Dipyridamole in Stroke Prevention
Effect of Dipyridamole on Blood Pressure

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Background and Purpose—Trial data suggest that dipyridamole, with or without aspirin, is more efficacious in the secondary prevention of stroke than of coronary events. This selective effect might be attributed to blood pressure lowering by dipyridamole. Therefore, we aimed to assess the effect on blood pressure in the setting of a randomized clinical trial in patients with cerebral ischemia of presumed arterial origin.

Methods—In this study, 591 patients with recent cerebral ischemia of arterial origin were randomly allocated to treatment with aspirin 30 to 325 mg/d or with the combination of aspirin and dipyridamole 400 mg/d in the European/Australian Stroke Prevention in Reversible Ischemia Trial. In an on-treatment analysis, the change in blood pressure measurements from baseline to values after at least 6 months of follow up was assessed with linear regression analysis.

Results—After an average period of 15 months, systolic blood pressure dropped 6.2 mm Hg in the aspirin plus dipyridamole group (n=273) and 6.2 mm Hg in the aspirin group (n=318), for a difference of 0.0 mm Hg (95% confidence interval, −3.8 to 3.7). Diastolic blood pressure dropped 3.6 mm Hg in the aspirin plus dipyridamole group compared with 2.7 mm Hg in the aspirin group, for a difference of 0.9 mm Hg (95% confidence interval, −1.0 to 2.9).

Conclusions—It is unlikely that dipyridamole leads to a permanent reduction in blood pressure and that this would explain why this drug might prevent strokes rather than coronary events. (Stroke. 2003;34:2339-2342.)

Key Words: blood pressure ■ dipyridamole ■ stroke ■ stroke prevention

The risk of recurrent stroke after cerebral ischemia of presumed arterial origin is 3.6% annually1 and 10.5% in the first year.2,3 The risk for all important vascular events in these patients is 4% to 11% annually.4 The Second European Stroke Prevention Study (ESPS-2)2,3 showed a relative risk reduction (RRR) of 24% (95% confidence interval [CI], 7 to 37) in the prevention of fatal and nonfatal stroke after cerebral ischemia of arterial origin in favor of the combination of aspirin plus dipyridamole versus aspirin alone. No blood pressure data from this trial are available. In contrast, the RRR for the prevention of myocardial infarction was not statistically significant: point estimate, 10% (95% CI, −41 to 43). The Antithrombotic Trialists’ Collaboration (ATT) analyzed the combination of aspirin plus dipyridamole compared with aspirin alone in general. Their findings confirm that the combination had more effect in the prevention of nonfatal stroke (RRR, 22%; 95% CI, 6 to 36) than of nonfatal coronary events (RR increases by 12%; 95% CI, −11 to 41).

Similar observations were made for the comparison of dipyridamole alone versus control, although the number of patients was smaller and no significant difference was found for either stroke or coronary events.

One of the pharmacological effects of dipyridamole is vasodilatation, which in turn may result in lowering blood pressure.7,8 Dipyridamole is a nucleoside transport inhibitor, which increases adenosine release by the myocardium and raises the interstitial fluid levels of adenosine, resulting in a vasodilator effect. This effect may result in myocardial ischemia in patients with coronary disease.

The strongest risk factor for cerebral ischemia is high blood pressure.9 Systematic reviews on the primary prevention of stroke show that a reduction in diastolic blood pressure by 5 to 6 mm Hg leads to a 35% to 50% lower stroke rate.10–12 In high-risk patients treated with ramipril, the Heart Outcomes Prevention Evaluation (HOPE) study group found a 32% RRR for stroke with reductions in systolic and diastolic blood pressures of only 3.8 and 2.8 mm Hg, respectively, on average.13 The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) group randomly treated patients after stroke with perindopril with or without indapamide and showed that an average blood pressure reduction of 9/4 mm Hg was associated with an 28% decrease in risk of subsequent stroke.14 The Framingham Heart Study again showed that the risk ratio per 10–mm Hg blood pressure increase was somewhat smaller for coronary heart disease than for stroke.15

The aim of this study was to investigate whether dipyridamole decreases blood pressure in patients after cerebral ischemia of presumed arterial origin in the long term (>6 months after start of treatment).
Patients and Methods
In the European/Australian Stroke Prevention in Reversible Ischemia Trial (ESPRIT), patients with cerebral ischemia of presumed arterial origin are randomized among 3 different treatment regimens: aspirin 30 to 325 mg/d, aspirin 30 to 325 mg/d combined with dipyridamole 200 mg twice daily, or oral anticoagulation with target international normalized ratio values of 2.0 to 3.0.16-17 Treatments are open, assessment of the primary outcome measure “vascular death, nonfatal stroke, nonfatal myocardial infarction, or major hemorrhage” is blinded.

Patient Characteristics
Eligible for ESPRIT are patients who are referred to a neurologist or general physician because of a transient ischemic attack or minor ischemic stroke (grade ≤3 on the modified Rankin Scale) within the preceding 6 months. Patients in whom a cause of cerebral ischemia other than atherosclerosis is demonstrated are excluded. Other exclusion criteria are indications for or contraindications against any of the treatment medications or diminished life expectancy. Further details are given elsewhere.16-17 Patients are informed about the background of the trial and its procedures, and informed consent is required. At baseline, data on the particulars of the ischemic event are collected, as well as information about vascular risk factors and medical history. Blood pressure taken at randomization is recorded on the baseline form.

Follow-Up
Every 6 months, follow-up data on clinical outcome events are collected. Most patients visit their neurologists or physicians for this purpose, but the study protocol allows follow-up by telephone as well. As of July 1999, we asked the ESPRIT centers to measure blood pressure at the follow-up visits, with the general justification that this would allow us to answer questions about the relation between the course of the blood pressure level after stroke and the risk of outcome events. Physicians were not aware of the aim of this particular substudy.

Statistical Analysis
Under the assumption of an SD of diastolic blood pressure of 13 mm Hg,1 a=0.05, and B=0.20, we calculated that we would need 167 patients per treatment arm to detect a 4-mm Hg difference with sufficient precision. With the same assumptions, detection of a 5-mm Hg difference would require 107 patients and a 3-mm Hg difference would require 297 patients per group. Hence, we decided to study ~200 patients per treatment arm to detect a clinically relevant difference in diastolic blood pressure.

The analysis was “on treatment” to evaluate the full pharmacological effect of dipyridamole on blood pressure. We included only those patients who had regularly used the medication anamnestic for at least 6 months at the time of blood pressure measurement on follow-up. The mean of the first 2 follow-up measurements was calculated as an estimate of “usual” blood pressure on follow-up. The difference between the baseline blood pressure and the average blood pressures on follow-up was compared between patients allocated to the combination of dipyridamole with aspirin and those on aspirin alone. Linear regression analysis was performed to calculate differences between the changes in blood pressure in the 2 treatment groups and corresponding 95% CIs. In addition, we used this regression technique to determine the influence of potential baseline imbalances between the 2 treatment groups by calculating adjusted differences.

Results
At the time of analysis (November 14, 2002), 1741 patients had been randomized between the treatment arms of aspirin combined with dipyridamole (n=862) or aspirin alone (n=879) (Figure 1). Almost all patients used the modified release form of dipyridamole. More than 1 blood pressure measurement after at least 6 months of follow-up was available for 325 patients on the combination treatment and 341 patients on aspirin alone. After exclusion of the patients who no longer followed the allocated treatment regimen, 273 remained in the combination group, and 318 were in the group on aspirin alone. Reasons for noncompliance were often headache and gastrointestinal complaints, furthermore dizziness, cardiac symptoms (palpitations or angina pectoris), or a new indication for oral anticoagulation. The mean follow-up time at the first blood pressure assessment was 349 days for both treatment groups. For the second blood pressure assessment, the follow-up time was 573 days for the combination treatment and 596 days for aspirin alone.

About two thirds of the included patients were male; mean age was ~62 years; and ~40% had been randomized within 1 month after the ischemic event (the Table). The qualifying event was a minor ischemic stroke in about two thirds and a transient ischemic attack or transient monocular blindness in the other patients. The mean systolic/diastolic blood pressure at baseline in the dipyridamole plus aspirin group was 152/86 mm Hg and in the aspirin group was 154/87 mm Hg. There were no major differences at baseline between the 2 treatment groups.

In the group on aspirin plus dipyridamole, the average systolic blood pressure dropped 6.2 mm Hg (95% CI, 3.4 to 9.0); in the aspirin group, it dropped 6.2 mm Hg (95% CI, 3.6 to 8.8) (Figure 2). The difference was 0.0 mm Hg (95% CI, -3.8 to 3.7). The average diastolic blood pressure dropped 3.6 mm Hg (95% CI, 2.3 to 5.0) in the group on combination therapy compared with 2.7 mm Hg (95% CI, 1.3 to 4.1) in the aspirin group (Figure 2). The difference was 0.9 mm Hg (95% CI, -1.0 to 2.9) in favor of the aspirin plus dipyridamole combination. After adjustment for baseline characteristics, the results were essentially similar.

Discussion
In our study, we found no clinically important decrease in blood pressure by long-term dipyridamole treatment in patients with recent cerebral ischemia of arterial origin. Our data make it highly unlikely that such a decrease would be
We found no previous studies that observed a permanent decrease in blood pressure after treatment with oral dipyridamole. Two randomized trials on dipyridamole for secondary prevention reported data on blood pressure at follow-up and did not show any important effect on blood pressure. In the Diabetic Microangiopathy Modification With Aspirin vs Dipyridamole (DAMAD) study, the difference in systolic blood pressure drop after 3 years was 0 mm Hg (95% CI, −8.6 to 8.8) between the group on aspirin plus dipyridamole (225 mg/d) and the group on aspirin alone. The difference in diastolic blood pressure drop was 3 mm Hg (95% CI, −1.4 to 7.4) in favor of the group on combination therapy. In the ESPS-I study, the systolic blood pressure drop difference after 2 years was 0.4 mm Hg (95% CI, −2.3 to 3.1) in favor of the placebo group compared with the group on aspirin plus dipyridamole (225 mg/d). The difference in decrease in diastolic blood pressure was 0.6 mm Hg (95% CI, −1.9 to 0.7) in favor of the combination treatment. The data in these 2 studies were analyzed according to the intention-to-treat principle.18,19

A minor limitation of our study is the unequal number of patients analyzed in the 2 treatment groups. This difference was caused by a lower compliance in the dipyridamole group. It is well known that headache is a frequent side effect of dipyridamole. In the ESPS-2 study, 28.3% stopped treatment with aspirin plus dipyridamole compared with 21.7% in the group on aspirin alone.2 Although the balance between the 2 groups achieved by randomization at baseline might have been disturbed by the selective dropout of patients, adjustments for differences in baseline characteristics did not alter the results.

Strong points of this study were assessment of blood pressure by physicians who where not aware of this study and the availability of 2 blood pressure measurements at least 6 months after the start of the trial medication.

In both treatment groups, a clinically relevant drop of ≥6/3 mm Hg was observed. An explanation for this blood pressure decrease in most patients may be the use of antihypertensive treatment, started after the presenting stroke, because physicians probably have treated blood pressure in a proportion of patients to a clinically safer target. However, even after a reduction of 6 mm Hg, systolic blood pressure remained high on follow-up, suggesting a potential for more intensive antihypertensive treatment. Another explanation for the decrease in blood pressure on follow-up may be the “wearing off” of the acute effects of the qualifying ischemic event. We do not consider regression to the mean an important explanation for the drop in blood pressure after randomization because our patients were not selected according to an elevated blood pressure.

In conclusion, we consider it unlikely that blood pressure effects of dipyridamole explain any selective effect in the prevention of stroke recurrence over that of new coronary events.

Appendix

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Acknowledgments

ESPRIT grant support came from the Netherlands Heart Foundation (No. 97.026), University Medical Center Utrecht, UK Stroke Association, French Ministry of Health, Janivo Foundation, Aegon, Netherlands Thrombosis Foundation (No. 20021), and the European Commission (No. QLK6-CT-2002–02332). We gratefully acknowledge the original idea and final comments of Professor C.P. Warlow, University Department of Clinical Neurosciences, Western General Hospital Edinburgh, (UK).

References

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Stroke. 2003;34:2339-2342; originally published online September 4, 2003;
doi: 10.1161/01.STR.000090346.45784.C3
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/34/10/2339

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