Prevention With Low-Dose Aspirin Plus Dipyridamole in Patients With Disabling Stroke

Diederik W.J. Dippel, MD, PhD; Lisette Maasland, MD; Patricia Halkes, MD, PhD; L. Jaap Kappelle, MD, PhD; Peter J. Koudstaal, MD, PhD; Ale Algra, MD, PhD; on behalf of the ESPRIT Study Group and the ESPS-2 Investigators

Background and Purpose—The combination of low-dose aspirin and dipyridamole is more effective than aspirin alone in reducing the risk of recurrent stroke and other major cardiovascular events in patients with a recent transient ischemic attack or minor stroke. It is unknown whether this also applies to patients with a disabling stroke.

Methods—We reanalyzed the data of 5700 patients from ESPRIT and ESPS-2 to study the effect of aspirin and dipyridamole according to modified Rankin scale (mRS) score at baseline. Primary outcome was vascular events (stroke, myocardial infarction, or vascular death). We used proportional hazards regression to estimate the treatment effect across mRS strata at baseline, and we tested for interactions with treatment.

Results—In total, 426 patients (7.5%) had mRS score of 4 or 5 at baseline. The risk of an outcome event increased with mRS score. The relative risk associated with the combination of aspirin and dipyridamole compared to aspirin alone in patients with mRS score 0 to 5 was 0.79 (95% confidence interval, 0.69–0.91). The relative risk according to mRS subcategory score 0 to 4 at baseline varied between 0.73 and 0.96 for vascular events and between 0.62 and 0.96 for stroke. The number of patients with mRS score 5 was too small for reliable estimates, but the data suggest a beneficial effect. There was no evidence of interaction between treatment effect and mRS score at baseline.

Conclusion—The beneficial effect of the combination of low-dose aspirin and dipyridamole was present in all subcategories of the mRS score.

Key Words: antiplatelet treatment ■ disabling stroke ■ transient ischemic attack

Two large, randomized, clinical trials have shown that the combination of aspirin and dipyridamole is more effective than aspirin alone in reducing the risk of stroke and other major vascular events in patients with a recent TIA or minor ischemic stroke.1,2 Patients who participated in these trials may not have been representative of patients with a recent TIA or ischemic stroke in general. We and others3–5 showed that patients in antiplatelet trials are generally younger, have less comorbidity, and less severe strokes than patients in hospital and population surveys. This may raise concerns about extrapolation of trial results to all patients with a recent TIA or minor ischemic stroke.

Of particular interest is stroke severity. Patients with disabling stroke may have a high risk of recurrent vascular events, including ischemic stroke in other vascular territories. However, more severely disabled patients may benefit less because of a limited lifespan and susceptibility to complications other than vascular complications. We reanalyzed the data of ESPRIT and ESPS-2 to study the effect of the combination aspirin and dipyridamole in relation to subcategories of the modified Rankin scale (mRS) score at baseline.

Materials and Methods

We pooled the data concerning patients treated with aspirin plus dipyridamole and aspirin alone from 2 multicenter, randomized, clinical trials. ESPRIT was an open-label multicenter, randomized, clinical trial in which the effect of low-dose aspirin (30–325 mg, daily) and dipyridamole (200 mg, twice daily) was compared with the effect low-dose aspirin alone. Patients with a TIA or minor ischemic stroke (mRS grade ≤3) in the previous 6 months were eligible for the trial.1 The mean follow-up was 3.5 years. ESPS-2 was a double-blind, multicenter, randomized, clinical trial with a 2×2 factorial design that compared low-dose aspirin (25 mg, twice daily) and dipyridamole (200 mg, twice daily) in combination or alone with placebo.2 Patients with a TIA or stroke that occurred in the preceding 3 months were included. All patients were followed-up for 2 years or until death.

The primary outcome was defined as vascular event, ie, the composite of nonfatal stroke, nonfatal myocardial infarction, or vascular death. We used Cox proportional hazards regression to estimate the effect of aspirin and dipyridamole vs aspirin alone for...
each outcome across mRS strata at baseline, and we tested for interaction between treatment and mRS.

Results

Information on the mRS at baseline was missing in 338 (5.6%) of 6038 patients included in the trials, leaving 5700 patients with complete baseline data for evaluation. In total, 426 patients (7.5%) had mRS score ≥3 at baseline. The risk of an outcome event increased with higher scores on the mRS (Table). The overall hazard ratio for vascular events associated with the combination of aspirin and dipyridamole compared to aspirin alone was 79% (relative risk reduction, 20.6%; 95% confidence interval, 8.9%–30.8%).

The hazard ratio for vascular events in mRS categories 0 to 4 ranged from 73% to 96% (Table). The hazard ratio for stroke in mRS categories 0 to 4 ranged from 62% to 96%. The number of patients in mRS category 5 was too small for precise estimates, but the data suggest a beneficial effect in this category. The relative risk reductions with 95% confidence intervals corresponding to the hazard ratios are displayed in the Figure. There was no evidence of interaction between the treatment effect and baseline mRS. More precisely, it could be estimated from the regression models that the probability of an interaction effect that would at least annihilate the effect of treatment on the occurrence of vascular events among patients with mRS score 4 would be 13% and the probability of a similarly sized interaction effect on stroke events would be 2.3%.

Discussion

Previous publications on the effect of dipyridamole and aspirin did not report on a differential effect according to disability at baseline. In most trials of antiplatelet treatment, the proportion of patients with severe stroke (mRS >3) was small. This can be explained by active exclusion of severely disabled patients, by a lower likelihood of being asked to participate, and by clustering of exclusion criteria. Also,

### Table. Effect of ASA and DIP Compared With ASA Alone

<table>
<thead>
<tr>
<th>Vascular events</th>
<th>N of Patients</th>
<th>Events/Patient-Year At Risk (Rate, %)</th>
<th>ASA (N=2861)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td>460/7091 (6.5)</td>
<td>0.80 (0.69–0.91)</td>
</tr>
<tr>
<td>mRS=0</td>
<td>1838</td>
<td>94/2593 (3.6)</td>
<td>107/2519 (4.2)</td>
<td>0.86 (0.65–1.13)</td>
</tr>
<tr>
<td>mRS=1</td>
<td>1790</td>
<td>95/2275 (4.2)</td>
<td>128/2239 (5.7)</td>
<td>0.73 (0.56–0.95)</td>
</tr>
<tr>
<td>mRS=2</td>
<td>1123</td>
<td>83/1352 (6.1)</td>
<td>116/1430 (8.1)</td>
<td>0.75 (0.57–1.00)</td>
</tr>
<tr>
<td>mRS=3</td>
<td>523</td>
<td>59/567 (10.4)</td>
<td>61/557 (10.9)</td>
<td>0.96 (0.67–1.38)</td>
</tr>
<tr>
<td>mRS=4</td>
<td>405</td>
<td>34/316 (10.8)</td>
<td>44/334 (13.2)</td>
<td>0.84 (0.54–1.31)</td>
</tr>
<tr>
<td>mRS=5</td>
<td>21</td>
<td>1/19.5 (5.1)</td>
<td>4/11.8 (34)</td>
<td>0.18 (0.02–1.59)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stroke</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Overall</td>
<td>255/7181 (3.6)</td>
<td>334/7161 (4.7)</td>
<td>0.76 (0.65–0.90)</td>
<td></td>
</tr>
<tr>
<td>mRS=0</td>
<td>1838</td>
<td>66/2609 (2.5)</td>
<td>67/2550 (2.6)</td>
<td>0.96 (0.69–1.35)</td>
</tr>
<tr>
<td>mRS=1</td>
<td>1790</td>
<td>76/2289 (3.3)</td>
<td>93/2258 (4.1)</td>
<td>0.80 (0.59–1.08)</td>
</tr>
<tr>
<td>mRS=2</td>
<td>1123</td>
<td>56/1375 (4.1)</td>
<td>90/1446 (6.2)</td>
<td>0.65 (0.46–0.90)</td>
</tr>
<tr>
<td>mRS=3</td>
<td>523</td>
<td>37/571 (6.5)</td>
<td>49/560 (8.8)</td>
<td>0.75 (0.49–1.15)</td>
</tr>
<tr>
<td>mRS=4</td>
<td>405</td>
<td>19/317 (6.0)</td>
<td>33/334 (9.9)</td>
<td>0.62 (0.35–1.09)</td>
</tr>
<tr>
<td>mRS=5</td>
<td>21</td>
<td>1/19.6 (5.1)</td>
<td>2/11.8 (16.9)</td>
<td>0.34 (0.03–3.74)</td>
</tr>
</tbody>
</table>

ASA indicates aspirin; CI, confidence interval; DIP, dipyridamole; HR, hazard ratio; mRS, modified Rankin scale. Data are expressed as events per patient-years at risk. Effects are expressed as HR with 95% CI adjusted for study.

![Figure](http://stroke.ahajournals.org/Downloaded from http://stroke.ahajournals.org/)

**Figure.** Relative risk reduction (RRR) with 95% confidence intervals for categories of the modified Rankin score at baseline with the combination of aspirin and dipyridamole compared with aspirin alone in a pooled analysis of data from ESPS-2 and ESPRIT.1,2 Upper graph, RRR for vascular events. Lower graph, RRR for stroke. The dashed lines indicate the point estimates for the effect of aspirin and dipyridamole. Both estimates were adjusted for study.
analyses of effects and adverse events were not specifically reported for this subgroup. 5

In the present study, we found that the beneficial effect of the combination of low-dose aspirin and dipyridamole compared with aspirin alone applied to all subcategories of the mRS. Therefore, optimal prevention in patients with disabling stroke should include the combination of aspirin and dipyridamole instead of aspirin alone.

Disclosure
Ale Algra has received speaker’s fees from Boehringer Ingelheim. The members of the ESPRIT Study Group and the ESPS-2 investigators are listed elsewhere.1,2

References
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