Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial

*The ESPRIT Study Group**

Summary

Background **Results of trials of aspirin and dipyridamole combined versus aspirin alone for the secondary prevention of vascular events after ischaemic stroke of presumed arterial origin are inconsistent. Our aim was to resolve this uncertainty.**

Methods **We did a randomised controlled trial in which we assigned patients to aspirin (30–325 mg daily) with (n=1363) or without (n=1376) dipyridamole (200 mg twice daily) within 6 months of a transient ischaemic attack or minor stroke of presumed arterial origin. Our primary outcome event was the composite of death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction, or major bleeding complication, whichever happened first. 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 **Mean follow-up was 3·5 years (SD 2·0). Median aspirin dose was 75 mg in both treatment groups (range 30–325); extended-release dipyridamole was used by 83% (n=1131) of patients on the combination regimen. Primary outcome events arose in 173 (13%) patients on aspirin and dipyridamole and in 216 (16%) on aspirin alone (hazard ratio 0·80, 95% CI 0·66–0·98; absolute risk reduction 1·0% per year, 95% CI 0·1–1·8). Addition of the ESPRIT data to the meta-analysis of previous trials resulted in an overall risk ratio for the composite of vascular death, stroke, or myocardial infarction of 0·82 (95% CI 0·74–0·91). Patients on aspirin and dipyridamole discontinued trial medication more often than those on aspirin alone (470 *vs* 184), mainly because of headache.**

Interpretation **The ESPRIT results, combined with the results of previous trials, provide sufficient evidence to prefer the combination regimen of aspirin plus dipyridamole over aspirin alone as antithrombotic therapy after cerebral ischaemia of arterial origin.**

Lancet 2006; 367: 1665–73

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Introduction

Patients with a transient ischaemic attack or non-disabling ischaemic stroke of presumed arterial origin have, without secondary preventive treatment, a yearly risk of a major vascular event of 4–16% in clinical trials[1,2] and of 9% in population-based studies.[3] Aspirin 30–300 mg daily prevents only 13–22%[1,2,4] of these vascular complications. Findings of studies[5,6] indicate no additional benefit of the combination of clopidogrel and aspirin compared with either of these drugs alone. The results of the Second European Stroke Prevention Study (ESPS 2)[7–9] show that the addition of modified-release dipyridamole 200 mg twice daily to aspirin 50 mg daily leads to a relative risk reduction of all major vascular events of 22% (95% CI 9–33) compared with aspirin alone. This finding contrasts with those of four earlier but smaller studies of the same treatment comparison, which showed no such benefit. The pooled analysis of data from the four earlier studies shows a relative risk reduction of dipyridamole and aspirin combined compared with aspirin alone of 3% (95% CI –22 to 22),[8,10–13] whereas a meta-analysis that included ESPS 2 resulted in a pooled relative risk reduction of vascular events of 16% (95% CI 3–28).[8] The uncertainty about the secondary preventive value of combined dipyridamole and aspirin is sustained by a Cochrane review,[14] showing that in patients with other types of vascular disease the combination was no more effective than aspirin alone. Because of these conflicting results, the routine use of the combination of dipyridamole and aspirin in the secondary prevention of vascular events after ischaemic stroke of presumed arterial origin is controversial.

Our aim, in the European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT), is to resolve this uncertainty by comparing dipyridamole and aspirin with aspirin alone in patients with a transient ischaemic attack or a minor ischaemic stroke of presumed arterial origin.[15,16]

Methods

Participants

Between July 1, 1997, and Dec 31, 2005, we did a randomised controlled trial. All patients who were referred to one of the participating hospitals within 6 months of a transient ischaemic attack (including transient monocular blindness) or minor ischaemic stroke (grade ≤3 on the modified Rankin scale[17,18]) of presumed arterial origin were eligible for the trial.

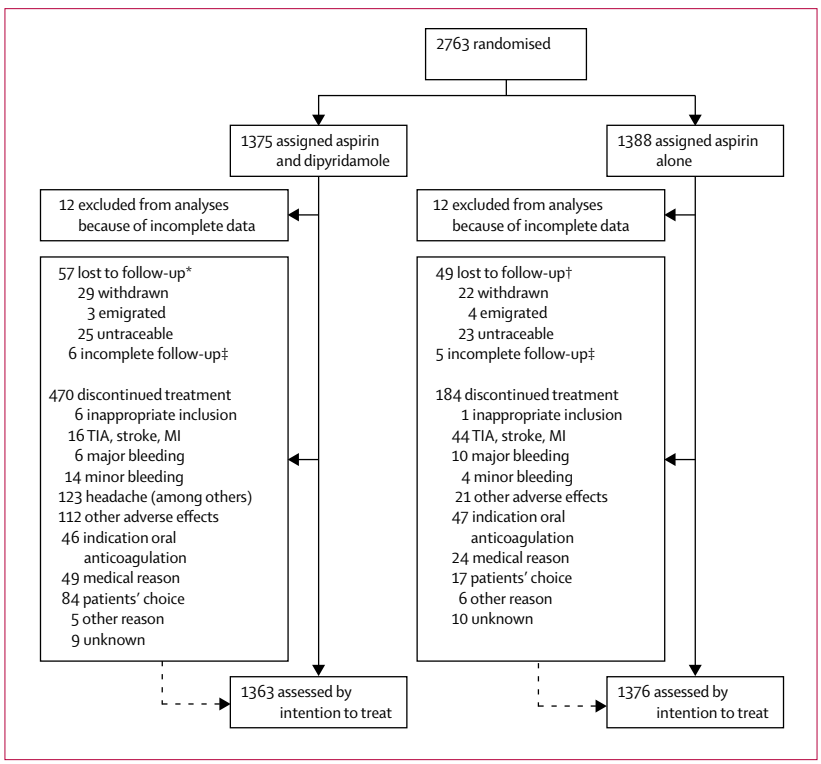

Figure 1: **Trial profile**

TIA=transient ischaemic attack. MI=myocardial infarction. *10 patients lost to follow-up before first follow-up: 7 untraceable, 1 withdrawn consent, 1 inappropriately included, 1 emigrated. †5 patients lost to follow-up before first follow-up: 3 untraceable, 1 withdrawn consent, 1 inappropriately included. ‡Incomplete follow-up because of close-out at date that all follow-up data were complete (four hospitals).

Exclusion criteria were a possible cardiac source of embolism (atrial fibrillation on ECG, 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, any contraindication for aspirin or dipyridamole, and a limited life expectancy.

The institutional medical ethics review boards of the participating hospitals approved the study protocol, and all patients provided written informed consent.

Procedures

We randomised patients between combination therapy of aspirin and dipyridamole and aspirin alone. Dipyridamole was prescribed in a dose of 200 mg twice daily, either as a fixed-dose combination of aspirin and dipyridamole or as a free combination. Dipyridamole was preferably used as an extended-release formulation. If no fixed-dose combination was prescribed, the aspirin dose was left to the discretion of local physicians provided it was between 30 mg and 325 mg per day, as was the case for patients allocated to aspirin alone. In addition to the comparison between the combination therapy and the monotherapy, ESPRIT addressed the efficacy of mild anticoagulation therapy (target international normalised ratio [INR] 2·0–3·0) versus aspirin.[15,16] Here we report only the main results of the comparison of aspirin plus dipyridamole versus aspirin alone.

We randomised patients by means of a telephone call, fax, or email to the central trial office. Our primary aim was to randomise patients in a three-arm randomisation scheme (anticoagulation therapy *vs* aspirin+dipyridamole *vs* aspirin), but a two-arm randomisation scheme (aspirin+dipyridamole *vs* aspirin) was permitted if there was a contraindication for anticoagulation therapy (age >75 years or leukoaraiosis on a brain scan), if a patient refused to participate because he or she did not want to use anticoagulation therapy, if the physician did not feel comfortable with prescribing anticoagulation therapy, or if regular assessment of INR values was impossible. Treatment allocation was by means of computer-generated randomisation codes stratified by hospital before the start of the trial. The randomisation codes and randomisation programme were generated by a clinical epidemiologist at the Academic Medical Center of the University of Amsterdam who was not otherwise involved in the trial. ESPRIT had an open, non-blinded study design to assess real-life treatment strategies.[19]

We obtained 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] antithrombotic drug use at the time of event, blood pressure, vascular risk factors, and vascular history. A CT or MR scan of the brain was mandatory in all patients except for those with transient monocular blindness. Three members of the scan committee reviewed and classified all scans at the central trial office. ECG was required, duplex scanning of the carotid arteries was optional. All baseline data were collected and checked at the central trial office and entered in a database. On the basis of CT or MR scan and clinical features, we classified patients as having large or small vessel disease. If a relevant ischaemic lesion was detected with imaging, classification was based on the characteristics of this lesion. If no lesion was detected, we used clinical symptoms for classification as in previous studies.[20,21] We classified patients with transient monocular blindness as having large vessel disease,[22] and patients with ischaemia in the posterior fossa (either on imaging or clinically) and patients with a large deep subcortical infarct as having unspecified vessel disease.

We asked all patients to return every 6 months for a consultation with their randomising physician or a trained trial nurse. If this was not possible, follow-up information was obtained by telephone contact with the patient or caregiver or from the family doctor. At each contact, the occurrence of possible outcome events, hospital admissions, and adverse events was recorded as well as current handicap (modified Rankin scale) and changes in trial medication. We gave centres the option to end further follow-up in patients who had completed

5 years in the trial. All remaining patients had a close-out visit between July 1, 2005, and Dec 31, 2005.

Our primary outcome event was the composite of death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction, or major bleeding complication, whichever happened first. Secondary outcome events included death from all causes, death from all vascular causes, death from all vascular causes and non-fatal stroke, all major ischaemic events (non-haemorrhagic death from vascular causes, non-fatal ischaemic stroke, or non-fatal myocardial infarction), all vascular events (death from vascular causes, non-fatal stroke, or non-fatal myocardial infarction), and major bleeding complications.

Outcome events defined post hoc were fatal and non-fatal ischaemic stroke and all cardiac events (fatal and non-fatal myocardial infarction, sudden death, and death from cardiac causes). 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, we classified the reason as vascular other, according to a-priori probabilities.[23] When a patient had a disabling stroke (modified Rankin scale >3) and died during follow-up, we classified the cause of death (stroke or the subsequent complication) as stroke, regardless of the interval between stroke and death, unless an unrelated other cause of death had been reported. In deceased patients who were still independent, at least in part, before their death, we attributed the cause of death to stroke only if the interval was less than 1 month.[24] Non-fatal ischaemic stroke was diagnosed in the case of sudden onset of a new or increasing neurological deficit that persisted 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 MR scan of the brain made within 2 weeks of the event. We used the same clinical criteria for the diagnosis of haemorrhagic stroke if a corresponding intracerebral haemorrhage was detected on CT or MR scan of the brain. If no brain imaging was done and clinical evidence of stroke was present, we classified the event as stroke, unspecified. We counted subdural and epidural haematomas as intracranial haemorrhages, but not as strokes, whereas we counted subarachnoid and intracerebral haemorrhages in both categories. The outcome event of myocardial infarction required at least two of the following characteristics: a history of chest discomfort for at least half an hour, level of specific cardiac enzymes more than twice the upper limit of normal, or the development of specific abnormalities (eg, Q waves) on the standard 12-lead ECG. The outcome event of major bleeding complication included all intracranial bleeding, any fatal bleeding, or any bleeding requiring hospital admission.

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; they 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 instances, a fourth member of the

	Aspirin+dipyridamole (n=1363)	Aspirin alone (n=1376)
Randomisation scheme		
Three arm	509 (37%)	516 (38%)
Two arm	854 (63%)	860 (63%)
Demographics		
Male	897 (66%)	892 (65%)
Age (years) (mean, SD)	63 (11)	63 (11)
Qualifying event		
Transient monocular blindness	62 (5%)	79 (6%)
Transient ischaemic attack	403 (30%)	376 (27%)
Minor ischaemic stroke	895 (66%)	921 (67%)
Time from longest event to randomisation		
<1 week	149 (11%)	151 (11%)
1 week to 1 month	303 (23%)	274 (20%)
1–6 months	890 (66%)	931 (69%)
Rankin grade		
0=no symptoms	588 (43%)	574 (42%)
1=minor symptoms; no limitations	450 (33%)	468 (34%)
2=some restrictions; no help needed	243 (18%)	249 (18%)
3=help needed; still independent	77 (6%)	84 (6%)
Additional investigations		
CT or MR scan of the brain*	1304 (96%)	1308 (95%)
Any infarct	623 (48%)	601 (46%)
Any relevant infarct	471 (36%)	446 (34%)
Ultrasound carotid arteries	1227 (90%)	1252 (91%)
Stenosis >50%	134 (11%)	112 (9%)
History		
Stroke	159 (12%)	155 (11%)
Angina pectoris	132 (10%)	130 (9%)
Myocardial infarction	91 (7%)	93 (7%)
Intermittent claudication	75 (6%)	53 (4%)
Vascular intervention	80 (6%)	79 (6%)
Diabetes mellitus	260 (19%)	252 (18%)
Hypertension	814 (60%)	817 (59%)
Hyperlipidaemia	634 (47%)	638 (46%)
Current cigarette smoking	484 (36%)	512 (37%)
Blood pressure (mm Hg)		
Systolic (mean, SD)	152 (24)	152 (23)
Diastolic (mean, SD)	86 (12)	86 (12)
Type of vessel involved		
Large vessel	405 (30%)	430 (31%)
Small vessel	687 (50%)	690 (50%)
Unspecified	271 (20%)	256 (19%)

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Antithrombotic drug use at time of event		
Aspirin	319 (23%)	309 (22%)
Oral anticoagulants	6 (<1%)	0
Other	16 (1%)	14 (1%)
None	1022 (75%)	1053 (77%)
Dose of aspirin		
30 mg	576 (42%)	635 (46%)
40 mg	2 (<1%)	1 (<1%)
50 mg	109 (8%)	2 (<1%)
75 mg	209 (15%)	206 (15%)
80 mg	61 (4%)	95 (7%)
100 mg	316 (23%)	340 (25%)
150 mg	26 (2%)	26 (2%)
160 mg	1 (<1%)	3 (<1%)
250 mg	2 (<1%)	2 (<1%)
300 mg	56 (4%)	62 (5%)
325 mg	5 (<1%)	4 (<1%)

Data are number (%) unless otherwise indicated. *Not required in patients with transient monocular blindness.

Table 1: **Baseline characteristics and dose of trial medication**

auditing committee was consulted before the executive committee decided.

Statistical analysis

Assuming a relative risk reduction of 20–25% for the combination of aspirin and dipyridamole by comparison with aspirin alone, we calculated that about 3000 patients should be followed up for a mean 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.[15]

During the trial, none of the investigators had any knowledge of event rates or complication rates according to treatment allocation. An independent data monitoring committee undertook five interim analyses, at intervals of 1500 patient-years of follow-up. This committee recommended continuation of the trial at each of these stages. A symmetrical stopping rule was used, according to O'Brien and Fleming.[25]

	Number on medication (%)/at risk	
	Aspirin+dipyridamole (n=1363)	Aspirin alone (n=1376)
At baseline	1334 (99%)/1353	1368 (100%)/1371
At 6 months	1059 (81%)/1307	1302 (97%)/1345
At 1 year	915 (77%)/1192	1153 (95%)/1220
At 1·5 years	780 (74%)/1053	1015 (93%)/1086
At 2 years	688 (73%)/938	875 (92%)/955
At 3 years	545 (71%)/767	688 (89%)/777
At 4 years	400 (69%)/581	504 (86%)/584
At 5 years	243 (66%)/366	318 (84%)/377

Table 2: **Treatment use over time**

We compared the occurrence of outcome events in the two groups in terms of the hazard ratio (HR), which can be interpreted as a relative risk since it is the average ratio of instantaneous risks (hazards) over time. We obtained HRs by means of the Cox proportional hazard model. The precision of the HR estimates is described with 95% CI obtained from the Cox model. We based analyses on the intention-to-treat principle. We also did an analysis of patients who used treatment (on-treatment analysis), in which we included only the outcome events that arose while study treatment was being taken or before the 28th day after the discontinuation of treatment. We included patients who were inappropriately enrolled in the trial in the intention-to-treat analysis, but excluded them from the on-treatment analysis.

We planned the following subgroup analyses in advance: randomisation scheme (three arm *vs* two arm), age (≤65 years *vs* >65 years), sex, history of ischaemic heart disease (previous myocardial infarction or history of angina pectoris *vs* no history of ischaemic heart disease), type of cerebral ischaemia (large vessel disease *vs* small vessel disease), and country (non-Asian *vs* Asian). Subgroup analyses devised post hoc were: dose of aspirin (<40 mg *vs* 40–100 mg *vs* >100 mg), preparation of dipyridamole (extended *vs* non-extended release), and interval between event and randomisation (<1 week *vs* 1 week to 1 month *vs* >1 month). We also planned to update our previous meta-analysis[8] of the comparison between aspirin plus dipyridamole versus aspirin alone with the new results.

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 (n=24) 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 (n=11), follow-up was closed at the time all data were complete. We used SPSS 12 for Windows for all analyses.

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.

Results

Figure 1 shows the trial profile. We randomly assigned and analysed 2739 patients; 1363 allocated to aspirin and dipyridamole and 1376 allocated to aspirin alone. Patients originated from 79 hospitals in 14 countries. Mean length

	Intention to treat			On treatment
	Aspirin+dipyridamole (n=1363)	Aspirin alone (n=1376)	HR (95% CI)	HR (95% CI)
Person-years of observation*	4498	4495		
Death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction, non-fatal major bleeding complication†	173	216	0·80 (0·66–0·98)	0·82 (0·66–1·02)
Death from all causes	93	107	0·88 (0·67–1·17)	0·98 (0·72–1·35)
Death from all vascular causes	44	60	0·75 (0·51–1·10)	0·86 (0·55–1·34)
Death from all vascular causes, non-fatal stroke†	132	171	0·78 (0·62–0·97)	0·83 (0·65–1·06)
Major bleeding complication	35	53	0·67 (0·44–1·03)	0·58 (0·35–0·97)
Non-fatal extracranial	21	32		
Fatal extracranial	2	0		
Non-fatal intracranial	9	17		
Fatal intracranial	3	4		
All major ischaemic events: non-haemorrhagic death from vascular causes, non-fatal ischaemic stroke, non-fatal myocardial infarction†	140	174	0·81 (0·65–1·01)	0·88 (0·69–1·12)
Death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction†	149	192	0·78 (0·63–0·97)	0·82 (0·65–1·04)
First ischaemic stroke	96	116	0·84 (0·64–1·10)	0·91 (0·68–1·22)
First cardiac event	43	60	0·73 (0·49–1·08)	0·87 (0·56–1·37)

*Years of follow-up until primary outcome event or end of follow-up. †Whichever event occurred first.

Table 3: **Occurrence of first outcome events, according to treatment**

of follow-up was 3·5 years (SD 2·0). In retrospect, we inappropriately enrolled 12 patients, of whom four were allocated to aspirin monotherapy; two had a brain tumour, one motor neuron disease, one multiple sclerosis, one syphilis, one peripheral nerve injury, one AIDS, and five patients were scheduled for carotid endarterectomy when entering the trial. Another 39 patients were enrolled more than 6 months after their last ischaemic cerebrovascular event (the majority within 9 months); we included these 39 patients in all analyses. 1025 patients (37%) were randomised in the three-arm scheme and 1714 patients (63%) in the two-arm scheme. Table 1 shows the baseline characteristics of the patients. About two-thirds of patients were men, the mean age was 63 years, and 450 (16%) patients were at least 75 years old. About one-third had had a transient ischaemic attack, including 5% with transient monocular blindness. CT or MR scan of the brain was available in 2612 patients; it showed a relevant ischaemic lesion in more than a third. In 90% of patients, ultrasound of the carotid arteries was undertaken, 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 835 (30%) patients and small vessel disease in 1377 (50%). In 527 patients (19%) the type of vessel involved was unspecified. Follow-up was incomplete in 117 (4%) patients (figure 1). These patients were censored at the time of the last follow-up. 93 patients (3%) who completed 5 years of follow-up were censored before July 1, 2005, because their randomising centres preferred a maximum follow-up of 5 years.

Data about the use of trial medication are summarised in figure 1 and tables 1 and 2. The distribution of prescribed doses of aspirin was similar in both groups (p=0·39 Mann-Whitney U test); the median dose was 75 mg (range 30–325). Of patients allocated to dipyridamole and aspirin, 1131 (83%) used extended-release dipyridamole. During the trial, 470 (34%) patients allocated the combination discontinued their trial medication, mainly because of adverse effects. 26% (n=123) of patients who discontinued the combination regimen reported headache as at least one of the reasons. Of patients allocated to aspirin alone, 184 (13%) discontinued their medication, mainly because of a medical reason, such as a new transient ischaemic attack or stroke or an indication for oral anticoagulant therapy.

During the trial, 389 patients had at least one primary outcome event: 173 assigned to combination therapy (13%) versus 216 assigned to monotherapy (16%; table 3). The absolute risk reduction of 1·0% per year (95% CI 0·1–1·8) corresponds with a number of patients needed

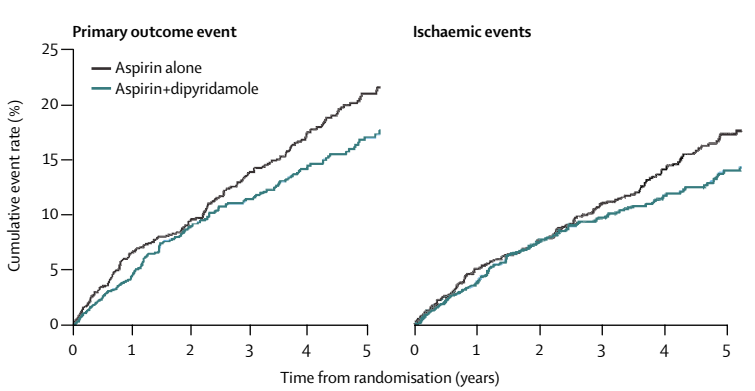

Figure 2: **Time-to-event curves for primary outcome event and all ischaemic events**

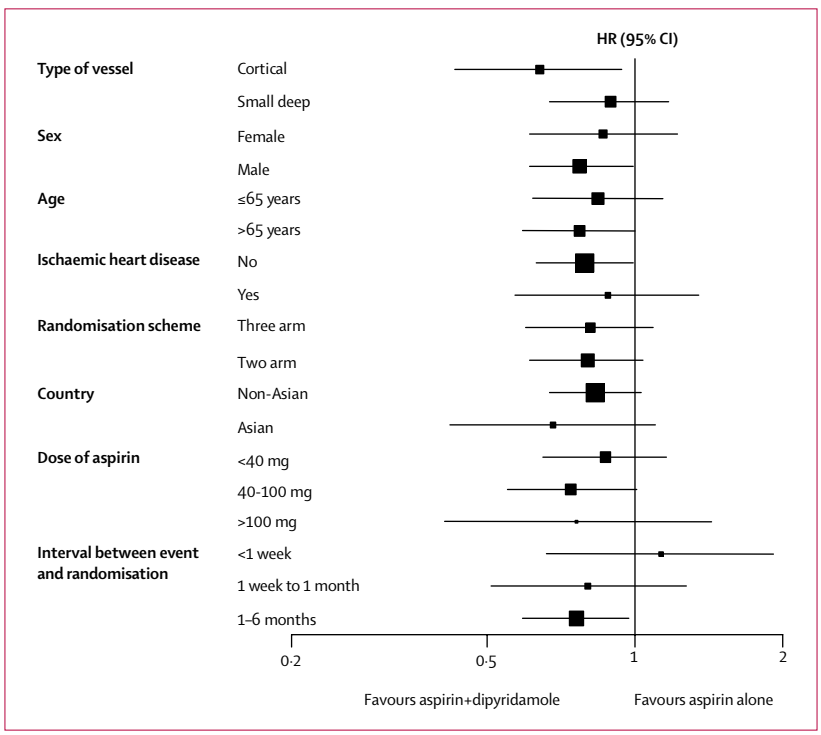

Figure 3: **Subgroup analyses for primary outcome event**

to treat with the combination regimen instead of with monotherapy to prevent death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction, or major bleeding complication of 104 (95% CI 55–1006) per year.

Ischaemic events were less frequent in the combination group than in the monotherapy group. The HR for death from all causes was 0·88 (table 3). There was no indication that there were differential effects according to cerebral or cardiac outcome event. Major bleeding complications arose in 35 patients allocated to aspirin and dipyridamole versus 53 patients allocated to aspirin alone, whereas minor bleeding was reported in 171 patients allocated to the combination regimen versus 168 patients allocated to aspirin (risk ratio 1·03; 95% CI 0·84–1·25). Figure 2 shows the time-to-event curves for the primary outcome event and for ischaemic events. In the on-treatment analysis, the HR for the primary outcome event was 0·82 (table 3).

Figure 3 shows the results of the planned and post hoc defined subgroup analyses for the primary outcome event; we noted no major differences between subgroups (smallest p value for interaction 0·18). Because all patients from non-Asian countries (with the exception of three patients from hospitals in Portugal, where extended release dipyridamole is not available) used slow-release dipyridamole, we did no additional analysis for this type of preparation.

Figure 4 shows an update of our previous meta-analysis in patients with cerebral ischaemia of presumed arterial origin for the composite outcome of vascular death, non-fatal stroke, or non-fatal myocardial infarction. The meta-analysis is now based on the data of six trials, including 3888 patients allocated to aspirin and dipyridamole and 3907 to aspirin alone; the total number of outcome events is 1158. The corresponding overall risk ratio is 0·82 (95% CI 0·74–0·91).

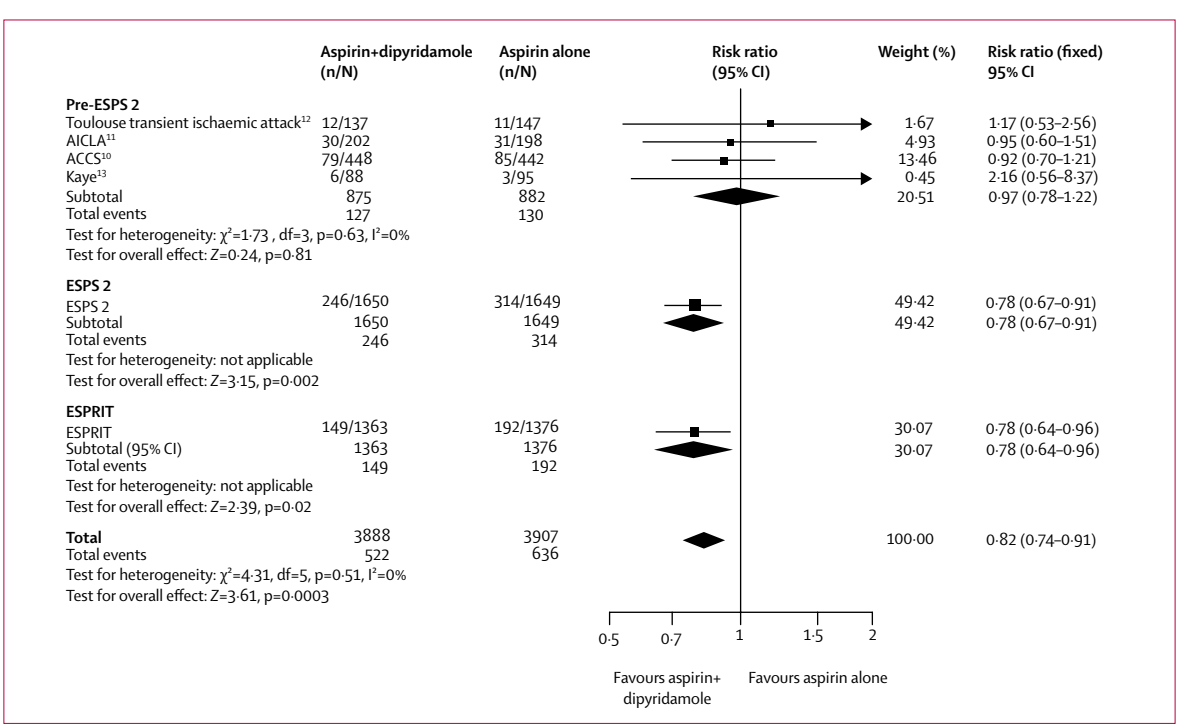

Figure 4: **Meta-analysis**

Discussion

Our findings show that the combination therapy of aspirin and dipyridamole is more effective than aspirin alone in the prevention of new serious vascular events in patients after non-disabling cerebral ischaemia of presumed arterial origin. These results are consistent with those of ESPS 2,[8] which also showed a benefit of the combination therapy over aspirin alone with respect to the occurrence of all vascular events.[8] Although four earlier, but smaller studies did not show such a benefit, the combined results of ESPS 2 and ESPRIT are consistent and provide robust evidence for the larger efficacy of the combination therapy (figure 4).

The smaller trials used an immediate-release formulation of dipyridamole, which is not as readily bioavailable as the extended-release formulation used in ESPS 2 and by most patients in ESPRIT.[26] The main difference between the treatment strategies in ESPS 2 and ESPRIT was that in the former trial all patients used the fixed-dose combination of aspirin and dipyridamole, with 25 mg aspirin twice daily in both treatment groups, whereas in our trial a maximum of 8% of patients allocated to the two drugs used this combination and most patients did not use 50 mg aspirin. Another difference between the trials was that, in ESPRIT, 83% of patients allocated to the combination regimen used extended-release dipyridamole, compared with all patients in the relevant group of ESPS 2. There were no differences, however, in the subgroup analyses, according to dose of aspirin or preparation of dipyridamole used. Since the results of both trials are similar, we believe both treatment strategies (fixed-dose combination and aspirin and dipyridamole prescribed separately) are equally effective.

A theoretical disadvantage of our trial is that treatment was not blinded. However, all members of the auditing committee for outcome events, who classified the outcome events, were unaware of allocated study treatment. Notification of potential outcome events might have been affected by treatment allocation, but we consider this bias unlikely since we recorded only major clinical outcome events (which are unlikely to go unnoticed). Another possible issue in ESPRIT—an academic trial—is that the patients were included for 8 years, which is much longer than the timespan of most industry-sponsored trials. The length of the study probably explains the relatively large proportion of patients with incomplete follow-up, but there is no reason to assume that this long duration has in any way biased the results. Another issue might be that there were no firm restrictions as to the dose of aspirin prescribed; any dose between 30 mg and 325 mg daily was allowed. However, since the dose of aspirin was similarly distributed in both treatment groups and since there were no major differences in the subgroup analysis according to dose, this factor can be discounted. Moreover, our liberal policy with respect to the dose of aspirin is an indication of variation in clinical practice, and allows broader generalisability of our findings. A fourth issue is the lower than anticipated rate of primary outcome events among patients treated with aspirin (4·8% per year observed *vs* 6·0% per year expected). Increased knowledge and changes in clinical practice regarding secondary prevention in patients after transient ischaemic attack or minor stroke could explain this finding—many patients received anti-hypertensive agents and statins apart from the trial medication. Because the total number of patient-years of observation (9722) was larger than planned (9000), the power of the trial was hardly compromised by the lower event rate. A fifth issue of ESPRIT is that we had to exclude 24 patients from one hospital because of incomplete data despite numerous reminders, and that we had to close follow-up for 11 patients from four hospitals at the last date that follow-up data of that hospital were complete. Since randomisation codes were stratified by hospital, however, both treatment groups will have been affected in the same way. Two-thirds of the patients were randomised 1–6 months after the event, whereas stroke recurrence is especially high in the first weeks after the event.[27] Finally, results of studies[28] indicate that the classification of large and small vessel disease based on clinical features is not the best method, since about 10–20% of strokes that are classified as lacunar on the basis of clinical features actually represent a cortical infarct and vice versa. Ideally, classification is based on diffusion weighted MR, which was unfortunately not routinely available for our patients.

An important concern with the combination of aspirin and dipyridamole is that a large number of patients discontinued treatment because of side-effects, mainly headache. A similar proportion of patients in ESPS 2 discontinued treatment because of side-effects.[7] In clinical practice, a titration scheme of dipyridamole at initiation could be used to try to resolve the problem of drug-induced headache.[29] This strategy, however, needs further study.

There are two surprising findings in ESPRIT. First, the overall benefit of the combination therapy was not larger in the on-treatment analysis than in the intention-to-treat analysis. This concurrence might be a chance finding; it cannot be explained by a difference in vascular risk profile between patients who continued to use trial medication and patients who did not, or by a difference in preventive medication after discontinuation of the trial medication. Second, patients allocated to aspirin and dipyridamole had fewer major bleeding complications than patients allocated to aspirin alone, though this finding was not significant. This difference cannot be explained by the prescribed dose of aspirin, which was similar in both treatment groups. Moreover, an equal rate of minor bleeding complications was reported in both groups. Since few major bleeding complications were reported in either group, and since the results of ESPS 2 show no difference in frequency of severe or fatal bleeding complications between the two groups,[9] we think this finding is probably a chance effect.

With our simple, pragmatic study design that had few exclusion criteria, we feel that a large proportion of patients with transient ischaemic attack or non-disabling stroke was probably eligible. On the basis of this reasoning, we

believe that the generalisability of our findings is equally broad. Contrary to the MATCH study,[6] vascular risk factors in ESPRIT patients were similar in most aspects to those of patients from one of the largest population-based studies on strokes, the OXVASC study.[30] Although our patients were slightly younger than those in the OXVASC study, we think they can be considered representative of all patients with transient or minor disabling cerebral ischaemia of arterial origin.The results of ESPRIT, combined with the results of previous trials in the new meta-analysis, provide sufficient evidence to prefer the combination therapy of aspirin and dipyridamole over aspirin monotherapy as antithrombotic therapy after cerebral ischaemia of arterial origin.

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P H A Halkes analysed and interpreted data and wrote the first draft of the paper. 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.

Conflict of interest statement
We declare that we have no conflict of interest.

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Acknowledgments
We thank Prof C P Warlow for his valuable comments on the manuscript, C L Franke for supervising the auditing process of outcome events, J G van der Bom for preparing the yearly reports for the data monitoring committee, and Prof C P L H Chen, E L L M De Schryver, Prof D Leys, Y M Ruigrok, and G S Venables and for help in obtaining funding for ESPRIT. This study was sponsored by: the Council of Singapore (NMRC/0702/2002, NMRC/0936/2005); European Commission (QLK6-CT-2002-02332); Janivo Foundation, Netherlands; The French Ministry of Health (Grant PHRC/1998); AEGON N V, Netherlands, The Netherlands Heart Foundation (grant 97.026); Thrombosis Foundation, Netherlands (grant 2002.1); UK Stroke Association (grant 24/96); University Medical Center Utrecht, Netherlands.

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