patients on anticoagulant drugs; 81, against 36 in the 665 patients treated with aspirin. The HR associated with the use of anticoagulants is 2.3 (95% CI, 1.6–3.5), the excess being attributable to a predominance of major bleeding complications in anticoagulated patients. Figure 2 shows the Kaplan–Meier curves for the primary outcome event (panel A) and major bleeding complications (panel B) in both

Table 1. Baseline Characteristics of the Study Patients, According to Assigned Treatment

	Anticoagulants	Aspirin
Number allocated	651	665
Male (%)	66	63
Age >65 yr (%)	47	48
Qualifying event (%)		
Transient monocular blindness	5	3
Transient ischemic attack	36	37
Minor ischemic stroke	58	60
Time from longest event to randomization (%)		
<1 wk	14	14
1 wk to 1 mo	34	33
1–6 mo	52	53
Rankin grade (%)		
0 = no symptoms	45	43
1 = minor symptoms; no limitations	27	29
2 = some restrictions; no help needed	19	21
3 = help needed; still independent	10	8
CT scan of the brain[a] (n)	624	646
Any infarct (%)	49	46
Any relevant infarct (%)	39	35
History (%)		
Stroke	9	8
Angina pectoris	9	12
Myocardial infarction	9	10
Intermittent claudication	5	7
Diabetes mellitus	11	13
Vascular intervention	7	6
Current cigarette smoking	46	44
Hypertension	39	46
Blood pressure (mm Hg)[b]		
Systolic	158 ± 24	158 ± 26
Diastolic	91 ± 13	91 ± 13
Cholesterol (mmol/L)[b]	6.1 ± 1.3	6.2 ± 1.3

[a] Not required in patients with transient monocular blindness.
[b] Mean ± SD.
CT = computed tomographic.

Table 2. When and Why Trial Medication Was Discontinued in the Study Patients

	Anticoagulants	Aspirin
On medication/at risk[a] (% on medication)		
At start trial	651/651 (100)	665/665 (100)
At 6 mo	451/511 (88)	483/510 (95)
At 1 yr	287/355 (81)	345/373 (92)
At 1.5 yr	165/200 (83)	197/215 (92)
At 2 yr	94/112 (84)	114/125 (91)
Reason for first discontinuation (n)	143[b]	44[b]
Inappropriate inclusion	6	1
Nonfatal stroke or MI	12	12
Nonfatal major bleeding complication	20	2
Minor bleeding complication	25	1
Other adverse effect	17	3
Start other antithrombotic drugs	2	21
Other medical reason	12	1
Hassle anticoagulation control	16	0
Other reasons	29	2
Unknown	4	1

[a] Patients alive at the start of the period.
[b] Thirty-one patients never received anticoagulants and 3 patients never received aspirin as allocated.
MI = myocardial infarction.

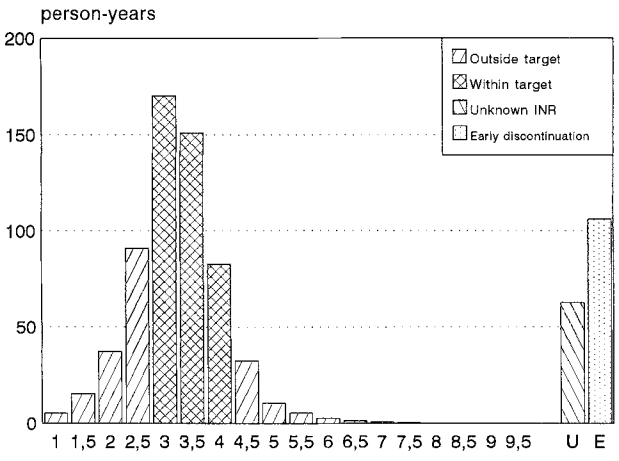

Fig 1. Distribution of time spent in each international normalized ratio class.

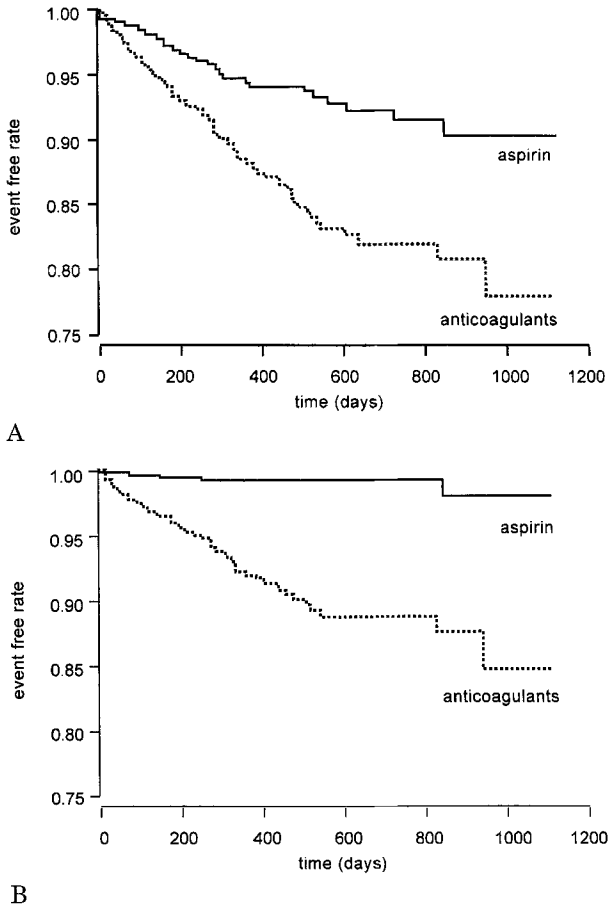

Fig 2. (A) Kaplan–Meier curves for the composite outcome event of "death from vascular causes, nonfatal stroke, nonfatal myocardial infarction, or nonfatal major bleeding complication," according to assigned treatment. The numbers of patients at risk are shown in Table 2. (B) Kaplan–Meier curves for major bleeding complications according to assigned treatment.

treatment groups. The HR for death from all causes was 2.4 (95% CI, 1.3–4.4). There was no statistically significant difference in the occurrence of major ischemic events (nonhemorrhagic death from vascular causes, nonfatal ischemic stroke, or nonfatal myocardial infarction). The crude HRs shown in Table 3 remained essentially the same after adjustment for major risk factors. We refrained from any of the planned subgroup analyses because of the limited numbers of outcome events.

Table 4 summarizes the types of major bleeding complications according to treatment group. Fourteen fatal brain hemorrhages occurred in the patients allocated to anticoagulants, against only 1 in the aspirin group. In the anticoagulated patients, 27 intracranial bleeding complications occurred of which 23 were intracerebral, 3 were subdural, and 1 was of unknown

Table 3. The Occurrence of First Outcome Events[a] According to Allocated Treatment (Intention-to-Treat Analysis)

	AC	ASA	HR	95% CI
Patients randomized	651	665		
Person-years of observation[b]	735	775		
Death from all vascular causes, nonfatal stroke, nonfatal MI, nonfatal major bleeding complication[c]	81	36	2.3	1.6–3.5
Death	35	15	2.4	1.3–4.4
Death from all vascular causes	24	11	2.3	1.1–4.6
Death from all vascular causes, nonfatal stroke[c]	48	29	1.7	1.1–2.7
Major bleeding complication	53	6	9.3	4.0–22
All major ischemic events: nonhemorrhagic death from vascular causes, nonfatal ischemic stroke, nonfatal MI	27	27	1.03	0.6–1.75

[a] One outcome event in the AC group and three in the ASA group were strokes that could be classified as neither ischemic nor hemorrhagic because no computed tomographic scan was available.
[b] Person-years are given for the primary outcome event. The number of person-years for the other outcome events are slightly higher.
[c] Whichever event occurred first.

AC = anticoagulants; ASA = aspirin; HR = hazard ratio; CI = confidence interval; MI = myocardial infarction.

Table 4. Bleeding Complications According to Treatment Group

Major Bleeding Complication	AC (n = 651)	ASA (n = 665)
Fatal intracerebral	14	1
Deep[a]	7	1
Lobar[a]	5	0
Cerebellar[a]	1	0
No CT scan[b]	1	0
Fatal subdural	1	0
Fatal gastrointestinal	0	0
Fatal other[c]	2	0
Nonfatal intracerebral	10	2
Deep[a]	4	2
Lobar[a]	3	0
Cerebellar[a]	3	0
Nonfatal subdural	2	0
Nonfatal gastrointestinal	10	2
Nonfatal urinary tract	7	0
Nonfatal other	7	1
Total	53	6

[a] Localization based on computed tomographic (CT) scanning or autopsy.
[b] Diagnosis based on clinical history: a 61-year-old man presenting with a right hemiparesis, aphasia, and progressive loss of consciousness died within 6 hours after onset of symptoms.
[c] One patient bled from an arteriovenous malformation in the liver hilus; another died from the sequelae of a massive bleed in a leg.

AC = anticoagulants; ASA = aspirin.

location. Fifteen intracranial breedings were deep intracerebral or cerebellar hemorrhages. Age of more than 65 years (HR, 2.5; 95% CI, 1.1–5.7) and leukoaraiosis centrally recorded for the baseline CT scan (HR, 7.5; 95% CI, 3.4–16) were the most important risk factors for intracerebral hemorrhages. There were no statistically significant differences in the incidence of intracerebral bleeding complications between patients with or without a history of hypertension, those with a lacunar or cortical infarction at their baseline CT scan, and those with a TIA versus a longer lasting qualifying event.

The incidence of major bleeding complications increased steeply with the achieved intensity of anticoagulation (Fig 3A). This is demonstrated clearly in a Poisson regression model; for each 0.5 INR unit the incidence increased by a factor of 1.43 (95% CI, 0.96–2.13). Figure 3B suggests a decrease of the incidence of ischemic events with increasing intensities of anticoagulation, although the CIs of the rate ratios are wide. The decrease in a Poisson model is 0.83 (95% CI, 0.65–1.07) for each 0.5 INR unit.

Discussion

This study was based on the premise that anticoagulant treatment would be more efficacious than aspirin in preventing recurrent episodes of cerebral ischemia, but

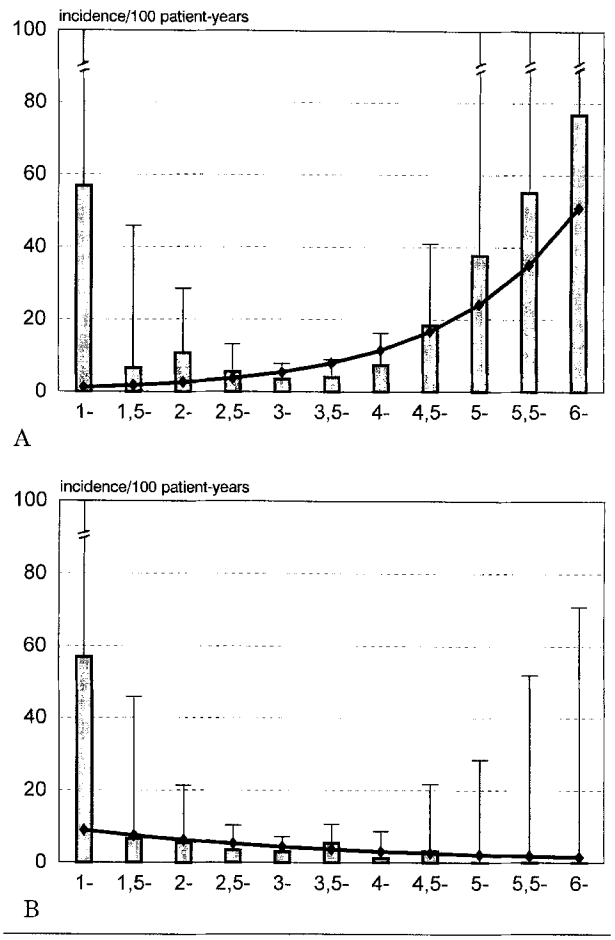

Fig 3. (A) International normalized ratio (INR)-specific incidence of major bleeding complications with upper limits of 95% confidence interval. The line results from a Poisson regression model. (B) INR-specific incidence of ischemic complications with upper limits of 95% confidence interval. The line results from a Poisson regression model.

the high rate of major bleeding complications led to the trial being terminated, at only 17% of its predetermined number of patient-years of observation. At the time of the interim analysis, the hemorrhagic complications were numerous enough to lead to a statistically significant difference in the primary, composite outcome event of the trial (death from all vascular causes, nonfatal stroke, nonfatal myocardial infarction, or major bleeding complication). The Data Monitoring Committee advised that this difference was sufficient reason to discontinue the trial because the original hypothesis assumed anticoagulants to be beneficial.

We aimed at a high target range of anticoagulation (INR values, 3–4.5) for two reasons; ie, (1) in The Netherlands as well as in other European countries this is the usual range for patients with arterial disease [5, 7, 13], and (2) the evidence available from studies based on measurement of actual (rather than intended) INR values suggests the rate of bleeding complications

increases only when INR values rise above 4.5. Indications for anticoagulant use in these studies included myocardial infarction [20], artificial heart valves [21], and atrial fibrillation in combination with transient ischemic attacks or a nondisabling stroke [22]. Safety data from the European Atrial Fibrillation Trial (EAFT) concerning patients with cerebral ischemia and atrial fibrillation appeared reassuring because the patients in that trial were relatively old (mean age, 71 years) and none of the strokes documented with CT scanning (16 of 20) in the anticoagulant group were hemorrhagic. Moreover, the use of oral anticoagulant drugs with a target INR range of 2.5 to 4.0 (and obtained INR range of 2.0–3.5) was associated with a risk reduction for major vascular events of 40% in comparison with aspirin [11].

Intracerebral hemorrhage was the most frequent type of major bleeding complication (52%) in the anticoagulated patients in this study. Why, then, were our patients so prone to intracerebral hemorrhage, when their TIAs or nondisabling strokes had not occurred in combination with atrial fibrillation? It is likely that these patients had preexisting damage to the cerebral arterial tree, whereas of those with cerebral ischemia due to atrial fibrillation, the majority will have emboli originating from the left atrium. An alternate explanation is that these events represented hemorrhagic transformation, but the preponderance of deep intracerebral or cerebellar hemorrhages (see Table 4) would be contrary to this in that large hemorrhagic infarcts would be expected to occur mainly in superficial areas, corresponding to the territory of major arteries or their branches. A third explanation would be that some qualifying events may, in fact, have been caused by small hemorrhages due to amyloid angiopathy [23], thus predisposing patients to large hemorrhages during anticoagulant treatment, as may occur after thrombolytic treatment for myocardial infarction. Again, if this were the case, a preponderance of lobar intracerebral hemorrhages rather than the predominantly deep sites of bleeding would be expected [24, 25]. Moreover, there was no excess risk of intracerebral hemorrhage in patients with TIAs compared with those with nondisabling ischemic strokes (in whom CT generally ruled out hemorrhages and showed positive evidence of infarction).

If neither hemorrhagic transformation nor previous small hemorrhages are causing the frequent occurrence of intracerebral hemorrhage in the anticoagulant-treated patients, is there preexisting damage to the wall of small perforating brain arteries? If this were the case, the risk of intracerebral bleeding would be especially high in patients whose clinical or radiological features at presentation suggested involvement of small vessels [26], i.e., lacunar or subcortical infarcts or, in the absence of evidence of infarction on CT scanning, "lacunar transient ischemic attacks." We could not demonstrate, however, a difference in the risk of intracerebral hemorrhage between patients with a lacunar or cortical infarction at their baseline CT scan. The only marker of small-vessel disease associated with the risk of intracerebral hemorrhage was the presence of diffuse ischemic damage to the white matter of the brain (as assessed on CT scans), and, to a much lesser extent, the patient's age and the presence of arterial hypertension.

The results of this trial can probably be generalized to all patients with TIAs or nondisabling ischemic strokes except those in atrial fibrillation or those with tight carotid stenosis requiring surgery, given that the two patient groups were well balanced for all major prognostic variables, and that the patients in the aspirin group were strikingly similar to those in a previous trial, in which we compared two different doses of aspirin [4]. The open design of our study might be regarded, by some, as a drawback, leading to information bias and thus detracting from the validity of our results; but as the assessment of outcome events was completely masked, we think this disadvantage has been overcome. What is more, there are advantages of an open trial with anticoagulant drugs. These lie not only in the simplicity of its organization, but also in that the comparison is truly that of strategies (one complex, the other simple) and not only of drugs (both with a complex mode of administration because of the use of double dummies), so that the results are fully analogous to clinical reality [27].

We do not expect that these results will end the debate about the use of anticoagulant treatment in the secondary prevention of stroke for patients in sinus rhythm. The hypothesis for this trial was that the rate of ischemic events in patients with TIAs or nondisabling strokes might be substantially lower with anticoagulant treatment than with aspirin, which drug prevents only 15 to 20% of all major vascular complications [2]. The numbers of outcome events of ischemic stroke, myocardial infarction, and nonhemorrhagic death from vascular causes were so low at the time the trial was stopped for safety reasons that the results are both compatible with a relative risk reduction of ischemic events by oral anticoagulants with 40% and with a relative risk reduction of ischemic events by aspirin with 43%; this is also reflected by the wide interval of the confidence interval of the slope of the Poisson regression line for the ischemic events. An ongoing trial in the United States [28] is comparing aspirin with anticoagulation with an INR target range of 1.4 to 2.8, and one would hope that this intensity is not only safe but also efficacious. In an observational study of patients with atrial fibrillation, the risk of stroke rose steeply at INR values measured to be lower than 2.0 [29], whereas in a randomized trial anticoagulation with an INR target range of 2.0 to 3.0 could

safely prevent ischemic stroke in high-risk patients with atrial fibrillation [30].

Calculation of INR-specific incidence rates [16, 20–22] has allowed us to estimate that shifting the target range of anticoagulation to an INR range of 2.0 to 3.0 (instead of 3.0–4.5) would reduce the rate of major bleeding complications by two-thirds. The results in Figure 1 indicate that the thrombosis centers were fairly successful in keeping patients within the target range of INR values; a considerable number of the outlying values were from the initial dosing titration. Excluding patients more than 75 years old and those with leukoaraiosis might also improve safety, although the intensity of anticoagulation is a much more powerful risk factor than age [31, 32]. Whether the remaining disadvantage would be outweighed by an even greater benefit in the prevention of ischemic events, compared with optimal antiplatelet treatment, is a question that can be settled only by a new trial of sufficient size. This trial, the European and Australian Stroke Prevention In Reversible Ischemia Trial (ESPRIT), started recently.

Appendix

The following centers and investigators participated in the Stroke Prevention in Reversible Ischemia Trial. The number of patients randomized at each center is given in parentheses.

Ziekenhuis De Wever and Gregorius Heerlen (126; C. L. Franke,*† and P. J. J. Koehler); Academisch Ziekenhuis Utrecht (111; J. W. Gorter,* L. J. Kappelle,*† G. J. E. Rinkel, H. C. Tjeerdsma,* and J. van Gijn,*†); Medisch Centrum Alkmaar (88; J. W. H. H. Dammers, H. J. S. Straatman, R. ten Houten, and M. M. Veering); Academisch Ziekenhuis Rotterdam Dijkzigt (79; S. L. M. Bakker, D. Dippel, P. J. Koudstaal,*† H. M. A. van Gemert, and J. C. van Swieten); Academisch Medisch Centrum Amsterdam (76; J. Horn, I. H. Kwa, M. Limburg, and J. Stam); Oosterschelde Ziekenhuis Goes (60; A. M. Boon, W. H. G. Lieuwens, and F. Visscher); Martini Ziekenhuis Groningen (58; C. Bouwsma, A. W. F. Rutgers, and J. W. Snoek); Medisch Spectrum Twente Enschede (44; P. J. A. M. Brouwers, J. Nihom, and H. Solleveld); Merwede-ziekenhuis Dordrecht (38; P. A. T. Carbaat, L. I. Hertzberger, R. P. Kleijweg, and V. M. H. Nanninga-van den Neste); St Jozefziekenhuis Kerkrade (38; A. J. H. van Diepen); St Lucas Andreas Ziekenhuis Amsterdam (37; W. H. J. P. Linssen, J. A. L. Vanneste, J. Vos, and H. C. Weinstein); Ziekenhuis Bethesda Hoogeveen (32; J. P. Schipper and W. K. van der Meer); De Lievensberg Bergen op Zoom (30; P. J. I. M. Berntsen); Zuiderzee Ziekenhuis Lelystad (30; E. M. de Vries-Leenders, J. P. Geervliet, and R. J. J. Tans); St. Deventer Ziekenhuizen Deventer (28; W. J. Feikema and H. J. M. M. Lohmann); Westeinde Ziekenhuis's-Gravenhage (26; V. van Kasteel); Ziekenhuis Rijnstate Arnhem (24; F. A. Jongebloed, Q. H. Leyten and P. J. M. van Wensen); Ziekenhuis De Gelderse Vallei Ede (24; C. Jansen and M. G. Smits); Holy Ziekenhuis Vlaardingen (24; J. J. M. Driesen, W. F. van Oudenaarden and J. C. B. Verhey); Streekziekenhuis Coevorden/Hardenberg (22; H. R. F. Bottger, M. F. Driessen-Kletter and F. Zwols); St Lucas Ziekenhuis Winschoten (22; J. B. van der Gaast and M. C. Wittebol); Academisch Ziekenhuis Maastricht (21; J. Lodder and R. J. van Oostenbrugge); Ziekenhuis Nij Smellinghe Drachten (19; K. D. Beintema, J. Hilbers and H. L. van der Wiel); St Anna Ziekenhuis Geldrop (18; H. B. M. van Lieshout); Diakonessenhuis Utrecht (17; W. Weststrate); Ziekenhuis St Jansdal Harderwijk (16; P. L. J. A. Bernsen); Canisius Wilhelmina Ziekenhuis Nijmegen (15; C. W. G. M. Frenken,*† and E. F. J. Poels); Twenteborg Ziekenhuis Almelo (14; S. F. Lindeboom); Streekziekenhuis Zevenaar (13; A. van der Steen); IJsselmeer Ziekenhuizen Emmeloord (12; W. F. Glimmerveen, E. I. F. Martens); St Franciscus Ziekenhuis Rotterdam (12; C. Bulens,* L. H. Penning de Vries-Bos); Royal Hallamshire Hospital Sheffield, UK (12; G. S. Venables*); Medisch Centrum Leeuwarden (11; J. G. Koster and L. G. F. Sinnige); Streekziekenhuis Midden Twente Hengelo (10; M. M. Klaver and J. C. Koetsveld-Baart); St Antonius Ziekenhuis Nieuwegein (10; H. W. Mauser); Kennemer Gasthuis-lokatie Zeeweg IJmuiden (10; J. A. Don); Beatrix Ziekenhuis Gorinchem (9; R. B. Alting van Geusau, M. H. Dijkman and W. J. J. F. Hoppenbrouwers); St James's University Hospital Leeds, UK (9; J. M. Bamford); Diaconessenhuis Leiden (9; P. E. Briët and J. L. A. Eekhof); Academisch Ziekenhuis V. U. Amsterdam (7; R. Witjes); Slotervaart Ziekenhuis Amsterdam (6; H. L. Hamburger and J. J. van der Sande); King's College Hospital London, UK (6; P. Bath); Royal Perth Hospital Perth, Australia (6; G. J. Hankey); N. H. Diaconessen Inrichting Meppel (5; E. Koning); Clinico Neurologica-Policlinic Perugia, Italy (5; S. Ricci); Catharina Ziekenhuis Eindhoven (4; J. N. Berendes); St Franciscus Ziekenhuis Roosendaal (4; L. J. M. A. Hooff, A. C. G. A. van Spreeken, and H. N. A. Wouters); Flevo Ziekenhuis Almere (3; A. R. Kuhler and G. N. Mallo); Onze Lieve Vrouwe Gasthuis Amsterdam (3; H. K. van Walbeek); Waterland Ziekenhuis Purmerend (3; J. C. Gauw); Diaconessenhuis Eindhoven (2; A. J. Vermeij); Schieland Ziekenhuis Schiedam (2; J. C. B. Verheij); Reinier de Graaf Gasthuis Delft (1; J. W. A. Swen); Hospital de Santa Maria Lisbon, Portugal (1; P. Canhao); Academisch Ziekenhuis Nijmegen (1; A. Keyser); Antonius Ziekenhuis Sneek (1; R. S. Holscher); Diaconessenhuis Voorburg (1; G. J. de Jong); and Lorentz Ziekenhuis Zeist (1; V. Kraaier).

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