Aspirin Plus Dipyridamole Versus Aspirin for Prevention of Vascular Events After Stroke or TIA
A Meta-Analysis

Piero Verro, MD, MS; Phillip B. Gorelick, MD, MPH; Danh Nguyen, PhD

Background and Purpose—This meta-analysis systematically reviewed randomized controlled trials comparing aspirin plus dipyridamole with aspirin alone in patients with stroke and TIA to determine the efficacy of these agents in preventing recurrent cerebral and systemic vascular events.

Methods—We performed separate analyses of the incidences of stroke alone and composite outcome of stroke, myocardial infarction, or vascular death. We also performed two subset analyses, planned a priori, to examine effect size based on trials using (1) exclusively immediate-release and (2) predominantly extended-release dipyridamole.

Results—The summary results indicate a significant reduction in the overall risk ratio in favor of aspirin plus dipyridamole for stroke alone with relative risk 0.77 (0.67 to 0.89) and the composite end point with relative risk 0.85 (0.76 to 0.94). Studies using immediate-release dipyridamole showed a nonstatistically significant trend in favor of the combination for stroke alone with relative risk 0.83 (0.59 to 1.15) and for the composite outcome with relative risk 0.95 (0.75 to 1.19). Studies using predominantly extended-release dipyridamole showed a statistically significant difference in favor of the combination for stroke alone with relative risk 0.76 (0.65 to 0.89) and for the composite outcome with relative risk 0.82 (0.73 to 0.92).

Conclusions—The combination of aspirin plus dipyridamole is more effective than aspirin alone in preventing stroke and other serious vascular events in patients with minor stroke and TIsAs. The risk reduction was greater and statistically significant for studies using primarily extended release dipyridamole, which may reflect a true pharmacological effect or lack of statistical power in studies using immediate release dipyridamole. (Stroke. 2008;39:1358-1363.)

Key Words: antiplatelet drugs ■ cerebrovascular accident ■ prevention ■ stroke management ■ transient ischemic attack

Secondary stroke prevention is an important concern for the 700,000 people in the United States who sustain strokes annually, especially because almost 30% of strokes that occur each year are recurrent.1–2 Antiplatlet therapy is a major strategy for preventing recurrent vascular events in patients with stroke or TIA of noncardioembolic etiology: in their present clinical practice guidelines, the American Heart Association, the American Stroke Association, the American College of Chest Physicians, and the American Academy of Neurology acknowledge the benefits of aspirin as well as prescription antiplatelet agents for secondary stroke prevention.2–4 These organizations assert that aspirin (50 to 325 mg/d), the combination of aspirin and extended-release dipyridamole, and clopidogrel are all acceptable options for initial therapy.

Aspirin is the most widely used antiplatelet agent for the prevention of recurrent stroke because of its low cost and acceptable adverse-effect profile. The effect of aspirin is small, however, because it prevents only about 13% to 22% of recurrent vascular events5,6 and only about 15% of recurrent stroke, independent of dose.7–8 The findings of the European Stroke Prevention Study 2 (ESPS-2) showed that, compared with aspirin, the combination of aspirin plus extended-release dipyridamole was 23% more effective than aspirin monotherapy in preventing subsequent stroke.9 A second comparative study, the European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT), which used the extended-release form of dipyridamole in a majority of patients, provided confirmatory data supporting the use of this combination.10 Older clinical trials using the immediate-release form of dipyridamole combined with aspirin showed no benefit in preventing secondary stroke compared with aspirin alone, possibly because of limited statistical power. The objective of our analysis was to systematically review...
randomized controlled trials comparing aspirin plus dipyridamole with aspirin alone in patients with minor stroke and TIA to determine the efficacy of these agents in preventing serious vascular events, including recurrent stroke.

Methods

Eligibility Criteria
Both published and unpublished studies were considered in this meta-analysis if they were randomized controlled trials that compared aspirin plus dipyridamole with aspirin monotherapy in patients with a history of stroke or TIA and assessed, at a minimum, the prevention of stroke as a primary end point. Additional end points could include myocardial infarction (MI) and vascular death or the composite end point of such events. Studies that used either immediate-release, extended-release dipyridamole, or both formulations were acceptable. The patient population was limited to patients with previous noncardioembolic stroke or TIA. High quality studies were defined as those having double blind concealment of treatment allocation, provided assessment of compliance and completeness of follow-up, and had blinded outcome adjudication.

Search Strategy for Identification of Studies
We performed a MEDLINE search (1966 to 2006) limited to randomized, controlled trials of human subjects using the terms “dipyridamole AND stroke,” “dipyridamole AND cerebrovascular accident,” “dipyridamole AND stroke AND aspirin,” “dipyridamole AND cerebrovascular accident AND aspirin,” and “dipyridamole AND stroke prevention,” to identify original studies and relevant review articles. We also searched the Cochrane Database of Systematic Reviews using the terms dipyridamole, stroke, stroke prevention, and vascular disease and identified the most recent review, from which we selected those clinical trials that met our eligibility criteria. Finally, we examined the reference lists of all relevant publications to locate additional studies meeting our eligibility criteria. From the identified trials, we extracted relevant clinical information regarding numbers of patients as well as numbers of defined outcome events identified in the Cochrane Database plus 1 additional relevant study.50 Fifty-six other studies identified through MEDLINE were excluded for the following reasons: 9 secondary stroke prevention studies did not compare aspirin plus dipyridamole versus aspirin control or recorded no end points, 15 did not study patients with cerebrovascular disease, 26 were analyses or commentaries of previously published data, and 6 were pharmacological studies. One additional study comparing dipyridamole plus aspirin versus aspirin alone in patients with cerebrovascular ischemia51 was identified by search of reference lists of published studies: it was excluded because it did not include stroke as a primary end point, and specifically stated that neurological assessment was inadequate.

Six randomized controlled trials met the inclusion criteria, with a total of 7648 patients; 3822 patients were allocated to aspirin plus dipyridamole and 3826 patients were allocated to aspirin monotherapy.9,10,17–20

Four trials9,17–19 were double-blinded and met our criteria for high quality studies. Specific weaknesses of individual trials were poor compliance of 71% to 80% in the ESPS-2 study,9 and 79% in the ACCSG19 study. The ESPRIT study10 used unblinded treatment allocation and thus did not qualify as high quality despite the fact that adjudication of end points was blinded; in addition it reported a 34% rate of medication discontinuation in the aspirin plus dipyridamole arm. In one small trial,20 blinding of treatment assignment and end point adjudication was not described, nor was compliance and completeness of follow-up: this trial clearly did not qualify as high quality.

Four trials used exclusively the immediate-release form of dipyridamole17–20 comprising a total of 1611 patients: their results were pooled to calculate the efficacy of immediate release dipyridamole combined with aspirin versus aspirin alone. The ESPS-2 trial used exclusively extended-release dipyridamole,9 and the ESPRIT trial used extended-release dipyridamole in 83% of patients and the immediate-release formulation in 17% of patients10: the pooled populations of these 2 trials treated 92% of participants with the extended-release form of dipyridamole and was used in the subanalysis

patients with cerebrovascular ischemia and did not specifically investigate secondary prevention of stroke. Five relevant studies were identified through the Cochrane Database search.17–20 The MEDLINE search identified 4 studies also found in the Cochrane Database plus 1 additional relevant study.50 Fifty-six other studies identified through MEDLINE were excluded for the following reasons: 9 secondary stroke prevention studies did not compare aspirin plus dipyridamole versus aspirin control or recorded no end points, 15 did not study patients with cerebrovascular disease, 26 were analyses or commentaries of previously published data, and 6 were pharmacological studies. One additional study comparing dipyridamole plus aspirin versus aspirin alone in patients with cerebrovascular ischemia51 was identified by search of reference lists of published studies: it was excluded because it did not include stroke as a primary end point, and specifically stated that neurological assessment was inadequate.

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Table 1. Aspirin and Dipyridamole: Total Daily Dose and Formulation

<table>
<thead>
<tr>
<th></th>
<th>ASA</th>
<th>ASA+DP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caneschi et al10</td>
<td>300 mg ASA 150 mg +IR-DP 225 mg</td>
<td></td>
</tr>
<tr>
<td>Guiraud-Chaumeil et al17</td>
<td>990 mg ASA 990 mg +IR-DP 150 mg</td>
<td></td>
</tr>
<tr>
<td>AICLA18</td>
<td>990 mg ASA 990 mg +IR-DP 225 mg</td>
<td></td>
</tr>
<tr>
<td>ACCSG19</td>
<td>1300 mg ASA 1300 mg +IR-DP 300 mg</td>
<td></td>
</tr>
<tr>
<td>ESPS-29</td>
<td>50 mg ASA 50 mg +ER-DP 400 mg</td>
<td></td>
</tr>
<tr>
<td>ESPRIT10</td>
<td>75 mg† ASA 75 mg† +DPT 400 mg</td>
<td></td>
</tr>
</tbody>
</table>

ASA indicates aspirin; IR-DP, immediate-release dipyridamole; ER-DP, extended-release dipyridamole.

†Median dose. Allowable dose of ASA 30–325 mg. ‡83% ER-DP, 17% IR DP.
comparing the extended-release form of dipyridamole plus aspirin to aspirin. The dosage of aspirin and dipyridamole varied among the various studies and is summarized in Table 1.

Definition of outcome events for 3 older studies17–19 varied, making pooling of data from such studies impossible. However, outcome data from these studies based on uniformly defined clinical events had been previously rigorously collected and published by the Antiplatelet Trialists’ Collaboration12; these data were used in our analyses. The study by Caneschi et al20 only published stroke incidence data; this study was thus excluded from the combined end point analysis. The definition of combined vascular events used in ESPS-2 did not correspond to that used by the Antiplatelet Trialists’ Collaboration: therefore, outcome data for each individual component of the combined vascular events were obtained from tables published in a related publication.21 These individual end points were combined to provide outcome data consistent with the Antiplatelet Trialists’ Collaboration definition of vascular events. For the ESPRIT study,10 we obtained additional outcomes information by personal communication with the corresponding author.

Stroke End Point for All Studies
Outcomes data for nonfatal ischemic and hemorrhagic stroke were available for all 6 studies9,10,17–20; the summary results indicate a significant reduction in the overall RR (RR, 0.77; 95% CI, 0.67 to 0.89) for dipyridamole combined with aspirin compared to aspirin alone (Figure 1A and Table 2). The test for heterogeneity of treatment effect across studies was not significant (\(\chi^2 = 1.82, \text{df } 5, P = 0.874\)), indicating no strong evidence of heterogeneity among the studies.

Composite Outcome: Stroke, MI, or Vascular Death for All Studies
A meta-analysis pooling the 5 studies that evaluated the composite outcome of nonfatal stroke, nonfatal myocardial infarction, and vascular death also indicates a significant reduction in the overall RR (RR, 0.85; 95% CI, 0.76 to 0.94) for dipyridamole combined with aspirin compared to aspirin alone (Figure 1B and Table 2). The test for heterogeneity of treatment effect across studies was not significant (\(\chi^2 = 1.78, \text{df } 4, P = 0.776\)).

Table 2. Results for Stroke-Alone End Point and the Composite End Point

<table>
<thead>
<tr>
<th>Study</th>
<th>Aspirin + DP Patients (n)</th>
<th>Aspirin Patients (n)</th>
<th>Aspirin + DP Events (n)</th>
<th>Aspirin Events (n)</th>
<th>RR (95% CI)</th>
<th>Aspirin + DP Events (n)</th>
<th>Aspirin Events (n)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caneschi et al20</td>
<td>22</td>
<td>14</td>
<td>3</td>
<td>3</td>
<td>0.64 (0.15–2.72)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Guiraud-Chaumeil et al17</td>
<td>138</td>
<td>147</td>
<td>1</td>
<td>4</td>
<td>0.27 (0.03–2.37)</td>
<td>12</td>
<td>11</td>
<td>1.17 (0.53–2.56)</td>
</tr>
<tr>
<td>AICLA18</td>
<td>202</td>
<td>198</td>
<td>16</td>
<td>16</td>
<td>0.98 (0.50–1.91)</td>
<td>30</td>
<td>31</td>
<td>0.95 (0.60–1.51)</td>
</tr>
<tr>
<td>ACCSG19</td>
<td>448</td>
<td>442</td>
<td>38</td>
<td>45</td>
<td>0.83 (0.55–1.26)</td>
<td>79</td>
<td>85</td>
<td>0.92 (0.70–1.21)</td>
</tr>
<tr>
<td>ESPS-28</td>
<td>1650</td>
<td>1649</td>
<td>137</td>
<td>186</td>
<td>0.74 (0.60–0.91)</td>
<td>272</td>
<td>321</td>
<td>0.85 (0.73–0.98)</td>
</tr>
<tr>
<td>ESPRIT10</td>
<td>1363</td>
<td>1376</td>
<td>99</td>
<td>127</td>
<td>0.79 (0.61–1.01)</td>
<td>149</td>
<td>192</td>
<td>0.78 (0.64–0.96)</td>
</tr>
<tr>
<td>Total Population</td>
<td>3823</td>
<td>3826</td>
<td>294</td>
<td>381</td>
<td>0.77 (0.67–0.89)</td>
<td>542</td>
<td>640</td>
<td>0.85 (0.76–0.94)</td>
</tr>
</tbody>
</table>

n indicates the No. of patients or events in each subgroup; DP, dipyridamole; MI, myocardial infarction; RR, relative risk.
Subset Analysis: Trials Using Exclusively Immediate-Release Dipyridamole

A prespecified meta-analysis performed based on the subset of 4 trials that used exclusively the immediate-release form of dipyridamole did not show a statistically significant reduction in overall RR with respect to either the stroke-alone end point (RR, 0.83; 95% CI, 0.59 to 1.15) or the composite outcome (RR, 0.95; 95% CI, 0.75 to 1.19; Figure 2A and 3A). Tests of heterogeneity were not significant.

Subset Analysis: Trials Using Primarily Extended-Release Dipyridamole

A prespecified meta-analysis based on data from the combined populations of the ESPS-2 and ESPRIT trials showed a significant reduction in the overall RR for stroke (RR, 0.76; 95% CI, 0.65 to 0.89; Figure 2B) and for the composite outcome (RR, 0.82; 95% CI, 0.73 to 0.92; Figure 3B).

Subset Analysis: High-Quality Trials

We performed our analysis combining data from the 4 studies considered high quality9,17–19: the results for the stroke alone end point (RR, 0.76; 95% CI, 0.64 to 0.91), and for the composite outcome end point (RR, 0.87; 95% CI, 0.78 to 0.99) for dipyridamole combined with aspirin compared to aspirin alone were both statistically significant and similar to the results obtained for all studies combined.

Discussion

The results of this meta-analysis show that the combination of aspirin plus dipyridamole is more effective than aspirin alone in preventing stroke and other serious vascular events in patients with minor stroke and TIA. When data from all 6 studies are pooled, the results show a statistically significant benefit in favor of aspirin plus dipyridamole compared with aspirin monotherapy for both the stroke-alone end point and the composite end point of stroke, MI, and vascular death. Our meta-analysis pooled data from high quality studies as well as those having a potential for bias because of weaknesses in study design: however, when our analysis was limited to the 4 studies considered high quality the results were essentially the same. It thus seems unlikely that bias introduced by the lower quality studies could explain the results of our meta-analysis.

In our analysis, estimates of efficacy for pooled results of studies that used exclusively the immediate-release formulation of dipyridamole were smaller and nonstatistically significant, whereas pooled results of the ESPS-2 and ESPRIT studies, which used mostly extended-release dipyridamole, showed larger point estimates which were statistically significant. However, the confidence intervals for these point estimates overlap, and the earlier studies using exclusively immediate-release dipyridamole enrolled a smaller combined cohort of 1611 patients, compared with 2739 subjects in Esprit, and 3299 in ESPS-2. Thus, because of a lack of statistical power in the combined analysis of the earlier studies we cannot draw conclusions regarding the relative efficacy of one formulation versus the other. Besides this purely statistical explanation for these discrepant estimates of efficacy, pharmacological differences between the older studies and the 2 more recent ones could have potentially influenced the results. These include differences in bioavailability22–24 and altered pharmacokinetics25,26 of the extended-release form of dipyridamole, as well as the lower doses of dipyridamole administered in the older trials (150 to 300...
mg/d) compared with the 400 mg daily dose used in both ESPS-2 and ESPRIT. Finally, the earlier trials used higher doses of aspirin (300 to 1300 mg), whereas approximately half of the subjects in the ESPRIT study used an aspirin dose of less than 75 mg, and ESPS-2 used a 50-mg dose. The efficacy of very low dose aspirin in prevention of ischemic vascular events is less well established compared to higher doses,27 thus it is possible that the higher doses of aspirin used in the early trials were more effective, leading to a smaller apparent benefit of combined treatment.

In summary, our meta-analysis of aspirin plus dipyridamole compared to aspirin alone for the secondary prevention of cerebrovascular ischemia shows a robust benefit for the combination compared to aspirin alone. The failure of trials using immediate release dipyridamole plus aspirin to show a benefit compared to aspirin alone may be because of a lack of statistical power, although the effects of different medication dosages and differences in formulation of the extended release form of dipyridamole cannot be excluded.

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Disclosures
Dr Verro has received speaking honoraria, research support, and serves as a consultant for Boehringer Ingelheim, and speaking honoraria from Bristol-Myers Squibb/Sanoﬁ Pharmaceuticals. Dr Gorelick has received speaking honoraria and serves as a consultant for Boehringer Ingelheim, Diadexus, and Bayer; he has received speaking honoraria from Bristol-Myers Squibb/Sanoﬁ Pharmaceuticals.

References


16. Kaye JA. A trial to evaluate the relative roles of dipyridamole and aspirin in the prevention of deep vein thrombosis in stroke patients. Bracknell, Boehringer Ingelheim (internal report); 1990.


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