ESPRIT
(European/Australasian Stroke Prevention in Reversible Ischaemia Trial)
and related studies

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ESPRIT
(European/Australasian Stroke Prevention in Reversible Ischaemia Trial)
en gerelateerde onderzoeken.
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. J.C. Stoof, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op dinsdag 30 september 2008 des middags te 4.15 uur

door

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geboren op 25 Maart 1976 te Nijmegen

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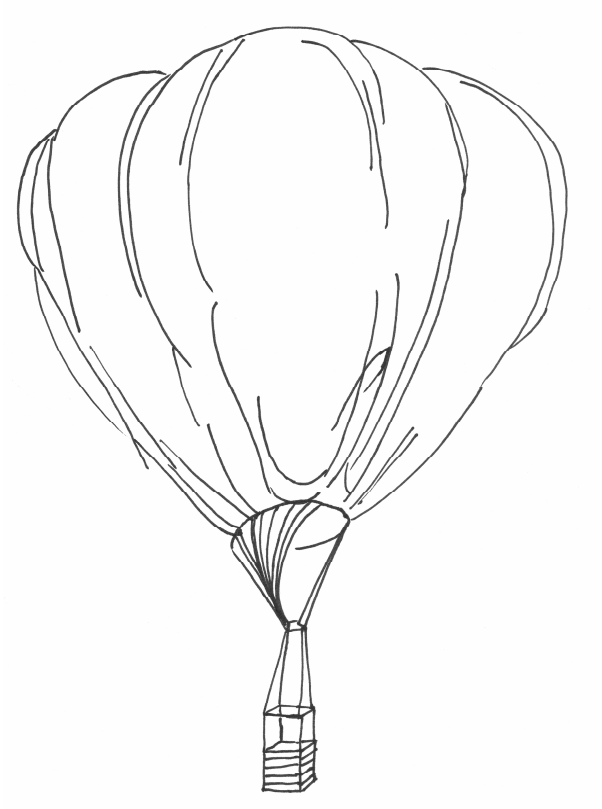
Chapter 1

General introduction



In the developed countries stroke is the third leading cause of death, after coronary heart disease and cancer. Among adults in the age between 45 and 69 years, heart disease and stroke are the leading causes of disease burden, as measured in disability-adjusted life years.[1] The World Health Organization estimates that there were, worldwide, 16 million first-ever strokes and 5.7 million stroke deaths in 2005. These numbers are expected to rise to 18 million and 6.5 million, respectively, in 2015.[1]

Ischaemic strokes

The vast majority of strokes is ischaemic, i.e. caused by an occluded instead of a ruptured vessel.[2] These ischaemic strokes can be classified in several ways. First, the duration of the neurological deficit can be used as the basis; if the symptoms last for less than 24 hours, the event is considered a transient ischaemic attack (TIA), in contrast to an ischaemic stroke in which the neurological deficit lasts longer than 24 hours. Second, ischaemic strokes can be classified according to cause. A simple division is made between strokes caused by cardiac disease and stroke of non cardioembolic, i.e. arterial, origin. A more detailed classification is based on the TOAST criteria, resulting in five subtypes of stroke: large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined origin or stroke of undetermined etiology.[3]
A third way to classify strokes is on basis of the size and location of the ischaemic lesion detected on imaging: lacunar versus cortical, assumed to be caused by small versus large vessel disease. In **chapter 2** we studied a third, intermediate, type, the large subcortical infarcts, and compared them with cortical and lacunar ones.

Secondary prevention

The overall incidence of first ever ischaemic stroke in a large population based study in England (the Oxford Vascular Study) was 1.42/1000/year.[4] Stroke is merely a disease of the elderly; the estimated lifetime risk of a healthy 55 year-old woman to suffer an ischaemic stroke is 18%, the corresponding risk for a man is 14%.[5]
After a TIA or minor ischaemic stroke patients are at risk for further vascular events; in the absence of secondary preventive measures the estimated annual risk of a major vascular event is 9% in population based studies.[6] This is probably an underestimation, because it is based on older series in which patients were not seen until some time after a TIA or minor ischaemic stroke,[2] whereas the risk is highest in the early phase after the event.[7] An important goal in treatment after a TIA or minor ischaemic stroke is to prevent further, possibly more serious or disabling, events, the so called secondary prevention.

A way to reduce the risk of serious vascular events after cerebral ischaemia is the use of antithrombotic medication. Aspirin, or acetylsalicylic acid, was first produced in its present form at the end of the 19th century as a pain killer. Bayer, the company that registered the trade mark aspirin, stated in one of the first aspirin advertisements that ‘the drug did not affect the heart’. It was not until the

1970s, however, that aspirin, which also inhibits platelet aggregation, was recognized as preventing heart attacks and strokes. Now we know that aspirin 30-300 mg daily prevents a substantial amount of the vascular complications after a TIA or stroke of arterial origin, with a relative risk reduction of 13-22%.[8-10]
A few decennia ago a new drug, dipyridamole, was released and registered as platelet aggregation inhibitor. Its usefulness in the secondary prevention after cerebral ischaemia, however, has been subject to debate. Four small trials performed in the 1980s did not show a benefit for the combination of aspirin plus dipyridamole compared with aspirin alone.[11-14] Pooled analysis of these trials showed a relative risk reduction of 3% (95% confidence interval (CI) -22 – 22).[15]
In 1996, the results of the Second European Stroke Prevention Study (ESPS 2) were published.[16] In this large trial the combination therapy of aspirin and dipyridamole was found more effective than aspirin alone in the prevention of vascular events after a TIA or minor stroke of arterial origin with a relative risk of 0.78 (95% CI 0.67-0.91). Because of these conflicting results, in combination with a Cochrane review showing that the combination was not more effective than aspirin alone in patients with other types of vascular diseases,[17] dipyridamole was not implemented in the routine care for patients after cerebral ischaemia of arterial origin.
In 1993 it was found that vitamin K antagonists (oral anticoagulants) with an aimed international normalized ratio (INR) between 2.5 and 4.0 reduce the risk of a serious vascular event after a TIA or stroke caused by atrial fibrillation with 47% (95% CI 24-64).[18] After this finding, it seemed a logical and relevant question to determine whether oral anticoagulants would be of the same benefit in patients after a TIA or minor stroke of arterial origin. This question was addressed in the Stroke Prevention in Reversible Ischaemia Trial (SPIRIT), where patients with cerebral ischaemia of arterial origin were randomized between anticoagulants (aimed INR 3.0-4.5) and aspirin 30 mg daily.[19] The trial was terminated at the first interim analysis as there appeared to be more major bleeding complications in patients who were allocated to oral anticoagulants. The question whether anticoagulants are more effective than aspirin in the secondary prevention after non cardioembolic stroke, however, was not completely answered by this trial. An observational study of 356 patients, who were routinely treated with anticoagulants after cerebral ischaemia of arterial origin, showed that the optimal intensity for these patients was an INR between 2.5 and 3.5.[20] The intensity used in SPIRIT was probably too high.

The above mentioned findings were the reason to initiate the European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT).[21,22] In this international, randomized controlled trial that included patients after a TIA or minor ischaemic stroke of arterial origin, three treatment strategies were compared: a combination therapy of aspirin plus dipyridamole, medium intensity oral anticoagulants and aspirin alone. The majority of the studies described in this thesis are based on the ESPRIT trial.

During ESPRIT all possible outcome events were reported to the central trial office, where a clinical report of the event was made by the trial coordinator. This report was subsequently sent to three members of the auditing committee for outcome events who independently classified the event. It struck us that they often disagreed on the classification of the cause of death in patients who previously had experienced a stroke, other than the qualifying event. In **chapter 3** we report on our consultation of stroke experts from all over the world to determine whether this is a common problem and to formulate a practical guideline for the auditing of death after stroke in clinical research.

The main results of the first part of ESPRIT, the comparison between the combination therapy of aspirin plus dipyridamole versus aspirin alone in the secondary prevention after stroke, are described in **chapter 4**. The second part of ESPRIT, the comparison between mild intensity oral anticoagulation and aspirin, was ended, before the planned number of patient-years had been reached, after publication of the results of the first part. **Chapter 5** describes the results of the second part.

After the completion of ESPRIT we pooled our data with the data from other published trials on the combination of aspirin plus dipyridamole versus aspirin in the secondary prevention after TIA or ischaemic stroke of arterial origin.[11-13,16] The subsequent meta-analysis, based on individual patient data, is presented in **chapter 6**. Thanks to the availability of extensive data sets we were also able to study the efficacy of aspirin plus dipyridamole and aspirin alone in different risk groups.

An important finding in ESPRIT was that many patients discontinue to use dipyridamole because of side effects, mainly headache. In an exploratory analysis in **chapter 7** we tried to identify risk factors for the discontinuation of dipyridamole because of non medical reasons, especially headache.

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Chapter 2

Large subcortical infarcts – Clinical features, risk factors and long-term prognosis compared with cortical and small deep infarcts

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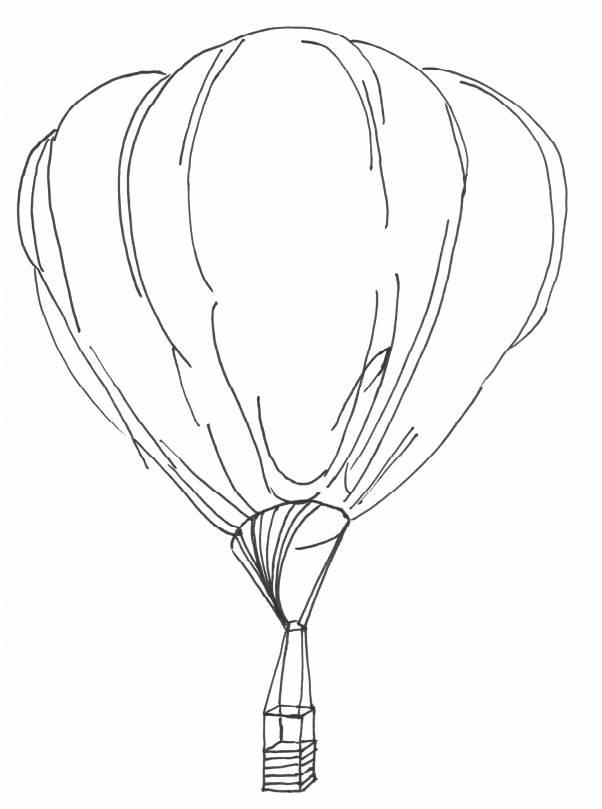

Abstract
Background and Purpose- In this study we compared risk factors, clinical features, and stroke recurrence in a large series of patients with large subcortical, cortical, or small deep infarcts.
Methods- Patients with a transient or minor ischemic attack (modified Rankin Scale grade of ≤ 3) who had a single relevant supratentorial infarct of presumed noncardioembolic origin on CT were classified as suffering from a large subcortical (n=120), small deep (n=324), or cortical (n=211) infarct. Mean follow-up was 8 years. Rates of recurrent stroke were compared with Cox regression.
Results- The clinical deficits caused by large subcortical infarcts resembled either those of a cortical or those of a small deep infarct. Risk factor profiles were similar in the 3 groups. The rate of recurrent stroke in patients with a large subcortical infarct (25/120; 21%) did not differ from that of patients with a cortical infarct (46/211; 22%) or with a small deep infarct (60/324; 19%). After adjustment for age, sex, and vascular risk factors, hazard ratios for recurrent stroke of large subcortical and cortical infarcts were 1.05 (95% CI, 0.65 to 1.70) and 1.17 (95% CI, 0.79 to 1.73), respectively, compared with small deep infarcts.
Conclusions- Clinical features, risk factor profiles, and stroke recurrence rate in patients with a large subcortical infarct only differ slightly from those in patients with small deep or cortical infarcts.

Introduction

Ischemic strokes are often categorized into small-vessel lesions and large-vessel lesions.[1,2] This distinction can usually be made by means of the clinical features[3,4] and more reliably by CT or MRI scanning. A third type of infarction is the large subcortical infarct, also termed *giant lacune*. They are located in the carotid territory, like most symptomatic small deep infarcts, but are larger and supposedly not caused by small-vessel disease.[5–8] Clinical features, risk factors, and long-term outcome of these infarcts have been studied in small series,[6–12] but without comparison with other types of infarction. In the present study we evaluated clinical features, risk factors, overall outcome, and type of recurrent infarction in a large series of patients with recent cerebral ischemia of presumed arterial origin who participated in a large clinical trial. We compared these characteristics with those of patients with a small deep infarct or with a cortical infarct.

Subjects and Methods

Patients participated in the Dutch TIA Trial, a multicenter trial performed in the Netherlands from 1986 to 1990.[13,14] In this randomized, double-blind, controlled trial, the preventive effects of 30 and 283 mg acetylsalicylic acid per day were compared in patients with a transient ischemic attack (TIA) or minor stroke (modified Rankin Scale score of ≤3). In addition, in eligible patients the effects of 50 mg of atenolol versus placebo were tested. A total of 3150 patients from 63 different hospitals were enrolled. Exclusion criteria were a possible cardioembolic source and clotting disorders. The mean follow-up was 2.6 years. Risk factors such as hypertension or hyperlipidemia were considered present if the patient had a history of this disorder or received treatment. A CT scan of the brain was mandatory for each patient, except for those with transient monocular blindness. Additional follow-up data were obtained from the Life Long After Cerebral ischemia (LiLAC) study, in which the follow-up of 2447 of 3150 Dutch TIA Trial participants was extended to a mean period of 10 years after inclusion in the Dutch TIA Trial.[15] During the study period, all patients received aspirin in a dose of 38 or 283 mg per day. The Dutch TIA Trial showed that both doses were equally effective in the prevention of vascular events.[14] After the trial, all patients were treated by their neurologist according to current international guidelines.

Stroke at Baseline

For the purpose of the present study, all baseline CT scans were rereviewed by a neurologist and a neurologist in training to select patients with a single “relevant” supratentorial infarct on the CT scan, i.e., the location of the infarct matched the clinical features. These infarcts were classified as large subcortical, small deep, or cortical. Large subcortical infarcts were diagnosed if they were located in the basal ganglia, internal capsule, or corona radiata, with a diameter between 15 and 40 mm. Small deep infarcts were defined according to the same locations but with a diameter of ≤15 mm. Cortical infarcts were defined as wedge-shaped, superficial ischemic lesions in the territory of one of the large major cerebral arteries or lesions in a border zone; the underlying white matter might be involved as well.

Stroke during Follow-Up

All patients in the Dutch TIA Trial visited their neurologist or general practitioner every 4 months. A stroke during follow-up was considered “definite” if relevant clinical features were accompanied by a fresh infarct or hemorrhage on a repeat CT scan and “probable” if clinical deficits without CT changes caused an increase in handicap of at least 2 grades on the modified Rankin Scale.[13,14,16] For the present study, clinical reports and CT scans of all strokes during the follow-up of the Dutch TIA Trial and LiLAC were reviewed again. Two investigators independently reviewed these and adjudicated, without any information on the baseline strokes, whether the infarcts on follow-up were caused by small- or large-vessel disease. If findings on the scan were not conclusive, they relied on clinical deficits. If the investigators did not agree, a third opinion of a neurologist with expertise in stroke was requested. Clinical features suggesting small-vessel disease were pure motor stroke, pure sensory stroke, sensorimotor stroke, or ataxic hemiparesis.[4] Large-vessel disease was assumed when cortical functions were involved, i.e., dysphasia, visuospatial disorder, or hemianopia, with or without motor or sensory deficits. Ischemia in the posterior fossa was diagnosed with at least 2 of following symptoms: vertigo, dysarthria, dysphagia, diplopia, and ataxia. If CT or MRI scans were not available, the scan report of the attending neurologist was used. If no detailed information on the recurrent event was available but stroke had been diagnosed by a physician in a nursing home, it was classified as “stroke with undetermined clinical syndrome.” If no physician had confirmed a stroke reported to us, it was considered “possible stroke” and excluded in our analysis.

Statistical Analysis

Baseline characteristics, vascular risk factors, clinical features at baseline, and clinical syndromes associated with subsequent strokes were compared between the 3 types of infarct with χ^2 values, *t* tests, and Mann-Whitney *U* tests. The frequency of recurrent stroke in the 3 groups was compared with Cox proportional hazards analysis and reported with hazard ratios and corresponding 95% CIs. In multivariate analysis, hazard ratios were adjusted for known risk factors of vascular disease.

Results

Of the 2899 patients with a transient or nondisabling ischemic attack who underwent CT scanning, 732 patients (25%) had a single relevant ischemic lesion at baseline. These were classified as large subcortical in 120 patients (16%), as small deep in 324 patients (44%), and as cortical in 211 patients (29%). In 77 patients (11%), the symptomatic infarct on the CT scan could not be assigned to any of these categories (i.e., combination of cortical and subcortical infarct or infarct in posterior fossa); these were excluded from the present study.

Baseline

Baseline characteristics and vascular risk factors of the 655 patients are summarized in Table 1. Patients with a large subcortical infarct only differed slightly with respect to the vascular risk factor profile from patients with a small deep infarct or a cortical infarct.

The clinical features of the stroke at baseline of patients with a large subcortical infarct were different in distribution from those of patients with a cortical or small deep infarct (Table 2). In this group, 63% presented with a lacunar syndrome versus 35% of patients with a cortical infarct and 78% of those with a small deep infarct ($P<0.05$). Patients with a cortical infarct more often showed features of cortical dysfunction than patients with a large subcortical infarct and patients with a small deep infarct (62% versus 32% versus 18%; $P<0.05$) and more often had a complete or partial hemianopia (29% versus 6% versus 2%; $P<0.05$).

Table 1. Baseline characteristics and vascular risk factors

	cortical (n=211)	**large sub-cortical (n=120)**	**small deep (n=324)**	**total (n=655)**	**X^2; p[a]**	**X^2; p[b]**
male gender (%)	144 (68)	79 (66)	221 (68)	444 (68)	0.20; 0.65	0.23; 0.64
mean age (SD)	63 (10.3)	66 (9.4)	65 (9.7)	65 (9.9)	0.05†	0.99†
history of hypertension (%)	88 (42)	58 (48)	146 (45)	292 (45)	1.36; 0.24	0.37; 0.54
untreated (%)	22 (25)	21 (37)	39 (27)	82 (28)		
current SBP ≥ 160 mm Hg (%)	90 (43)	64 (53)	182 (56)	336 (51)	3.51; 0.06	0.29; 0.59
current DBP ≥ 90 mm Hg (%)	139 (66)	77 (64)	221 (68)	437 (67)	0.10; 0.75	0.65; 0.42
current smoking (%)	96 (46)	61 (51)	149 (46)	306 (47)	0.87; 0.35	0.83; 0.36
diabetes mellitus (%)	18 (9)	14 (12)	35 (11)	67 (10)	0.86; 0.35	0.67; 0.80
history of hyperlipidemia (%)	5 (2)	3 (3)	10 (3)	18 (3)	0.01; 0.94	0.11; 0.75
history of MI (%)	24 (11)	11 (9)	24 (7)	59 (9)	0.39; 0.53	0.37; 0.54
history of claudication (%)	11 (5)	4 (3)	13 (4)	28 (4)	0.63; 0.43	0.11; 0.74
history of vascular surgery (%)	8 (4)	1 (1)	15 (5)	24 (4)	2.53; 0.11	3.63; 0.06
heart rate ≥ 70 bpm (%)	125 (59)	77 (64)	191 (59)	393 (60)	0.78; 0.38	1.00; 0.32
left ventricular hypertrophy (%)*	5 (2)	5 (4)	15 (5)	25 (4)	0.89; 0.35	0.06; 0.82
white matter lesion on CT (%)	12 (6)	10 (8)	47 (15)	69 (11)	0.86; 0.35	0.98; 0.08

*a: large subcortical versus cortical; b: large subcortical versus small deep; SBP : systolic blood pressure; DBP: diastolic blood pressure; MI: myocardial infarction; *: known for 638 patients; †: P, independent samples t test*

Table 2. Baseline event: characteristics and symptoms

	cortical (n=211)	**large sub-cortical (n=120)**	**small deep (n=324)**	**total (n=655)**	**X^2; p[a]**	**X^2; p[b]**
baseline event					0.99; 0.32	0.53; 0.47
TIA (%)	27 (13)	11 (9)	23 (7)	61 (9)		
stroke (%)	184 (87)	109 (91)	301 (93)	594 (91)		
attack frequency*					0.96†	0.99†
1 (%)	170 (81)	97 (81)	262 (81)	529 (81)		
2-3 (%)	33 (16)	18 (15)	50 (15)	101 (15)		
4-10 (%)	6 (3)	5 (4)	9 (3)	20 (3)		
> 10 (%)	2 (1)	0	3 (1)	5 (1)		
modified Rankin scale					0.94†	0.28†
0 (%)	49 (23)	34 (28)	86 (27)	169 (26)		
1 (%)	82 (39)	40 (33)	134 (41)	256 (39)		
2 (%)	59 (28)	27 (23)	85 (26)	171 (26)		
3 (%)	20 (10)	16 (13)	18 (6)	54 (8)		
4 or 5 (%)	1 (1)	3 (3)	1 (0)	5 (1)		
lacunar syndrome (%)	74 (35)	76 (63)	253 (78)	403 (62)	24.7; 0.00	9.9; 0.00
cortical functions involved (%)	131 (62)	38 (32)	57 (18)	226 (35)	28.3; 0.00	10.3; 0.00
no motor- or sensory symptoms (%)	66 (31)	4 (3)	10 (3)	80 (12)	35.8; 0.00	0.02; 0.90
(quadrant) hemianopia (%)	62 (29)	7 (6)	5 (2)	74 (11)	25.7; 0.00	6.1; 0.01
speech disturbance (%)[$]	107 (51)	69 (58)	149 (46)	325 (50)	1.42; 0.23	4.6; 0.03

*a: large subcortical versus cortical; b: large subcortical versus small deep; *: number of ischemic episodes before inclusion in the study; $: dysarthria, dysphasia or a combination of these; †: P, Mann-Whitney U test*

Follow-Up

In the Dutch TIA Trial, no patients were lost to follow-up. For the patients selected for LiLAC, follow-up was nearly complete: 99%. Of the 655 patients, 503 (77%) also participated in LiLAC. For these patients, a mean follow-up of 9.2 years was available versus 2.8 years for the remaining 152 patients. A total of 131 patients suffered a recurrent stroke (Table 3). Of patients with a cortical infarct at baseline, 46 (22%) had a recurrent stroke; of those with a large subcortical infarct at baseline, 25 (21%) had a recurrent stroke; and of those with a small deep infarct at baseline, 60 (19%), had a recurrent stroke. The adjusted hazard ratio for recurrent stroke was 1.05 (95% CI, 0.65 to 1.70) for patients with a large subcortical infarct at baseline and 1.17 (95% CI, 0.79 to 1.73) for patients with a cortical infarct at baseline compared with patients with a small deep infarct at baseline. The 2 investigators who adjudicated the stroke findings on follow-up agreed on classification in all but 2 cases. In 46% of patients with recurrent stroke, after a subcortical infarct at baseline the new clinical syndrome was cortical. This was the case for 67% of patients with a cortical infarct at baseline and for 37% of patients with a small deep infarct at baseline ($P<0.05$). Of the patients with recurrent stroke and a large subcortical infarct at baseline, a lacunar syndrome was found in 42% versus 14% of patients with a cortical infarct at baseline and 41% of patients with a small deep infarct at baseline ($P<0.05$).

The patients with a large subcortical infarct at baseline had their recurrent stroke after a median interval of 2.4 years after the index event. New small deep infarcts occurred after a longer interval (median=5.1 years) than recurrent cortical strokes (median=1.7 years). For patients with a small deep infarct at baseline, the recurrent stroke occurred after a median of 4.3 years (4.7 years for small deep strokes and 2.8 years for cortical strokes), and for patients with a cortical infarct at baseline, the stroke occurred after a median interval of 2.8 years (4.6 years for small deep strokes and 2.1 years for cortical strokes).

Discussion

We found no significant differences in vascular risk profile, clinical features, and the rate of recurrent stroke between patients with a large subcortical infarct and those with a cortical or small deep infarct. The generalisability of our study results may be limited by the selection processes of the study population. All patients were referred to a neurologist and consented to participate in a clinical trial. Patients, however, originated from 50 centers in the Netherlands, both university medical centers (5) and general hospitals (45). The generalisability is also somewhat limited by the fact that only patients with a relevant ischemic lesion that was visible on a CT scan were included in our study, but this was the only way that large subcortical infarcts could be identified.

Part of our data were also used in a previous study, in which the clinical course in patients with an infarct caused by small-vessel disease was compared with that in patients with an infarct caused by large-vessel disease.[17] In that study, patients with a large subcortical infarct were included among those with large-vessel disease. The number of patients in the present study was much smaller because the inclusion criteria were stricter than those in the previous study. This was

Table 3. Stroke and death during follow-up

	cortical (n=211)	**large sub-cortical (n=120)**	**small deep (n=324)**	**total (n=655)**	**X^2; p[a]**	**X^2; p[b]**
total stroke(%)	46 (22)	25 (21)	60 (19)	131 (20)	0.04; 0.84	0.30; 0.58
crude Hazard ratio (95% CI)	1.03 (0.70-1.52)	1.08 (0.68-1.72)	reference			
adjusted[§] Hazard ratio (95% CI)	1.14 (0.77-1.68)	1.06 (0.66-1.70)	reference			
adjusted[∫] Hazard ratio (95% CI)	1.17 (0.79-1.73)	1.05 (0.65-1.70)	reference			
assessment of stroke (n,%*)						
ischemic stroke	38 (82)	20 (80)	47 (78)	105 (80)		
hemorrhagic stroke	3 (7)	1 (4)	5 (8)	9 (7)		
stroke, unknown cause	0	0	1 (2)	1 (1)		
fatal ischemic stroke	1 (2)	1 (4)	1 (2)	3 (2)		
fatal hemorrhagic stroke	1 (2)	0	4 (7)	5 (4)		
fatal stroke, unknown cause	3 (7)	3 (12)	2 (3)	8 (6)		
CT scan (n,%*)						
ischemia	25 (54)	9 (36)	26 (43)	60 (46)		
hemorrhage	4 (9)	1 (4)	9 (15)	14 (11)		
no ischemia/hemorrhage	12 (26)	11 (44)	15 (25)	38 (29)		
no scan made	5 (11)	4 (16)	10 (17)	19 (15)		
clinical syndrome (n,%)**						
cortical	28 (67)	11 (46)	19 (37)	58 (50)	2.74; 0.10	0.50; 0.48
lacunar	6 (14)	10 (42)	21 (41)	37 (32)	6.2, 0.01	0.00; 0.97
vertebrobasilar	3 (7)	1 (4)	7 (14)	11 (9)	0.24; 0.63	1.56; 0.21
undeterminable	5 (12)	2 (8)	4 (8)	11 (9)		
median interval baseline-follow-up stroke (years)	2.8	2.4	4.3	3.2	0.61[†]	0.30[†]
death from all causes (%)	110 (52)	62 (52)	162 (50)	334 (51)	0.73; 0.39	0.24; 0.62

*a: large subcortical versus cortical; b: large subcortical versus small deep; §: adjusted for age and gender; ∫: adjusted for age, gender, history of hypertension, white matter lesions on CT or MRI scan and for left ventricular hypertrophy; *: percent of all strokes during follow-up; **: percent of non hemorrhagic strokes during follow-up; †: p, Mann-Whitney U test*

because in the present study only patients with a single symptomatic infarct at baseline scan were included, whereas the distinction between small- and large-vessel disease in the previous study was based on clinical features if the CT scan was not conclusive. The number of events, however, was much larger in the present study because of the extended follow-up.[15] Although the relatively small number of patients in this study might limit the conclusions, our study cohort represents the largest series of patients with a large subcortical infarct.

Four methodological issues merit consideration. First, the definition of large subcortical infarcts differs between studies. We defined all infarcts in the subcortical region with a diameter between 15 and 40 mm as large subcortical,[5,6,10,18] whereas others used a diameter of 20 mm as the lower limit.[8,9,11,12] Second, in previous studies by others, approximately half of the patients with a large subcortical infarct had a potential cardioembolic source. Because these patients were excluded from the Dutch TIA Trial, our analyses of the risk factor profile apply only to patients with cerebral ischemia of noncardioembolic origin. Whereas in our study the vascular risk profile of patients with a large subcortical infarct did not differ from that of patients with a small deep infarct or with a cortical infarct, in patients with subcortical infarcts of both noncardioembolic and cardiac origin the risk profile may more closely resemble that of a cortical infarct because of the greater proportion of cardioembolic sources in these types of infarcts.[6,8–10,12] Moreover, in a recent large systematic review, atrial fibrillation and carotid stenosis were the only 2 risk factors shown to differ between patients with lacunar and nonlacunar infarcts.[19] Unfortunately, in the Dutch TIA Trial we did not collect information about the presence of a carotid stenosis. Consequently, we unfortunately could not determine whether such a difference also exists in our cohort, which would have been interesting because it would have provided a clue about the most likely pathogenesis of the large subcortical infarcts. Third, in previous studies a higher stroke recurrence rate was found in patients with large-vessel disease than in patients with small-vessel disease, whereas in our study there is no difference in recurrence rate between the 3 groups. This is probably the result of our inclusion criteria. On the one hand, we only included patients with a relevant ischemic lesion on CT scan, which probably resulted in relatively few patients with small, lacunar TIAs, who are probably less likely to experience a recurrent stroke. On the other hand, in the Dutch TIA Trial all patients with a modified Rankin Scale score >3 were excluded, i.e., patients who were severely disabled as result of the stroke. That group includes many patients with large cortical infarcts and a high risk of recurrence. Exclusion of the extremes of the stroke severity spectrum probably resulted in a more or less similar prognosis for the patients with large- and with small-vessel disease in the present study. Another explanation for the lower than expected recurrence rate is the definition of recurrent stroke in this study. We used the definition that was adopted in the Dutch TIA Trial, when patients had to have a (temporary) change in Rankin Scale score of ≥2 points when there was no detectable lesion on CT scan. This may have led to an underestimation of recurrent strokes that caused minor symptoms, which are often associated with small, lacunar strokes.[20] A final possible explanation for the similar recurrence

rate is that recent evidence suggests that there might be no difference in recurrence rates between lacunar and nonlacunar infarction in the long term.[21] Fourth, ideally, stroke classification in epidemiological studies is based on MRI. Because of the time period of this study, no MRI was performed. Moreover, not all patients with a recurrent stroke had a CT at the time of the recurrent stroke. This might have influenced the classification of recurrent stroke because ≈10% to 20% of strokes that are lacunar clinically are actually due to cortical infarct and vice versa.[22] Future studies in this field should preferably use MRI for the classification of both index and recurrent stroke.

Our study supports the notion that a distinction between large subcortical and other infarcts is difficult to make on clinical grounds alone. Patients with a large subcortical infarct can have signs of cortical involvement, such as aphasia or hemineglect,[6,7,10] but also signs of a small deep infarct, for example, a pure motor stroke.[7,8] The vascular risk factors of patients with large subcortical infarcts fail to show a distinctive profile.[6,7,10–12] Our study shows that recurrence rates and clinical syndromes of recurrent strokes also show overlap with those of either small deep infarcts or cortical infarcts. We conclude from the data in this study that the clinical distinction between large subcortical infarcts and other infarcts in the acute stage seems to be unreliable and does not appear to have clear practical implications.

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Chapter 3

Classification of cause of death after stroke in clinical research

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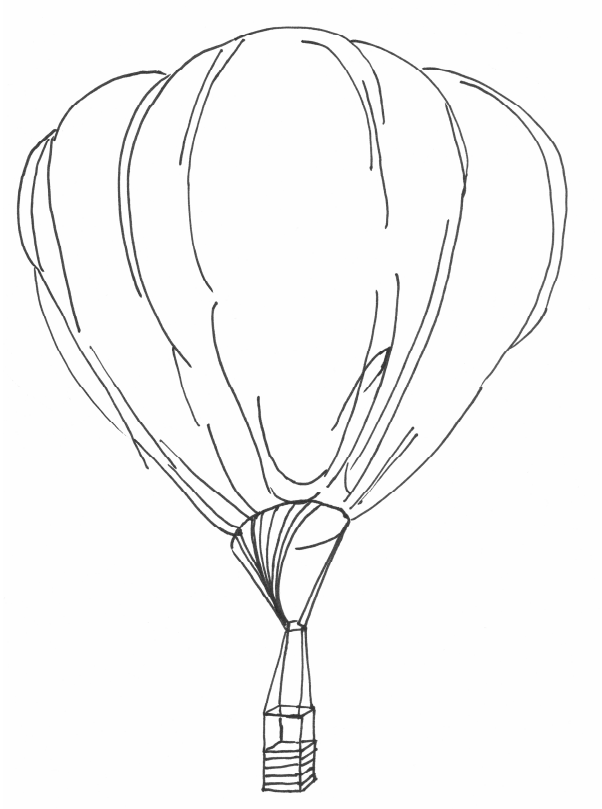

Abstract
Background and Purpose- Classification of outcome events is essential in clinical research. The Executive Committee of the European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT), a secondary prevention trial in patients with cerebral ischemia, repeatedly encountered problems in classifying the cause of death after a stroke if the interval between these events was relatively long. We aimed to develop guidelines for classifying such events.
Methods- Twenty-nine neurologists with a special interest in stroke filled out a questionnaire and audited 5 case vignettes. On the basis of this information, we developed a proposal for classifying causes of death after stroke. This proposal was evaluated in an interobserver analysis in which 10 neurologists or residents in neurology assessed 20 of 100 case vignettes.
Results- Initially, there was great variation in classifications of the case vignettes, mainly because the correspondents strongly disagreed about the relative importance of the interval between stroke and death, the degree of disability after stroke, the discharge destination (home or institutional care), and the coexistence of infection. In the new proposal, the main criteria were “interval after stroke” (cutoff point at 1 month) and “best Rankin grade after stroke” (cutoff at 3). In the interobserver analysis, good agreement was obtained among the 5 pairs of neurologists who assessed the 20 case vignettes (κ 0.80 95% CI, 0.68 to 0.92).
Conclusions- In the absence of guidelines, neurologists show striking variation in the classification of causes of death in patients who die after a stroke. With precise rules, agreement in the classification of death after stroke strongly improved.

Introduction

In clinical trials of secondary prevention, the main outcome events are recurrent stroke, myocardial infarction, and death. Such outcome events are also often used in observational studies. In most such studies, an auditing committee classifies these events according to prespecified criteria. The executive committee of the European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT)[1] repeatedly encountered problems in classifying the cause of death in patients who had previously experienced a stroke. An example is a patient who remained dependent in a nursing home after a brain infarct, developed pneumonia and heart failure, and eventually died 4 months after the stroke (Table 1, case vignette 2). Members of the auditing committee could not agree whether the subsequent pneumonia, heart failure, and ultimately death should be attributed to the initial stroke or whether these events should be regarded as separate complications.

The difficulty in reaching consensus arose because some neurologists tended to attach most importance to the long interval between stroke and death, whereas others put the emphasis on stroke-related disability. Because we could not find appropriate references in the literature, we decided to consult with stroke experts from all over the world, with the aim to formulate a practical guideline for the auditing of death after stroke in clinical research.

Methods

We sent a message to 43 experts with a special interest in secondary prevention after stroke and with expertise in auditing outcome events in clinical trials. We explained our problem and asked whether they were willing to answer 5 questions on the classification of the cause of death after a stroke (Table 3) and to audit 5 cases. All cases were based on true patient data from the ESPRIT trial. The case vignettes are described in Table 1. A single item could be chosen from a list with 12 predefined causes of death (Table 2).

Table 1. Case vignettes

Case 1: male, 79 years of age Presented with dysphasia, right-sided paralysis of face, arm and leg. There was no recovery of the neurological deficits. He developed pneumonia after 3 days and died, despite of antibiotic treatment, after 2 weeks.
Case 2: female, 77 years of age Presented with sudden dysarthria, left-sided facial weakness, and confusion. There was no recovery at all; the patient returned to the nursing home where she was living because of cognitive impairment. After 4 months, her level of consciousness suddenly decreased and she developed a Cheyne Stokes breathing pattern. Only symptomatic treatment was given. She developed pneumonia and heart failure and died one week later.

Table 1 continued

Case 3: female, 65 years of age
Presented with forced deviation of head and eyes to the right, neglect for the left side, left hemianopia and facial weakness and hemiplegia on the left side. There was almost no recovery of the neurological symptoms and she was discharged to a nursing home with a Rankin disability score of 5 and remained dependent. Four months later she suddenly failed to react to speech, had a decreased level of consciousness and an increased neglect. There was some recovery of these deficits, but she refused (intentionally) to eat or drink anything and died suddenly 2 months later.

Case 4: female, 73 years of age
Presented with aphasia and hemiplegia on the right side; computed tomography showed ischaemic lesion of the middle cerebral artery territory in the left hemisphere. There was no recovery and patient was discharged to a nursing home. At the time of discharge, she was given antibiotics because of a possible respiratory infection. After three months she died, according to the institute physician as a result of aspiration pneumonia.

Case 5: male, 67 years of age
Presented with headache, nausea, hemianopia and hemihypesthaesia on the left side, with computed tomography showing an ischemic lesion with haemorrhagic transformation in the middle cerebral artery territory of the right hemisphere. The neurological symptoms were progressive, and in the following days his level of consciousness decreased, he developed a left hemiplegia and a Cheyne Stokes breathing pattern. One week later, his temperature rose to 41.5ºC and he had severe hypertension and tachypnoea. Despite antibiotics, he died 7 days after the event

After having studied the completed questionnaires and opinions, we formulated a proposal with guidelines for classifying the cause of death after stroke (Table 4). This proposal was sent to all participating neurologists for approval.
In the second stage of this study, the proposed guidelines were tested by means of an interobserver analysis. From several stroke trials and studies coordinated by the stroke trial office in Utrecht (ESPRIT,[1] Dutch TIA Trial (DTT),[2] and Life Long After Cerebral Ischaemia (LiLAC)[3]), case histories of 100 patients were selected who experienced a stroke and died during follow-up. For each patient, a short report summarized the qualifying event, the stroke during follow-up, and the circumstances at the time of death. Seven Dutch neurologists and 3 residents in neurology, all with a special interest in stroke (see Appendix), consented to audit 20 case reports and to classify the causes of death as “stroke” or “other cause” on the basis of the proposed guidelines in Table 4. In this way, each case report was classified by 2 different physicians. Interobserver agreement on causes of death was assessed with κ statistics.

To compare the agreement of the initial classifications of the participants in the questionnaire with the agreement in the classifications in the interobserver analysis, based on the new criteria, we reclassified the initial classifications. If the classified cause of death was “fatal cerebral infarction,” “fatal cerebral hemorrhage” or “fatal stroke,” we reclassified it as “stroke”; if another classification was chosen, we classified it as “other cause.” The neurologists were divided in 2 groups according to order of response (first responder in group 1, second in group 2, third in group 1, etc), resulting in 70 classification couples (one responder was excluded for this analysis to obtain an even number of responders). Interobserver agreement on these classified causes of death was assessed with κ statistics.

Table 2. Audited causes of death

	case number				
	1	**2**	**3**	**4**	**5**
fatal cerebral infarction	5	2	5	15	18
fatal cerebral haemorrhage					11
fatal stroke	19	9	6		
fatal myocardial infarction		1			
definite sudden death			6		
probable sudden death			5		
other cardiac cause					
other vascular cause		6	1		
infection	4	3		12	
malignancy					
death from non-natural cause			1		
other nonvascular		4	4		
combination of causes	1	3	1	1	
no answer		1		1	

Results

Twenty-nine (see Appendix) of 43 international experts filled out the questionnaire. The answers on the questions are summarized in Table 3, and the assigned causes of death for the 5 test cases are shown in Table 2. The length of the interval between stroke and death appeared to be important for 26 of 29 of adjudicators, but there was no consensus on the interval between stroke and death, beyond which stroke no longer should be regarded as a cause of death. Five experts commented that the length of this period depends on the type and severity of the stroke and on the so-called “direct cause of death” (for example, brain herniation, aspiration pneumonia, or heart failure). Three neurologists who did specify a maximum interval breached their own rule when they audited the cases. With regard to the degree of disability according to the modified Rankin scale,[4,5] most neurologists indicated that it should be taken into account, but again, there was no agreement on the cutoff point for dependence below which stroke always should be taken as cause of death. Also, there was much difference of opinion on the importance of the discharge destination of the patient (home versus nursing home). There was more agreement about the importance of co morbidity at the time of the stroke and on whether the patient experienced

an infection at the time of death; a clear majority thought these conditions should be taken into account.

Table 3. Questions on auditing death after stroke and responses from 29 neurologists

if you audit a clinical event in a secondary prevention trial after TIA or minor non-disabling stroke, in a patient who died after a stroke, do you take into account:		
question	**answer**	**number (total = 29)**
the amount of time between stroke and death?	no	3
	yes	26
if yes: what is the maximum period between stroke and death to count the stroke as the cause of death?	≤ 1 week	3
	1 week – 1 month	9
	1 month – 1 year	6
	variable / no answer	8
the maximum level of disability of the patient at discharge after the stroke?	no	5
	yes	24
if yes: what level of disability (Rankin scale 0-5) should a patient obtain to show enough recovery of his stroke to **not** consider it as cause of death?	1	1
	2	7
	3	9
	4	3
	no answer	4
whether the patient suffers from co-morbidity?	no	3
	yes	26
whether the patient suffers from an infection at the time of death?	no	8
	yes	19
	no answer	2
whether the patient was discharged to his own home after admission for the stroke or to a nursing home?	no	16
	yes	12
	no answer	1

Not surprisingly, there was great variation in the way neurologists classified the cause of death in the 5 case vignettes (Table 2). Only in cases 1 and 5 was there substantial agreement. The κ of the interobserver analysis of these initial classifications was 0.31 (95% CI, 0.10 to 0.54), which reflects poor agreement. After having weighed all different opinions and answers, we proposed a new guideline for classifying the cause of death after stroke (Table 4). All but 2 of the 29 correspondents agreed with the proposal without major objections.

Table 4. Suggested classification-scheme for classifying death after stroke

		best Rankin after stroke	
		≤ 3	> 3
time since stroke	≤ 1 month	stroke[1]	stroke[2]
	> 1 month	other[3]	stroke[4]

1,2,4: cause of death is stroke, unless an undeniable other cause (e.g., myocardial infarction, malignancy, car accident) is the obvious cause of death
3: cause of death can be stroke if the mechanisms leading to death are clearly related to the stroke

In the second phase of the study, in which 5 pairs of neurologists each classified 20 different case histories, there was agreement on the cause of death in 90 of the 100 patients (Table 5), resulting in a κ value of 0.80 (95% CI, 0.68 to 0.92).

Table 5. Classified causes of death in interobserver analysis

	classification observer 2		
	stroke	other	total
classification observer 1			
stroke	49	5	54
other	5	41	46
total	54	46	100

Discussion

Our study shows that in the absence of clear guidelines, there was very little agreement among world experts on the classification of cause of death in patients who die after a stroke in the setting of a clinical trial. On the basis of all these opinions, we designed a simple set of criteria (Table 4) on which most experts who participated in our study (27 of 29) agreed. Moreover, a subsequent interobserver study among neurologists in a single country showed there was excellent agreement in classification of cause of death when this set of criteria was used. In our study, a κ of 0.80 was obtained, whereas in general, a kappa between 0.61 and 0.80 is considered to reflect substantial agreement, and a kappa between 0.81 and 1.00 reflects almost perfect agreement.[6,7] The World Health Organization (WHO) published the *International Statistical Classification of Diseases and Related Health Problems*,[8] a manual with rules and guidelines for the coding of mortality and morbidity for the purpose of statistical analysis. According to their general principles, all deaths should be attributed to the primary cause of a sequence leading to the fatal disease. In this way, death in a patient dying of aspiration pneumonia after a stroke should, for example, be attributed to atherosclerosis. However, modification rules can override these general principles, and special “Sequelae of ” codes are provided, for instance, a “Sequelae of cerebrovascular disease” code, which can be used if a patient dies as a consequence of the stroke. There is no time limit or other restriction to this

WHO code that can be consulted if “there is evidence that death occurred from residual effects of this condition rather than from those of its active phase.” This leaves a wide margin of uncertainty for all physicians when classifying and reporting causes of death in a given patient. Although the number of neurologists who participated in the questionnaire was limited to 29, they represent a fair sample of the 43 world experts we consulted, and the range of answers and classifications could have been only wider in a larger sample. Most disagreement was related to the interval between stroke and death, the disability level of the patient after the stroke, the existence of infection at the time of death, and of the discharge destination after stroke. The disagreement on this last item may partly be caused by intercultural differences because care for the elderly and disabled differs between countries, even within the Western world. The other items seem to be more essential for the purpose of this questionnaire, but the answers we initially received differed not only between but also within correspondents, given some discrepancies between opinion and actual classification.

The agreement in the interobserver analysis may have been influenced by the single country background of the participants, resulting in an exaggeration of the agreement. Although the observers work in 5 different hospitals in The Netherlands, their Dutch medical training may have resulted in a better agreement than would have been obtained in an international analysis. However, from the difference between this analysis and the analysis of the initial classifications, we can infer that the “gut feeling” of stroke experts has a strong individual basis and does not result in agreement in consensus-based classifications.

To study whether application of the new criteria changes the original classifications, we compared the classifications of the cases in the interobserver analysis with those in the studies from which they were derived (DTT, LiLAC, and ESPRIT). Of the 90 cases in which there was agreement on classification in the interobserver analysis, 20 were differently classified in the original study. In all these, death was classified as “stroke” in the interobserver analysis, whereas the original classification was “other cause.”

The results of previous secondary prevention trials probably have not been substantially influenced by disagreement about the cause of death after stroke because in most of these studies, only the first vascular event a patient experiences is included in the primary analysis. In the study cases, all first vascular events would be stroke, and the event of death would be analyzed only for secondary survival analysis.

When our new set of criteria is applied to the 5 original case vignettes in the questionnaire, all 5 would be classified as stroke deaths (cerebral infarction, cerebral hemorrhage, or stroke of unspecified nature). This is in contrast with the classification of the majority of participating neurologists except in 2 cases (vignettes 1 and 5) in which death occurred within 2 weeks after stroke. In the other cases, other classifications were initially prompted by the presence of co morbidity and a long interval between stroke and death. There is no universal truth in this matter. To quote one of our correspondents: I always ask myself the question “Would this patient have died if he would not have suffered that stroke?”

To answer that question, we devised an admittedly arbitrary but pragmatic set of criteria to simplify the work of auditing committees in clinical studies. The proposed guideline was developed and tested by neurologists, whereas in some countries, stroke patients are cared for by general physicians or geriatricians. Nevertheless, we think the weighing of causal factors in the chain of events between stroke and death is not likely to depend on medical discipline. It is not designed to determine the “one and only” true cause of death in patients participating in a clinical study. Nevertheless, if the same criteria are used in different studies, the results of these studies can be compared more reliably. Moreover, from the perspective of internal validity, it is no problem to use criteria with some arbitrary aspects in clinical trials as long as these rules are applied in the same way to all treatments. Because the majority of correspondents agreed with our proposed criteria, and the criteria proved to be workable and reliable in the interobserver analysis, we conclude that we succeeded in our goal to formulate a practical guideline for the auditing of death after stroke in clinical research.

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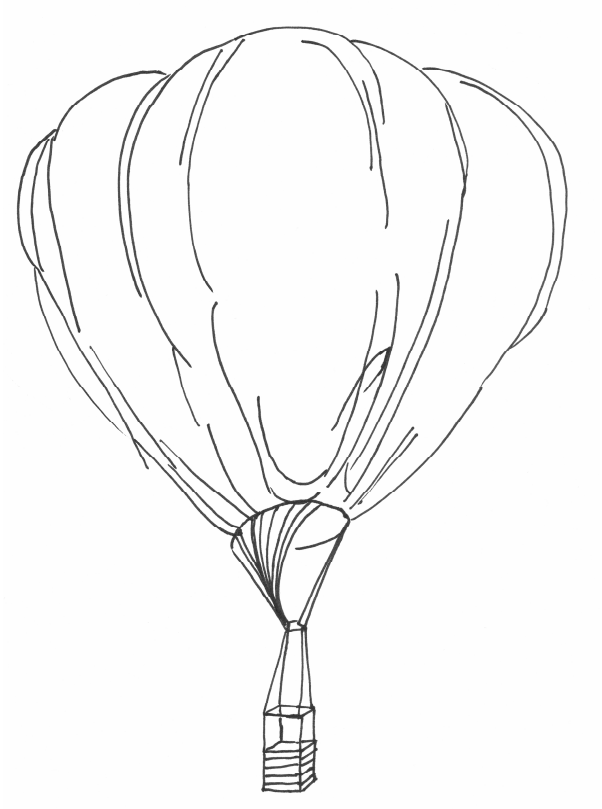
Chapter 4

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

The ESPRIT Study Group (members listed in appendix)

Lancet 2006;367:1665-73



Abstract
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.

Introduction

Patients with a transient ischaemic attack or nondisabling 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. 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 normalized 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 program 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, nonfatal 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 (nonhaemorrhagic death from vascular causes, non-fatal ischaemic stroke, or non-fatal myocardial infarction), all vascular events (death from vascular causes, nonfatal stroke, or non-fatal myocardial infarction), and major bleeding complications. Outcome events defined post hoc were fatal and nonfatal 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 hours, 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 (e.g., 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 auditing committee was consulted before the executive committee decided.

Statistical analysis

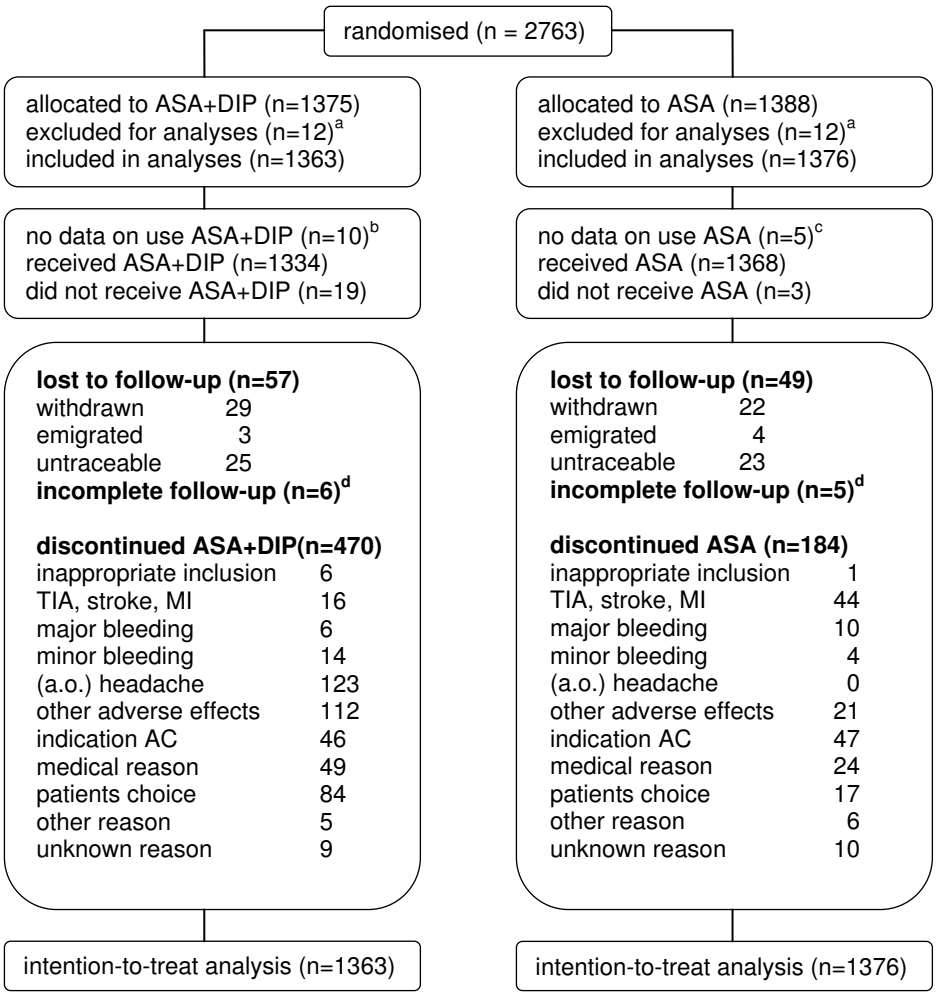
Assuming a relative risk reduction of 20–25% for the combination of aspirin and dipyridamole by comparison with aspirin alone, we calculated that about 3000 patients should be followed up for a mean of 3 years, resulting in 9000 patient-years of follow-up. This calculation was based on a type 1 error 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] 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 arms *vs.* two arms), 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—i.e., 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).

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.

Figure 1. Trial profile



ASA+DIP: combination therapy of acetylsalicylic acid and dipirydamole; ASA: monotherapy with acetylsalicylic acid; AC: oral anticoagulation; MI: myocardial infarction; a.o.: among others; a: patients from one excluded hospital; b: lost to follow-up before first follow-up: 7 untraceable, 1 withdrawn consent, 1 inappropriately included, 1 emigrated; c: lost to follow-up before first follow-up: 3 untraceable, 1 withdrawn consent, 1 inappropriately included; d: incomplete follow-up because of close-out at the date that all follow-up data were complete (four hospitals)

Patients originated from 79 hospitals in 14 countries. Mean length 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.

Table 1. Baseline characteristics and dose of ASA trial medication

	ASA+DIP (n=1363)	**ASA (n=1376)**
randomisation scheme		
three-arm scheme	509 (37)	516 (38)
two-arm scheme	854 (63)	860 (62)
demographics		
male (%)	897 (66)	892 (65)
mean age (± 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 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 (n)[a]	1304	1308
any infarct (%)	623 (48)	601 (46)
any relevant infarct (%)	471 (36)	446 (34)
ultrasound carotid arteries (n)	1227 (90)	1252 (91)
stenosis > 50% (%)	134 (11)	112 (9)

Table 1 continued

	ASA+DIP (n=1363)	ASA (n=1376)
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)
hyperlipidemia	634 (47)	638 (46)
current cigarette smoking	484 (36)	512 (37)
blood pressure (mm Hg)[b]		
systolic	152 ± 24	152 ± 23
diastolic	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)
antithrombotic drug use at time of event (%)		
aspirin	319 (23)	309 (23)
oral anticoagulants	6	0
other	16 (1)	14 (1)
none	1022 (75)	1053 (77)
dose of aspirin (%)		
30 mg	576 (42)	635 (46)
40 mg	2	1
50 mg	109 (8)	2
75 mg	209 (15)	206 (15)
80 mg	61 (5)	95 (7)
100 mg	316 (23)	340 (25)
150 mg	26 (2)	26 (2)
160 mg	1	3
250 mg	2	2
300 mg	56 (4)	62 (5)
325 mg	5	4

ASA+DIP: combination therapy of acetylsalicylic acid and dipyridamole; ASA: monotherapy with acetylsalicylic acid; a: not required in patients transient monocular blindness; b: mean ± SD

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 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.

Table 2. Proportion of patients on allocated medication during the trial

	ASA+DIP n=1363	**ASA n=1376**
on medication/ at risk (%)		
at trial start	1334/1353 (99)	1368/1371 (100)
at 6 months	1059/1307 (81)	1302/1345 (97)
at 1 year	915/1192 (77)	1153/1220 (95)
at 1.5 year	780/1053 (74)	1015/1086 (93)
at 2 years	688/938 (73)	875/955 (92)
at 3 years	545/767 (71)	688/777 (89)
at 4 years	400/581 (69)	504/584 (86)
at 5 years	243/366 (66)	318/377 (84)

ASA+DIP: combination therapy of acetylsalicylic acid and dipyridamole; ASA: monotherapy with acetylsalicylic acid

*Table 3. The occurrence of first outcome events according to allocated treat*ment

			intention to treat		on treatment	
	ASA+DIP	ASA	HR	95% CI	HR	95% CI
patients randomised	1363	1376				
person-years of observation[a]	4498	4495				
death from all vascular causes, nonfatal stroke, nonfatal MI, nonfatal major bleeding complication[b]	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, nonfatal stroke[b]	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
nonfatal extracranial (%)	21 (60)	32 (60)				
fatal extracranial (%)	2 (6)	0				
nonfatal inctracranial (%)	9 (26)	17 (32)				
fatal intracranial (%)	3 (9)	4 (8)				
all major ischaemic events: nonhaemorrhagic death from vascular causes, nonfatal ischaemic stroke, nonfatal MI[b]	140	174	0.81	0.65-1.01	0.88	0.69-1.12
death from all vascular causes, nonfatal stroke, nonfatal MI[b]	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

a: years of follow-up until primary outcome event or end of follow-up; b: whichever event occurred first; ASA+DIP: combination therapy of acetylsalicylic acid and dipirydamol; ASA: monotherapy with acetylsalicylic acid; HR: hazard ratio; CI: confidence interval; MI: myocardial infarction

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 2. Time to event curves for primary outcome event (left) and all ischaemic events (right)

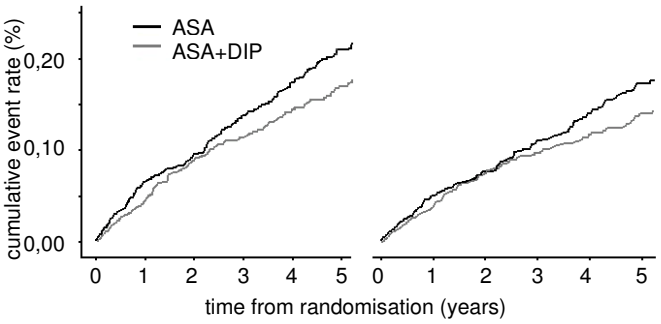


Figure 3 shows the results of the planned and post hoc defined subgroup analyses for the primary outcome event; we noted no major differences between subgroups (smallest p value for interaction 0.18). Because all patients from non-Asian countries (with the exception of three patients from hospitals in 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, nonfatal 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 3. Subgroup analyses for the primary outcome event (HR with corresponding 95% CI)

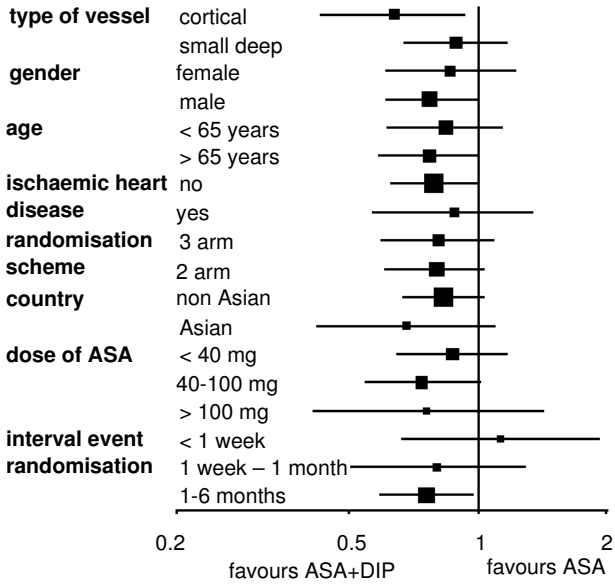
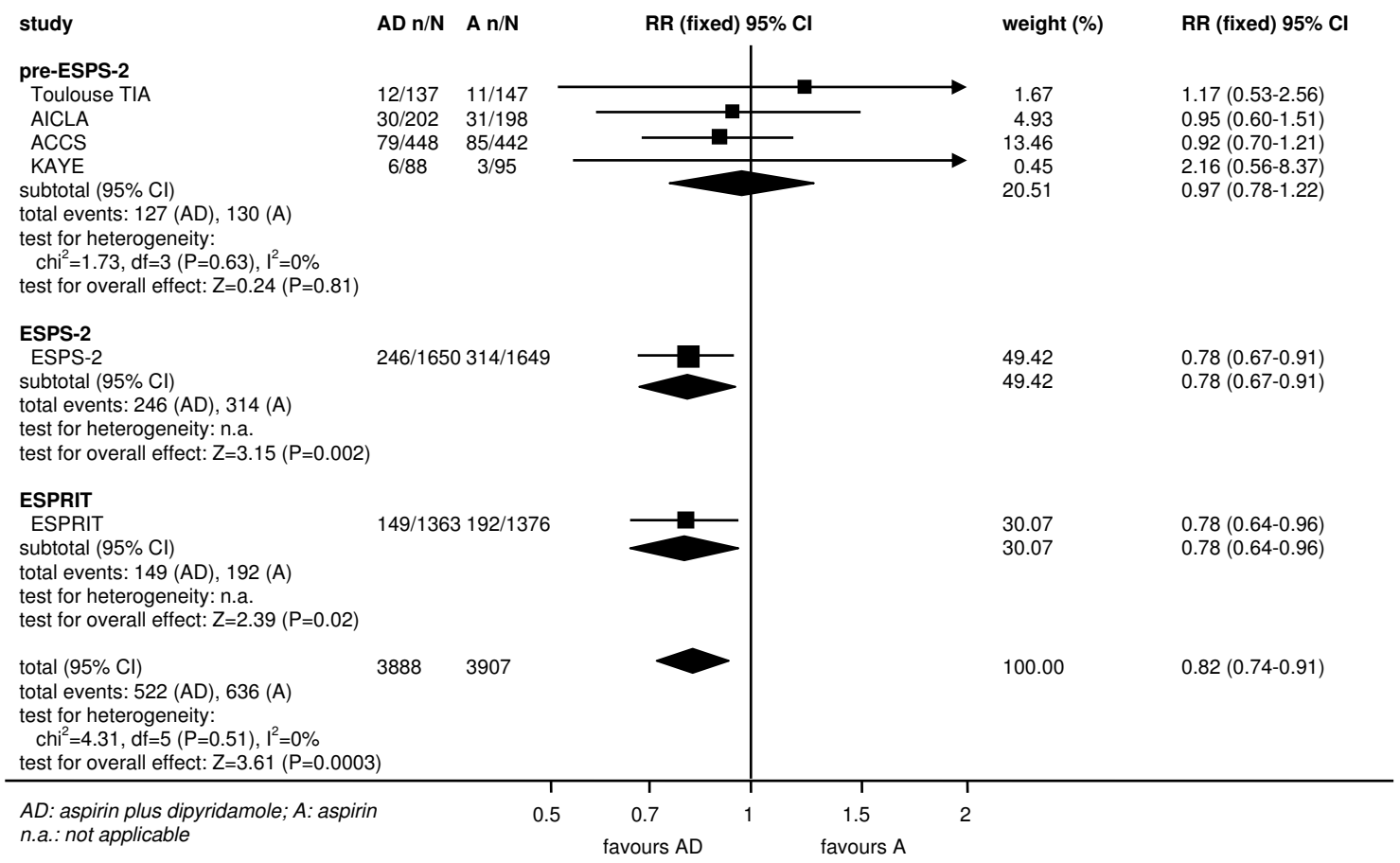


Figure 4. Meta-analysis of all trials comparing aspirin plus dipyridamole with aspirin alone in the secondary prevention after TIA or minor stroke or arterial origin;composite outcome of vascular death, nonfatal stroke, or non-fatal myocardial infarction



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 bio-available 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 antihypertensive 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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Chapter 5

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

The ESPRIT Study Group (members listed in appendix)

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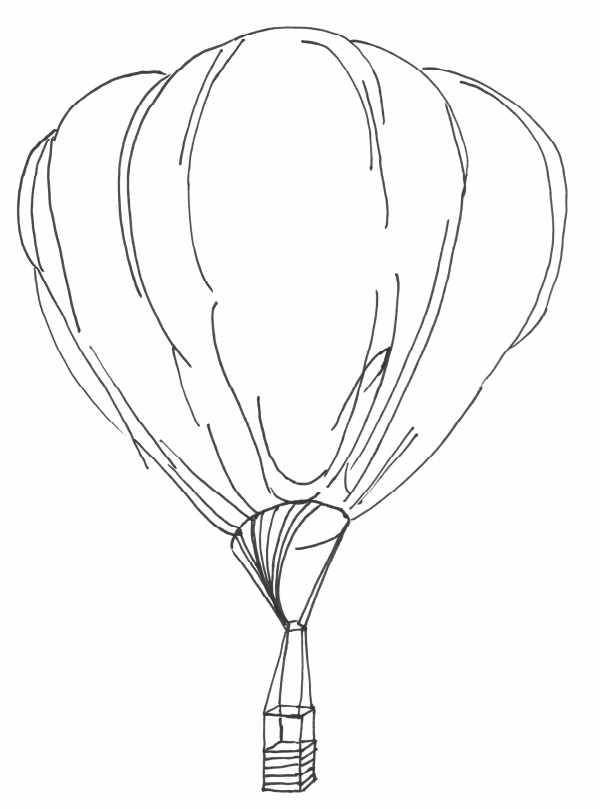


Abstract
Background- Oral anticoagulants are better than aspirin for secondary prevention after myocardial infarction and after cerebral ischaemia in combination with non-rheumatic atrial fibrillation. The European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) aimed to determine 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 off set by increased bleeding complications.

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 randomizing 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 day15 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

secondary outcome events

pre-specified

- death from all causes
- death from all vascular causes
- death from all vascular causes and nonfatal stroke
- all major ischaemic events: death from any ischaemic vascular condition or nonfatal ischaemic stroke or MI
- all vascular events: death from all vascular causes, nonfatal stroke or MI
- major bleeding complications

post hoc defined

- fatal and nonfatal ischaemic stroke
- all cardiac events: fatal and nonfatal MI, sudden death and death from cardiac cause
- fatal bleeding complication

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 (e.g., 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 hospitalization. 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 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.

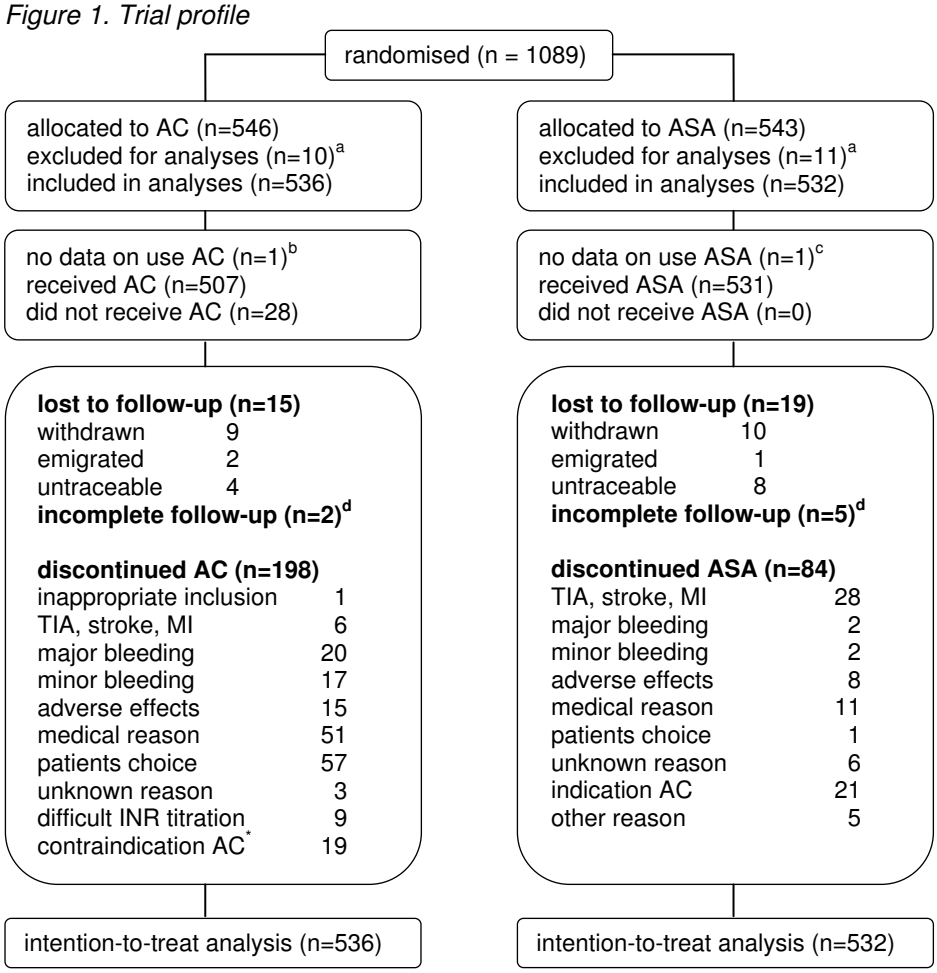
The occurrence of outcome events in the groups was compared in terms of the hazard ratio (HR), which may be interpreted as a relative risk. HRs were obtained with the Cox proportional hazard model. The precision of the HR estimates was described with 95% CIs. Analyses were based on the intention-to-treat 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, 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- i.e., 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).

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).

Figure 1. Trial profile



*AC: anticoagulants; ASA: aspirin; MI: myocardial infarction; a.o.: among others; a: patients from one excluded hospital; b: lost to follow-up before first follow-up: 1 untraceable; c: lost to follow-up before first follow-up: 1 inappropriately included; d 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 during the trial and patients who in retrospect had leukoaraiosis on the CT scan of their brain, both were exclusion criteria for the use of AC in ESPRIT*

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. Most patients (97%) were enrolled in the three-arm randomisation scheme (table 1). More than two-thirds of patients were men and the mean age was 61 years.

Table 1. Baseline characteristics according to allocated treatment

	AC (n=536)	**ASA (n=532)**
randomisation scheme (%)		
three arm	523 (98)	516 (97)
two arm	13 (2)	16 (3)
demographics		
men (%)	385 (72)	345 (65)
mean age (± 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 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 MR scan of the brain[a] (%)	514 (96)	503 (95)
any infarct (%)	254 (49)	242 (48)
any relevant infarct (%)	184 (36)	196 (39)
ultrasound carotid arteries (n)	487 (91)	480 (90)
stenosis > 50% (%)	57 (12)	44 (9)

Table 1 continued

	AC (n=536)	ASA (n=532)
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)
hyperlipidemia	251 (47)	243 (46)
current cigarette smoking	220 (41)	225 (42)
blood pressure (mm Hg)[b]		
systolic	153 (22)	152 (22)
diastolic	87 (12)	87 (12)
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	n.a.	301 (57)
50 mg	n.a.	1
75 mg	n.a.	79 (15)
80 mg	n.a.	34 (6)
100 mg	n.a.	65 (12)
150 mg	n.a.	16 (3)
250 mg	n.a.	1
300 mg	n.a.	34 (6)
325 mg	n.a.	1

AC: anticoagulants; ASA: aspirin; a: not required in patients with transient monocular blindness; b: mean ± SD

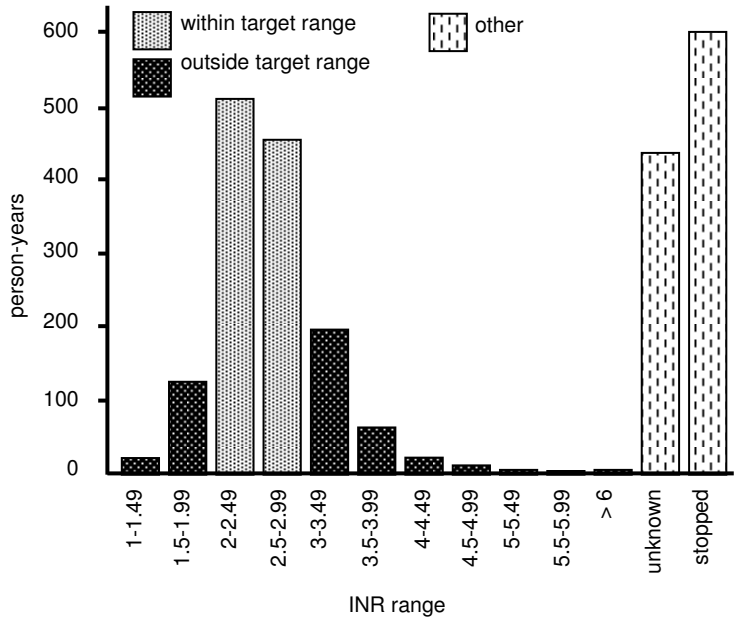
About a third had a transient ischaemic attack, including 5% with transient monocular blindness. CT or MRI of the brain was available for 1017 patients and showed a relevant ischaemic lesion in more than a third. Most patients without a CT or MRI scan had had transient monocular blindness as a qualifying 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. Data about the use of trial medication are summarised in figures 1 and 2 and in tables 1 and 2. A total of 25030 INR

Table 2. Proportion of patients on allocated medication during the trial

	AC n=536	**ASA n=532**
on medication/ at risk (%)		
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)

AC: anticoagulants; ASA: aspirin

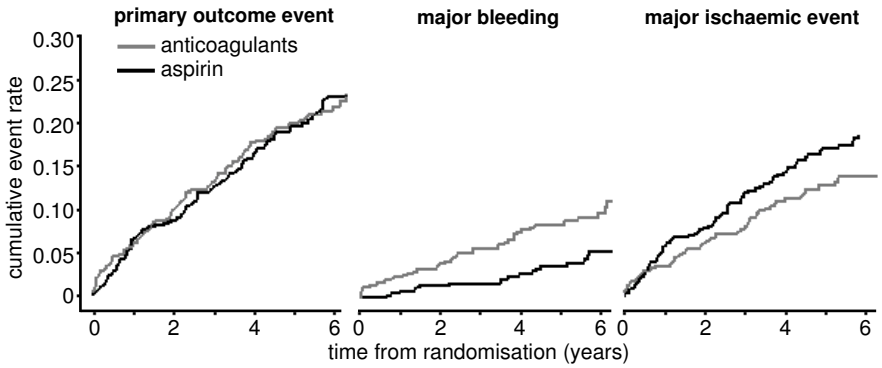
Figure 2. Distribution of time spent in each class of 0.5 INR unit



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.

Figure 3. Time to event curves



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 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.

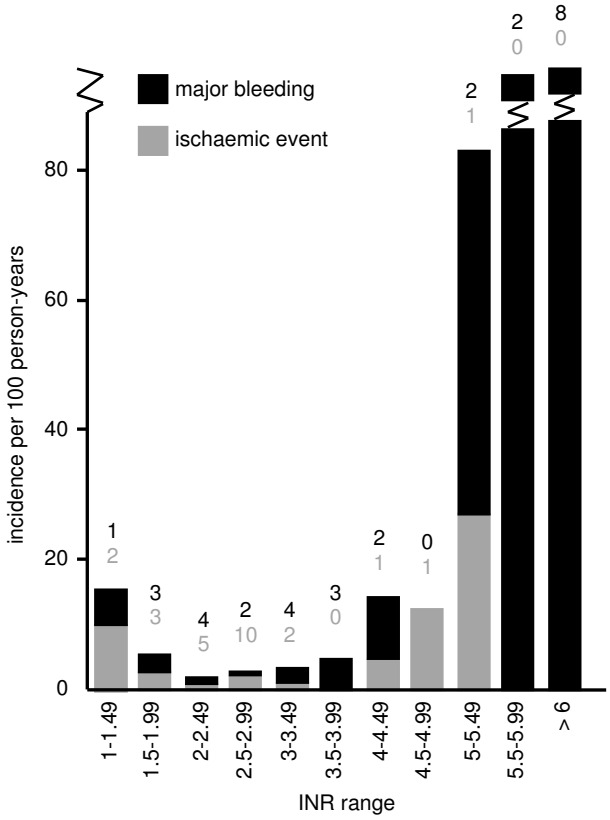
Table 3. The occurrence of first outcome events according to allocated treatment: anticoagulants versus aspirin

			intention to treat		on treatment	
	AC	ASA	HR	95% CI	HR	95% CI
patients randomised	536	532				
person-years of observation[a]	2204	2227				
death from all vascular causes, nonfatal stroke, nonfatal MI, nonfatal major bleeding complication[b]	99 (18.5%)	98 (18.4%)	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 all vascular causes	31	24	1.31	0.77-2.23	1.43	0.73-2.78
death from all vascular causes, nonfatal stroke[b]	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				
intracranial (%)	18	9				
fatal bleeding complication[*]	11	4	2.8	0.9-8.8	5.5	1.2-25.4
all major ischaemic events: nonhaemorrhagic death from vascular causes, nonfatal ischaemic stroke, nonfatal MI[b]	62	84	0.73	0.52-1.01	0.72	0.50-1.04
death from all vascular causes, nonfatal stroke, nonfatal MI[b]	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	0.8	0.50-1.22
first cardiac event*	25	33	0.77	0.46-1.29	0.81	0.44-1.51

*AC: anticoagulants; ASA: aspirin; a: years of follow-up until primary outcome event or end of follow-up; b: whichever event occurred first, 8 strokes (5 in the anticoagulant group and 3 in the aspirin group) of unspecified origin were included; HR: hazard ratio; CI: confidence interval; MI: myocardial infarction; *: post hoc defined outcome events*

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 plus dipyridamole.

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 (black) and ischaemic events (grey) in the INR range. Incidence in INR range 5.5-5.99=133, incidence in INR range >6=308.

Table 4. The occurrence of first outcome events according to allocated treatment: anticoagulants versus aspirin plus dipyridamole

			intention to treat		on treatment	
	AC	AD	HR	95% CI	HR	95% CI
patients randomised	523	509				
person-years of observation[a]	2394	2443				
death from all vascular causes, nonfatal stroke, nonfatal MI, nonfatal major bleeding complication[b]	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 all vascular causes	34	24	1.42	0.84-2.40	1.19	0.64-2.20
death from all vascular causes, nonfatal stroke[b]	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	3.16-20.4
extracranial (%)	28	10				
intracranial (%)	19	1				
fatal bleeding complication[*]	11	2	5.53	1.22-24.9	n.e.	n.e.
all major ischaemic events: nonhaemorrhagic death from vascular causes, nonfatal ischaemic stroke, nonfatal MI[b]	67	70	0.94	0.67-1.31	0.83	0.57-1.21
death from all vascular causes, nonfatal stroke, nonfatal MI[b]	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

*AC: anticoagulants; AD: aspirin plus dipyridamole; a: years of follow-up until primary outcome event or end of follow-up; b: whichever event occurred first, 6 strokes (5 in the anticoagulant group and 1 in the aspirin plus dipyridamole group) of unspecified origin were included; HR: hazard ratio; CI: confidence interval; MI: myocardial infarction; n.e.: not estimable; *: post hoc defined outcome events*

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 off set 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] 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 nonrheumatic atrial fibrillation28,29 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 off set 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 anti-coagulation 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.

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Chapter 6

Dipyridamole plus aspirin versus aspirin alone in the secondary prevention after TIA or stroke: a meta-analysis by risk

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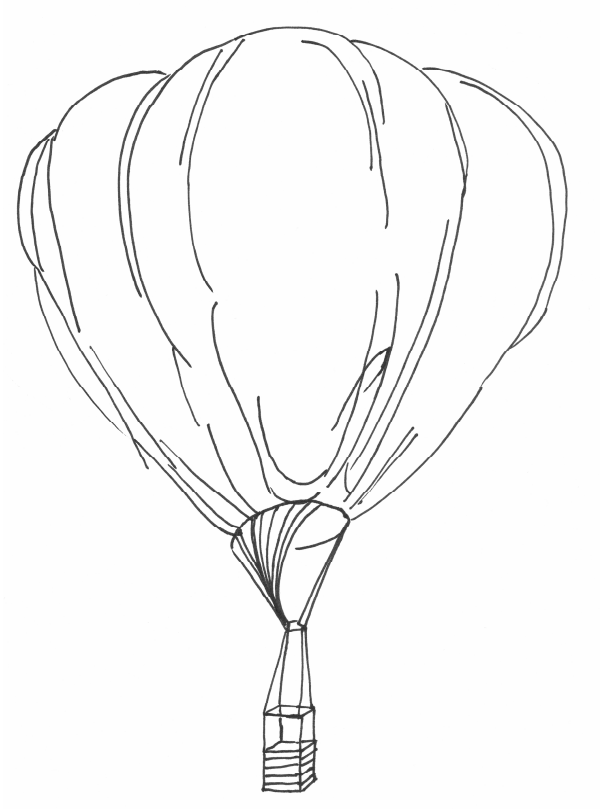


Abstract
Objectives- Our aim was to study the effect of combination therapy with aspirin and dipyridamole (A+D) over aspirin alone (ASA) in secondary prevention after transient ischemic attack or minor stroke of presumed arterial origin and to perform subgroup analyses to identify patients that might benefit most from secondary prevention with A+D.
Data sources- The previously published meta-analysis of individual patient data was updated with data from ESPRIT (N=2,739); trials without data on the comparison of A+D versus ASA were excluded.
Review methods- A meta-analysis was performed using Cox regression, including several subgroup analyses and following baseline risk stratification.
Results- A total of 7,612 patients (5 trials) were included in the analyses, 3,800 allocated to A+D and 3,812 to ASA alone. The trial-adjusted hazard ratio for the composite event of vascular death, non-fatal myocardial infarction and non-fatal stroke was 0.82 (95% confidence interval 0.72-0.92). Hazard ratios did not differ in subgroup analyses based on age, sex, qualifying event, hypertension, diabetes, previous stroke, ischemic heart disease, aspirin dose, type of vessel disease and dipyridamole formulation, nor across baseline risk strata as assessed with two different risk scores. A+D were also more effective than ASA alone in preventing recurrent stroke, HR 0.78 (95% CI 0.68 – 0.90).
Conclusion- The combination of aspirin and dipyridamole is more effective than aspirin alone in patients with TIA or ischemic stroke of presumed arterial origin in the secondary prevention of stroke and other vascular events. This superiority was found in all subgroups and was independent of baseline risk.

Introduction

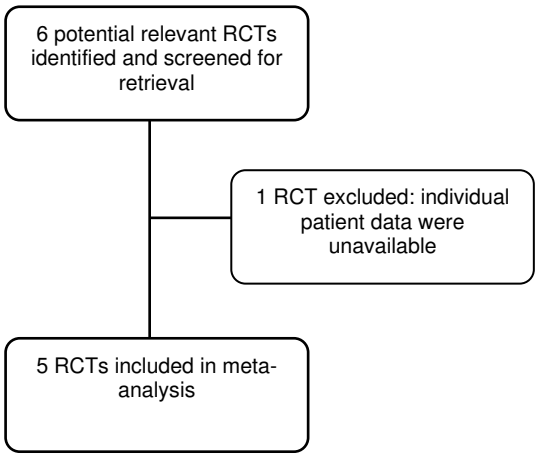
After a transient ischemic attack (TIA) or stroke of presumed arterial origin patients have an annual risk of a serious vascular event (recurrent stroke, myocardial infarction or death from vascular cause) of 9% in population based studies.[1] Treatment with aspirin, in a dose between 30 and 300 mg daily, reduces this risk by 13-22%.[2-4] In one study, treatment with dipyridamole alone was found to reduce risk by a similar amount.[5] Although clopidogrel was marginally superior to aspirin in the CAPRIE trial, no statistically significant difference was seen in the subset of patients with previous ischemic stroke (average event rate per year 7.15% for clopidogrel versus 7.71% for aspirin, relative-risk reduction of 7.3% (95% CI -5.7-18.7).[6] Furthermore, there is no indication for an additional benefit of combining aspirin and clopidogrel as compared with either drug alone,[7,8] or for anticoagulation treatment with any INR range.[9-13] The combination of aspirin and dipyridamole has been tested in several trials although early results did not show any beneficial effect over aspirin alone.[14-17] In contrast, the 'Second European Stroke Prevention Study' (ESPS 2) found that the addition of dipyridamole (extended release 200 mg twice daily) to aspirin (50 mg daily) reduced serious vascular events by 22% (95% confidence interval [CI] 9-33%) in comparison with aspirin alone.[5,18] The positive results of two meta-analyses on this comparison were based mainly on the results of ESPS 2, which was by far the largest trial included.[19,20] Subsequently, the European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT)[21] confirmed the results of ESPS 2; the hazard ratio for the primary outcome event (vascular death, recurrent stroke, myocardial infarction, or major bleeding complication) was 0.80 (95% CI 0.66-0.98).[21]
We have updated the earlier meta-analysis based on individual patient data (IPD)[20] with the inclusion of ESPRIT and aimed to identify patients who may benefit most from the combination of aspirin and dipyridamole. In particular, we wished to assess whether a patient's baseline risk would modify the efficacy of combination therapy.

Methods

Searching and selection

The search strategy to identify all eligible randomized controlled trials on the effectiveness of dipyridamole in the secondary prevention after TIA or minor stroke of arterial origin has been described previously.[20] We selected trials which compared, at a minimum, the combination therapy of aspirin and dipyridamole with aspirin alone. The principal investigators of each included trial shared individual patient data for use in the current analysis.

Figure 1. Trial flow



Data abstraction

Data from the different trials were merged into a single data set for analysis. This database contained information on demography (age, sex), qualifying event (TIA or stroke, clinical features of the event, findings on brain imaging), vascular risk profile (history by of hypertension, diabetes, ischemic heart disease or stroke and blood pressure at baseline), prescribed trial medication (dose of aspirin and formulation of dipyridamole) and the occurrence of serious events ((vascular) death, myocardial infarction or stroke) during the trial. On the basis of findings on brain imaging (CT or MRI) and clinical features, we classified patients as having small or large vessel disease. If a relevant ischemic 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.[22,23]

Study characteristics

The primary outcome event was the composite of death from all vascular causes, non-fatal stroke and non-fatal myocardial infarction. Secondary outcome events were the composite of death from all vascular causes or non-fatal stroke, all death, death from vascular causes, fatal and non-fatal stroke, and fatal and non-fatal myocardial infarction. Prespecified subgroup analyses for the primary outcome event were performed according to age (<65 years vs. ≥65 years), sex (male vs. female), qualifying event (TIA vs. stroke), type of vessel disease in qualifying event (small vs. large), dose of aspirin (<75 mg vs. ≥75 mg), formulation of dipyridamole (immediate vs. extended release), time between qualifying event and randomization (< 1 week vs. 1 week-1 month vs. 1-6 months) and history of hypertension, diabetes, stroke or ischemic heart disease.

In addition we did a subgroup analysis according to baseline risk as assessed with two different risk models. The first model used three risk factors: age 65 years or older, stroke as a qualifying event and a history of hypertension; the risk of stroke increased with an increasing number of risk factors (0-3) in the previous IPD meta-analysis.[20] The area under the receiver operator characteristics curve (AUC-ROC) for this model in the current data set was 0.59 (95% CI 0.57-0.60) The second model was developed with data from the Dutch TIA Trial (DTT), a secondary stroke prevention trial with a factorial design comparing two doses of aspirin, and atenolol, with placebo.[24,25] We

Table 1. Cross-tabulation for the risk scores from the two models used (both scores known for 5,967 patients)

risk score quintiles*	risk score based on 3 risk factors†			
	0	**1**	**2**	**3**
1	237	594	365	2
2	116	392	521	164
3	58	273	556	310
4	15	180	547	449
5	2	81	469	636

**: quintiles based on risk score calculated with formula: 0.532*sex (0: female, 1: male) + 0.037*age (years) + 0.757*diabetes (0: no, 1: yes) + 0.383*history of ischemic heart disease (0: no, 1: yes) + 0.007*systolic blood pressure (mm Hg); †: n of risk factors: age 65 years or older, stroke as a qualifying event and a history of hypertension*

used those characteristics identified previously to be associated with new vascular events[26] and that were available in the present dataset, resulting in a risk score: 0.532*sex (0: female, 1: male) + 0.037*age (years) + 0.757*diabetes (0: no, 1: yes) + 0.383*history of ischemic heart disease (0:no, 1: yes) + 0.007*systolic blood pressure (mm Hg); its AUC-ROC was 0.62 (95% CI 0.60-0.64). Based on this risk score, patients were divided into 5 risk-quintiles. Subgroup analyses were performed based on the different risk groups from these two models. The numbers needed to treat were calculated for each subgroup. In Table 1 a cross-tabulation for the risk scores from the two models is shown to give an impression of the agreement of risk between the models.

Quantitative data synthesis

Data were analyzed according to the intention-to-treat principle. The occurrence of outcome events was compared between patients allocated to combined aspirin and dipyridamole versus patients allocated to aspirin in terms of the hazard ratio (HR, with 95% CI), calculated with Cox proportional hazard modeling. To adjust for a possible heterogeneity between the trials we stratified the Cox model with trial as the stratification factor.[27] All analyses were in duplicate performed, independently, by two investigators (PH, LG).
Analyses were performed with Stata version 8 and SPSS version 12.0.02.

Results

Trial flow and study characteristics

Five randomized controlled trials comparing the combination of aspirin and dipyridamole with aspirin alone in the secondary prevention after cerebral ischemia of arterial origin were identified (Figure 1).[5,14-16,21] In two trials, randomization was only done between combination therapy and aspirin alone;[16,21] whereas the other trials also compared combination therapy with placebo,[5,14,15] or dipyridamole alone.[5] The dose of aspirin was fixed in four trials: 25 mg twice daily,[5] 300 mg three times daily,[14] 325 mg three times daily[16] or 330 mg three times daily.[15] In ESPRIT the dose of aspirin was left to the discretion of the treating physician, provided it was between 30 and 325 mg daily. The dose of dipyridamole was 50 mg three times daily[14], 75 mg three[15] or four[16] times daily or 200 mg twice daily.[5,21] In three trials all patients used the immediate release formulation of dipyridamole,[14-16] and in one trial all patients used the extended release formulation.[5] In ESPRIT the majority of patients (83%) used the extended release formulation and the remaining patients used the immediate release formulation.[21] One trial only included patients with a TIA;[16] the others also included patients with a minor stroke.[5,14,15,21] The five trials included 3,800 patients allocated to combined aspirin and dipyridamole, and 3,812 patients allocated to aspirin alone. Table 2 shows the baseline characteristics for the different trials and for the combined data. Apart from the differences mentioned above (dose of aspirin, formulation of dipyridamole and type of qualifying event), the main difference between the samples was that the mean age was higher in ESPS 2 (mean age 67 versus 62-63 in the other trials) and the fact that in the

Table 2. Trial characteristics for included trials

trial year	FU	trt.	n	male (%)	age*	QE (%)	stroke (%)	HT (%)	SBP*	DBP*	IHD	DM
Toulouse	36-72	**AD**	137	112 (82)	62 (10)	81 (60)	-	-	-	-	-	-
1982[14]		**A**	147	126 (86)	62 (9)	92 (63)	-	-	-	-	-	-
AICLA	36	**AD**	202	146 (72)	63 (10)	169 (84)	-	119 (59)	149 (20)	90 (10)	-	51 (25)
1983[15]		**A**	198	131 (66)	63 (10)	68 (85)	-	129 (65)	150 (21)	90 (12)	-	44 (22)
ACSSG	24-60	**AD**	448	306 (68)	63 (10)	0	-	214 (48)	-	-	-	70 (16)
1985[16]		**A**	442	288 (65)	63 (10)	0	-	205 (46)	-	-	-	49 (11)
ESPS 2	24	**AD**	1650	956 (58)	67 (11)	1246 (76)	439 (27)	979 (60)	150 (22)	85 (12)	573 (35)	254 (15)
1996[5]		**A**	1649	956 (58)	67 (11)	1257 (76)	464 (28)	983 (60)	151 (21)	86 (11)	571 (35)	240 (15)
ESPRIT	mean	**AD**	1363	897 (66)	63 (11)	895 (66)	159 (12)	814 (60)	152 (24)	86 (12)	179 (13)	260 (19)
2006[21]	42	**A**	1376	892 (65)	63 (11)	921 (67)	155 (11)	817 (59)	152 (23)	86 (12)	177 (13)	252 (18)
total	31	**AD**	3800	2417 (64)	65 (11)	2391 (63)	598 (20)†	2126 (58)†	151 (23)†	86 (12)†	749 (25)†	635 (17)†
		A	3812	2393 (63)	65 (11)	2438 (64)	619 (21)†	2134 (58)†	151 (22)†	86 (12)†	748 (25)†	585 (16)†

*FU: duration of follow-up (months;, trt.: allocated treatment; n: number of patients; *: mean (SD); QE: stroke as qualifying event; stroke: stroke before qualifying event; HT: history of hypertension; SBP: systolic blood pressure; DBP: diastolic blood pressure; IHD: history of ischemic heart disease; DM: history of diabetes mellitus; AD: aspirin plus dipyridamole; A: aspirin, †: total limited to the trials with data for this characteristic*

Toulouse trial there were more males included (more than 80% versus less than 70% in the others). In total, almost two-thirds of patients were male with a mean age of 65 years. In the majority the qualifying event was a stroke. There were no major differences in the prevalence of vascular risk factors between the different trials. The mean length of follow-up was 2.6 years (range 0-8.21 years).

Quantitative data synthesis
In the combined aspirin and dipyridamole group 475 patients (12.5%) had a primary outcome event, compared with 579 patients (15.2%) in the aspirin group, resulting in an adjusted HR of 0.82 (95% CI 0.72-0.92) (Table 3).

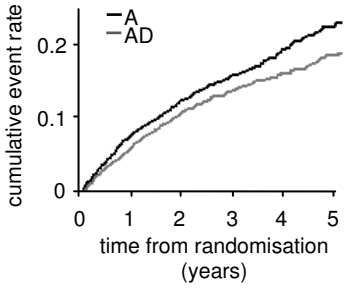
Table 3. Occurrence of outcome events, according to treatment

	ASA+DIP n = 3800	ASA n = 3812	HR	95% CI
person-years of observation	9441	9396		
vascular death, non-fatal stroke or non-fatal myocardial infarction	475 (12.5%)	579 (15.2%)	0.82	0.72-0.92
vascular death or non-fatal stroke	434	528	0.81	0.72-0.92
all death	358	360	1.01	0.87-1.17
vascular death	175	187	0.96	0.78-1.18
recurrent stroke	341	429	0.78	0.68-0.90
myocardial infarction	81	87	0.94	0.69-1.27

ASA+DIP: aspirin and dipyridamole; ASA: aspirin; MI: myocardial infarction; HR: hazard ratio adjusted for trial; CI: confidence interval

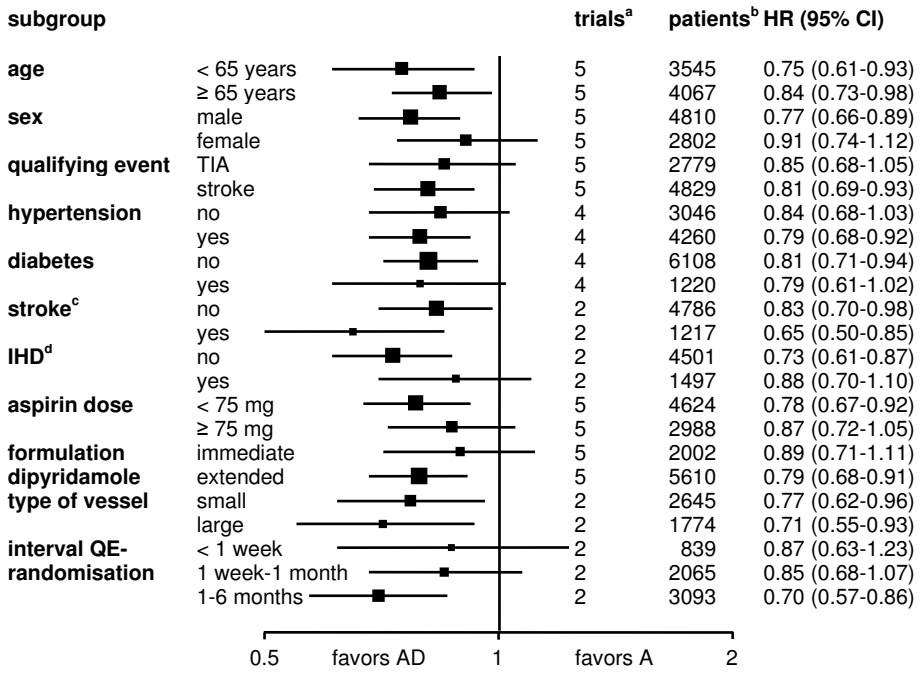
The adjusted HR for the composite event of death from vascular cause or non-fatal stroke was 0.81 (95% CI 0.72-0.92), that for vascular death 0.96 (95% CI 0.78-1.18) and for recurrent stroke 0.78 (95% CI 0.68-0.90). The number needed to treat (1/absolute risk reduction*100) with aspirin plus dipyridamole instead of aspirin alone to prevent one serious vascular event to happen is 100 per year.
Figure 2 shows the time-to-event curve for the primary outcome event.
Figure 3 shows the results of the subgroup analyses according to age, sex, qualifying event, hypertension, diabetes, stroke, ischemic heart disease, dose of aspirin, type of vessel

Figure 2. Time to event curve for the primary outcome event: the composite of death from all vascular causes, non-fatal stroke and non-fatal myocardial infarction



disease, formulation of dipyridamole and interval between qualifying event and randomization for the primary outcome event. No major differences between the subgroups were found (smallest p value for interaction 0.14). The only slight differences in the estimated hazard ratios for the subgroups confirm the superior efficacy of aspirin plus dipyridamole in all groups.

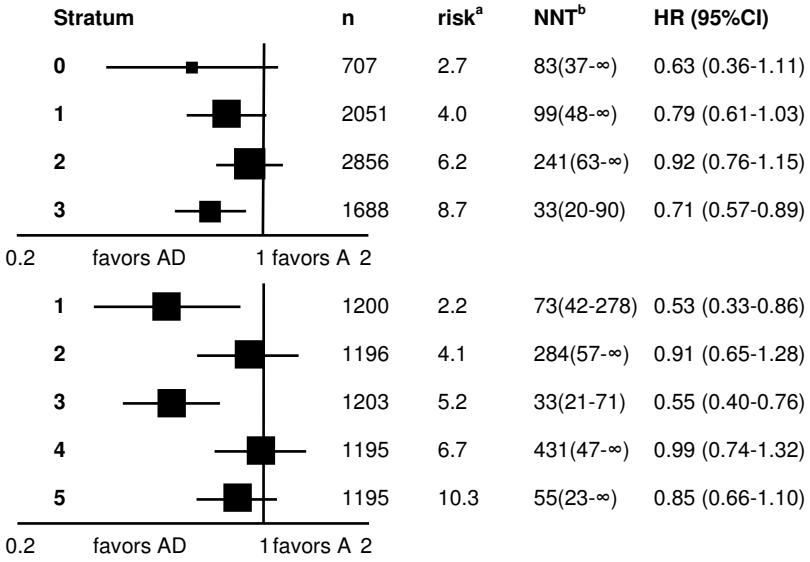
Figure 3. Subgroup analyses for the primary outcome event: the composite of death from all vascular causes, non-fatal stroke and non-fatal myocardial infarction; according to risk factors



a: number of trials for which the characteristic is known; b: number of patients in subgroup; c: stroke before qualifying event; d: history of ischemic heart disease; QE: qualifying event; AD: aspirin plus dipyridamole; A: aspirin

Figure 4 shows the subgroup analyses according to the number of risk factors present at baseline (known for 7,302 patients) and according to the risk score derived from the DTT-risk model (known for 5,989 patients). The HRs were broadly similar in all risk groups and not different from the overall HR (smallest p value for interaction 0.11). The numbers needed to treat with dipyridamole and aspirin instead of aspirin alone to prevent one major vascular event per year are shown as well; no major differences were found here either.

Figure 4. Subgroup analyses for the primary outcome event: the composite of death from all vascular causes, non-fatal stroke and non-fatal myocardial infarction; analyses according to risk groups based on presence of 3 risk factors (above) and according to risk groups based on DTT-risk model (below)



a: risk (%) on a major vascular event (vascular death, nonfatal stroke or nonfatal myocardial infarction) per year; NNT: numbers needed to treat with aspirin and dipyridamole instead of with aspirin alone to prevent one major vascular event per year; HR: hazard ratio; CI: confidence interval; AD: aspirin plus dipyridamole; A: aspirin

Discussion

This individual patient data meta-analysis confirms that the combination of aspirin and dipyridamole is more effective than aspirin alone in secondary vascular prevention after TIA or minor stroke from arterial origin. From figure 2 we can conclude that the advantage of the combination therapy of aspirin plus dipyridamole starts early on and remains present over time. Importantly, analyses in prognostic subgroups, including age, sex and vascular history, found no differential effects between groups of patients whereas currently there may be a selection of patients who receive dipyridamole in addition to aspirin.
Quantitatively, combined aspirin and dipyridamole reduce vascular events by 18%, and stroke by 22%, as compared with aspirin alone, results which do not differ materially from earlier meta-analyses,[19-21] In contrast, dual antiplatelet therapy had no advantage over aspirin in preventing total death, vascular death, or myocardial infarction; importantly, the combination of aspirin and dipyridamole did not increase the incidence of myocardial infarction.
The number needed to treat found in this meta-analysis is 100 per year, which is about the same as the number needed to treat for aspirin versus placebo.

Whether this NNT is cost-effective for aspirin plus dipyridamole should be formally assessed in a cost-effectiveness analysis.

The risk models we used did not have a strong discriminatory ability with regard to prediction of major vascular events, as is obvious from the AU ROCs (0.59 and 0.62 respectively). Unfortunately, there are no stronger prediction models for vascular events after a TIA or minor stroke.[28] Moreover, we could only use those variables that were available in the included trials.

Previous subgroup analyses in ESPS 2 suggested that the relative efficacy for combination therapy was greater in patients at high risk of recurrence than those at lower risk.[29,30] In our larger individual patient data meta-analysis, in contrast, we found that relative efficacy for vascular events was not related to the estimated baseline risk. Moreover, the numbers needed to treat varied between the different risk groups, but there was no indication that these numbers were higher in low risk patients. The independence of relative risk reduction from baseline risk is important since the risk of recurrence has fallen with time in patients randomized to aspirin (overall, 6.1% per year versus 4.3% per year in ESPRIT), this presumably reflecting improved non-antiplatelet prophylaxis.

The main difference between the five trials was the prescribed trial medication. Aspirin doses varied reflecting historical and geographical variations in practice. Since lower doses of aspirin (30-75 mg daily) are no less effective at preventing vascular recurrence than higher doses,[2,24] this variation is unlikely to have influenced the results. Similarly, the dose and formulation of dipyridamole varied between the trials; older studies used short acting (immediate release) dipyridamole give 3-4 times per day[14-16] whereas all patients in ESPS 2 and most (83%) in ESPRIT received extended release dipyridamole twice daily.[5,21] This difference might explain, in part, the difference seen in efficacy between older and newer trials with dipyridamole. However, our subgroup analyses do not show any differences in efficacy of aspirin and dipyridamole between different doses of aspirin or different formulations of dipyridamole.

The results of meta-analyses may be confounded if data from unpublished trials are not available for inclusion; notably, these trials are more likely to be neutral or negative in outcome leading to publication bias. Missing trials have never been reported to us following our previous meta-analyses[19,20] so it is very unlikely that any medium-sized to large trials are missing here. However, data on risk factors were not available for all five trials so the subgroup analyses involve fewer patients for some analyses. Nevertheless, meta-analysis allows the total evidence to be assessed and the use of individual patient data, as here, is superior to the use of summary group data.[31]

The superiority of combination aspirin and dipyridamole over aspirin alone in secondary vascular prevention after TIA or stroke is now well supported. The hazard ratio found in this individual patient data meta-analysis is consistent with the two largest clinical trials and does not appear to differ in subgroups of patients. Combination therapy with aspirin and dipyridamole should be preferred over aspirin alone in all patients after a TIA or minor stroke of presumed arterial origin, as supported by several national guidelines.

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Chapter 7

Risk indicators for development of headache during dipyridamole treatment after cerebral ischaemia of arterial origin

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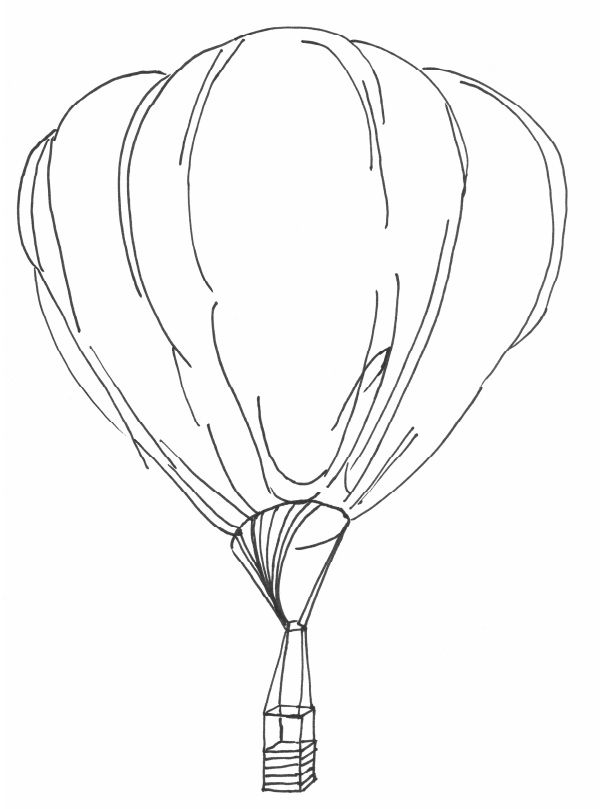

Abstract
Background- A considerable proportion of patients discontinue dipyridamole because of headache. We aimed to identify risk indicators for the development of dipyridamole induced headache by means of an exploratory analysis of data from the European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) and the Second European Stroke Prevention Study (ESPS 2).
Results- In ESPRIT dipyridamole induced headache was significantly associated with female sex, absence of hypertension and non-smoking (area under the ROC curve: 0.63 (95% CI 0.58-0.68)) and in ESPS 2 with female sex and absence of ischaemic lesions on imaging (area under the ROC curve: 0.64 (95% CI 0.59-0.69)).
Interpretation- Development of dipyridamole induced headache might be related to the integrity of vascular endothelium.

Introduction

In a meta-analysis of all trials comparing aspirin plus dipyridamole with aspirin in the secondary prevention after a Transient Ischaemic Attack (TIA) or minor stroke of arterial origin an overall risk ratio for the composite event 'vascular death, nonfatal stroke or nonfatal myocardial infarction' of 0.82 (95% confidence interval 0.74-0.91) was found,[1] resulting in the prescription of this therapy to many patients. An important drawback of treatment with dipyridamole, however, is that a substantial proportion of patients discontinue this medication because of side effects, mainly headache. Previous studies reported 24-70% of patients on dipyridamole to develop headache.[2-4] The pathophysiology of this dipyridamole-associated headache is unknown, but similarities with the headache in migraine or nitrate administration have been noted.[5,6] An initial titration phase with a lower dose of dipyridamole might help to avoid the headache.[6] Moreover, a study in healthy volunteers implied that in most patients the headache decreases with continued use.[7] We aimed to identify risk indicators associated with the development of headache during treatment with aspirin plus dipyridamole by means of an exploratory analysis of data from the European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) and the Second European Stroke Prevention Study (ESPS 2).[1,3]

Methods

We included all patients randomised for the combination therapy of aspirin plus dipyridamole in ESPRIT (n=1353) and ESPS 2 (n=1650), two trials on the secondary prevention after TIA or minor stroke of arterial origin. For detailed information on the methods of these trials we refer to the original publications.[1,3] In ESPRIT patients used aspirin in any dose between 30 and 325 mg daily, in combination with dipyridamole 200 mg twice daily (83% used the extended release preparation).[1] In ESPS 2 patients used aspirin 25 mg twice daily plus extended release dipyridamole 200 mg twice daily.[1,3]

All demographic data, data on vascular risk factors and on history of vascular disease of the patients were collected at the time of inclusion in the trials. Results of baseline imaging (CT or MRI) were available for 96% of ESPRIT patients and for 81% of ESPS 2 patients. For 90% of the ESPRIT patients it was recorded whether there was a stenosis of more than 50% of one of the carotid arteries. The results of carotid ultrasound were available for 52% of ESPS 2 patients; they were classified as normal or abnormal.

During follow-up of ESPRIT patients were asked if they still used the trial medication. If they discontinued it, the reason for discontinuation was recorded in the patient's or physician's words. For the purpose of the analysis of ESPRIT all forms were reviewed and the reasons for discontinuation were classified into 9 categories, one of which was headache (alone or in combination with other adverse events). During follow-up of ESPS 2 patients were systematically questioned with regard to several adverse events, one of which was headache. In case of discontinuation of the trial medication a pre-specified reason for discontinuation had to be chosen, one of which was 'adverse events'. For the purpose of this study we assumed that all patients who discontinued trial

medication because of adverse events and who also reported headache while taking the medication discontinued it, at least partly, because of headache. We explored the association between demographic data, vascular risk factors and symptoms at baseline on the one hand and discontinuation of dipyridamole because of headache on the other. Because of differences in definitions of risk factors and of discontinuation because of headache we performed separate analyses for the two trials. We related the baseline factors to discontinuation by means of Cox proportional hazard modelling, as patients were followed for different periods and discontinuation occurred at various times. Hazard ratio's (which can be interpreted as relative risk) are reported with the corresponding 95% confidence interval. If a factor protected against discontinuation (i.e., hazard ratio and upper limit of the confidence interval <1), we used the inversed factor as predictor for discontinuation. To construct a prediction model, variables selected from the univariable analysis (p for hazard ratio <0.20) were entered into a multivariable model; all variables with a significant influence on the model were retained. The discriminatory power of this model was analysed with receiver operator characteristic (ROC) curves and corresponding area under the curve.

Results

In ESPRIT 123 (9%) of the 1353 patients allocated to the combination therapy of aspirin and dipyridamole discontinued this medication because of headache, against 158 (10%) of the 1650 patients in ESPS 2. Figure 1 shows the time to event curve for headache induced discontinuation in both trials. The majority of patients who stopped, did this within 3 months from randomisation (76% of ESPRIT and 80% of ESPS 2 patients).

Figure 1. Time to event curve for discontinuation of trial medication because of headache in EPSRIT and ESPS 2

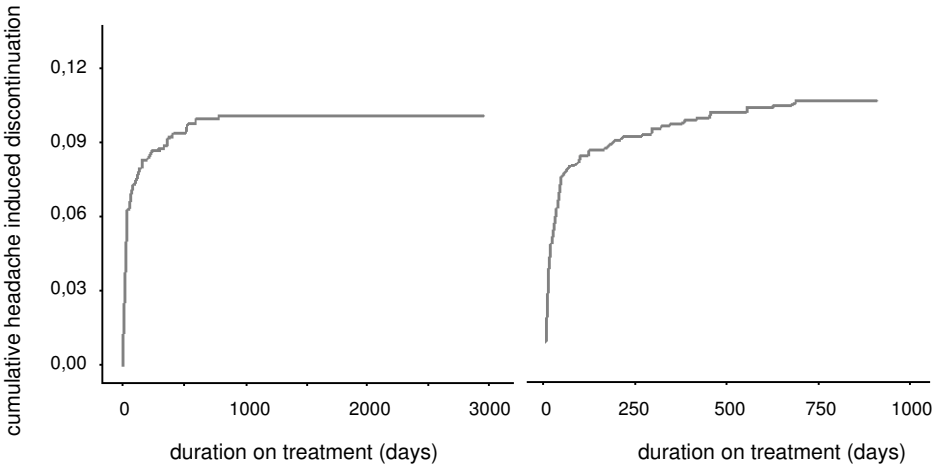

Table 1 shows the relation between baseline characteristics and headache induced discontinuation.

Table 1. Relation between baseline characteristics and headache induced discontinuation of dipyridamole.

	ESPRIT		ESPS 2	
	Hazard ratio	95% CI[a]	Hazard ratio	95% CI[a]
demographics				
female sex	**2.03**	**1.42-2.89**	**1.82**	**1.33-2.50**
age (per 10 years)	**1.17**	**1.00-1.38**	0.89	0.78-1.02
baseline investigations				
abnormalities on carotid ultrasound	0.39[b]	0.16-0.95	0.69[c]	0.42-1.15
no abnormalities on carotid ultrasound	**2.58**	**1.05-6.34**		
ischaemic lesion on CT or MRI	0.63[d]	0.42-0.95	0.52[e]	0.37-0.72
no ischaemic lesion on CT or MRI	**1.58**	**1.05-2.39**	**1.93**	**1.37-2.71**
history				
stroke	0.80	0.44-1.45	1.07	0.76-1.51
ischaemic heart disease	0.82[f]	0.43-1.57	0.76[g]	0.52-1.12
myocardial infarction	0.82	0.38-1.77	0.57	0.29-1.12
intermittent claudication	0.73	0.30-1.78	0.79	0.52-1.18
diabetes mellitus	0.68	0.41-1.13	0.71	0.43-1.16
smoking	0.57	0.38-0.86	0.68	0.46-1.01
no smoking	**1.76**	**1.16-2.65**	**1.47**	**1.00-2.18**
hypertension	0.66	0.47- 0.94	0.96	0.70-1.31
no hypertension	**1.51**	**1.06-2.15**		
hyperlipidemia	0.92	0.64-1.31	0.87	0.60-1.26

a: CI = confidence interval; b: defined as stenosis carotid artery(ies) > 50%; c: defined as any abnormality on carotid duplex; d: only relevant, i.e. symptomatic, lesions; e: any ischaemic lesion; f: defined as angina pectoris; g: history of any ischaemic heart disease, other than myocardial infarction

Factors that showed a positive relation with discontinuation because of headache in ESPRIT were female sex, age, absence of stenosis >50% of the carotid arteries, absence of a relevant ischaemic lesion on imaging, non-smoking and absent history of hypertension. In the multivariable model for headache-induced discontinuation, the association was statistically significant for female sex, absence of hypertension and non-smoking. The area under the ROC curve for the

model with these factors was 0.63 (95% CI 0.58-0.68).Factors that had a positive relation with discontinuation because of headache in ESPS 2 were female sex, absence of any ischaemic lesion on brain imaging and non-smoking. In the multivariable model for headache-induced discontinuation, the association was statistically significant for female sex and absence of ischaemic lesions on imaging. The area under the ROC curve for the model with these factors was 0.64 (95% CI 0.59-0.69).

Discussion

This exploratory analysis identified several factors associated with the development of headache when dipyridamole was combined with aspirin after a TIA or minor ischaemic stroke. Associations that were consistent between the two trials were female sex, the absence of (relevant) ischaemic lesions on brain imaging and non-smoking. The joint discriminative power of the factors, however, was limited.

The association with the absence of stenosis of the carotid arteries found in ESPRIT was not found in ESPS 2, where fewer patients underwent ultrasound investigation of the carotid arteries. Moreover, in ESPS 2 no distinction was made according to the degree of stenosis, whereas in ESPRIT only a stenosis >50% was considered abnormal. In ESPRIT there also was an association with absent history of hypertension, which was not found in ESPS 2.

There are at least two proposed mechanisms of action of dipyridamole on the vascular system. First, it inhibits the reuptake of adenosine by red blood cells, platelets and the endothelium, increasing the extracellular level of adenosine. Adenosine in turn activates adenylate cyclase and causes a rise in cAMP.[5,8] Secondly, it inhibits phosphodiesterase (PDE) in various tissues, thereby increasing cGMP production by endothelium-derived relaxing factor (i.e. nitric oxide). Either action can also result in vasodilatation and, consequently, headache. As both actions are mediated by endothelium, this dipyridamole-induced vasodilatation is probably more pronounced in patients with a healthy endothelial function. The majority of factors we identified in this study as predictors for the development of headache also interact with endothelial function. Patients with presumably healthier endothelial function, such as non smokers, were found more prone to headache. Conversely, the factors that were associated with absence of headache correspond with a less healthy endothelium. This does not apply to female sex, as there is no reason to assume that females have a healthier endothelium than men. The association with female sex, however, may be caused by the same mechanisms that cause a higher risk of migraine in women, as there are probably similarities between migraine and dipyridamole induced headache.

The ESPRIT and ESPS 2 trials were not designed to perform an analysis on risk predictors for the development of headache in patients taking dipyridamole, which has probably resulted in an underestimation of the number of patients who discontinued dipyridamole because of headache. On the other hand, when the trials were designed, no preventive measures for the development of headache

were planned, which possibly led to more patients discontinuing dipyridamole than necessary.
We did not aim to develop an approach to avoid non-adherence to dipyridamole in clinical practice. Therefore we cannot offer evidence-based advice on how to avoid headache in dipyridamole treatment. Future studies on dipyridamole-induced headache should focus on the physiological and biochemical factors involved, as well on the clinical characteristics that predict the development of headache. These studies may confirm or refute our hypothesis that development of headache is related to the integrity of vascular endothelium.

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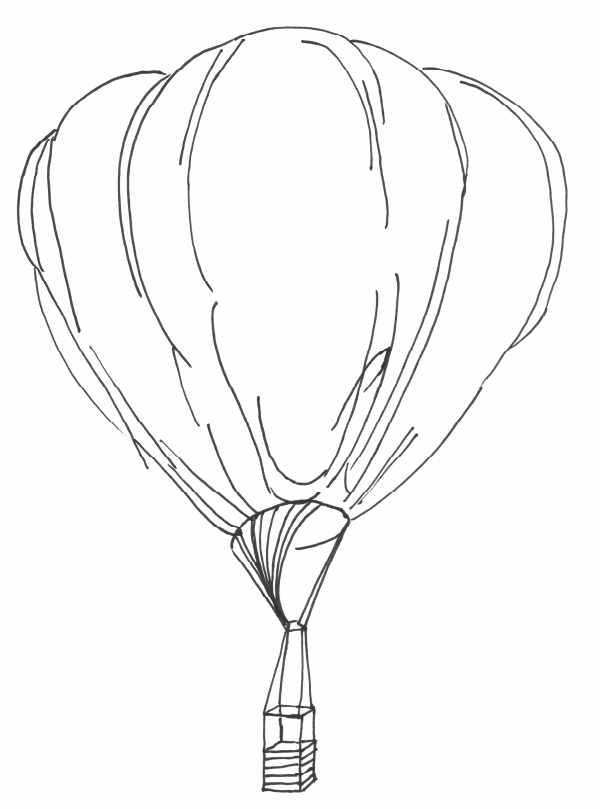
Chapter 8

General discussion



Secondary prevention; the ESPRIT trial

The main finding of this thesis is the superiority of the combination therapy of aspirin plus dipyridamole over aspirin alone in the secondary prevention after TIA or minor ischaemic stroke of presumed arterial origin. In the ESPRIT trial, described in **chapters 4 and 5**,[1-4] we found that the combination therapy was superior to aspirin alone in the prevention of serious vascular events (death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction and major bleeding complication). When we compared mild intensity oral anticoagulants (aimed INR 2.0-3.0) with aspirin alone, we found no difference in the prevention of serious events; there was a trend towards less ischaemic complications in patients allocated to anticoagulants, but this was offset by more bleeding complications in this group. In a post hoc analysis, oral anticoagulants were compared with the combination therapy of aspirin plus dipyridamole. Although the power of this analysis was limited, the combination was more effective than oral anticoagulants.

The publication of these results had major clinical implications. Many 'non-believers' of the efficacy of dipyridamole, including some of the members of the Steering Committee of ESPRIT, had to reconsider their believe. The standard therapy in the secondary prevention after TIA or non-disabling stroke had to change in many countries. Monotherapy with aspirin was no longer the preferred treatment, but was replaced by the combination of with aspirin plus dipyridamole in many guidelines and protocols, amongst others the guidelines of the American Heart Association/ American Stroke Association (AHA/ASA) and the European Stroke Organisation.[5,6]

Several criticasters commented on the non-blinded study design, where patients and treating physicians knew which medication the patient used.[7-11] This design might, in theory, have influenced the investigators' interpretation of potential endpoints, and might have led to under- or over reporting of outcome events. As the endpoints were 'major' i.e. unlikely to miss because of the serious clinical implications for the patient, and because most of the participating neurologists participated because they had doubt about the best treatment strategy, we do not think the unblinded design has had a major influence on the results of ESPRIT. Moreover, the members of the auditing committee for outcome events who classified the outcome events were blind for allocated treatment.

Another point of extensive discussions was the dose of aspirin.[7,12] In ESPRIT, the treating physician was free to decide which dose, within the range of 30-325 mg daily, he or she would prescribe. This is a reflection of daily practice, where doses of aspirin in secondary prevention differ between and even within countries. No matter how firm the evidence for equal efficacy of different doses of aspirin is,[13-16] some people are not convincible and still think the minimum effective dose is more than 30 mg,[12] which was prescribed to many (Dutch) ESPRIT patients. Moreover, as the dose of aspirin was similar in both groups studied in ESPRIT,

the effect we found can be considered the effect of adding dipyridamole to aspirin, no matter what dose of aspirin used.

After the analysis of the first part of ESPRIT the Steering and Executive Committee of ESPRIT decided to end the second part of the trial, the comparison between oral anticoagulants and aspirin, before the aimed number of patients had been accrued. The accrual rate for this part of the trial had always been lower than that for the other part. When we learned about the superiority of aspirin plus dipyridamole we reasoned that the power of the trial, even if we would be able to include the aimed number of patients, would be too small to detect a possible benefit of anticoagulants over aspirin plus dipyridamole, the new standard in our opinion. Moreover, we found it unethical to continue randomisation for aspirin while we knew there was a better treatment option.
The role of oral anticoagulants in the secondary prevention after TIA or ischaemic stroke of arterial origin is now defined; there is no reason to prescribe this treatment for this indication. Results of earlier studies, combined with those of ESPRIT, leave no INR target range that might be more effective than aspirin, let alone than aspirin plus dipyridamole.[2,17-19] In the secondary stroke prevention, oral anticoagulants should be reserved for patients with potential sources of embolism in the heart such as atrial fibrillation. For these patients the benefits of treatment outweigh the adverse effects of the medication by far.[20-23] Maybe one day, if new classes of anticoagulants will be available that have a lower rate of bleeding complications, we have to redo the ESPRIT trial, with the combination therapy of aspirin plus dipyridamole as reference treatment.

Cumulative evidence
After completion of the ESPRIT trial, we combined our data with data from all other trials that compared the efficacy of aspirin plus dipyridamole with aspirin alone in the secondary prevention after TIA or minor stroke of presumed arterial origin in **chapter 6**.[24-27] Although earlier trials suggested a differential efficacy of the combination treatment in patients with different vascular risk profiles,[28,29] this meta-analysis based on individual patient data showed that the combination therapy is the preferred treatment for all patients, irrespective of baseline risk, type of vessel disease or vascular risk profile.
These findings were not surprising, as subgroup analyses in the ESPRIT trial showed the same results. The power of the analysis, however, was larger with the addition of data of several other trials. After the publication of these results, there seems no need for further research on the efficacy of the combination therapy of aspirin plus dipyridamole after TIA or ischaemic stroke of arterial origin, compared with aspirin alone. The cost-effectiveness of treatment with aspirin plus dipyridamole in the different subgroups should be studied in a formal analysis. Previous analyses, however, suggested that the combination therapy is cost-effective in the secondary prevention after TIA or minor ischaemic stroke, at least in the first five years after the event.[30-33]

The spectrum of ischaemic strokes is wider than that of patients included in ESPRIT and the other trials in our meta-analysis. Patients with a major stroke of arterial origin, i.e. patients who remain dependent in their daily activities as a consequence of the stroke, were excluded. There is, however, no reason to assume that the combination therapy is not the preferred one in the secondary prevention in these patients as the pathophysiological mechanisms leading to stroke are the same as in the patients included in ESPRIT with a minor stroke.

A more difficult question to answer is whether the combination therapy is also superior in patients with different stroke aetiology. In patients with a cardio-embolic source of embolism oral anticoagulation has proven its superiority compared with several antiplatelet agents.[20-23] No direct comparison between the combination of aspirin plus dipyridamole and oral anticoagulation has been made, but the large benefit of anticoagulation in the trials that were done makes it unlikely that the combination therapy would win such a contest.
In ESPRIT patients with a significant and symptomatic narrowing of one of the carotid arteries were excluded, as there is enough evidence to treat these patients with carotid endarterectomy which reduces the risk of serious vascular events.[34-36] In the trials from which this evidence derives most patients, whether they were surgically treated or not, also used antiplatelet therapy for secondary prevention.[34,35] It is plausible to prescribe the combination therapy to patients after carotid surgery as it is reasonable to assume that the atherosclerotic mechanisms that caused the carotid narrowing are also important in the aetiology of other ischaemic strokes of arterial origin.
In patients with an ischaemic stroke as a result of cervical artery dissection there is no need for long term secondary prevention as the risk of recurrence is less than 1% per year.[37-40] In the first weeks to months after the dissection, however, the risk of recurrent stroke from the unhealed dissection is higher and preventive medication is needed. The widespread preference for oral anticoagulation instead of antiplatelet therapy in this period is empirical rather than evidence-based.[38] In recently published systematic reviews on oral anticoagulation versus antiplatelets after cervical artery dissection no randomised clinical trials were included, because no such trials were available. The included observational studies showed no significant difference in the outcome event ‘disability or death’ and ‘stroke or death’.[38,41] As the incidence rate of cervical artery dissection is low (less than 3 per 100.000), a trial on the best secondary preventive medication would be very difficult if not impossible to perform. Moreover, in patients with cervical artery dissection there are several mechanisms leading to ischaemic stroke (embolism originating from the injured intima and as a result from haemodynamic compromise). If, however, a physician decides to treat a patient with a TIA or stroke as a result of a cervical artery dissection with antiplatelets instead of oral anticoagulation, treatment with the combination therapy of aspirin plus dipyridamole could be justified. As the results from ESPRIT showed that there is no higher risk of major bleeding complications during this treatment compared with aspirin, we do probably not need to be afraid of enlargement of the mural bleed leading to an increase of the narrowing of the vessel lumen.

Other causes of ischaemic stroke are more rare than the ones mentioned above, for example vasculopathies or haematological disorders. For these patients secondary preventive strategies should be determined on a per patient basis. Whether the combination therapy of aspirin plus dipyridamole plays a role is hard to say and will probably never be the subject of research.

Cerebral infarcts are not only categorised based on aetiology. Frequently a distinction is made between small, i.e. lacunar, infarcts and large, i.e. cortical, infarcts. Cortical infarcts are lesions in the (partial) supply area of one of the large major cerebral arteries or in the borderzone area and are presumed to be caused by large vessel disease. Lacunar infarcts are located in the basal ganglia, internal capsule, corona radiata or brainstem and result from occlusion of a small penetrating artery, so called small vessel disease. The distinction between these types can usually be made by means of the clinical features,[42,43] and more reliably by CT or MRI scanning. A third, less frequently studied, type of infarct is the large subcortical infarct, also termed giant lacune. They are located in the same area as the small deep infarcts, but are larger and supposedly not caused by small-vessel disease.[44-47] In **chapter 2**[48] we found that this type of infarct can mimic the clinical features of both lacunar and cortical infarcts and that large subcortical infarcts had the same vascular risk profiles and rate of recurrent stroke as their small vessel or large vessel counterparts. The choice for secondary prevention strategies, however, should be based on the cause of the infarct rather than on the territory or size of the infarct.

The reverse side of the medal

The most effective treatment is not always the best tolerated by patients. In ESPRIT we found that a considerable proportion of patients allocated to aspirin plus dipyridamole discontinued this medication because of side effects, mainly headache. As headache as side effect of dipyridamole was also found in earlier studies,[26,49,50] we searched for predictors for the development of headache during dipyridamole treatment in ESPRIT and in the Second European Stroke Prevention Study (ESPS 2) (**chapter 7)**. The predictors we identified were female sex, no (relevant) ischaemic lesion on brain imaging and not smoking.

In daily practice there is not much we can do with these predictors; we have to warn all patients, not only the ones with these characteristics, that there is a fair chance to develop headache when using dipyridamole. Maybe, however, our findings can be of help in the search for the pathophysiological mechanism of the headache, which is still unknown. For clinical practice, it is also important that future studies will try to confirm the suggestion that the dipyridamole associated headache decreases with continued use.[51] There is also need for more research on titration schemes of dipyridamole that might help to avoid the headache.[52] In the meanwhile, we have to inform patients about the possibility of headaches and stimulate them to initially keep taking dipyridamole, because the headache may spontaneously disappear within two weeks. If patients decide to stop taking dipyridamole, we can try to motivate them to start again with a lower dose as the risk reduction achieved by adding dipyridamole to aspirin is large enough to give it

a second try. If, despite these efforts, the headache persists, we should consider prescribing aspirin mono therapy. At this moment there is no reason to prescribe the more expensive drug clopidogrel, with or without aspirin, in these patients,[53-55] except in those who cannot tolerate aspirin, but this might change when the results of the ongoing PRoFESS trial are published.[56]

Outcome events in stroke research

The main goals in stroke research are improving treatment in the acute phase and optimizing secondary prevention. In both research areas an important and recurrent discussion point is the definition of outcome in these studies. The difference between life and death is important, but the difference between 'life' and 'life', i.e. with or without restrictions and handicaps, might be at least as important, as is the experienced quality of life. The latter, however, is more difficult to measure and depends on many more factors than disease and handicap per se.

During the execution of the ESPRIT trial, we discovered that the definition of the so called 'firm outcome events' can also be subject to debate, when it concerns the cause of death in patients who have died after a stroke. With the help of stroke experts from all over the world we designed guidelines for the classification of cause of death after stroke in clinical research **(chapter 3)**.[57] When using these guidelines, stroke is held responsible for death if a patient dies within 1 month after the stroke or if a patient never reaches a certain level of independency after (and as a result of) the stroke.

The question whether death can be attributed to a stroke is mainly theoretical and has no direct consequences for patients or treatment. The guidelines, however, can be used in clinical research to simplify the auditing of outcome events and to improve comparability, especially when used in multiple studies.

The use of composite outcome events is another point of discussion in the world of clinical trials. It is very appealing to use composite outcomes, as this increases the incidence of event rates and the power of the trial. Moreover, also from the patients perspective it seems logical to a certain extent; a treatment that prevents one serious illness is less attractive if it increases the chance of another.

Recently a systematic review of randomised controlled trials in the field of cardiovascular disease was published, in which the authors addressed problems with the use of composite endpoints.[58] In the majority of the 114 trials studied there was a large or moderate gradient in importance of outcomes to patients, for example a composite event of death, doubling of serum creatinine concentration and end stage renal disease. As the clinical implications of these separate events are not comparable (how to compare doubling of serum creatinine concentration with death?) it seems unfair to combine them in the main analysis of a clinical trial. In 54% of the 84 trials in which also data on the individual outcomes were available there was a substantial gradient in both importance to patients and the effect of treatment across the components. Less important components showed higher event rates and larger treatment effects. In the above mentioned study treatment gave a substantial and significant risk reduction for the composite outcome event. This reduction, however, was mainly caused by a decrease in the

number of patients who had a doubling of the serum creatinine concentration, a frequently encountered outcome event, whereas there was an increase in all cause mortality in the group on study treatment. This could result in wrong interpretation of study results by less intensive readers. The primary outcome event in ESPRIT was also a composite of events we hoped to prevent by treatment (ischaemic events) and events that could possibly be an adverse effect of the same treatment (major bleeding complications). One could debate whether the definition of major bleeding complications in ESPRIT was too liberal for the purpose of the trial as every bleeding that resulted in admission in a hospital was counted, inclusive for example a nose bleed. From patients and physicians perspective it seems unfair to compare these bleedings with major events as death or stroke, as the implications of these events are incomparable. In the design of ESPRIT this problem was anticipated by defining multiple secondary endpoints, thus avoiding to mislead readers by showing only composite outcomes with a gradient in importance of its components. Though the power of the analyses of secondary endpoints in ESPRIT was smaller than that of the main analysis because of a lower incidence, there was a clear trend towards superiority of the combination of aspirin plus dipyridamole in all analyses.

Funding of stroke research

A problem we repeatedly encountered during ESPRIT was to obtain sufficient funding. As ESPRIT was an academic trial, i.e. it was done independently of pharmaceutical industries, we depended completely on charities and governmental bodies for the money necessary to execute such a large trial. We were able to complete the trial partly because of the generosity of the participating physicians who were not paid for the inclusion and follow-up of patients, which is usually done in industry-funded trials (and we had to compete with many industry based trials targeting at the same patient group in the same period![53,55,56]). The problem of funding of stroke research, however, is common. An analysis of funding of stroke research in nine European countries showed that it is poor compared to funding of research in cancer and coronary heart disease,[59] a finding that was confirmed in a worldwide study.[60] In the Netherlands, for example, the total funding of stroke research by nationally based organisations was only 2% of the total funding of cancer research.[59] This may seem logical, as stroke is the third most common cause of death, after coronary heart diseases and cancer, in the developed world. However, mortality data underestimate the true burden of stroke. In contrast to coronary heart disease and cancer,[55] the major burden of stroke is chronic disability rather than death.[61] Many stroke survivors remain functionally dependent and stroke leads to secondary problems as epilepsy, dementia, depression and falls. Moreover, with increasing possibilities to treat stroke in the acute phase, such as thrombolytic agents, endovascular treatment and hemicraniectomy for space occupying middle cerebral artery infarcts, an increasing proportion of patients will survive stroke and become –more than the average person- health care consumers. These arguments, together with the still far-from-ideal secondary prevention strategies, will hopefully lead to increasing appreciation and, consequently, funding of stroke research in the future.

The future

As the role of dipyridamole in the secondary prevention is well established by now, the road is open for a definite cost-effectiveness analysis of this treatment. Moreover, more research is needed to study the prevention and treatment of side effects of the drug, especially headache.

Despite the superiority of the combination of aspirin plus dipyridamole found in this study, the search for the best antithrombotic treatment is not completed. There are still major vascular events left to prevent! In the near future the results of the Prevention Regimen For Effectively avoiding Second Strokes Trial (PRoFESS) are expected.[56] In this largest secondary stroke prevention trial ever conducted, the efficacy of aspirin plus dipyridamole is compared with clopidogrel 75 mg once daily. Although earlier trials were not able to show a benefit of a combination of aspirin plus clopidogrel over either of these medications alone,[53,55] no direct comparisons between clopidogrel and aspirin plus dipyridamole have been published yet.

No new antithrombotic drugs have been approved in several years, but maybe there will be new, more powerful, antithrombotic agents developed in the future.

In addition to treatment with antithrombotic agents there are other strategies to prevent further events in patients who suffer a TIA or ischaemic stroke. For patients with symptomatic narrowing of an internal carotid artery, carotid endarterectomy has proven its value.[34-36] Although the first results of trials comparing endarterectomy with carotid stenting in these patients showed no benefit of the latter treatment,[62,63] more trials on this comparison are on their way.[64,65]

Life style modification is at least as important as antithrombotic medication and so is treatment of conditions that increase the risk of vascular events, like hypertension and diabetes mellitus. Hopefully more vascular risk factors with corresponding treatment will be identified in the future, possibly starting with the results of the Vitamins To Prevent Stroke (VITATOPS) study,[66] which will answer the question whether treatment with vitamin supplements (folic acid, vitamin B6 and vitamin B12) is effective in the secondary prevention.

Finally, with an increasing proportion of patients surviving stroke and with an increasing life expectancy after stroke, studies should not only focus on secondary prevention, but also on ways to improve quality of life after stroke, because it is very unlikely that there will be a time that we will be able to prevent all ischaemic strokes!

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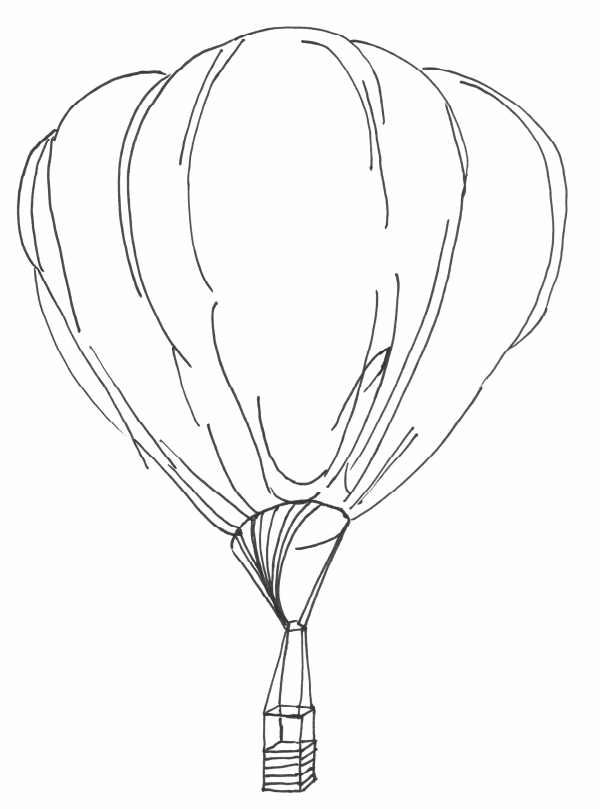
Summary



In **chapter 1**, the general introduction, we described background information and the rationale for the research described in this thesis.

In **chapter 2** we compared 120 patients who had had a large subcortical infarct with 324 who had had a small deep infarct and with 211 who had had a cortical infarct from the same cohort. Infarcts were classified based on CT scan findings. We found no differences in risk factor profiles between the three groups, nor a difference in stroke recurrence rate.

In **chapter 3** we demonstrated, by means of a questionnaire filled in by 29 neurologists with special interest in stroke, that there is very little agreement on the classification of cause of death in patients who die after a stroke in the setting of a clinical trial. Based on this questionnaire, we developed guidelines for the classification of the cause of death after stroke, with the criteria 'interval between stroke and death' (cutoff point at 1 month) and 'best Rankin grade after stroke' (cutoff at 3). An interobserver analysis of these guidelines showed a strong improvement in agreement on the cause of death.

Chapter 4 describes the results of the first part of the European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT). Patients who suffered a Transient Ischaemic Attack (TIA) or non disabling ischaemic stroke of presumed arterial origin were randomized between the combination therapy of aspirin plus dipyridamole (n=1363) and aspirin alone (n=1376). Less patients assigned to the combination therapy (173, 13%) than to aspirin alone (216, 16%) suffered the primary outcome event, which was the composite of death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction, or major bleeding complication, whichever happened first. The corresponding hazard ratio was 0.80 (95% confidence interval 0.66-0.98).

In **chapter 5** the results of the second, prematurely halted, part of ESPRIT are presented. In this part a comparison was made between medium intensity oral anticoagulants (aimed international normalized ratio (INR) 2.0-3.0) and aspirin in the secondary prevention after TIA or non disabling ischaemic stroke of arterial origin. There was no difference in the incidence of the primary outcome event (the composite of death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction, or major bleeding complication, whichever happened first) between patients who were assigned to anticoagulation (99 of 536 patients, 19%) and patients who were assigned to aspirin (98 of 532, 18%). There were, however, more major bleeding complications in patients assigned to anticoagulation (45 vs. 18, hazard ratio 2.56 (95% confidence interval 1.48-4.43).

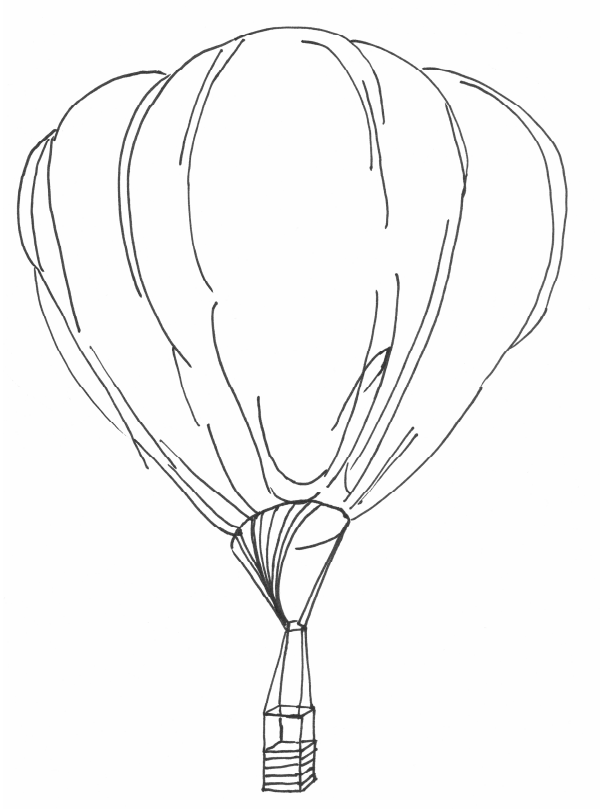
Chapter 6 summarizes the results of an individual patient data based meta-analysis of all trials that compared the combination therapy of aspirin plus dipyridamole with aspirin alone in the secondary prevention after TIA or stroke of arterial origin. Data from 7612 patients (3800 allocated to aspirin plus dipyridamole and 3812 to aspirin alone) were available for this analysis. The

hazard ratio for the composite event of vascular death, non-fatal myocardial infarction and non-fatal stroke was 0.82 (95% CI 0.72-0.92). Hazard ratios did not differ in subgroup analyses based on patient characteristics, nor across baseline risk strata as assessed with two different risk scores.

In **chapter 7** we did an exploratory analysis on data from ESPRIT and from the Second European Stroke Prevention Study (ESPS 2), another trial on the efficacy of aspirin plus dipyridamole in the secondary prevention after TIA or stroke of arterial origin, with the aim to identify risk factors for the development of headache during treatment with dipyridamole. The factors we found to be associated with discontinuation of dipyridamole because of headache were female sex, no (relevant) ischemic lesion on brain imaging and not smoking.

In **chapter 8**, the general discussion, the implications and drawbacks of the studies described in this thesis are outlined. An overview and limitations of secondary prevention are presented, as well as some practical issues in stroke research. Finally, suggestions for future research are given.

Samenvatting



Beroertes komen veel voor; wereldwijd zijn zij de op twee na meest voorkomende doodsoorzaak. Daarnaast zorgen beroertes voor veel handicaps en beperkingen onder degenen die een beroerte overleven. Het merendeel van de beroertes zijn herseninfarcten waarbij een bloedstolsel een slagader in het hoofd afsluit. Deze stolsels kunnen afkomstig zijn uit het hart, maar veel vaker zijn ze het gevolg van atherosclerose of lokale trombose (van arteriële oorsprong).

In **hoofdstuk 2** wordt een onderzoek beschreven waarin 120 patiënten met een zogenaamd 'groot subcorticaal infarct', een relatief groot infarct waarbij de cerebrale cortex (hersenschors) gespaard blijft, vergeleken worden met 324 patiënten met een lacunair herseninfarct en met 211 patiënten met een corticaal herseninfarct. Er bleek geen verschil te zijn voor wat betreft vasculaire risicofactoren of optreden van recidief herseninfarcten tussen deze groepen.

Na een Transient Ischaemic Attack (TIA) of herseninfarct hebben patiënten een verhoogd risico op een nieuw herseninfarct en op andere vasculaire aandoeningen zoals een hartinfarct. Om dit risico te verlagen worden patiënten behandeld met medicijnen die de vorming van een stolsel voorkomen. Om duidelijkheid te krijgen welk medicijn het beste is voor patiënten met een TIA of een herseninfarct van arteriële origine werd de European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) gedaan, een internationaal gerandomiseerd onderzoek, waarin drie verschillende medicijnen met elkaar vergeleken werden.

In **hoofdstuk 4** staan de resultaten van het eerste deel van ESPRIT, de vergelijking tussen 1363 patiënten die enkele jaren behandeld werden met de combinatiebehandeling van aspirine en dipyridamol en 1376 patiënten die met alleen aspirine behandeld werden. Gevonden werd dat de combinatiebehandeling beter beschermt tegen de gecombineerde uitkomstmaat 'recidief beroerte, myocardinfarct, ernstige bloeding of overlijden door vasculaire oorzaak'. De gevonden hazard ratio (te interpreteren als relatief risico) was 0.80 (95% betrouwbaarheidsinterval (BI) 0.66-0.98).

Na afronding van het eerste deel van ESPRIT hebben we de gegevens ervan gecombineerd met alle eerdere onderzoeken waarin deze twee therapieën werden vergeleken in deze patiëntengroep. In de hieruit volgende meta-analyse, beschreven in **hoofdstuk 6**, werden 7612 patiënten geïncludeerd. Uit deze analyse bleek dat de combinatietherapie effectiever is bij het voorkomen van vasculaire complicaties voor alle patiënten met een TIA of herseninfarct van arteriële oorsprong, onafhankelijk van andere vasculaire risicofactoren.

In **hoofdstuk 5** worden de resultaten van het tweede deel van ESPRIT beschreven. Hierin wordt een vergelijking gemaakt tussen 536 patiënten die behandeld werden met orale antistolling met een matige intensiteit (streefwaarde voor de International Normalised Ratio (INR) 2.0-3.0) en 532 patiënten die behandeld werden met aspirine. Er was geen verschil in voorkomen van de

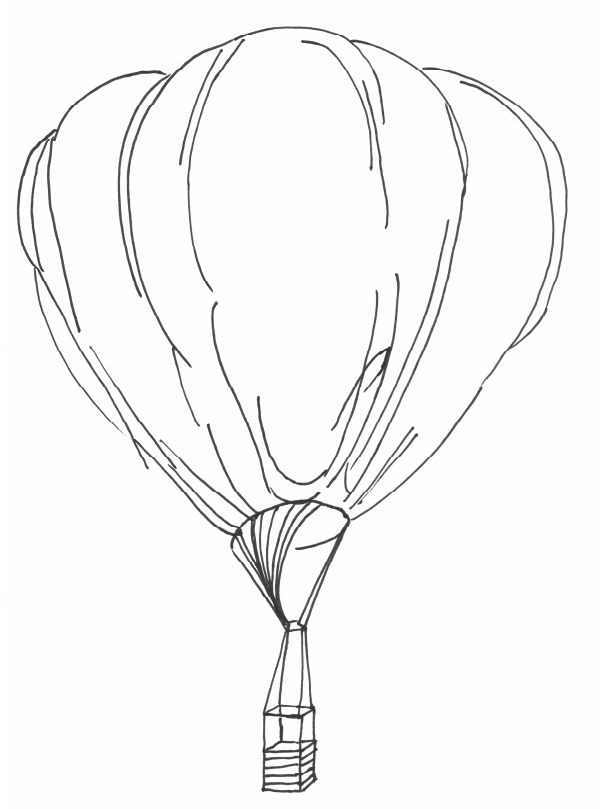
gecombineerde uitkomstmaat met een hazard ratio van 1.02 (95%-BI 0.77-1.35). Er waren minder ischemische complicaties bij patiënten die antistolling gebruikten (62 versus 84, hazard ratio 0.73, 95% BI 0.52-1.01). Dit effect werd echter teniet gedaan door meer bloedingscomplicaties in deze groep (45 versus 18, hazard ratio 2.56, 95% BI 1.48-4.43).

Tijdens ESPRIT maakten wij regelmatig mee dat degenen die de uitkomstmaten moesten classificeren het niet eens waren over de doodsoorzaak als patiënten overleden nadat ze een ernstige recidief beroerte hadden door gemaakt. Wij hebben dit nader onderzocht in **hoofdstuk 3**, waarin we beschrijven hoe we een vragenlijst hebben gestuurd naar 29 neurologen die zich regelmatig met dit soort onderzoeken bezighouden. Wij vroegen hen een paar vragen te beantwoorden over het classificeren van doodsoorzaken bij wetenschappelijk onderzoek en om 5 casus te beoordelen. Hieruit bleek dat er ook onder hen geen overeenstemming was in de beoordelingen. Hierop hebben we richtlijnen ontwikkeld voor het beoordelen van de doodsoorzaak na een beroerte, waarbij de criteria ‘interval tussen beroerte en overlijden’ en ‘beste Rankin score (maat voor invaliditeit)’ na de beroerte gebruikt worden. De richtlijnen zijn getest in een interobserver analyse waaruit goede overeenstemming in beoordelingen bleek.

In ESPRIT, en in eerdere onderzoeken, stopten veel patiënten met het gebruik van dipyridamol omdat ze er hoofdpijn van kregen. In **hoofdstuk 7** beschrijven we een onderzoek waarin we gezocht hebben naar risicofactoren voor het ontwikkelen van hoofdpijn bij patiënten die deelnamen aan ESPRIT en aan de ‘Second European Stroke Prevention Study (ESPS 2)’. Risicofactoren voor hoofdpijn bleken ‘vrouwelijk geslacht’, ‘geen ischemische afwijking op CT- of MRI-scan van de hersenen’ en ‘niet roken’.

In **hoofdstuk 8**, de algemene discussie, worden de gevolgen en de nadelen van de verschillende onderzoeken besproken. Tevens gaat deze over secundaire preventie na een TIA of een herseninfarct in het algemeen en over onderzoek hiernaar in het bijzonder. Tot slot worden enkele suggesties voor toekomstig onderzoek gedaan.

Dankwoord



Promoveren is net het echte leven; je hoeft het gelukkig niet allemaal alleen te doen! Een aantal mensen zonder wie het niet zo ver gekomen zou zijn wil ik hier graag noemen.

Professor Algra, beste Ale. Veel positiefs over jou als promotor is al door anderen geschreven; en het is allemaal waar! Je jeugdige enthousiasme, je betrokkenheid, je continue beschikbaarheid en je opbouwende kritieken zijn onbetaalbaar. Onze soms nachtelijke 'chat-sessies' via de e-mail maakten altijd weer dat er structuur kwam in mijn soms wat chaotische gedachtengang. Ik ben er trots op dat ik de laatste pleegmoeder van jouw 'kindje' ESPRIT mocht zijn.

Professor Kappelle, beste Jaap. Het is fijn een promotor te hebben die bewijst dat een goed onderzoeker zijn niet uit hoeft te sluiten dat je een uitmuntend clinicus bent. Die combinatie bewonder ik zeer in je. Het was heel prettig dat ik ook met alle klinische problemen die je bij patiënt-gebonden onderzoek tegenkomt bij jou terecht kon.

Gegevens van zoveel patiënten uit zoveel ziekenhuizen uit zoveel landen verzamelen en structuren is geen sinecure. Daar kunnen de dames van het trialbureau over meepraten.
Moniek, volgens mij zou jij alle (ruim 400) ESPRIT-patiënten uit het UMC op straat herkennen en zij jou! Volgens mij hebben er velen alleen doordat ze elk half jaar een gesprek met jou mochten voeren het zolang vol gehouden. Ik hoop nooit meer (al dan niet met jou) een vliegtuig te missen, maar wil best nog eens met jou bij zo'n vriendelijke oude Engelse meneer op de gang douchen…
Jammer voor het trialbureau dat ze jou als onderzoeksverpleegkundige zijn kwijt geraakt, maar fijn voor de oude mensen dat jij je nu om hen bekommert!
Gré, ik hoef je niet te vertellen hoe ik het bewonder dat jij na je zestigste, zonder enige computerervaring, de stap waagde onderzoeks-secretaresse van ESPRIT te worden, een functie waarbij je nauwelijks achter de computer vandaan komt. En je hebt het met verve gedaan! De beruchte 'lijstjes van Gré' die je uit de printer liet rollen, soms in combinatie met de hele database van ESPRIT, maakten dat bij mij het overzicht bleef bestaan. Je werklust en je altijd goede humeur maken je tot een gouden lid van elk team, daar kunnen ze in het halve UMC over meepraten.
Gelukkig werden deze dames en ik regelmatig geholpen door Paut, Marrit en Dorien, die eveneens onmisbaar zijn geweest voor het slagen van ESPRIT!

Beste professor van Gijn, u weet hoe jammer ik het vind dat de datum van uw pensionering samenviel met de datum dat ik in het UMC met mijn opleiding begon. Graag had ik ook in witte jas onder uw begeleiding gewerkt. Ik troost me met de gedachte dat ik optimaal heb kunnen genieten van u als onderzoeks-begeleider. Tijdens ESPRIT-vergaderingen kreeg u in één keer helder waar ik al een tijd over nadacht en uw gevoel voor de Engelse taal heeft denk ik menig manuscript net dat beetje extra gegeven wat het nodig had.

Professor Koudstaal, beste Peter. Je was het enige lid van het uitvoerend comité van ESPRIT buiten het UMC. Hierdoor hadden we voornamelijk mail-contact, maar daarin ben je van grote waarde gebleken. Niemand reageerde zo snel op e-mailtjes of op manuscripten als jij, zelfs vanaf het andere eind van de wereld. Bedankt voor je grote inhoudelijke bijdrage aan dit proefschrift.

Een onderzoek als ESPRIT staat of valt bij de bereidwilligheid van patiënten om deel te nemen. Wereldwijd, maar met name in Nederland, hebben ruim 3000 patiënten de gok gewaagd. Zonder hen zou dit proefschrift hier niet voor u liggen. Ik ben blij dat ESPRIT een uitkomst heeft gekregen waar de patiënten ook daadwerkelijk iets aan hebben!

We zouden nooit voldoende patiënten hebben kunnen includeren als ESPRIT niet gedragen werd door vele neurologen en onderzoeksverpleegkundigen over de hele wereld. Een groot deel van het werk is door hen gedaan, waarvoor veel dank.

ESPRIT was een al rijdende trein toen ik als trialcoördinator begon; ik hoefde alleen maar de laatste kilometers te sturen en vervolgens het station binnen te rijden. Ik wil dan ook de machinisten voor mij, te weten Cyrille, Els, Geert-Jan, Jan Willem en Ynte bedanken dat ze de trein op het goede spoor hebben gestart en gehouden.

Professor Wokke, bedankt dat u mij een paar jaar geleden heeft aangenomen voor de opleiding tot neuroloog. Ik kijk er naar uit me de komende jaren onder uw bezielende (op)leiding verder te ontwikkelen.

Het lijkt misschien raar om een website te bedanken in je proefschrift, maar Google is voor dit onderzoek zo belangrijk geweest dat ik overwoog mijn proefschrift eraan op te dragen. Welk probleem ik ook had; een statistische term of berekening die ik niet kende, een patiënt die van de aardbodem verdwenen leek of een deelnemend ziekenhuis dat aangeschreven moest worden, Google vond de oplossing!

Collega-assistenten en neurologen, ook dank. Niet alleen voor het attenderen op patiënten die misschien aan ESPRIT mee konden doen en voor het beoordelen van scans of eindpunten, maar ook voor de nodige gezelligheid en voor het creëren van het fijne werk- en opleidingsklimaat waar ik de komende jaren nog in mag vertoeven.

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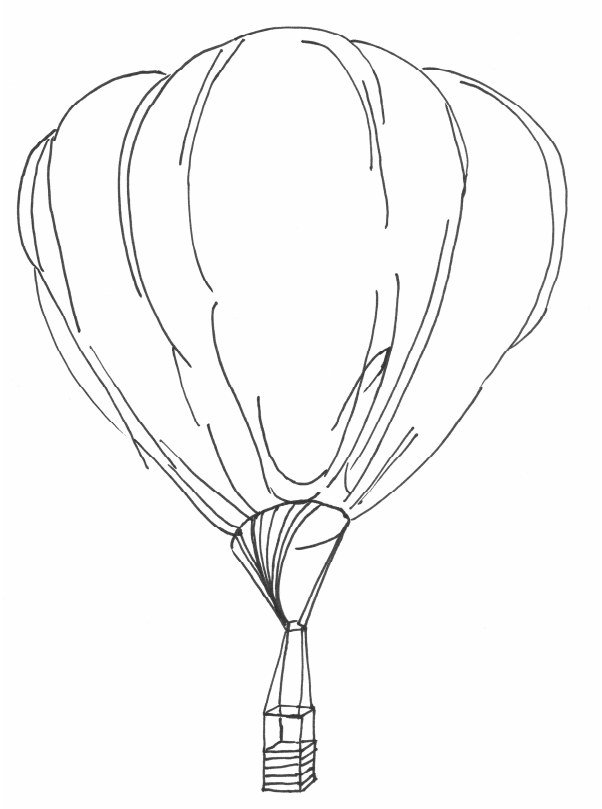
List of publications



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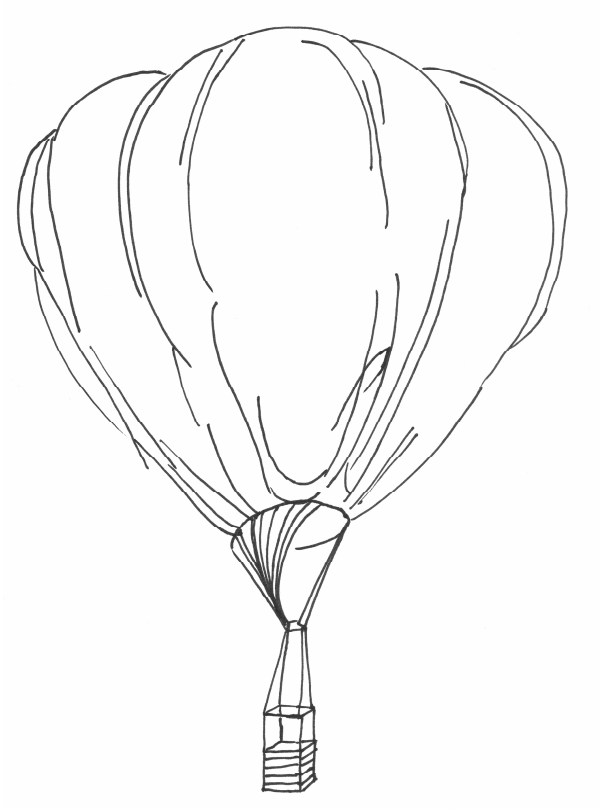
Curriculum Vitae



Curriculum Vitae

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Appendix chapter 3

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