Medium intensity oral anticoagulants versus aspirin after cerebral ischaemia of arterial origin (ESPRIT): a randomised controlled trial

*The ESPRIT Study Group**

Summary

Background Oral anticoagulants are better than aspirin for secondary prevention after myocardial infarction and after cerebral ischaemia in combination with non-rheumatic atrial fibrillation. The European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) aimed to determine whether oral anticoagulation with medium intensity is more effective than aspirin in preventing future vascular events in patients with transient ischaemic attack or minor stroke of presumed arterial origin.

Methods In this international, multicentre trial, patients were randomly assigned within 6 months after a transient ischaemic attack or minor stroke of presumed arterial origin either anticoagulants (target INR range 2·0–3·0; n=536) or aspirin (30–325 mg daily; n=532). The primary outcome was the composite of death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction, or major bleeding complication, whichever occurred first. In a post hoc analysis anticoagulants were compared with the combination of aspirin and dipyridamole (200 mg twice daily). Treatment was open, but auditing of outcome events was blinded. Primary analysis was by intention to treat. This study is registered as an International Standard Randomised Controlled Trial (number ISRCTN73824458) and with ClinicalTrials.gov (NCT00161070).

Findings The anticoagulants versus aspirin comparison of ESPRIT was prematurely ended because ESPRIT reported previously that the combination of aspirin and dipyridamole was more effective than aspirin alone. Mean follow-up was 4·6 years (SD 2·2). The mean achieved INR was 2·57 (SD 0·86). A primary outcome event occurred in 99 (19%) patients on anticoagulants and in 98 (18%) patients on aspirin (hazard ratio [HR] 1·02, 95% CI 0·77–1·35). The HR for ischaemic events was 0·73 (0·52–1·01) and for major bleeding complications 2·56 (1·48–4·43). The HR for the primary outcome event comparing anticoagulants with the combination treatment of aspirin and dipyridamole was 1·31 (0·98–1·75).

Interpretation Oral anticoagulants (target INR range 2·0–3·0) are not more effective than aspirin for secondary prevention after transient ischaemic attack or minor stroke of arterial origin. A possible protective effect against ischaemic events is offset by increased bleeding complications.

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Introduction

Oral anticoagulants in patients with arterial vascular disease are effective for several indications. They reduce the risk of a serious vascular event by up to 50% more than aspirin in patients after myocardial infarction.[1] In patients with non-rheumatic atrial fibrillation and transient ischaemic attack or minor ischaemic stroke, the risk reduction for anticoagulants compared with aspirin is 40% (95% CI 13–59).[2] Moreover, adjusted dose warfarin proved more efficacious than fixed-dose warfarin plus aspirin[3] and a combination of aspirin and clopidogrel[4] in high-risk patients with non-rheumatic atrial fibrillation. After infrainguinal bypass surgery, oral anticoagulation is better than aspirin for the prevention of infrainguinal-vein-graft occlusion and for lowering the rate of ischaemic events.[5]

Since atherosclerosis is a substantial cause of both myocardial infarction and cerebral ischaemia, an obvious hypothesis is that anticoagulants are also more effective than aspirin after a transient ischaemic attack or minor ischaemic stroke of presumed arterial origin. Without secondary prevention measures these patients have an annual risk of vascular events (death from vascular causes, non-fatal stroke, or non-fatal myocardial infarction) ranging between 4% and 16% in clinical trials[6,7] and of 9% in population-based studies.[8] This risk is reduced by no more than 20% with aspirin.[6,7,9]

The Stroke Prevention in Reversible Ischemia Trial (SPIRIT), in which high-intensity anticoagulation (international normalised ratio [INR] target range 3·0–4·5) was compared with aspirin in patients after transient ischaemic attack or minor stroke of presumed arterial origin, was stopped early because of an excess in major bleeding complications in the anticoagulation group.[10] Calculation of INR-specific incidence rates in SPIRIT led to the conclusion that shifting the target range to INR 2·0–3·0 would reduce the rate of major bleeding complications by two-thirds to incidence rates similar to those for other indications.[11] Another lesson learned from SPIRIT was that patients older than 75 years and those with severe leukoaraiosis had an excess risk of major bleeding.[12]

In the European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT),[13,14] medium intensity anticoagulant treatment (with an INR target range of 2·0–3·0) was compared with aspirin (in any dose between

30 mg and 325 mg daily)[15] in patients after a transient ischaemic attack or minor stroke of presumed arterial origin. To study real life treatment strategies ESPRIT had an open design.[16]

In another completed group of ESPRIT we showed that the combination of aspirin and dipyridamole was more effective than aspirin alone in preventing major vascular events.[17] Since the power of the trial might well be insufficient to detect a possible benefit of anticoagulants over the combination of aspirin and dipyridamole, which from then on would be regarded by many as the new standard in our opinion, we consulted the data monitoring committee. They agreed to end the trial before the planned number of patient-years had been reached.

Methods

Participants

In this international multicentre trial we included patients within 6 months after a transient ischaemic attack (including transient monocular blindness) or minor ischaemic stroke (grade ≤3 on the modified Rankin scale)[18,19] of presumed arterial origin. Exclusion criteria were a possible cardiac source of embolism (atrial fibrillation on electrocardiogram, valvular heart disease, or recent myocardial infarction), cerebral ischaemia associated with high-grade carotid stenosis for which carotid endarterectomy or endovascular treatment was planned, any blood coagulation disorder, moderate or severe diffuse ischaemic damage to the white matter of the brain (leukoaraiosis),[20] any contraindication for any of the study drugs, and a reduced life expectancy. Patients older than 75 years were preferably excluded, unless the randomising physicians felt that a lower "biological age" allowed treatment with oral anticoagulants. Patients with intracerebral haemorrhage were not included in the trial. The institutional medical ethical review boards of the participating hospitals approved the study protocol and all patients provided written informed consent.

Procedures

Patients were randomly assigned oral anticoagulants, aspirin, or the combination of aspirin and dipyridamole. The preferred anticoagulant drug was phenprocoumon because more stable anticoagulation is expected with this drug than with other anticoagulants, but acenocoumarol and warfarin were also allowed. The INR target range was 2·0–3·0. The aspirin dose was left to the discretion of the treating physician provided it was between 30 mg and 325 mg per day[15] and remained fixed for the duration of the trial. Dipyridamole was prescribed in a dose of 200 mg twice daily, preferably in the extended release formulation, either in a fixed-dose or in a free combination with aspirin.

ESPRIT had an open, non-blinded study design.[16] Treatment allocation was done by means of computer-generated randomisation codes, stratified by hospital before the start of the trial. Patients were randomised by means of a telephone call, fax, or e-mail to the central trial office. Our primary aim was to randomise patients in a three-arm randomisation scheme (anticoagulation *vs* aspirin plus dipyridamole *vs* aspirin alone). Randomisation in a two-arm scheme of aspirin plus dipyridamole versus aspirin was possible if there was a contraindication for anticoagulation treatment (age older than 75 years or leukoaraiosis on a brain scan), if patients refused to participate because they did not want to use anticoagulation treatment, if the physician did not feel comfortable with prescribing anticoagulation treatment, or if regular assessment of INR values was impossible. Randomisation in a two-arm scheme of anticoagulation treatment versus aspirin was possible in countries where dipyridamole was not available. Data from patients randomised in the two-arm scheme of aspirin and dipyridamole (n=854) versus aspirin (n=860) were accounted for in the previous report of ESPRIT.[17]

We gathered data on the clinical features of the longest episode of focal neurological deficits in the preceding 6 months by means of a checklist. The baseline form recorded demographic data, disability score on the modified Rankin scale,[18,19] antithrombotic drug use at the time of the event, blood pressure, vascular risk factors, and vascular history. The diagnosis of transient ischaemic attack or stroke was based on the duration of the symptoms of the qualifying event; if they lasted less than 24 h the event was deemed a transient ischaemic attack and if they lasted more than 24 h it was judged to be a stroke. CT or MRI of the brain was mandatory in all patients apart from those with transient monocular blindness. All scans were rereviewed and classified at the central trial office by three members of the scan committee.[21] An ischaemic lesion on the CT or MRI was thought to be relevant if it corresponded with the symptoms of the qualifying event. Electrocardiography (ECG) was required, but duplex scanning of the carotid arteries was optional. All baseline data were gathered and checked at the central trial office and entered in a database. On the basis of CT or MRI scans and clinical features, patients were classified as having large-vessel or small-vessel disease or ischaemia in the posterior fossa. If a symptomatic ischaemic lesion was identified with imaging, classification was based on the characteristics of this lesion. If no symptomatic lesion was identified, the symptoms were used for classification, as was done in previous studies.[22,23] Patients with transient monocular blindness were classified as having large-vessel disease,[24] whereas we used the classification of unspecified vessel disease for patients with a large, deep, subcortical infarct.

All patients were asked to return every 6 months for a consultation with their randomising physician or a trained trial nurse. If patients were unable to attend, follow-up information was obtained by telephone contact with the patient or caregiver or, if this was not possible, from their family practitioner. At each contact, the occurrence of possible outcome events, hospital admissions, and adverse events were recorded, as well as current disability (according to the modified Rankin scale[18,19]) and changes in

trial medication. Centres were given the option to end further follow-up for patients who had completed 5 years in the trial. All remaining patients randomly assigned aspirin had a close-out visit between July 1 and Dec 31, 2005. After the presentation of the results of the first part of ESPRIT,[17] which showed a clear benefit of aspirin and dipyridamole over aspirin, patients allocated aspirin were advised to switch their medication to aspirin and dipyridamole and they were no longer followed for the trial. For the purpose of the post hoc analysis between anticoagulants and the combination treatment of aspirin and dipyridamole, all patients allocated to either of these treatment groups had a final follow-up between Jan 1 and Sept 1, 2006. For the purpose of the primary analysis of this report (anticoagulants *vs* aspirin) the follow-up period for patients allocated anticoagulants ended on Dec 31, 2005.

The primary outcome was the composite of death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction, or major bleeding complication. The panel summarises the secondary outcome events. Death from vascular causes included death caused by cerebral infarction, intracranial haemorrhage, unspecified stroke, myocardial infarction, heart failure, pulmonary embolism, arterial bleeding, or sudden death. If no information was available about the cause of death, it was classified as vascular other, according to a priori probabilities.[25] When a patient had a disabling stroke (modified Rankin scale >3) and died during follow-up, the cause of death (stroke or the subsequent complication) was classified as stroke, irrespective of the interval between stroke and death, unless an unrelated other cause of death had been reported. In patients who were independent before their fatal illness, the cause of death was attributed to stroke only if the interval was less than 1 month.[26] Non-fatal ischaemic stroke was diagnosed in case of a new or increasing neurological deficit with sudden onset and persisting for more than 24 h, resulting in an increase in handicap of at least one grade on the modified Rankin scale and no signs of haemorrhage on CT or MRI of the brain undertaken within 2 weeks after the event. The same clinical criteria were used for the diagnosis of haemorrhagic stroke if a corresponding intracerebral haemorrhage was identified on CT or MRI of the brain. If no brain imaging was done while clinical evidence of stroke existed, the event was classified as stroke, unspecified. The outcome event myocardial infarction needed at least two of the following characteristics: a history of chest discomfort for at least half an hour; concentration of specific cardiac enzymes more than twice the upper limit of normal; or the development of specific abnormalities (eg, Q waves) on a standard 12-lead ECG. The outcome event major bleeding complication included all intracranial bleeding, any fatal bleeding, or any bleeding requiring hospitalisation.

Outcome events were reported to the central trial office where all relevant data, including brain scan or ECG, were obtained from the physician in charge. A clinical report of the outcome event was prepared by the trial coordinator who removed all information about the allocated treatment and subsequently presented the report to three members of the auditing committee for outcome events who independently classified the event. If the three classifications differed, the outcome event was discussed by the executive committee who made a decision by majority vote. In some cases, a fourth member of the auditing committee was consulted before the executive committee decided.

During the trial all INR values for patients allocated anticoagulants were regularly obtained from the randomising physician or, in the Netherlands, from regional anticoagulation clinics. The number of patient-years that a certain intensity of INR (subdivided according to intervals of 0·5 INR units) had been achieved by the patient population was calculated.[11] Intensity-specific incidences for major bleeding complications and ischaemic events were calculated as the ratio of the number of events that took place in each interval and the number of patient-years in that interval. The INR value at the time of an outcome event was obtained from the hospital records. If this measurement had not been done or could not be retrieved, the last INR measurement at the anticoagulation clinic was used if it was within 8 days before the event. If this information was not available, the event was not included in the analysis of INR values in relation to events.

Statistical analysis

Assuming a relative risk reduction of 20–25% for anticoagulants in comparison with aspirin, we calculated that about 3000 patients should be followed up for a mean period of 3 years, resulting in 9000 patient-years of follow-up. This calculation was based on a type 1 error of 5%, a type 2 error of 20%, and a presumed incidence of the primary outcome event of six per 100 patient-years in the aspirin group.[13]

During the trial, none of the investigators were aware of event or complication rates according to treatment group. An independent data monitoring committee undertook

***Panel:* Secondary outcome events**

Prespecified

- Death from all causes
- Death from all vascular causes
- Death from all vascular causes and non-fatal stroke
- All major ischaemic events: death from any ischaemic vascular condition or non-fatal ischaemic stroke or non-fatal myocardial infarction
- All vascular events: death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction
- Major bleeding complications

Post hoc defined

- Fatal and non-fatal ischaemic stroke
- All cardiac events: fatal and non-fatal myocardial infarction, sudden death and death from cardiac cause
- Fatal bleeding complication

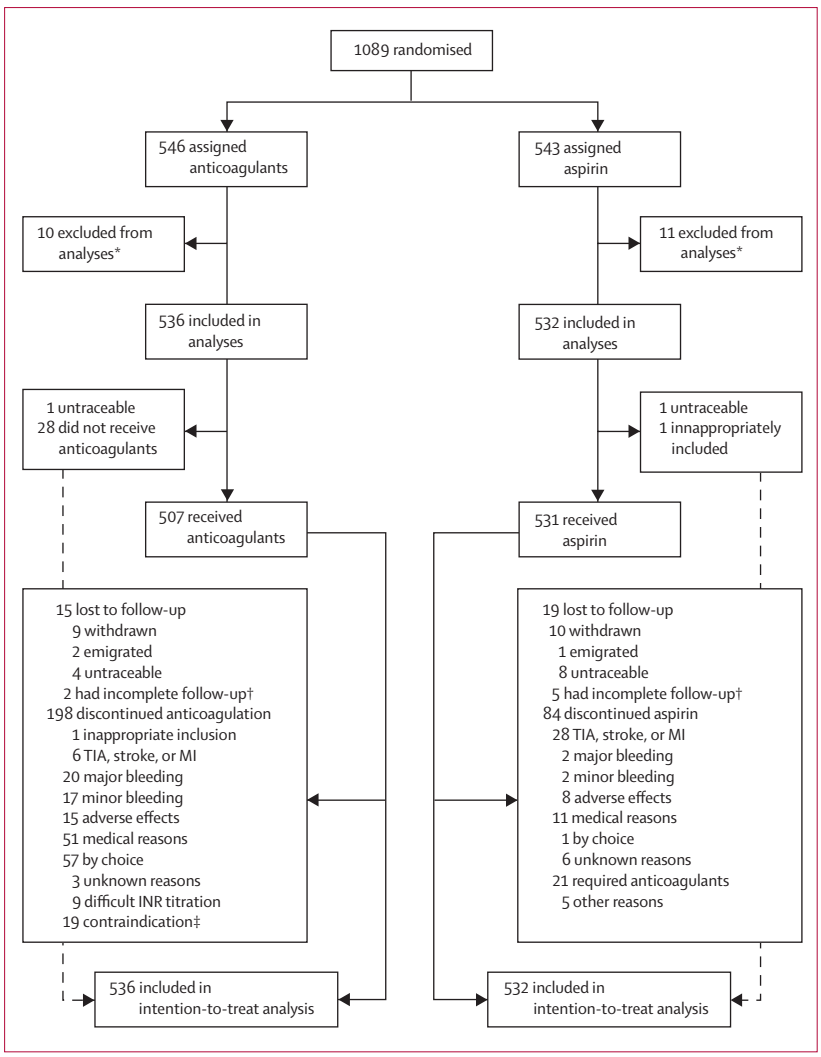

***Figure 1*: Flow-chart anticoagulants versus aspirin**
TIA=transient ischaemic attack. MI=myocardial infarction. *Patients from one excluded hospital. †Incomplete follow-up because of close-out at the date that all follow-up data were complete (four hospitals). ‡Patients who reached the age of 75 years during the trial and patients who in retrospect had leukoaraiosis on CT; both were exclusion criteria for use of anticoagulants in ESPRIT.

	Anticoagulants (n=536)	Aspirin (n=532)
Randomisation scheme		
Three arm	523 (98%)	516 (97%)
Two arm	13 (2%)	16 (3%)
Demographics		
Men	385 (72%)	345 (65%)
Mean age, years (SD)	62 (10)	61 (9)
Qualifying event		
Transient monocular blindness	29 (5%)	28 (5%)
Transient ischaemic attack	164 (31%)	140 (26%)
Minor ischaemic stroke	343 (64%)	364 (68%)
Time from longest event to randomisation		
<1 week	61 (12%)	54 (10%)
1 week to 1 month	119 (23%)	116 (22%)
1–6 months	345 (66%)	358 (68%)
Modified Rankin grade		
0=no symptoms	228 (43%)	223 (42%)
1=minor symptoms; no limitations	167 (31%)	176 (33%)
2=some restrictions; no help needed	106 (20%)	104 (20%)
3=help needed; still independent	32 (6%)	29 (6%)
Additional investigations		
CT or MRI scan of the brain*	514 (96%)	503 (95%)
CT	433 (84%)	423 (84%)
MRI	81 (16%)	70 (16%)
Any infarct	254 (49%)	242 (48%)
Any relevant infarct	184 (36%)	196 (39%)
Ultrasound carotid arteries	487 (91%)	480 (90%)
Stenosis >50%	57 (12%)	44 (9%)
History		
Stroke	61 (11%)	49 (9%)
Angina pectoris	62 (12%)	54 (10%)
Myocardial infarction	35 (7%)	38 (7%)
Intermittent claudication	25 (5%)	27 (5%)
Vascular intervention	30 (6%)	25 (5%)
Diabetes mellitus	98 (18%)	77 (15%)
Hypertension	316 (59%)	282 (53%)
Hyperlipidaemia	251 (47%)	243 (46%)
Current cigarette smoking	220 (41%)	225 (42%)
Mean blood pressure, mm Hg (SD)		
Systolic	153 (22)	152 (22)
Diastolic	87 (12)	87 (12)

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three interim analyses, after each 1500 patient-years of follow-up. This committee advised to continue the trial at all of these analyses. A symmetrical stopping rule was used according to O'Brien and Fleming.[27] The trial was stopped early (when 55% of the planned number of patient years had been reached) for reasons outlined earlier.

In a separate and recently completed arm of ESPRIT, we showed that combination of aspirin and dipyridamole was more effective than aspirin alone in preventing major vascular events. We considered it relevant to present a post hoc comparison of anticoagulants with the combination of aspirin and dipyridamole because many neurologists regard the combination treatment to be the new standard.

The occurrence of outcome events in the groups was compared in terms of the hazard ratio (HR), which may be interpreted as a relative risk. HRs were obtained with the Cox proportional hazard model. The precision of the HR estimates was described with 95% CIs. Analyses were based on the intention-to-treat principle. Additionally, we undertook an analysis of patients who used treatment (on-treatment analysis), in which we included only outcome events that occurred while study treatment was being taken or within 28 days after discontinuation of treatment. Patients who were inappropriately enrolled in the trial were included in the intention-to-treat analysis but were excluded from the on-treatment analysis. Subgroup analyses according to randomisation scheme, age, sex,

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Type of vessel involved		
Large vessel	180 (34%)	175 (33%)
Small vessel	255 (48%)	255 (48%)
Posterior fossa	80 (15%)	77 (14%)
Unspecified	21 (4%)	25 (5%)
Antithrombotic drug use at time of event		
Aspirin	131 (24%)	120 (23%)
Oral anticoagulants	5 (1%)	0
Other	7 (1%)	10 (2%)
None	393 (73%)	402 (76%)
Aspirin dose		
30 mg	..	301 (57%)
50 mg	..	1
75 mg	..	79 (15%)
80 mg	..	34 (6%)
100 mg	..	65 (12%)
150 mg	..	16 (3%)
250 mg	..	1
300 mg	..	34 (6%)
325 mg	..	1

Data are number (%) or mean (SD). *Not required in patients with transient monocular blindness.

***Table 1*: Baseline characteristics**

history of ischaemic heart disease, type of cerebral ischaemia, and country were planned, but were not undertaken in view of the low number of outcome events. A post hoc defined subgroup analysis was done according to stroke subtype at baseline (large-vessel *vs* small-vessel disease) because patients with small-vessel disease might be more prone to intracerebral bleeding complications. In addition to our primary analysis, anticoagulation versus aspirin, we decided post hoc to do an analysis of anticoagulation versus aspirin and dipyridamole.

Before unblinding of the data, the executive committee reviewed all baseline and follow-up data obtained at the central trial office. Because of incomplete data, patients from one hospital (21 patients) were excluded from all analyses. From four other hospitals follow-up data were incomplete—ie, not all patients had a close-out visit between July 1 and Dec 31, 2005. For these hospitals (seven patients), follow-up was closed at the time all data were complete. The corresponding numbers for the post hoc comparison between anticoagulants and the combination treatment are 22 patients excluded from all analyses and seven patients from four hospitals with early termination of follow-up.

This study is registered as an International Standard Randomised Controlled Trial (number ISRCTN73824458) and with ClinicalTrials.gov (NCT00161070).

Role of the funding source

None of the sponsors had a commercial interest in the outcome of the study. The sponsors had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

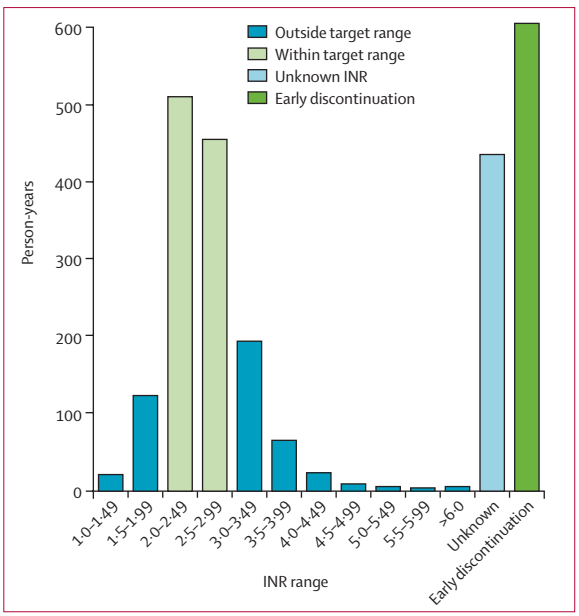

***Figure 2*: Distribution of time spent in each class of 0·5 INR unit**

Results

Between July 1, 1997, and July 1, 2005, 1068 patients from 75 hospitals in 14 countries were randomly assigned anticoagulants (n=536) or aspirin (n=532) and were subsequently analysed (figure 1). Mean length of follow-up was 4·6 years (SD 2·2), corresponding to a total of 4912 patient-years. In retrospect, five patients, of whom three were allocated anticoagulants, were inappropriately enrolled in ESPRIT; one had AIDS, one had a brain tumour, one had syphilis, one had a source of embolism in the heart, and in one patient the qualifying event turned out to be a rapidly progressive stroke that was fatal within several days after inclusion. Another 15 patients were enrolled more than 6 months after their qualifying event (most within 9 months); they were included in all analyses.

	On medication/at risk (% on medication)	
	Anticoagulants	Aspirin
At trial start	507/535 (95%)	531/531 (100%)
At 6 months	440/519 (85%)	507/518 (98%)
At 1 year	395/487 (81%)	457/484 (94%)
At 1·5 year	356/458 (78%)	431/460 (94%)
At 2 years	330/428 (77%)	395/436 (91%)
At 3 years	284/385 (74%)	345/393 (88%)
At 4 years	245/346 (71%)	286/338 (85%)
At 5 years	181/267 (68%)	238/279 (85%)

***Table 2*: Proportion of patients on allocated medication during the trial**

	Intention to treat				On treatment	
	Anticoagulants	Aspirin	HR	95% CI	HR	95% CI
Patients randomised	536	532				
Person-years of observation*	2204	2227				
Death from any vascular cause, non-fatal stroke, non-fatal myocardial infarction, or non-fatal major bleeding complication†	99 (19%)	98 (18%)	1·02	0·77–1·35	1·11	0·82–1·50
Death from all causes	59	44	1·36	0·92–2·01	1·13	0·70–1·84
Death from vascular causes	31	24	1·31	0·77–2·23	1·43	0·73–2·78
Death from vascular causes or non-fatal stroke†	71	78	0·90	0·65–1·24	0·93	0·65–1·33
Major bleeding complication	45	18	2·56	1·48–4·43	3·43	1·82–6·45
Extracranial	27	9				
Inctracranial	18	9				
Fatal bleeding complication‡	11	4	2·8	0·9–8·8	5·5	1·2–25·4
All major ischaemic events: death from any ischaemic vascular condition, non-fatal ischaemic stroke, non-fatal myocardial infarction†	62	84	0·73	0·52–1·01	0·72	0·50–1·04
Death from vascular causes or non-fatal stroke or non-fatal myocardial infarction†	79	92	0·85	0·63–1·15	0·88	0·63–1·22
First ischaemic stroke‡	41	53	0·76	0·51–1·15	0·78	0·50–1·22
First cardiac event‡	25	33	0·77	0·46–1·29	0·81	0·44–1·51

*Years of follow-up until primary outcome event or end of follow-up. †Whichever event occurred first; eight strokes (five in the anticoagulant group and three in the aspirin group) of unspecified origin were included. ‡Post hoc defined outcome events.

***Table 3*: Occurrence of first outcome events according to allocated treatment for the comparison between anticoagulants and aspirin**

Most patients (97%) were enrolled in the three-arm randomisation scheme.

More than two-thirds of patients were men and the mean age was 61 years (table 1). About a third had a transient ischaemic attack, including 5% with transient monocular blindness. CT or MRI of the brain was available for 1017 patients and showed a relevant ischaemic lesion in more than a third. Most patients without a CT or MRI scan had had transient monocular blindness as a qualifying event. In 90% an ultrasound study of the carotid arteries was done, with 10% of these showing a stenosis of more than 50% in one or both arteries. The vascular risk profiles and vascular history were similar in the two treatment groups. Large-vessel disease was diagnosed in 355 (33%) patients, small-vessel disease in 510 (48%), and ischaemia in the posterior fossa in 157 (15%). The type of vessel involved was unspecified in the remaining 46 (4%) patients.

Follow-up was censored before the formal end of the trial in 17 patients allocated anticoagulants and in 24 patients allocated aspirin (figure 1). Another 86 patients were censored before July 1, 2005, because the participating centres in question preferred a maximum follow-up of 5 years.

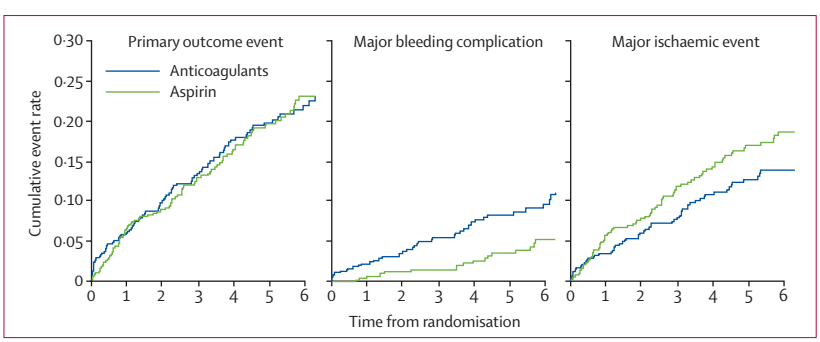

***Figure 3*: Time-to-event curves**

Data about the use of trial medication are summarised in figures 1 and 2 and in tables 1 and 2. A total of 25 030 INR measurements were obtained with a mean INR of 2·57 (SD 0·86). Close to 70% of time spent in the different INR ranges was within the proper intensity range (2·0–3·0). The median dose of aspirin was 30 mg (range 30–325 mg). Of the patients allocated anticoagulants, 198 (37%) discontinued this medication compared with 84 (15%) patients allocated aspirin. Most patients in either group discontinued trial medication because of a medical reason.

During the trial, 197 patients had at least one primary outcome event: 99 (19%) allocated anticoagulants and 98 (18%) allocated aspirin (table 3). In the primary outcome event, eight strokes (five in the anticoagulation group and three in the aspirin group) of unspecified origin were included because of lack of brain imaging within 2 weeks after the stroke. Ischaemic events were less common in the anticoagulant group than in the aspirin group. Major bleeding complications, both intracranial and extracranial, were most common in the anticoagulant group. There was no indication that there were differences with regard to cerebral or cardiac outcome events between the two treatment groups. Figure 3 shows the time-to-event curves for the primary outcome event, for major bleeding complications, and for ischaemic events. In the on-treatment analysis the HR for the primary outcome event was 1·11 (95% CI 0·82–1·50). In the subgroup analysis according to stroke subtype a HR for the primary outcome event of 0·91 (0·61–1·37) and a HR for major bleeding complications of 2·97 (1·33–6·64) was found in patients with small-vessel disease at baseline. The corresponding

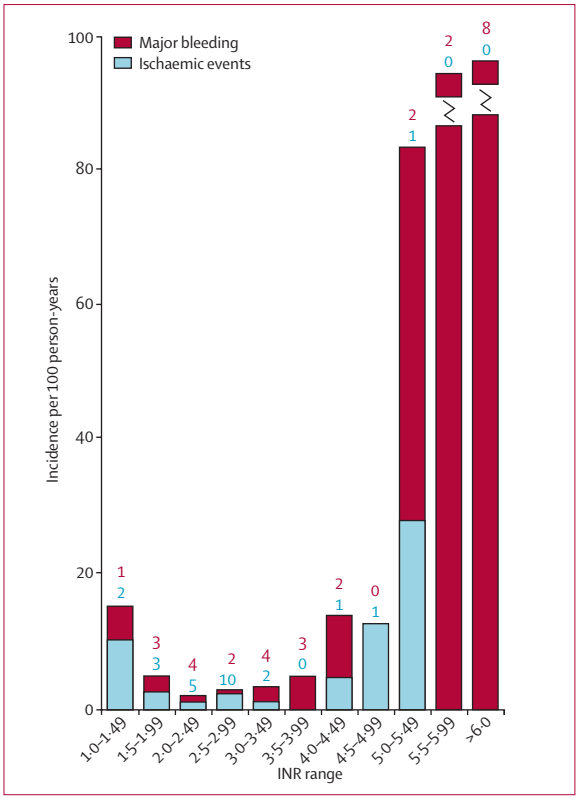

***Figure 4*: INR-specific incidence of major bleeding complications and ischaemic events**
Incidences are an underestimation as there are outcome events for which the INR value was unknown. Numbers are absolute numbers of major bleeding complications (red) and ischaemic events (blue) in the INR range. Incidence in INR range 5·5–5·99=133, incidence in INR range >6=308.

HRs for patients with large-vessel disease at baseline were 1·17 (0·72–1·92) for the primary outcome event and 1·64 (0·60–4·51) for major bleeding complications. The incidence of major bleeding complications in patients on anticoagulants increased with the achieved intensity of anticoagulation (figure 4), whereas there tended to be no clear relation between the intensity of anticoagulation and the incidence of ischaemic events.

Table 4 shows incidences and HRs for the post hoc defined analysis of anticoagulants versus the combination of aspirin and dipyridamole. During this part of the trial 106 of 523 patients allocated anticoagulants (20%) had a primary outcome event, compared with 82 of 509 patients (16%) allocated combination treatment of aspirin and dipyridamole. There were more major bleeding complications in patients allocated anticoagulants than in those allocated aspirin. The baseline table for this comparison as well as the flowchart and the time-to-event curves are incorporated in webfigures 1 and 2 and the webtable.

See **Online** for webfigures 1 and 2 and webtable

Discussion

ESPRIT shows that oral anticoagulation with a target INR of 2·0–3·0 is not more effective than aspirin in the prevention of new serious vascular events in patients after non-disabling cerebral ischaemia of presumed arterial origin. The possible beneficial effect in the prevention of ischaemic events is completely offset by an excess of major bleeding complications.

The excess in major bleeding complications in ESPRIT is less extreme than that observed in SPIRIT in which patients with a transient ischaemic attack or minor ischaemic stroke of presumed arterial origin were randomly assigned high-intensity anticoagulation (target INR 3·0–4·5) or aspirin.[10]

	Intention to treat				On treatment	
	Anticoagulants	Aspirin plus dipyridamole	HR	95% CI	HR	95% CI
Patients randomised	523	509				
Person-years of observation*	2394	2443				
Death from any vascular cause, non-fatal stroke, non-fatal myocardial infarction, or non-fatal major bleeding complication†	106 (20·3%)	82(16·1%)	1·31	0·98–1·75	1·37	0·99–1·89
Death from all causes	67	48	1·39	0·96–2·02	1·03	0·65–1·62
Death from vascular causes	34	24	1·42	0·84–2·40	1·19	0·64–2·20
Death from vascular causes or non-fatal stroke†	78	64	1·21	0·87–1·69	1·18	0·82–1·71
Major bleeding complication	47	11	4·37	2·27–8·43	8·03	3·16–20·37
Extracranial	28	10				
Intracranial	19	1				
Fatal bleeding complication‡	11	2	5·53	1·22–24·9	..	..
All major ischaemic events: death from any ischaemic vascular condition, non-fatal ischaemic stroke, or non-fatal myocardial infarction†	67	70	0·94	0·67–1·31	0·83	0·57–1·21
Death from vascular causes or non-fatal stroke or non-fatal MI†	85	73	1·16	0·85–1·58	1·12	0·79–1·58
First ischaemic stroke‡	45	45	0·98	0·65–1·48	0·90	0·57–1·41
First cardiac event‡	27	25	1·07	0·62–1·85	0·87	0·47–1·61

*Years of follow-up until primary outcome event or end of follow-up. †Whichever event occurred first; six strokes (five in the anticoagulant group and one in the aspirin plus dipyridamole group) of unspecified origin were included. ‡Post hoc defined outcome events.

***Table 4*: Occurrence of first outcome events according to allocated treatment for the comparison between anticoagulants and aspirin plus dipyridamole**

The overall incidence of major bleeding complications with anticoagulants was indeed lower in ESPRIT than in SPIRIT (1·8% per year *vs* 7·2% per year), but was still higher than that found in patients taking aspirin (0·7% per year). The rate of major bleeding complications is similar to that reported in primary prevention trials in patients with non-rheumatic atrial fibrillation[28,29] and in a secondary prevention trial in patients with non-rheumatic atrial fibrillation and ischaemic stroke.[2] Any interpretation of the absolute rate of major bleeding should take into account that all haemorrhages requiring hospital admission were counted as major bleeding; this criterion included not only intracranial haemorrhages but also nose bleeds. But even if non-fatal extracranial bleeding complications were not taken into account in the primary outcome event, the positive trend with regards to a reduction of ischaemic events would be offset by an excess of fatal intracranial haemorrhages. About 85% of the patients randomised into ESPRIT had a CT as their baseline brain scan. In the SPIRIT trial,[12] where we found that leukoaraiosis was a strong risk factor for anticoagulant-related intracranial bleeding, virtually all baseline scans were done with CT. We therefore made CT-based leukoaraoisos an exclusion criterion for ESPRIT and think that we thus excluded most patients with an increased risk of intracranial haemorrhage on the basis of leukoaraiosis. We cannot exclude, however, the possibility that an MRI-based definition of leukoaraiosis could have refined this selection process. The subgroup analysis according to stroke subtype suggested no higher risk for vascular events in patients with small-vessel disease at baseline, although the confidence intervals were wide because of the limited size of the subgroup.

Against the background of other studies, there is no intensity of anticoagulation in which the beneficial effect in preventing ischaemic events exceeds the inevitable haemorrhagic complications. In the Warfarin-Aspirin Recurrent Stroke Study (WARSS)[30] patients were randomly assigned anticoagulants (INR target range 1·4–2·8) or aspirin. No differences in efficacy were shown, with a mean achieved INR of 1·9. The rates of major haemorrhage with this INR target range were similar to those found in ESPRIT and did not differ between treatments: 2·2% per year in the anticoagulant group and 1·5% per year in the aspirin group. In the Warfarin-Aspirin Symptomatic Intracranial Disease Trial (WASID),[31] patients with a transient ischaemic attack or minor stroke caused by angiographically verified 50–99% stenosis of a major intracranial artery were randomly assigned anticoagulants (INR 2·0–3·0) or aspirin (1300 mg daily). WASID was stopped early because of a higher rate of adverse events and no benefit in patients allocated anticoagulants.

The design of ESPRIT may be considered unusual because of the possibility of randomisation in different randomisation schemes. This design, however, has been used before[2] and does not compromise the internal validity of the trial. A theoretical disadvantage of ESPRIT is that treatment allocation was not blinded. However, all members of the auditing committee for outcome events, who classified the outcome events, were completely masked for allocated study treatment. A theoretical disadvantage of the open design is selective reporting of outcome events, but on the other hand all participating physicians were motivated by doubt about the best antithrombotic strategy. A disadvantage of a blinded design with sham anticoagulation is distortion of usual practice; the hassle of anticoagulation titration does not reflect future practice when done for sham purposes. Because ESPRIT, an academic trial, had to compete with other, industry-sponsored, trials, inclusion lasted 8 years, which was longer than anticipated. This long duration provides a ready explanation for the relatively large proportion of patients with incomplete follow-up (4%), but there is no reason to assume that this has in any way biased the results. Unfortunately, we had to exclude 21 patients from one hospital because of severely incomplete data despite several reminders and we had to curtail follow-up for seven patients from four hospitals at the last date that follow-up data of that hospital were complete. However, as randomisation codes were stratified by hospital, both treatment groups were affected in the same way. We regarded the enrolment of 15 patients more than 6 months after their qualifying event as a minor protocol violation and we therefore included these patients in all analyses.

The choice for the primary outcome event, which included both ischaemic and haemorrhagic events, was made to meet the patients' perspective. In our opinion, such an outcome event takes into account both the beneficial and harmful effects of a treatment and hence facilitates interpretation and communication of the study results. For more pathophysiologically oriented interpretations of the data, however, we provided data for ischaemic and haemorrhagic events in isolation.

An issue in ESPRIT might be that there was no fixed dose of aspirin other than that it should be between 30 mg and 325 mg daily. However, a large trial and a meta-analysis in patients with various vascular diseases have shown no difference in efficacy between several doses of aspirin.[9,15] Moreover, our liberal policy for the dose of aspirin is indicative of variation in clinical practice and allows broader generalisation of our findings. Two-thirds of patients were randomised 1–6 months after the event, whereas stroke recurrence is especially high in the first weeks after the event.[32] Because of the inclusion criteria the results of ESPRIT only apply to patients aged 75 years or younger with a non-disabling ischaemic stroke of presumed arterial origin and with no signs of marked leukoaraiosis.

The question whether anticoagulants (INR 2·0–3·0) are more effective than aspirin in the secondary prevention after transient ischaemic attack or minor stroke was no longer clinically relevant because the other arm of the ESPRIT trial showed that the combination of dipyridamole and aspirin was more effective than aspirin alone.[17] Despite the premature ending of the comparison of anticoagulation and aspirin, we feel that some conclusions are warranted.

The HR for ischaemic events found in ESPRIT was 0·73 (95% CI 0·52–1·01). Although ESPRIT was underpowered to detect a possible beneficial effect of oral anticoagulants compared with aspirin in the prevention of ischaemic events, this confidence interval suggests that such an effect is not unlikely. This possible beneficial effect, however, does not outweigh the excess of major bleeding complications in patients treated with anticoagulation. Second, the combination treatment of aspirin and dipyridamole is probably better than anticoagulants and is definitely better than aspirin for secondary prevention after cerebral ischaemia. We therefore prefer combination treatment over anticoagulants or aspirin alone for secondary prevention after a transient ischaemic attack or minor stroke of presumed arterial origin. With the completion of WARSS, WASID, SPIRIT, and ESPRIT, the role of oral anticoagulants in patients with cerebral ischaemia of arterial origin has become clear: there is no indication for that treatment, not even in patients who cannot tolerate dipyridamole since easier, safer, and cheaper treatment with aspirin is equally effective.

Contributors

P H A Halkes analysed and interpreted data and wrote the first draft of the manuscript. A Algra, J van Gijn, and L J Kappelle obtained funding. A Algra, J van Gijn, L J Kappelle, and P J Koudstaal conceived, designed, and supervised the study and contributed to subsequent versions of the manuscript. A Algra analysed and interpreted data. All members of the writing committee approved the final report.

Conflicts of interest

After completion, full analysis, and publication of the first part of ESPRIT, in which the combination treatment of aspirin and dipyridamole was compared with aspirin alone in the secondary prevention after transient ischaemic attack or minor stroke, we accepted financial support from Boehringer Ingelheim for post hoc exploratory analyses of the ESPRIT trial data. These post hoc analyses pertain to the comparison of dipyridamole and aspirin versus aspirin alone; we negotiated complete scientific freedom in the contract. There are no other conflicts of interest.

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