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European Stroke Prevention Study 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke [1]

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Abstract

In 1988, we undertook a randomized, placebo-controlled, double-blind trial to investigate the safety and efficacy of low-dose acetylsalicylic acid (ASA), modified-release dipyridamole, and the two agents in combination for secondary prevention of ischemic stroke. Patients with prior stroke or transient ischemic attack (TIA) were randomized to treatment with ASA alone (50 mg daily), modified-release dipyridamole alone (400 mg daily), the two agents in a combined formulation, or placebo. Primary endpoints were stroke, death, and stroke or death together. TIA and other vascular events were secondary endpoints. Patients were followed on treatment for two years. Data from 6,602 patients were analysed. Factorial analysis demonstrated a highly significant effect for ASA and for dipyridamole in reducing the risk of stroke ($p \leq 0.001$) and stroke or death combined ($p < 0.01$). In pairwise comparisons, stroke risk in comparison to placebo was reduced by 18% with ASA alone ($p = 0.013$); 16% with dipyridamole alone ($p = 0.039$); and 37% with combination therapy ($p < 0.001$). Risk of stroke or death was reduced by 13% with ASA alone ($p = 0.016$); 15% with dipyridamole alone ($p = 0.015$); and 24% with the combination ($p < 0.001$). The treatment had no statistically significant effect on the death rate alone. Factorial analysis also demonstrated a highly significant effect of ASA ($p < 0.001$) and dipyridamole ($p < 0.01$) for preventing TIA. The risk reduction for the combination was 36% ($p < 0.001$) in comparison with placebo. Headache was the most common adverse event, occurring more frequently in dipyridamole-treated patients. All-site bleeding and gastrointestinal bleeding were significantly more common in patients who received ASA in comparison to placebo or dipyridamole. We conclude that (1) ASA 25 mg twice daily and dipyridamole, in a modified-release form, at a dose of 200 mg twice daily have each been shown to be equally effective for the secondary prevention of ischemic stroke and TIA; (2) when co-prescribed the protective effects are additive, the combination being significantly more effective than either agent prescribed singly; (3) low-dose ASA does not eliminate the propensity for induced bleeding.

Keywords: Stroke; Transient ischemic attack; Secondary prevention; Acetylsalicylic acid; Dipyridamole

1. Introduction

In a recent review, Bonita (1992) describes stroke incidence and related mortality. Using selected studies from USA, New Zealand and Europe, she demonstrates that age-standardized incidence rates for first-ever stroke increase steeply from about 20 per 10,000 for people aged 50–64 year up to more than 200 per 10,000 for people aged 85 and over. Stroke mortality has been declining over the years but not necessarily stroke prevalence. In the same review, Bonita points out that an extrapolation from the Auckland Stroke Study suggests that in a population of 1 million, 1250 persons will have a first stroke each year and 350 will suffer a recurrent stroke. A large proportion of these people will remain handicapped and dependent. These factors together with a projected increase in the population older than 65 years, suggest a major burden on the community with respect to the care of stroke patients and the costs of acute and recurrent stroke.

Many investigators have sought to confirm that antiplatelet treatment would be of value for preventing secondary stroke and/or TIA with considerable uncertainty as to the outcome, including the trials named AICLA (Bousser et al., 1983), AITIA (Fields et al., 1977), UK-TIA (UK-TIA Study Group, 1991), SALT (SALT Collaborative Group, 1991) and ESPS-1 (ESPS Group, 1987). The Anti-platelet Trialists' Collaboration (1994a); Anti-platelet Trialists' Collaboration (1994b), Anti-platelet Trialists' Collabora-

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[1] ESPS-2 Writing Committee

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tion (1994c) performed a meta-analysis of all the randomized antiplatelet trials and demonstrated that ASA was efficacious in preventing recurrent thrombotic events and particularly in patients who had had prior myocardial infarction and prior cerebrovascular events. The analysis could not detect the merits of particular regimen, e.g. dose of ASA, usefulness of other agents etc., but the data did suggest that high doses of ASA were not more efficacious than lower doses. In addition, clinical pharmacological studies have suggested that very low doses of ASA may also be effective showing in healthy volunteers that 50 mg ASA per day and 400 mg dipyridamole per day significantly reduce ex vivo thrombus formation and have an additive effect in combination (Weisenberger, Nehmiz and Su, personal communication; Müller et al., 1990). Ticlopidine in two studies (Gent et al., 1989; Hass et al., 1989) has been shown to be effective in reducing risk of secondary stroke but is associated with significant adverse events and has not been universally approved for clinical use.

Two studies, from the American–Canadian Co-operative Study Group (1983) and AICLA (Bousser et al., 1983), on stroke secondary prevention involving a direct comparison of ASA alone to ASA combined with dipyridamole had been published. Neither of them did show a superiority of the combination over ASA alone. But both lacked the power to detect a small difference. Similarly the Anti-platelet Trialists' Collaboration (1988) failed to show a superiority of the combination over ASA alone in stroke prevention.

In 1987 the European Stroke Prevention Study was published (ESPS Group, 1987). In this trial dipyridamole at a daily dose of 225 mg (75 mg three times daily) was co-prescribed with ASA 990 mg daily (330 mg three times daily), for two years, in patients whose eligibility for the trial was determined by a prior ischemic stroke or TIA. The combination treatment showed a striking 38% reduction in secondary stroke over the group treated with placebo. This reduction was substantially more than that found in the analysis of trials using ASA alone.

In view of the conflicting data from the individual stroke prevention trials and the more recent debate with respect to the best dosing of ASA, it was felt by the study group that a placebo control arm could not be avoided for assessing this low dose (25 mg twice daily) of ASA. The ESPS-1 investigation had not shown the relative contribution of ASA and dipyridamole alone to the combination results. The protocol was considered and approved by the Ethics Committees of each participating centre and the central ethics review board.

The second European Stroke Prevention Study (ESPS-2) was designed to answer the following questions; (1) how effective are dipyridamole and ASA alone for prevention of secondary stroke, (2) is the combination of treatments superior to each agent given alone, (3) does ASA at the low dose of 50 mg eliminate the propensity to induce bleeding? ESPS-2 was a randomized, 2×2 factorial, double-blind, placebo-controlled, multicenter trial carried out at 59 sites in 13 countries between February 1989 and March 1995.

2. Patients and methods

2.1. Patient recruitment and eligibility

Patients were eligible for the trial if they were more than 18 years old and had experienced a TIA (clinical neurological symptoms persisting for less than 24 h) or a completed ischemic stroke (clinical neurological deficit lasting more than 24 h), within the preceding three months. Diagnosis based on clinical neurological examination only was acceptable but computed tomography (CT) or magnetic resonance imaging (MRI) were recommended to confirm the diagnosis. General medical examination was performed and included blood pressure measurement and an electrocardiogram. Blood chemistry studies and a complete blood count were performed for each patient to screen for exclusion criteria and to provide baseline values. Patients with a recent history of peptic ulcer or other gastrointestinal bleeding, hypersensitivity or intolerance to either study medication, bleeding disturbances, any condition requiring continued use of ASA or anticoagulants, or any life-threatening condition were excluded from the study. Upon entering the study, each patient's past general medical and neurological history was recorded. All underwent a detailed medical and neurological examination. The severity of the qualifying stroke was assessed on a modified Rankin scale (Van Swieten et al., 1988).

2.2. Trial medication and randomization

Treatment group allocation was determined by a randomization system based on the minimization technique and taking into account the following factors: qualifying event, sex, age, and study centre. Randomization was performed at a central location: the data centre of the European Organization for Research and Treatment of Cancer (EORTC), which was linked through the X25 network to computer terminals at each study site. Once inclusion and exclusion criteria were assessed, eligible patients were randomly assigned a number corresponding to one of the preprogrammed treatment packages available at that centre. Randomization distributed patients equally among the following four treatment groups: ASA (25 mg twice daily); modified-release dipyridamole (DP, Persantin® Retard, 200 mg twice daily); the combination of ASA (25 mg twice daily) and modified-release dipyridamole (200 mg twice daily); or matched placebo.

2.3. Clinical data and follow-up

Each patient was followed for two years, regardless of compliance with study medication or occurrence of a non-fatal endpoint. Over the course of the trial, only 42/6602 patients (0.64%) were lost to follow-up. Follow-up examinations took place one month after inclusion in the trial and then at three-month intervals for the duration of the trial, beginning with the third month. At each follow-up visit, patients were systematically questioned with regard to adverse events. Bleeding, gastrointestinal complaints, and headache were asked for in particular.

Compliance with study medication was assessed in three ways: (1) at follow-up visits, patients were asked whether they had taken the study medication according to the directions received; (2) at medication renewal their remaining supply of capsules was counted; (3) patients were randomly selected for drug assay (15% sample). The ASA metabolite salicylic acid and plasma dipyridamole concentrations were measured.

Patients, investigators, and the steering and monitoring committees overseeing the study were blinded to the treatment group assignments until the code was broken in August 1995. While the study was ongoing, treatment labels were shuffled in order to avoid identification of treatment groups in safety reports prepared by the statistical department of the Free University of Brussels. The laboratory that conducted the salicylic acid and DP plasma concentration assays also was blinded to treatment group assignment.

2.4. Endpoint definitions

Primary endpoints were three: stroke; death; stroke and/or death. Stroke included fatal and non-fatal strokes, death was from all causes, while stroke and/or death from any cause allowed the first event to be counted for 'survival' analysis but avoided the patient being counted twice. TIA was a secondary endpoint, as were myocardial infarction, ischemic events and other vascular events. The term 'ischemic events' allowed the inclusion of stroke, myocardial infarction and sudden death (presumed to be thrombotic in origin). All endpoints were reviewed on a blinded basis by a Morbidity and Mortality Assessment Group (MMAG).

2.5. Statistical methodology

ESPS-2 was organized according to a 2×2 factorial design (Pocock, 1983). This design was chosen in order to maximize the power of the study to detect the relative contribution of the single treatments being tested. It provides more information than would be obtained from a similar trial involving only pairwise comparisons of treatments as it allows for an assessment of any statistical interaction between ASA and DP. Lack of a statistical interaction suggests that the effects of the two agents are additive when co-administered. In addition, pairwise statistical analyses also were conducted.

The study was designed to achieve 80% power to detect a 25% risk reduction (RR) at the 5% level of statistical significance. The sample size was calculated using the endpoint incidence and frequency of treatment cessations observed in ESPS-1 (ESPS Group, 1987; ESPS Group, 1990): it was assumed that these figures could be extrapolated to ESPS-2. Computer simulations, which employed sensitivity analyses with parameters based on the ESPS-1 data, indicated that 1,250 patients per treatment group would provide the required study power. The study protocol called for a single interim analysis to assess the validity of the previous assumptions with respect to sample size. This analysis was carried out after data cut-off in May 1991, after 3,690 patients had been recruited. The sample size was recalculated thus requiring 1,750 patients per group to provide the necessary statistical power. This new requirement was accepted by the Steering Committee. All statistical analyses were conducted according to the intention-to-treat principle; each patient was analysed according to the original treatment group assignment, regardless of whether eligibility was confirmed by the MMAG, the patient's degree of compliance, or whether the study medication was stopped during the course of the trial. Between-group comparisons were made by descriptive analysis, cross-tabulation and analysis of variance, whenever applicable. Endpoint risk reductions were calculated. Endpoints were assessed by the statistical technique of survival analysis. A 'survivor' at any given time is someone for whom the specified outcome, death or stroke, has not been observed. Survival curves for each treatment group and endpoint were derived using the actuarial method, which incorporates all survival information (including losses to follow-up and treatment withdrawals) with survival data being grouped into 24 intervals of one month (Miller, 1981). Overall statistical comparison of survival curves was performed by the Wilcoxon-Gehan test. A Cox model (Miller, 1981) analysis of survival data was also employed to identify the most important covariates associated with endpoint occurrence.

2.6. Exclusion of data

Prior to unblinding of the data, the ESPS-2 data quality control unit identified two issues that required investigation: (1) Fourteen randomization numbers were issued that did not correspond to existing patients. (2) Serious inconsistencies in patient case record forms and compliance assay determinations led the Steering Committee to question the reliability of data from one centre which had randomized 438 patients in total. Because reliability of these data could not be established by audit, the Steering Committee made the decision to exclude this centre from the study before unblinding the data. Therefore, the results

presented in this report are based on 6,602 patients and not the total 7,054 said to have been enrolled. It should be emphasized that statistical analyses were performed for the original 7,054-patient data base as well as the 6,602-patient data base. The excluded patients had no impact on the results reported in this paper.

2.7. Issues arising from other clinical trials

During the course of ESPS-2, new data became available regarding the management of certain patient subgroups. These data were made known to all the ESPS-2 investigators and clinical management options were suggested but left to their discretion. Specifically, data from the European Atrial Fibrillation Trial (EAFT), published in 1993, showed that anticoagulation rather than ASA was the treatment of choice in patients with non-rheumatic atrial fibrillation who developed stroke or TIA (EAFT Group, 1993). Investigators participating in ESPS-2 were informed of the findings from these studies and were told that patients with atrial fibrillation participating in ESPS-2 could be switched to anticoagulation, at the investigators' judgement.

3. Results

3.1. Demographic characteristics

The patients were recruited between February 1989 and March 1993 in 59 clinical centres from 13 European countries. The origin and the baseline characteristics of the ESPS-2 population have already been described in detail (Bertrand-Hardy et al., 1995). Data from 6,602 patients were analysed. There were no significant differences among the four treatment groups in terms of baseline characteristics, including age, sex, weight, nature and severity of qualifying event, concomitant diseases, and risk factors. These characteristics are given in Table 1.

Overall, 76.3% of patients entered the trial with an ischemic stroke; 23.7% had a TIA. Mean age was 66.7 years. Gender composition was 58.0% male and 42.0% female. In patients whose qualifying event was stroke the ischemic insult had a cerebral hemispheric location in 82.9%, a brainstem location in 14.0%, and was of uncertain location in 3.1%. The figures for TIA patients are 74.9%, 14.6%, and 10.5%, respectively.

Regarding other baseline characteristics, hypertension (defined by history or current use of antihypertensive medication, or blood pressure of at least 160/95 mm Hg at entry) was present in 60.5% of patients. Ischemic heart disease (defined by history or electrocardiographic evidence at entry) was diagnosed in 35.1% of patients. Of the 15.3% of patients with diabetes mellitus, 20.9% were insulin-dependent.

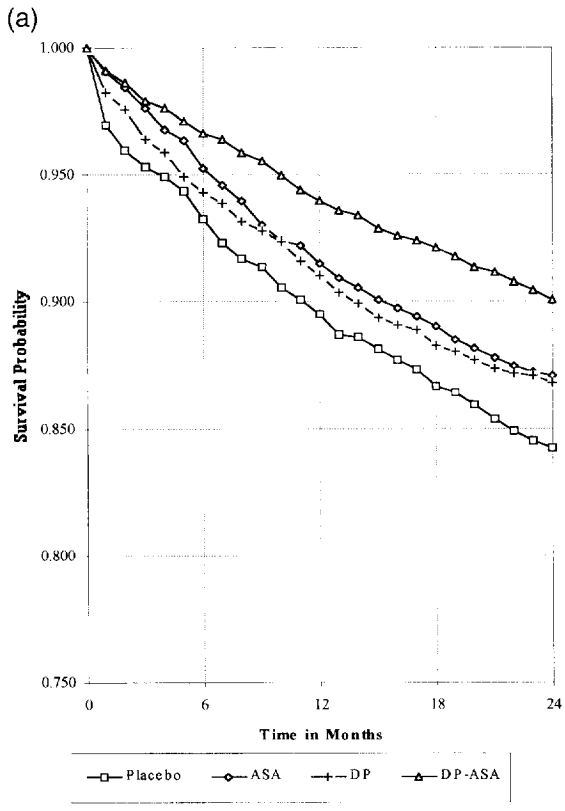
3.2. Analysis

During the two year follow-up, 12.5% of patients experienced stroke and 11.5% died, overall. The 24 month stroke rate was 12.9% in the ASA-alone group, 13.2% in the dipyridamole-alone group, 9.9% in the combination

Table 1
Demographic characteristics

Characteristic	Placebo (n = 1649)		ASA (n = 1649)		DP (n = 1654)		DP-ASA(n = 1650)		p-Value	Total (n = 6602)	
Age (mean, years)	66.6		66.8		66.7		66.8		0.92	66.7	
Males	951	(57.7)	956	(58.0)	965	(58.3)	956	(57.9)	0.98	3828	(58.0)
Females	698	(42.3)	693	(42.0)	689	(41.7)	694	(42.1)		2774	(42.0)
Qualifying event											
Stroke	1270	(77.0)	1257	(76.2)	1265	(76.5)	1246	(75.6)	0.80	5038	(76.3)
TIA	379	(23.0)	392	(23.8)	388	(23.5)	403	(24.4)		1562	(23.7)
Stroke severity (modified Rankin scale)											
Grades 0 + 1 + 2	871	(68.7)	862	(68.6)	885	(70.0)	864	(69.3)	0.89	3482	(69.1)
Grade 3	192	(15.1)	177	(14.1)	169	(13.4)	179	(14.4)		717	(14.2)
Grades 4 + 5	205	(16.2)	218	(17.3)	211	(16.7)	203	(16.3)		837	(16.6)
Associated diseases and risk factors											
Hypertension	1022	(62.0)	983	(59.6)	1012	(61.2)	980	(59.4)	0.16	3997	(60.5)
Ischemic heart disease	577	(35.0)	571	(34.6)	598	(36.2)	573	(34.7)	0.68	2319	(35.1)
Cardiac failure	138	(8.4)	134	(8.1)	143	(8.6)	140	(8.5)	0.86	555	(8.4)
Atrial fibrillation	107	(6.5)	104	(6.3)	114	(6.9)	104	(6.3)	0.89	429	(6.5)
Peripheral vascular disease	363	(22.0)	362	(22.0)	371	(22.4)	358	(21.7)	0.95	1454	(22.0)
Diabetes	239	(14.5)	240	(14.6)	278	(16.8)	254	(15.4)	0.22	1011	(15.3)
Insulin dependent	53	(3.2)	58	(3.5)	49	(3.0)	50	(3.0)	0.28	210	(3.2)
Non-insulin dependent	186	(11.2)	182	(11.0)	229	(13.8)	204	(12.4)		801	(12.1)
Hypercholesterolemia	347	(21.0)	377	(22.9)	375	(22.7)	410	(24.8)	0.08	1509	(22.9)
Current smokers	386	(23.5)	388	(23.5)	395	(23.9)	422	(25.6)	0.77	1591	(24.1)
Alcohol (> 5 units/day)	96	(5.8)	87	(5.3)	100	(6.0)	84	(5.1)	0.59	367	(5.6)

Values are numbers and (in parentheses) percentages. ASA = acetylsalicylic acid; DP = dipyridamole; DP-ASA = combination of DP and ASA.



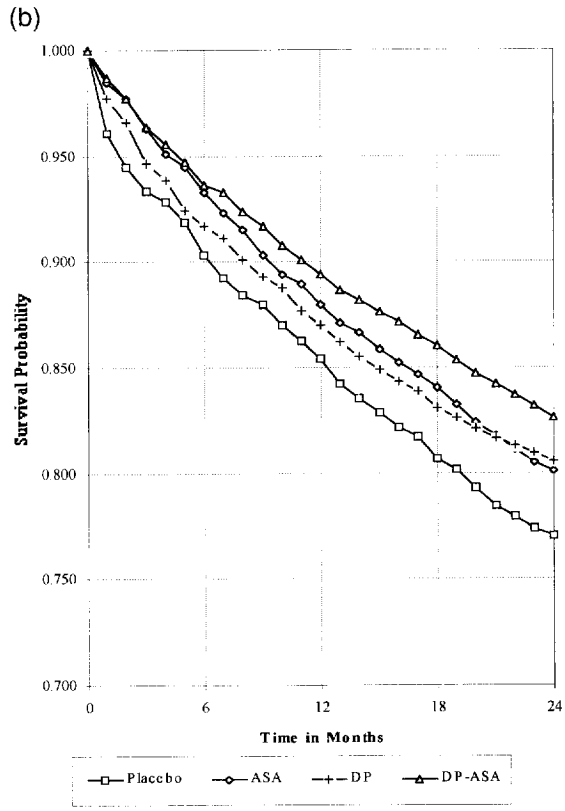


Fig. 1. Endpoint-free survival curves for the endpoints (a) stroke, (b) stroke or death, and (c) death in patients with prior stroke or TIA treated with ASA, DP, DP-ASA, or placebo ($n = 6{,}602$). (a) Stroke. All cases. (b) Stroke and/or death. All cases. (c) Death. All cases.

Fig. 1 (continued).

group, and 15.8% in the placebo group. Survival curves of time to stroke, stroke or death and death are presented in Fig. 1. There was a clear, progressive divergence of the curves for the endpoint stroke and the combined endpoint of stroke or death, demonstrating a higher probability of endpoint-free survival with the combination regimen than with either agent alone. Placebo treatment was associated with the lowest probability of endpoint-free survival. The number of events and event-free survival at two years are presented in Table 2.

The overall difference among the four groups was significant for the endpoint stroke ($p < 0.001$) and the combined endpoint stroke or death ($p < 0.001$). There was no significant difference among the groups for the endpoint death ($p = 0.616$). The factorial analysis showed a significant effect for ASA and for DP in reducing the risk of recurrent stroke ($p < 0.001$ for each) and stroke or death ($p = 0.003$ and $p = 0.002$, respectively). There was no significant statistical interaction between the effects of ASA and DP in reducing stroke or stroke or death, suggesting that the effects of the two agents are additive. Results for pairwise comparisons of the treatment groups confirm the findings of the factorial analysis. Relative risk reductions and significance levels are presented in Table 3.

Stroke risk was significantly reduced by 18.1% ($p =$

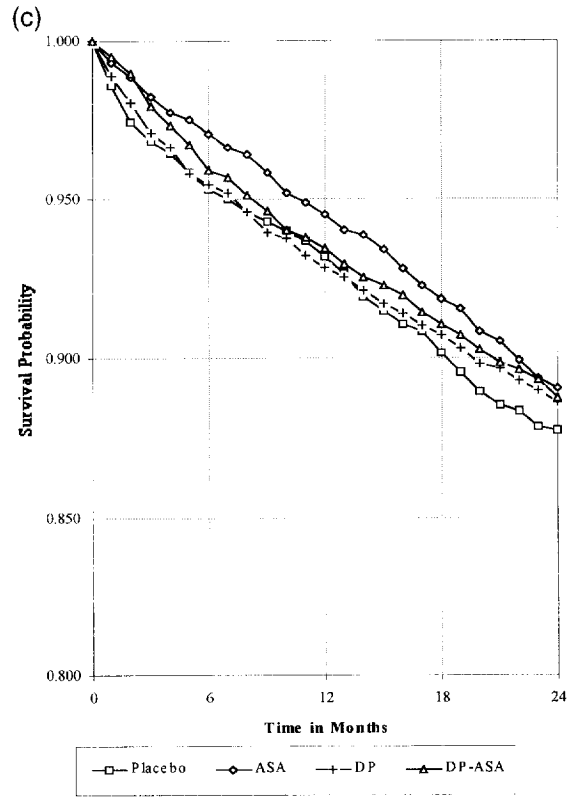


Fig. 1 (continued).

Table 2
Number of events and 24-month event-free survival (%) for principal endpoints

	Number of patients	Number of strokes			24-Month survival (%)	Number of strokes or deaths	24-Month survival (%)	Number of deaths	24-Month survival (%)
		Non-fatal	Fatal	Total					
ASA	1649	186	20	206	87.07	330	80.07	182	89.06
DP	1654	183	28	211	86.79	321	80.56	188	88.61
DP-ASA	1650	137	20	157	90.05	286	82.63	185	88.76
Placebo	1649	228	22	250	84.22	378	77.03	202	87.72
Total	6602	734	96	824	–	1315	–	757	–

ASA = aspirin; DP = dipyridamole; DP-ASA = combination of DP and ASA.

0.013) with ASA alone, by 16.3% ($p = 0.039$) with DP alone, and by 37.0% ($p < 0.001$) with combination therapy, when compared with placebo. The relative risk reductions for the combined endpoint of stroke or death were 13.2% ($p = 0.016$) with ASA, 15.4% ($p = 0.015$) with DP, and 24.4% ($p < 0.001$) with the combination. None of the treatments significantly reduced the risk of death alone or of fatal stroke. Comparisons of combination therapy versus each agent alone yielded a significant 23.1% reduction in stroke risk over ASA alone ($p = 0.006$), and a significant 24.7% reduction over DP alone ($p = 0.002$). For stroke or death, the risk reductions achieved with combination therapy versus each agent alone reached respectively 12.9 and 10.7%, only approaching statistical significance ($p = 0.056$ for ASA and $p = 0.073$ for DP). As with placebo comparisons, the observed reductions in death were not statistically significant.

Odds ratios (ORs) and 95% confidence intervals (CIs)

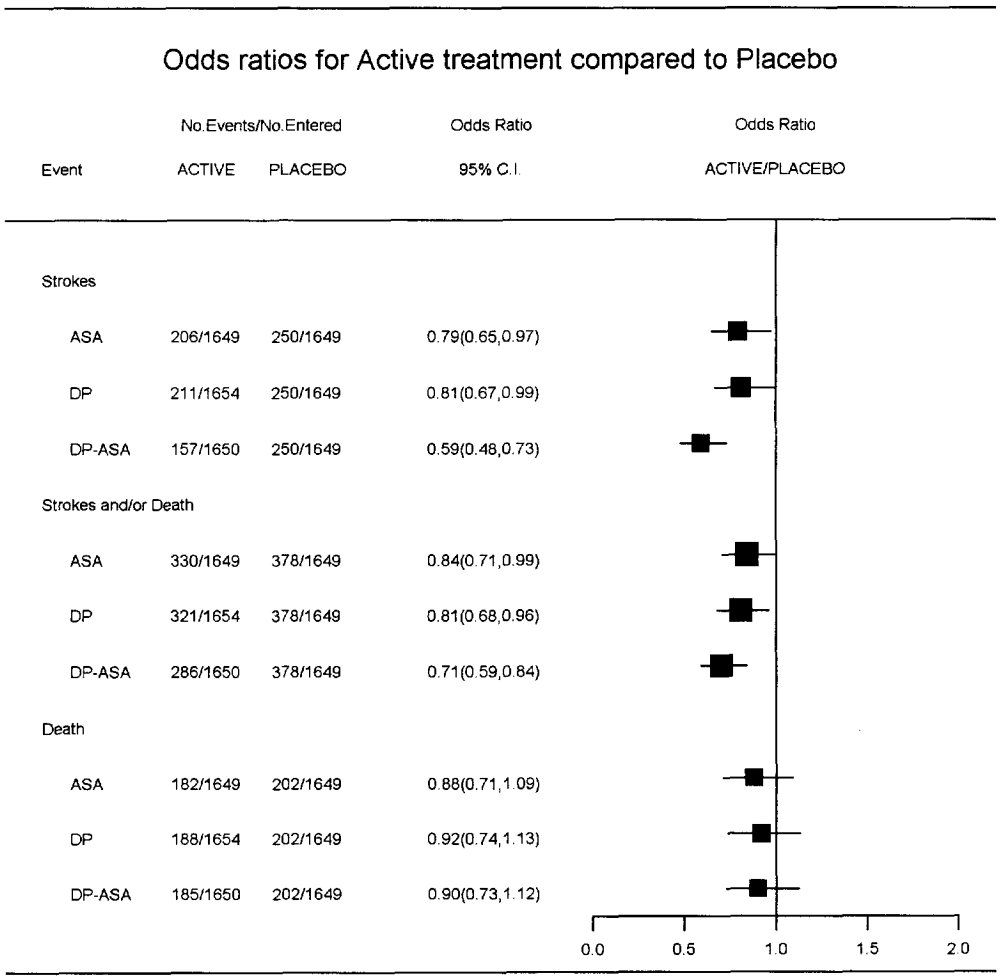


Fig. 2. Odds ratios and 95% confidence intervals for the effect of active treatment versus placebo on the principal endpoints: stroke, stroke or death, and death.

Table 3
Relative risk reductions and standard error estimates for factorial analysis and pairwise comparisons

	Stroke			Stroke or death			Death		
	RRR	se	p	RRR	se	p	RRR	se	p
Factorial design									
ASA effect	21.0	5.3	< 0.001	12.0	4.4	0.003	6.3	6.4	0.287
DP effect	19.3	5.4	0.001	14.2	4.3	0.002	2.5	7.2	0.732
Pairwise comparisons									
ASA vs Pl	18.1	7.2	0.013	13.2	5.8	0.016	10.9	8.6	0.204
DP vs Pl	16.3	7.3	0.039	15.4	5.7	0.015	7.3	8.8	0.453
DP-ASA vs Pl	37.0	6.0	< 0.001	24.4	5.3	< 0.001	8.5	8.8	0.324
DP-ASA vs ASA	23.1	7.1	0.006	12.9	6.0	0.056	-2.7	9.6	0.777
DP-ASA vs DP	24.7	7.0	0.002	10.7	6.1	0.073	1.3	9.3	0.815

ASA = aspirin; DP = dipyridamole; DP-ASA = combination of DP and ASA; Pl = placebo;vs = versus; RRR = relative risk reduction; se = standard error; p = p-value.

for the three principal endpoints are presented in Fig. 2, and confirm the risk reduction pattern observed.

The calculated risk reductions also can be examined in a fashion that provides greater clinical meaning: by translating them into the number of events avoided per thousand patients treated over two years. These figures are provided in Table 4, and clearly illustrate the additive effect of combination therapy. Nearly twice as many events are avoided with ASA-DP therapy than with ASA or DP given alone.

In order to determine the individual impact of baseline patient characteristics and treatment group assignment on survival at 24 months, the Cox model for evaluating survival data was employed. This model allows interpretation of the effects of covariates e.g. prior risk factors, demographic data, as well as assigned treatment on the risk of end-point occurrence.

According to the model, the most powerful predictor of a stroke at 24 months was a cerebrovascular event occurring before the qualifying event ($c = 1.62$). Other strong predictors included alcohol consumption ($c = 1.51$), smoking ($c = 1.22$), and concomitant diseases such as diabetes ($c = 1.40$) or myocardial infarction ($c = 1.27$). The model shows that use of either ASA ($c = 0.79$) or DP ($c = 0.77$) was associated with a significant reduction in risk.

Applying the Cox model to the endpoint death failed to show any significant effect of treatment on survival; this was consistent with the results seen with the survival analysis. In addition, the model revealed that smoking ($c = 1.51$), atrial fibrillation ($c = 1.91$), and ischemic heart disease ($c = 1.50$) exerted a negative influence on survival. When the Cox model was applied to the combined endpoint of stroke or death, administration of either ASA or DP was found to be an independent covariate significantly associated with endpoint risk reduction ($c = 0.86$ for ASA; $c = 0.80$ for DP). As expected, a previous stroke ($c = 1.43$), diabetes ($c = 1.45$) and atrial fibrillation ($c = 1.67$) had an important negative impact on this combined endpoint.

Table 4
Number of events prevented per thousand patients treated for two years

	Stroke	Stroke or death	Death
ASA vs placebo	29	30	13
DP vs placebo	26	35	9
DP-ASA vs placebo	58	56	10
DP-ASA vs ASA	30	26	−3
DP-ASA vs DP	33	21	2

ASA = aspirin; DP = dipyridamole; DP-ASA = combination of DP and ASA; vs = versus.

Table 6
Other secondary endpoints

	Placebo	ASA	DP	DP-ASA	Total	p
Number of patients	1649	1649	1654	1650	6602	
Myocardial infarction	45	39	48	35	167	NS
Other vascular events *	54	38	35	21	148	$p < 0.01$
Ischemic events †	307	266	271	206	1050	$p < 0.001$

* Combined endpoint: Lung embolism, deep venous thrombosis, obstruction of peripheral arteries, and retinal artery occlusion.
† Combined endpoint: stroke and/or MI and/or sudden death.

3.3. Transient ischemic attack

In every patient occurrence or recurrence of TIAs was recorded on systematic enquiry during the follow-up period. 860 patients reported having had at least one TIA. It is clear from Table 5 that the category with TIA decreased with ASA and/or DP when compared to the placebo group. The factorial analysis indicated that both ASA and DP were significantly effective (both $p < 0.01$) with risk reduction being respectively 21.9% and 18.3%, while the interaction was not significant. The risk reduction for the combination was 35.9% compared to placebo ($p < 0.001$). These observations are consistent with the drug effects on the stroke endpoint.

Table 5
TIA occurrence according to treatment

	Placebo	ASA	DP	DP-ASA	Total
Number of patients	1622	1631	1628	1631	6512
Patients without TIAs during 2 years of FU	1355	1425	1413	1459	5652
Patients with TIA during 2 years of FU	267	206	215	172	860
% Patients with TIA	16.46	12.63	13.21	10.55	

Table 7
Number of patients reporting at least one adverse event during the study (stratified by treatment group)

	Placebo ($n = 1649$)	ASA ($n = 1649$)	DP ($n = 1654$)	DP-ASA ($n = 1650$)	p-Value (treatment groups overall comparisons)
Any adverse event	933	990	1034	1056	$p < 0.001$
Gastrointestinal event	465	502	505	541	$p = 0.042$
Nausea	226	204	245	254	$p = 0.064$
Dyspepsia	266	283	274	290	$p = 0.70$
Vomiting	109	93	119	133	$p = 0.046$
Gastric pain	219	242	240	274	$p = 0.06$
Diarrhea	154	109	254	199	$p < 0.001$
Headache	534	546	615	630	$p < 0.001$
Bleeding any site (total)	74	135	77	144	$p < 0.001$
Mild	52	82	53	84	
Moderate	15	33	18	33	
Severe or fatal	7	20	6	27	
Dizziness	509	481	498	486	$p = 0.72$

ASA = aspirin; DP = dipyridamole; DP-ASA = combination of DP and ASA.

3.4. Other secondary endpoints

The data with regard to other secondary endpoints, including myocardial infarction, other vascular events and ischemic events also tend to confirm the value of antiplatelet treatment (see Table 6).

3.5. Adverse events

Analysis of adverse events noted upon systematic enquiry yielded up to one third of patients in all treatment groups including placebo reporting headache and gastro-intestinal disturbances, including diarrhoea, at any of the follow-up visits. This form of enquiry, concentrating on effects known or expected to be associated with DP and/or ASA produced a large number of reports which included mild and insignificant events reported repeatedly and almost equally in patients receiving placebo (see Table 7). A more useful analysis proved to be of those patients who withdrew from treatment because of adverse events (see Table 8). In addition analyses of time to adverse event proved helpful in assigning events to particular treatments. These analyses showed that headache and gastrointestinal events predominated as a reason for early discontinuation of treatment in patients receiving a dipyridamole-containing regimen.

Bleeding episodes were significantly more frequent and more often moderate or severe/fatal in both ASA-containing regimen. In the ASA alone group 135 (8.2%) patients reported bleeding and for DP-ASA 144 (8.7%), while in the DP alone and placebo groups bleeding was reported by 77 (4.7%) and 74 (4.5%) patients respectively. Of these, moderate to severe/fatal bleeds were as follows: ASA 53/135 (39.3%); DP-ASA 60/144 (41.7%); DP 24/77 (31.2%); placebo 22/74 (29.7%). Bleeding was most commonly reported as epistaxis, 'other' sites, proctorrhagia, melaena, haematuria, haematemesis and purpura in descending order. In contrast to the adverse events more commonly associated with DP which were generally reported early, analysis of time to reported bleed showed that

Table 8
Primary reason for premature cessation of study medication

	Placebo	ASA	DP	DP-ASA	p-Value (treatment groups overall comparisons)
Number of patients in each group	1649	1649	1654	1650	
Number of cessations	360	366	485	479	$p < 0.001$
Reasons for cessation					
Medical	275	290	385	398	$p < 0.001$
Any adverse events ‡	127	141	249	262	$p < 0.001$
Gastrointestinal event	60	61	102	116	$p < 0.001$
Headache	39	31	132	133	$p < 0.001$
Bleeding any site, any severity	5	20	3	21	$p < 0.001$
Other medical reason	148	149	136	136	NS
Non-medical	81	72	95	79	NS
Unknown	4	4	5	2	–

‡ One patient may have had one or more adverse events.
ASA = aspirin; DP = dipyridamole; DP-ASA = combination of DP and ASA.

the risk of ASA-induced bleeding persisted throughout treatment exposure.

Laboratory measurements performed throughout the follow-up period and assessment of the safety data by organ system (WHO-preferred term) were unremarkable.

3.6. Compliance

Compliance with study medication was excellent overall. According to plasma assays, compliance was confirmed in 84% of patients assigned to ASA and in 97% of patients taking DP. The apparent poorer compliance in the ASA-treated patients may represent the assay limit of detection for salicylic acid given the low ASA dose employed and sampling being carried out beyond the time period for detection.

4. Discussion

The second European Stroke Prevention Study has shown that dipyridamole modified-release formulation, 200 mg, given twice daily is effective in the secondary prevention of stroke and transient ischemic attack, when compared to placebo; further, that ASA 25 mg also given twice daily, a dose hitherto untested for clinical endpoints, is equally effective; that the co-prescription of the two agents provides a truly additive benefit, thus confirming the results of ESPS-1 (ESPS Group, 1987) a study which compared the co-administration of high-dose ASA combined with a standard-release formulation of dipyridamole. In ESPS-2 the relative risk reduction for stroke due to ASA was 18.1% ($p = 0.013$), due to dipyridamole modified-release was 16.3% ($p = 0.039$) and with the combination was 37.0% ($p < 0.001$) when each is compared with placebo. The combination was also significantly more effective than the two components prescribed singly. Factorial analysis also confirms the effect of each agent ($p \leq 0.001$) without evidence of statistical interaction. This absence of interaction reflects the different mode of action of ASA which inhibits thromboxane formation and of dipyridamole which reduces platelets aggregation by raising antiplatelet level of cyclic adenosine monophosphate (c-AMP) and cyclic guanosine monophosphate (c-GMP). Raised levels of c-AMP and c-GMP have an anti-aggregating effect (Alheid et al., 1989). As for the remaining primary end-points, the combined stroke or death endpoint was also significantly different for each treatment but presumably because of the saving in strokes since there was no significant treatment effect on all-cause death. The same benefits are also seen for TIA which although a secondary end-point was also a qualifying event for entry to the study. TIA is considered by most authorities to have qualitatively the same arterial pathology as minor and possibly major ischemic stroke. Investigation of other single thrombotic endpoints merely confirmed a trend in favour of the value of antiplatelet treatment but endpoints were generally too few in occurrence to draw further conclusions.

Previous trials of antiplatelet treatment in patients suffering from cerebrovascular disease have sought to establish the level of benefit to be expected from ASA. While differing analyses pointed to an ASA benefit in terms of endpoint reduction, (UK-TIA (1991), SALT (1991); OR = 0.82) almost all because of sample size limitations had confidence intervals which included unity. The Antiplatelet Trialists' Collaboration by their meta-analysis reduce the 95% confidence intervals and confirm a level of ASA-related benefit with respect to all vascular events corresponding to a risk reduction of 22%. In considering the importance of the results of ESPS-2 it is only possible to compare exactly the benefit seen in prior studies of stroke/TIA with respect to non-fatal stroke. The Antiplatelet Trialists' Collaboration record in their meta-analysis an Odds reduction of 23% for all 18 trials quoted. The comparable figures in ESPS-2 are, for ASA 21.7%, for dipyridamole 22.7% and for the combination 43.7%.

Prior to ESPS-2 it could only be said that doses in the range of 75–325 mg were appropriate. This study, in conjunction with pharmacological evidence that platelet cyclooxygenase is fully inhibited by ASA 25 mg, is the first to show that 25 mg twice daily is independently clinically effective in secondary stroke prevention thus supporting the position of Patrono and Roth (Patrono et al., 1996). The hope that such a dose would be free of haemorrhagic complications was not realised although the incidence of serious gastro-intestinal adverse events and bleeding was low. Of interest was the finding that ASA-induced bleeding is a risk throughout exposure to the drug. Dipyridamole modified release at 200 mg twice daily was associated with headache and gastro-intestinal disorders, particularly diarrhoea, generally early in the trial.

Given that hypertension, age > 65 years and previous episode of stroke remain major risk factors for ischemic stroke and that patients with TIA are known to be at risk of ischemic stroke, the findings of ESPS-2 that dipyridamole modified release formulation and ASA at low dose are both effective in prevention, are most welcome for a disease that is so prevalent in our society. The co-prescription of the two agents raises the expectation of preventive treatment to some 35% or more reduction in risk and therefore sets a new standard for effective medication.

Acknowledgements

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Appendix A. Trial organization

A.1. Organization structure

A.1.1. Steering Committee

Blard JM, MD. Centre Gui de Chauliac, Dept of Neurology A, Montpellier, France.

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Galvin R, MD, MRCP. Cork University Hospital, Dept of Neurology, Cork, Ireland.

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Bovim G, MD, PhD. Trondheim University Hospital, Regionsykehuset, Dept of Neurology, Trondheim, Norway.

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A.1.2. Co-ordinating Committee

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A.2.2. Finland

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A.2.4. Germany

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