Stroke is the leading cause of disability in industrialized countries and poses an increasing burden on public and private healthcare systems. Owing to increasing life expectancy, the rate of first stroke is expected to continue to rise.1 In contrast, the rate of recurrent stroke is more susceptible to medical prevention strategies and therefore could be effectively reduced. In addition to control of the classic cardiovascular risk factors, both oral anticoagulants (vitamin K antagonists) and platelet inhibitors have been shown to decrease the relative risk of stroke recurrence by 13% to 67%.2 Several antiplatelet drugs have been investigated for the secondary prevention of stroke, including aspirin, ticlopidine, clopidogrel, and dipyridamole (DP). In addition, the combination of DP plus aspirin has been compared versus aspirin and the combination of clopidogrel plus aspirin versus aspirin or clopidogrel.4

In the following section, I will review the results from clinical trials investigating the benefit and risk of the combination of aspirin and DP versus placebo and aspirin monotherapy. In addition, I will compare the study design and results of the European Stroke Prevention Study 2 (ESPS2)5 and the recently published European/Australian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) study.6

Early studies investigating the combination of DP plus aspirin versus aspirin monotherapy failed.7–9 Those trials used a rapid-release form of DP and were apparently underpowered in terms of sample size.

ESPS2 was a randomized, double-blind, placebo-controlled trial that compared aspirin (50 mg daily), modified-release DP alone (200 mg twice daily), aspirin plus DP, and placebo in the secondary prevention of stroke.5,10 Patients (N=6602) who had experienced either a transient ischemic attack (TIA) or stroke were randomized. ESPRIT was randomized but open, and it compared aspirin in doses of 30 to 325 mg daily with and without 200 mg DP twice daily.11 Patients (N=2763) with TIA or minor stroke participated. ESPS2 was the last prevention trial that included a placebo group. Therefore, it was possible to prove that a low dose of 50 mg aspirin was superior to placebo. The variable dose of aspirin used in ESPRIT reflects clinical practice. Meta-analyses were unable to show a relation between the dose of aspirin and clinical efficacy for secondary stroke prevention.12,13 An open trial like ESPRIT again reflects clinical reality. In a trial with hard end points, such as stroke or myocardial infarction, and blinded evaluation, an open trial design will not bias the outcome (in contrast to trials wherein subjective outcome measure such as pain are used). However, headache as a side effect of DP early during treatment would have “unblinded” both investigators and patients. Slow-release DP was used in 83% of the patients in ESPRIT.

ESPS2 included patients with all types of stroke severity, whereas ESPRIT recruited patients with TIA and nondisabling stroke. In ESPS2, stroke severity at inclusion was not a predictor of outcome when the 4 treatment arms were compared. The primary end point in ESPS2 was stroke. The reason why this end point was chosen was because of results from the first European Stroke Prevention Study,14 which showed a benefit of combination therapy versus placebo and which served to perform the power calculation for ESPS2. The primary end point in ESPRIT was a combined end point of vascular death, nonfatal stroke, nonfatal myocardial infarction, and bleeding complications. There is ongoing debate whether the primary end point should reflect the benefit or whether it should also include the risk of treatment. As both studies have shown, both approaches are feasible. The 2-year relative risk reduction of stroke in the aspirin plus DP group (37.0%) was significantly higher than in the aspirin-only group (18.1%). The 2-year rate of recurrent stroke was 9.5% with aspirin plus DP, 12.5% with aspirin alone, 12.8% with DP alone, and 15.2% with placebo. In ESPRIT, the 3.5-year risk of reaching the primary end point was 13% for combination therapy and 16% for monotherapy. The relative risk reduction was 20%. For the end point of first ischemic stroke, the difference of 96 versus 116 strokes was not significant.

Until now trials, that tested a combination of 2 antiplatelet drugs, like aspirin and clopidogrel, have shown a higher bleeding rate than aspirin monotherapy. This is true for stroke prevention3,4 and for the treatment of acute coronary syndrome.15 The combination of anticoagulants and aspirin also leads to a higher bleeding rate.16,17 Interestingly, in both ESPS2 and ESPRIT, the bleeding rate was similar with monotherapy and combination therapy. This could mean that the preventive...
action of DP has other mechanisms of action than antiplatelet activity.

In the past, intravenous DP was used as a stress test in patients with severe coronary heart disease. This practice created the assumption that DP might be harmful in patients with coronary heart disease who were included in stroke prevention trials. Both trials showed that this was not the case. In ESPS2, 35 patients in the combination therapy group and 39 in the aspirin monotherapy group experienced a myocardial infarction. The respective numbers in a first cardiac event in ESPRIT were 43 and 60. The explanation is that DP in slow-release from does not cause a transient ischemic attack.

Headache is a frequent side effect of DP early during treatment. This effect caused a considerable number of patients to withdraw from both trials. Meanwhile, however, clinicians have learned how to resolve this problem. If patients are instructed that headache can occur and that this is a transient phenomenon, like headache caused by nitrate use, the dropout rate attributable to headache is much lower. In the ESPS2 trial, in which the dropout rate attributable to headache is much lower, the explanation is that DP in slow-release from does not cause a coronary steal phenomenon.

The ESPRIT trial was published in one of the most prestigious medical journals, The Lancet. The ESPS2 manuscript was rejected by The Lancet 11 years ago with the argument that it was unethical to use a placebo arm. None of the 59 ethics committees and review boards shared this view. One should remember that at the time when ESPS2 was initiated, it had not been shown that a dose as low as 50 mg aspirin was effective in secondary stroke prevention.

ESPS2 was funded by Boehringer Ingelheim. The protocol, however, was designed by the steering committee, and the analysis was performed by an academic institution. ESPRIT was funded by bodies with no relationship to the pharmaceutical industry. The results of both trials are nevertheless almost identical. ESPRIT had 1 participating center with incomplete data, and 24 patients had to be excluded before data analysis. In ESPS2, 1 investigator had falsified data from 438 patients. This was detected by monitoring before the database was closed. As it turned out, that same investigator had falsified data for many earlier trials but was identified only through ESPS2. The results of ESPS 2, however, were not influenced by inclusion or exclusion of the falsified data.

In summary, it has been shown in 2 independent trials with different designs, inclusion criteria, end points, and funding that the combination of DP and aspirin is superior to aspirin alone for the secondary prevention of TIA and ischemic stroke without a higher risk of bleeding. Therefore, in my opinion, it is no longer appropriate to promote aspirin monotherapy as the treatment of first choice for secondary stroke prevention.

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