Dipyridamole for Preventing Recurrent Ischemic Stroke and Other Vascular Events
A Meta-Analysis of Individual Patient Data From Randomized Controlled Trials

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Background and Purpose—Results from randomized controlled trials of dipyridamole, given with or without aspirin, for secondary prevention after ischemic stroke or transient ischemic attack (TIA) have given conflicting results. We performed a meta-analysis using individual patient data from relevant randomized controlled trials.

Methods—Randomized controlled trials involving dipyridamole in patients with previous ischemic stroke or TIA were sought from searches of the Cochrane Library, other electronic databases, references lists, earlier reviews, and contact with the manufacturer of dipyridamole. Individual patient data were merged from 5 of 7 relevant trials involving 11,459 patients. Results were adjusted for age, gender, qualifying event, and history of previous hypertension.

Results—Recurrent stroke was reduced by dipyridamole as compared with control (OR, 0.82; 95% CI, 0.68 to 1.00), and by combined aspirin and dipyridamole versus aspirin alone (OR, 0.78; 95% CI, 0.65 to 0.93), dipyridamole alone (OR, 0.74; 95% CI, 0.60 to 0.90), or control (OR, 0.61; 95% CI, 0.51 to 0.71). The point estimates obtained for the comparisons of aspirin and dipyridamole versus control (OR, 0.63; significant) or versus aspirin (OR, 0.88; nonsignificant) were similar if the data from the largest trial, ESPS II (which provided 57% of data), were excluded. Similar findings were observed for nonfatal stroke. The combination of aspirin and dipyridamole also significantly reduced the composite outcome of nonfatal stroke, nonfatal myocardial infarction, and vascular death as compared with aspirin alone (OR, 0.84; 95% CI, 0.72 to 0.97), dipyridamole alone (OR, 0.76; 95% CI, 0.64 to 0.90), or control (OR, 0.66; 95% CI, 0.57 to 0.75). Vascular death was not altered in any group.

Conclusions—Dipyridamole, given alone or with aspirin, reduces stroke recurrence in patients with previous ischemic cerebrovascular disease. The combination of aspirin and dipyridamole also reduces the composite of nonfatal stroke, nonfatal myocardial infarction, and vascular death as compared with aspirin alone. (Stroke. 2005;36:162-168.)

Key Words: aspirin ▪ dipyridamole ▪ stroke prevention ▪ transient ischemic attack

Aspirin is recommended for use in patients with previous ischemic stroke or transient ischemic attack (TIA) to reduce the risk of recurrence.1 In a meta-analysis, the Anti-Thrombotic Trialists (ATT) found that aspirin reduced the relative odds of further vascular events by 22%.5 However, the side effects of aspirin (principally gastrointestinal disturbance and bleeding) and its modest efficacy mean that alternative or additional antiplatelet agents might be useful clinically. A number of alternative antiplatelet agents exists for use after ischemic stroke, including dipyridamole and clopidogrel.3,4 The routine use of dipyridamole in secondary prevention after cerebrovascular events has been controversial. First, a key trial, European Stroke Prevention Study (ESPS) II,3 was criticized on a number of grounds;5 although these criticisms do not necessarily invalidate the primary results that combined aspirin and dipyridamole was superior to both aspirin alone (ie, AD versus A) and dipyridamole alone (ie, AD versus D) in preventing further stroke. Second, ATT did not find that the combination of aspirin and dipyridamole was superior to aspirin alone in reducing a composite vascular
outcome (comprising nonfatal stroke, nonfatal myocardial infarction, and vascular death) in patients with previous vascular disease. The aim of this systematic review was to assess whether dipyridamole, given with or without aspirin, reduced stroke in patients with previous ischemic cerebrovascular disease. To maximize the statistical power and facilitate subgroup analyses, we used individual patient data from all trials involving patients with previous ischemic stroke or TIA.

Methods

Search Strategy

A comprehensive literature search was performed to identify all eligible randomized controlled trials, whether published or unpublished, of dipyridamole given for the purposes of secondary prevention in patients with previous cerebrovascular disease. Electronic searches of the Cochrane Library (Issue 4, 2002), MEDLINE (1966 to 2001 inclusive), EMBASE (1980 to 2002), and Web of Science (1981 to 2002) were performed using the key words “dipyridamole,” “stroke,” “prevention,” and “cerebrovascular” in combination with the recommended search routine for identifying randomized controlled trials. Reference lists from the identified publications and earlier reviews of dipyridamole in stroke were also searched, and the trialists and manufacturer of dipyridamole (Boehringer Ingelheim) were contacted. No restrictions on the language of the publication were made. Nonrandomized or confounded trials were excluded, as were those that involved nonstroke patients or did not include dipyridamole in one of the treatment arms. Study status was determined by 2 reviewers (J.L.-B., P.B.).

Data Management

The principal investigator from each trial was approached and asked if they would share their individual patient data with the collaboration. Data were exchanged electronically. The data included information on demography (age, gender), clinical presentation (qualifying event, history of hypertension or myocardial infarct, blood pressure [BP], treatment assignment (aspirin, dipyridamole, control/placebo), treatment findings (BP at baseline and 1 month, major bleeding, headache, and dropouts on treatment), and outcome at end of trial (nonfatal and fatal stroke, nonfatal and fatal myocardial infarction, and death).

The quality of each trial was assessed on the basis of method of randomization, concealment of allocation, completeness of follow-up, and blinding of outcome assessment.

Statistical Analysis

The data were initially analyzed as performed in the trial publication to ensure consistency. Trialists were contacted to resolve any differences or ambiguities. Data were re-coded and merged into a single data set for analysis. The primary outcome measure was stroke (combined fatal and nonfatal) at the end of study follow-up in randomized trials. Stroke was chosen a priori as the primary outcome because it is the most common vascular event in patients with recent cerebrovascular events and was a component of the primary outcome, either alone or with other events, in each of the dipyridamole trials. Secondary outcome measures included nonfatal stroke, combined fatal and nonfatal myocardial infarction, vascular death, and a composite outcome of nonfatal stroke, nonfatal myocardial infarction, and vascular death.

The following comparisons were performed by treatment group: dipyridamole versus control/placebo (D/C), combined aspirin and dipyridamole versus control (AD/C), combined aspirin and dipyridamole versus aspirin (AD/A), and combined aspirin and dipyridamole versus dipyridamole (AD/D). Data were analyzed by intention-to-treat using a logistic regression model with random effects to account for heterogeneity between trial results and fixed effects for treatment assignment. Aspirin and dipyridamole were coded within a single variable (0, control; 1, aspirin; 2, dipyridamole; 3, dual therapy) in each model. Multivariate models were adjusted for trial and 4 prognostic factors: age (younger than 65, 65 years or older), gender, qualifying event (ischemic stroke, TIA), and history of previous hypertension chosen a priori. Subgroup analyses were performed on the same 4 prognostic factors. Sensitivity analyses were performed on the primary outcome (total stroke) by formulation of dipyridamole (conventional, modified release), risk of recurrence, removal of each trial in turn to assess its importance in the overall model, inclusion of a nonrandomized clinical controlled study, and inclusion of tabular data from a trial in which no individual patient data were available. The effect of dipyridamole, aspirin, and their combination on BP, treatment dropouts, major bleeding, and headache were also studied. Analyses relating the effect of dipyridamole on BP and stroke used treatment group and change in BP as covariates with a random effect for trial.

Descriptive data are reported as mean (SD) or frequency (%). The results from the logistic regression are presented as odds ratios (OR) and 95% confidence intervals (95% CI); results with \( P < 0.05 \) were considered significant. Analyses were performed using SAS for Windows, version 8.02 (SAS Institute Inc). Egger test for asymmetry was used to assess for missing trials based on the OR for stroke recurrence.

Results

Trials

Seven completed randomized controlled trials involving 11 459 patients were identified that assessed dipyridamole in the secondary prevention of stroke (Table 1, Figure 1). Individual patient data from 2 small studies (n = 169 and n = 50; amounting to 1.9% of total data) were unavailable. Data from a nonrandomized controlled clinical study were only included in sensitivity analyses (Table 1). Two ongoing studies were excluded: ESPRIT (AD/A) and PRoFESS, the latter compared combined aspirin and dipyridamole with clopidogrel alone. A trial comparing short-term use of combined aspirin and dipyridamole with aspirin alone in the prevention of deep vein thrombosis (rather than prevention of stroke recurrence) in patients with acute stroke was also excluded. There was no evidence of missed trials caused by publication bias as assessed using Egger test for asymmetry on the OR for stroke recurrence at end of the trial (\( P = 0.43 \)). Six of the 7 trials were deemed to have a high level of quality by satisfying at least 3 of the criteria. The remaining trial and nonrandomized study were given lower levels of quality.

Five trials were placebo-controlled and 6 assessed the efficacy of the combination of dipyridamole and aspirin and compared this with aspirin, dipyridamole, and/or control; 4 studies had \( > 2 \) groups of patients (Table 1). Two formulations of dipyridamole were assessed: conventional (daily dose 150 to 300 mg) in 6 trials, and modified release (daily dose 400 mg) in 1. The daily dose of aspirin ranged between 50 and 1300 mg. Follow-up was performed at 15 to 72 months after enrollment. Three trials were reported as being positive on their primary outcome measure. The trials were balanced for baseline prognostic factors such as age, gender, and history of hypertension. The percentage of patients whose qualifying event was ischemic stroke varied considerably.
between the trials (Table 1); one trial only recruited patients with a qualifying event of TIA.\textsuperscript{16}

In the combined data set, patients received either aspirin alone (n=2450), dipyridamole alone (n=1838, modified release 90%), combined aspirin and dipyridamole (n=3861, modified release 1650, 43%), or placebo/control (n=3343). The average age was 65.4 years (SD 11.0), and 6895 (60%) of patients were male. Time from stroke onset to recruitment averaged 33.8 days (SD 64.7). Data for baseline systolic and diastolic BPs were recorded in 2 of the trials;\textsuperscript{3,18} the average diastolic BP was 152.3 (22.4)/87.5 (11.9) mm Hg.

### Outcomes

The overall stroke rate was 11.8% in patients receiving control and was 5 times more common than myocardial infarction (2.3%) as an outcome event. In a multivariate analysis, male patients had a 22% higher risk of stroke recurrence than females (P<0.002), whereas the risk of stroke increased by 3% for every year increase in age (P<0.0001). Patients with a qualifying event of ischemic stroke had a 30% higher risk of recurrence than those with TIA (P<0.001); a previous history of hypertension was associated with a 22% increase in risk of recurrence (P<0.002, n=10 546, excluding 1 trial\textsuperscript{14}).

When assessed using a multivariate intention-to-treat analysis adjusting for age, gender, and qualifying event, patients receiving dipyridamole had a 18% lower risk of stroke than those randomized to control (Table 2) (P=0.046). Similarly, those taking the combination of aspirin and dipyridamole had 22%, 26%, and 39% lower risks of stroke as compared with those receiving aspirin alone, dipyridamole alone, or control, respectively. Inclusion of tabular data from the 2 missing trials\textsuperscript{13,17} did not change the results qualitatively for this outcome (recurrence D/C: OR, 0.82; 95% CI, 0.68 to 0.99; P=0.039; AD/D: OR, 0.74; 95% CI, 0.61 to 0.91; P=0.003; AD/A: OR, 0.78; 95% CI, 0.65 to 0.93; P=0.005; AD/C: OR, 0.61; 95% CI, 0.52 to 0.72; P<0.001). The data for stroke were similar if any single trial, other than ESPS II, was removed from the analysis. With the ESPS II data removed, comparison of combined aspirin and dipyridamole with control (AD/C) remained significant (OR, 0.63; 95% CI, 0.48, 0.82), whereas that with aspirin alone (AD/A) had a nonsignificant trend (OR, 0.88; 95% CI, 0.64, 1.19). These data also apply to analysis of drug formulation and dose because only ESPS II used a modified-release version of dipyridamole at a daily dose of 400 mg; the other studies all used a conventional formulation at daily doses <400 mg.

When including the controlled clinical study of Matias-Guiu et al.,\textsuperscript{19} stroke was significantly reduced in all comparisons (D/C, AD/C, AD/A, AD/D). Inclusion of hypertension as an additional covariate (necessitating the removal of 1 trial because of missing data\textsuperscript{4}) did not alter the results for stroke recurrence (OR): D/C, 0.82; AD/C, 0.60; AD/A, 0.77; AD/D, 0.74 (all P<0.05). The addition of other prognostic covariates such as diabetes, ischemic heart disease, peripheral artery disease, and smoking was not possible because data on them were inconsistently present in the trial data sets.

In other analyses, dipyridamole reduced nonfatal stroke as compared with control (D/C), whereas the combination of aspirin and dipyridamole reduced both nonfatal stroke and the composite vascular outcome of nonfatal stroke, nonfatal myocardial infarction, and vascular death in comparison with aspirin alone (AD/A) (Table 2). When assessed against control, dual antiplatelet therapy reduced myocardial infarc-
tation as well as nonfatal stroke and the composite vascular outcome (AD/C).

Subgroups and Sources of Heterogeneity

The effect of dipyridamole in reducing stroke recurrence was independent of prognostic factors (Figure 2). Three of these factors—age 65 years or older, stroke as a qualifying event, and a previous history of hypertension—were used to build a risk model in which patients could have 0 to 3 factors present. The crude odds reductions seen for stroke were broadly similar in each risk group and not different from the overall OR (Table 3).

BP

Data for baseline and on-treatment (at 1 month) BP were obtained for 2 trials, ESPS and ESPS II. These data had significant terminal digit preference present, ie, rounding of data when the percentage of final digits in BP measurements ending in a “0” (ESPS 65.8%, ESPS II 78.7%) or “5” (21.7%, 15.0%, respectively) was disproportionate. Terminal digit preference significantly reduces the power of statistical analyses. Baseline systolic, but not diastolic, BP was positively associated with the rate of stroke recurrence: 10 mm Hg higher BP equivalent to 4% higher stroke ($P=0.003$). The percentage change in diastolic, but not systolic, BP was positively associated with the risk of stroke recurrence: 10% lower diastolic and systolic BP were associated with 10% ($P=0.015$) and 3% ($P=0.19$) reduced recurrence rates. Dipyridamole, with or without aspirin, significantly but modestly lowered BP by 1.1/0.9 mm Hg (0.7/0.6%) ($P=0.037$, $P=0.001$). The reduction in stroke seen with dipyridamole was not statistically related to the fall in BP ($P=0.37$).

Dropouts and Adverse Events

Information on dropouts was available for all trials and that for adverse events was present for 2 trials, ESPS and ESPS II.3,18 Patients were more likely to drop-out of trials or have a significant headache develop if they received dipyridamole (with or without aspirin) as compared with aspirin alone or control (Table 4). In contrast, bleeding rates were highest with aspirin therapy (with or without dipyridamole).

Discussion

Our meta-analysis of dipyridamole in patients with previous ischemic stroke or TIA shows that it is effective in reducing the risk of subsequent stroke. The odds of stroke was reduced with dipyridamole as compared with control (D/C, 18%), and the

<table>
<thead>
<tr>
<th>Events</th>
<th>Odds Ratio (95% CI)</th>
<th>D/C</th>
<th>AD/C</th>
<th>AD/A</th>
<th>AD/D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>4,913</td>
<td>6946</td>
<td>6123</td>
<td>5341</td>
<td></td>
</tr>
<tr>
<td>Stroke, all</td>
<td>0.82 (0.68, 1.00)</td>
<td>0.61 (0.51, 0.71)</td>
<td>0.78 (0.65, 0.93)</td>
<td>0.74 (0.60, 0.90)</td>
<td></td>
</tr>
<tr>
<td>Stroke, non-fatal</td>
<td>0.75 (0.59, 0.94)</td>
<td>0.59 (0.49, 0.72)</td>
<td>0.73 (0.59, 0.90)</td>
<td>0.80 (0.63, 1.02)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction, all</td>
<td>0.97 (0.66, 1.42)</td>
<td>0.67 (0.48, 0.95)</td>
<td>0.95 (0.66, 1.37)</td>
<td>0.70 (0.47, 1.04)</td>
<td></td>
</tr>
<tr>
<td>Vascular death</td>
<td>1.08 (0.82, 1.42)</td>
<td>0.91 (0.73, 1.12)</td>
<td>1.02 (0.81, 1.29)</td>
<td>0.84 (0.64, 1.10)</td>
<td></td>
</tr>
<tr>
<td>Vascular event</td>
<td>0.86 (0.73, 1.03)</td>
<td>0.66 (0.57, 0.75)</td>
<td>0.84 (0.72, 0.97)</td>
<td>0.76 (0.64, 0.90)</td>
<td></td>
</tr>
</tbody>
</table>

Relationship between treatment group and outcome adjusted for age, gender, and qualifying event. The composite outcome of vascular event consists of nonfatal stroke, nonfatal myocardial infarction, and vascular death. Odds ratio (OR) and 95% confidence intervals (95% CI) less than unity indicate a reduced risk in the event in the patients receiving the first specified treatment group in the Table.

Bold figures indicate a significant result ($P<0.05$).

A indicates aspirin; D, dipyridamole; C, placebo/control.
combination of aspirin and dipyridamole in comparison with aspirin alone (AD/A, 22%). The combination of aspirin and dipyridamole gave twice the reduction when compared with control (AD/C, 39%) suggesting the effects of each antiplatelet agent are additive. These results are in line with those of previous meta-analyses in stroke patients using group rather than individual patient data.8–10 The effect of dipyridamole, with or without aspirin, on nonfatal stroke appeared to be similar in magnitude to that for all stroke. Additionally, the reduction in stroke appeared to be independent of underlying risk, although these analyses had limited statistical power. A potential criticism of ESPS II and some other large trials such as Perindopril Protection Against Recurrent Stroke Study (PROGRESS)23 is their use of stroke, rather than the composite of nonfatal stroke, nonfatal myocardial infarction, and vascular death, as the primary outcome. Importantly, the analyses found that combined aspirin and dipyridamole reduced the composite

Figure 2. Unadjusted comparison of (a) dipyridamole versus control/placebo and (b) combined aspirin and dipyridamole versus aspirin on stroke by subgroups age, gender, qualifying event, and history of hypertension.
vascular outcome as compared with aspirin alone (AD/A) or control (AD/C). Monotherapy also appeared to reduce the composite vascular outcome as compared with control: significantly so with aspirin (AD/D), as seen in ATT,2 and nonsignificantly with dipyridamole (D/C).

The findings contrast with the neutral results for dipyridamole in systematic reviews that included trials involving groups of patients other than just stroke, eg, those with myocardial infarction,2–4 a situation that is not surprising. First, the epidemiology of stroke and IHD are different quantitatively—stroke patients are older and more likely to be female, whereas stroke has a stronger relationship with its principal modifiable risk factor, hypertension, than does myocardial infarction. Second, ischemic stroke is of mixed cause (large artery disease, cardioembolic, small vessel disease), whereas myocardial infarction largely follows coronary artery plaque rupture and thrombosis. Third, the main risk after stroke is of having another stroke, as seen in this analysis, whereas patients with a myocardial infarction are more likely to have a further cardiac event. Last, trials of primary prevention have consistently shown a differential treatment effect so that reducing BP is more effective in reducing stroke than myocardial infarction: 40% versus 15% reduction for a 10/6 mm Hg reduction in BP.

Because the ESPS II trial provided 57% of data in this review and was positive, it is possible that this trial is the primary driver for the findings reported here. When excluding the ESPS II data, assessment of combined aspirin and dipyridamole versus control (AD/C) remained positive, whereas other comparisons became nonsignificant, although the point estimates for the dipyridamole-based therapies (D/C, AD/A) support efficacy for this agent. That the earlier trials individually failed to find a positive effect of dipyridamole on stroke is not surprising because they were all much smaller with lower statistical power (type II error).

Dipyridamole did not alter the rate of myocardial infarction in patients with previous ischemic stroke or TIA, either when compared with control (D/C) or when administered in combination with aspirin and compared with aspirin alone (AD/A). In contrast, aspirin reduced the risk of myocardial infarction nonsignificantly by 30% (AD/D), a finding that is compatible with the ATT findings for aspirin.2 Considerable discussion, largely based on the results of ESPS II, has focused on whether dipyridamole has selective effects on stroke. These possible differential effects on vascular events have also been observed for antihypertensive agents, eg, calcium channel blockers may reduce stroke more than myocardial infarction, whereas angiotensin-converting enzyme inhibitors appear to have the opposite effect.25 The neutral rather than negative result for oral dipyridamole on myocardial infarction (as reported specifically in ESPS II26) is reassuring in view of the perception, based on the use of intravenous dipyridamole in cardiac stress testing,27 that it might cause myocardial ischemia.

High-dose dipyridamole administered intravenously is known to lower BP in addition to its antiplatelet activity. These actions reflect the inhibitory effect of dipyridamole on adenosine uptake by red cells and type V phosphodiesterase, thereby preventing the metabolism of cyclic GMP. Both adenosine and cyclic GMP are vasodilators, so the finding that oral dipyridamole lowered BP by a modest amount is not surprising, although a new finding. The reduction in BP of 1.1/0.9 mm Hg (at 1 month) would explain <10% of the witnessed decrease in stroke, assuming that a 10/6 mm Hg decline in BP leads to a 40% relative reduction in stroke. Nevertheless, the power of the analyses for BP is weakened considerably by inadequate measurement of BP, demonstrated by the presence of significant terminal digit preference. As a result, the relationships of BP with stroke and effect of dipyridamole on BP are probably underestimated. Recently, dipyridamole was reported to have no effect on BP (at >1 year) in an interim analysis involving data from 591 patients in the ongoing European/Australian Stroke Prevention in Reversible Ischemia Trial (ESPRIT) trial.20,28 The small size and possible presence of terminal digit preference mean that this may be a false neutral finding.28 Alternatively, the effect of dipyridamole on BP may be temporary.

Meta-analyses based on individual patient data have been described as the gold standard.29 They allow for consistent methods of data checking, categorization of patients, and analyses to be performed. They also allow for analyses to be performed, which would not be possible if using summary statistics alone, eg, on subgroups,
as we did here. Finally, they have more statistical power than conventional analyses based on summary data.

Systematic reviews are susceptible to missing unpublished trials or those that are published in non-English journals, so-called publication bias. Many such studies will be neutral or negative in outcome, and reviews will then have positively biased results. We performed a comprehensive multilingual search strategy, used the publication lists of existing trials and reviews, and contacted the pharmaceutical company that manufactures dipyridamole to help identify relevant trials. Additionally, we found no statistical evidence of publication bias. Hence, the identified trials probably represent the totality of trial evidence relating to dipyridamole in patients with cerebrovascular disease, and it is unlikely that the results are biased by a failure to include relevant studies. Bias may also result if data from some identified studies are unavailable, as occurred here with 2 studies, although the missing data comprised <2% of the total data set. Including tabular data from these trials did not alter the results. Finally, we were not able to adjust for all prognostic factors, eg, previous ischemic heart disease and time from event to treatment, because these data were not available for most trials. Hence, some sources of heterogeneity will not have been explained.

In summary, dipyridamole alone (when compared with aspirin), or especially in combination with aspirin (when compared with aspirin alone), reduces recurrence in patients with previous ischemic stroke or TIA. The data are internally consistent (internal validity). Dipyridamole has a place in secondary prevention after ischemic stroke or TIA, as recommended in current national and international guidelines. However, which antiplatelet regimen physicians prescribe—aspirin, clopidogrel, or dipyridamole alone, or combined aspirin and dipyridamole—will depend on patient-specific factors such as underlying risk, patient experience on existing antiplatelet drugs, tolerance, or allergies to each of the drugs and their cost.

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References

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