

## FROM FIRST TO THE SECOND EUROPEAN STROKE PREVENTION STUDY

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### SUMMARY

A number of recent publications have shown that secondary prevention of cerebrovascular ischemic brain events is possible with anti-aggregating drugs. Comparison between the different studies is difficult, but the results obtained with using a combination therapy with aspirin (ASA) and dipyridamole (DP) seem to be superior to the results obtained with ASA alone. The first European Stroke Prevention Study (ESPS 1), that used 990 mgASA and 225 mg DP a day, showed this clearly. In an attempt to minimise the side effects of a large dose ASA and possibly even to improve the efficacy, ESPS 2 was established. ESPS 2 will compare 50 mgASA, 400 mgDP, the combination of both, and placebo.

### ASPIRIN VERSUS ASPIRIN+DIPYRIDAMOLE

Possible superiority of secondary prevention using a combination of ASA with DP has already been mentioned by FitzGerald (1) and can be confirmed by comparing the four main studies of secondary prevention after an ischemic lesion of the nervous system. Among the main studies we accepted only those that have included more than 1000 patients. They are the United Kingdom Transient Ischemic Attack (UK-TIA) Study (2), the Canadian American Ticlopidine Study (CATS) (3), the Swedish Aspirin Low Dose Trial (SALT) (4) and the first European Stroke Prevention Study (ESPS 1) (5). Even if these four studies differ in many respects from each other, the risk reductions for similar endpoints are comparable. For the two common endpoints (stroke/myocardial infarction or death and vascular death), the best risk reduction was

achieved with the combination of ASA and DP (ASA+DP) (Table 1). About the vascular death, ASA+DP and ticlopidine had efficacy.

**Table 1.**

*Comparison of risk reduction (%) of similar endpoints in the four main studies of secondary prevention of cerebrovascular*

Endpoint	ESPS 15	UK-TIA2	CATS3	SALT4
	(ASA)	Study (ASA)	Study (Ticlopidine)	Study (ASA)
Stroke +myocardial infarction + death	33	16	17	14
Vascular death	26	5	22	8

To demonstrate the possible significant differences between the treatment regimens, we underwent a meta-analysis of seven studies that have used ASA vs. placebo and two studies using ASA+DP vs. placebo (6). The efficacy of the treatment was analysed using five endpoints (all strokes, fatal strokes, important vascular events, all deaths, vascular deaths). The risk reduction was found only in three of them in the studies using ASA alone (all deaths, all strokes, important vascular events). In the studies using

AS A+DP, risk reduction was found in all five endpoints analysed. In addition, risk reduction was always higher in the ASA+DP group. The difference in risk reduction between the two series was statistically significant in three of the analysed endpoints (all strokes, fatal strokes, important vascular events), but it was not significant in all deaths and vascular deaths.

The efficacy of the combination therapy used in ESPS 1 is well documented. What is then the reason to organize a second European Stroke Prevention Study (ESPS 2)?

### THE REASONS TO ESTABLISH ESPS 2

- There is a demonstrable significant difference in the main results in ESPS 1 between intention-to-treat analysis and explanatory analysis (Table 2). Intention-to-treat analysis takes into account results in all randomized patients, and explanatory analysis was based only on results in patients who were eligible and complied with the protocol. Even if the difference between these two types of analyses is not remarkable, it would be desirable to minimize the differences between intention-to-treat and explanatory analyses.

**Table 2.**

*Risk reduction of ischemia events in the European Stroke Prevention Study J (All patients, stroke or death from any reason as the endpoint).*

Method of analysis	ASA+DP	Placebo	Risk Reduction
Intention-to-treat analysis (2,500 patients)	15.2%	22.6%	33.5%, P<0.001
Explanatory analysis (1,861 patients)	10.8%	17.0%	36.5%, P<0.001

The drop-outs in ESPS 1 reached 34 % in the treatment group, but only 30 % in the placebo group, which difference is statistically significant. Some of the interruptions of the treatment were due to non-medical reasons, some to intercurrent diseases. However, in more than 40 % of the patients with ASA+DP in whom the treatment was stopped, it was due to the side effects. In the placebo group, the cessation for this reason was necessary only in 27 % of the patients.

Most of the adverse events were equally distributed between the two treatment groups. Some were, however significantly increased in the active treatment group (Table 3), and most probably were due to the influence of ASA. Among the most important ones are the bleedings. The information about bleedings, coming from different ASA studies in comparison with placebo, shows that they are twice as frequent in the treatment group as in the placebo group (Table 4). The bleedings may reach even 7 to 8 %, twice as much in the active than the placebo group. The bleedings are probably dose dependent (7, 8). Reducing the dosage of ASA could improve the results of the treatment by decreasing the incidence of the side effects.

**Table 3.**

*Adverse effects due to ASA in the European Stroke Prevention Study I*

Adverse effect	ASA+DP (N)	Placebo (N)	Statistical significance
Stomach pain	171	96	P<0.001
Vomiting	26	8	P<0.001
Dyspepsia	233	155	P<0.001
Ulcerus	13	2	P<0.001
Bleedings	79	41	P<0.001

**Table 4.**

*Frequency of bleedings in aspirin studies (%).*

Study	Low ASA (<325 mg)	High ASA (>325 mg)	Placebo
UK-TIA2	5.3	7.9	3.1
ESPS 15	-	7.3	3.8
SALT4	7.2	-	3.2
Dutch TIA7	5.0	8.7	-

Thus, the main reasons to organize a new study (ESPS 2) are: 1) To test, whether the risk reduction observed in ESPS 1 can be achieved with a lower dose of ASA, thereby preventing the high incidence of ASA-related adverse effects seen in the first trial, 2) to test, whether ASA or DP given alone, rather than in combination, can achieve a signifi-

cant reduction in cerebrovascular events, 3) to improve and computerize the data collection and handling. We hope with the new methodology to minimize the differences between intention-to-treat and explanatory analysis.

**THE METHODOLOGICAL IMPROVEMENTS IN ESPS 2**

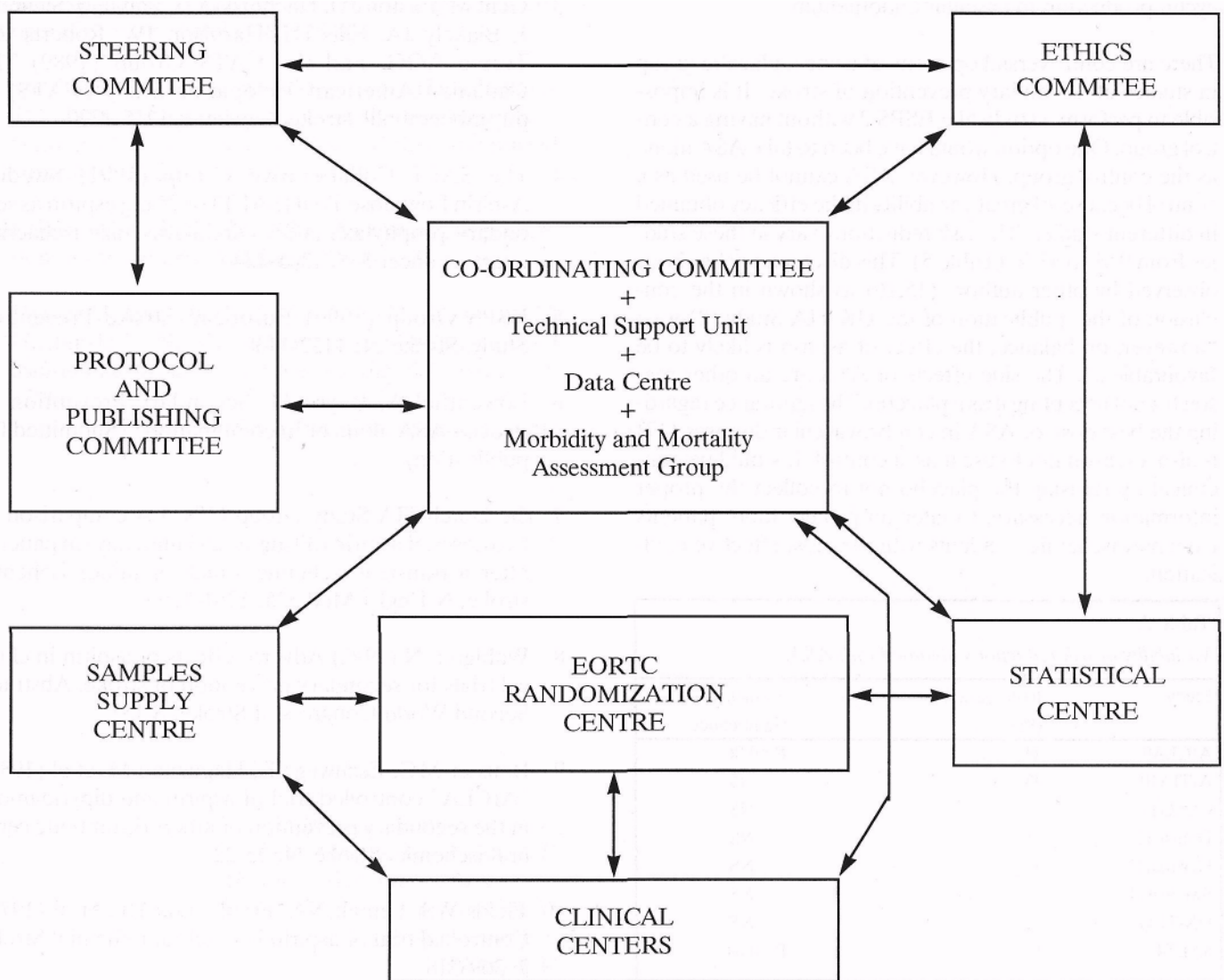
- Since ESPS 1 was organized in 1977 and ESPS 2 ten years later, one can understand that in ESPS 2 more computerized methods are used. The computerization allows the usage of a completely automated study design (Fig. 1). The patients are recruited in one of the 55 cen-

tres that are connected to the randomization centre by computer. The trialist has to answer to more than 20 questions in case of a new possible patient aimed to be recruited to the study, and send this information by computer to the European Organization for Research and Treatment of Cancer (EORTC) in Brussels. If a patient is accepted to the study, the answer is sent to the clinical trialist, to the sample supply centre and to the statistical centre. All information issued from the randomization or the follow-up visits of the patients is sent later to the Coordinating Committee. The Coordinating Committee informs all the other committees including the Steering Committee, the

**ESPS2 ORGANIZATION**

Figure 1.

Flowchart of the European Stroke Prevention Study 2.



Ethics Committee and the Protocol and Publishing committee. The Coordinating Committee works with two subcommittees: the Technical Support Unit (TSU) and the Morbidity and Mortality Assessment Group (MMAG).

## HOW TO DIMINISH THE SIDE EFFECTS OF ASA?

- It was decided that the ESPS 2 will have four arms: placebo, ASA 50 mg a day, DP 400 mg a day and ASA 50 mg+DP 400 a day. The usage of 50 mg of ASA was accepted due to the modern view favouring low-dose aspirin. Aspirin inhibits the synthesis of thromboxane A<sub>2</sub> in platelets by irreversibly acetylating the active site of cyclooxygenase while simultaneously inhibiting the production of prostacyclin. To avoid this "aspirin dilemma", low doses of aspirin are now widely recommended based on the assumption that a low dose can inhibit thromboxane synthesis in platelets with much less effect on prostacyclin production in vascular endothelium.

There are controversial opinions of using a placebo group in studies of secondary prevention of stroke. It is impossible to perform a study like ESPS 2 without having a control group. One option would have been to take ASA alone as the control group. However, ASA cannot be used as a control because of great variability in the efficacy obtained in different studies. The risk reductions vary in these studies from 9 % to 43 % (Table 5). This discrepancy has been observed by other authors (15,16) as shown in the conclusion of the publication of the UK TIA Study (2) was: "however, on balance, the effect of aspirin is likely to be favourable...". The side effects of ASA are an other reason for not accepting it as a placebo. The ignorance regarding the best dose of ASA in cerebrovascular diseases (17) is also a reason not to use it as a control. It would be non-ethical by refusing the placebo not to collect the proper information necessary, to later on protect more patients from new ischemic accidents with the most effective medication.

Study	Risk reduction (%)	Statistical significance
AICLA9	24	P<0.06
AITIA10	43	NS
CCSG11	7	NS
Danish12	-6	NS
German13	33	NS
Swedish14	-9	NS
UK-TIA2	12	NS
SALT4	19	P<0.04

The ESPS 2 study began in February 1989. An interim analysis was done at the end of 1991. From this analysis, no definite conclusion was yet possible about the risk reductions among the four treatment arms. Practically same number of patients with same frequency of physiological and pathological characteristics were included. This perfect randomization is due to the good quality of the methodology used in the study.

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