Cochrane Review: Dipyridamole for Preventing Major Vascular Events in Patients With Vascular Disease

E.L.L.M. De Schryver, MD; A. Algra, MD; J. van Gijn, MD

Background—Patients enrolled in clinical trials after nondisabling cerebral ischemia have an annual risk of vascular events (death from all vascular causes, nonfatal stroke, or nonfatal myocardial infarction) of 4% to 11%. Aspirin reduces the incidence by 13%. Many trials in patients presenting with vascular disease investigated the efficacy of (addition of) dipyridamole in secondary prevention. We systematically compared the efficacy and safety of dipyridamole versus control in the presence and absence of other antiplatelet drugs in clinical trials on the secondary prevention of vascular events in patients with vascular disease.

Summary of Review—Randomized trials with concealed treatment allocation in patients with a nonembolic arterial vascular disease were selected. Therapy consisted of dipyridamole in the presence or absence of other antiplatelet drugs compared with no drug or an antiplatelet drug(s) other than dipyridamole. Twenty-six trials were included, with a total of 19,842 patients. Dipyridamole was not more efficacious in the prevention of vascular death (relative risk [RR], 1.02; 95% CI, 0.90 to 1.17). It appeared more efficacious in the prevention of vascular events (RR, 0.90; 95% CI, 0.83 to 0.98), but this result only reached statistical significance because of 1 large trial in patients presenting with cerebral ischemia. Combination treatment of dipyridamole and aspirin compared with aspirin had an RR of 1.03 (95% CI, 0.87 to 1.22) for vascular death and an RR of 0.90 (95% CI, 0.80 to 1.00) for vascular events.

Conclusions—For patients who presented with arterial vascular disease, there was no evidence that dipyridamole, in the presence or absence of another antiplatelet drug (chiefly aspirin), reduced the risk of vascular death, although it may reduce the risk of further vascular events. However, this benefit was found only in a single large trial and only in patients presenting after cerebral ischemia. There was no evidence that dipyridamole alone was more efficacious than aspirin. Further trials comparing the effects of the combination of dipyridamole plus aspirin with aspirin alone are justified.

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Key Words: dipyridamole ■ stroke ■ vascular diseases

Patients with transient ischemic attacks (TIA) and minor ischemic strokes are at risk of serious vascular events (death from all vascular causes, nonfatal stroke, or nonfatal myocardial infarction). A systematic review of all trials of antiplatelet agents by the Antithrombotic Trialists’ Collaboration (ATT) provided very strong evidence that, in patients with a history of a vascular disease, antiplatelet drugs reduce the risk of serious vascular events by approximately 25%.1 Aspirin was the most widely tested antiplatelet drug. By comparison with the very large number of trials of aspirin, there were relatively few trials that assessed the efficacy of dipyridamole. Dipyridamole is a nucleoside transport inhibitor that increases adenosine release by the myocardium and raises the interstitial fluid levels of adenosine, resulting in a vasodilator effect that in turn may lower blood pressure.

A number of trials included in the review assessed whether the combination of dipyridamole with aspirin might be more effective than aspirin alone, but it appeared that, in high-risk patients, there was virtually no difference between the aspirin-dipyridamole combination and aspirin alone.1 We therefore sought to examine the trial data with a somewhat different approach to assess the effects of dipyridamole in greater detail.

The most appropriate way to make that more detailed assessment has been the subject of some debate. Is it better to assess the efficacy of medication for secondary prevention of vascular complications by looking at subgroups of high-risk patients or at all these patients together?2 A similar discussion applies to the most appropriate combination of vascular outcome events, ie, vascular death, nonfatal myocardial infarction, and nonfatal stroke.

Patients who enrolled in clinical trials after a TIA or nondisabling ischemic stroke have an annual risk of important vascular events of between 4% and 11%.3,4 The corresponding estimate for population-based studies is 9% per year.5 The ATT showed an absolute risk reduction of 22 to 36...
per 1000 high-risk patients treated with antiplatelet therapy for 2 years; this number was 36 per 1000 patients after cerebral ischemia. Aspirin alone, in a daily dose of ≥30 mg, offers only modest protection after cerebral ischemia: it reduces the incidence of major vascular events by 13% in such patients. In direct comparisons of different doses of aspirin, no differences were found in the efficacy between doses of 300 and 1200 mg or between doses of 30 and 283 mg. The efficacy of dipyridamole, an alternative antiplatelet agent, was assessed in the European Stroke Prevention Study 2 (ESPS-2), a randomized, placebo-controlled, double-blind trial with 4 treatment arms: aspirin (50 mg daily), dipyridamole (400 mg daily), both drugs, or neither. The combination treatment showed a relative risk (RR) reduction of 22% of major vascular events over aspirin. However, a meta-analysis of the 4 previous studies that compared the efficacy of the combination therapy with aspirin alone showed a RR of 0.97. This review seeks to extend and update those analyses to include all the data available in 2002 to provide the most up-to-date estimate of effect. Thus, the aim of this review was to assess the efficacy and safety of dipyridamole versus control in the secondary prevention of vascular events in patients with vascular disease in the presence and absence of other antiplatelet drugs.

Methods

We selected randomized long-term secondary prevention trials with concealed treatment allocation, for >1 month, started within 6 months after presentation of a vascular disease. The patients had to present with an arterial vascular disease: coronary artery disease, myocardial infarction, angina pectoris, retinopathy, nephropathy, peripheral arterial disease, stroke, TIA, or amaurosis fugax. Patients with presumed embolism from the heart were excluded. Therapy consisted of dipyridamole in any dose in the presence or absence of other antiplatelet drugs. Outcome measures searched for were vascular death, nonfatal stroke, nonfatal myocardial infarction, or major bleeding complication and death (all causes).

To identify trials for this review, we used the specialized register of controlled trials of the Cochrane Stroke Review Group. In addition, the trials register of the ATT was searched, and contact was made with other relevant Cochrane Review Groups (Heart and Peripheral Vascular Diseases). We searched the Cochrane Controlled Trials Register (Cochrane Library, 2002, Issue 2), MEDLINE (1966 to April 2002), and EMBASE (1980 to April 2002) with dipyridamole as a controlled vocabulary term and dipyridamole and its specific brand names as text words.

We contacted the following Dutch manufacturers of dipyridamole in the search for other published and unpublished studies: Boehringer Ingelheim, Centrafarm, Dumex, Genfarma, ICN Pharmaceuticals, Katwijk Farma, Multipharma, Pharbita, Pharmachemie, and Stephar.

Two reviewers independently selected those trials that met the inclusion criteria and extracted details of randomization, methods, blinding of treatments and assessments, whether intention-to-treat analysis was possible from the published data, whether treatment groups were comparable with regard to major prognostic factors, the number of patients who were excluded or lost to follow-up, definition of outcome events, and entry and exclusion criteria. The methodological quality of each trial was assessed by the 2 reviewers on the basis of these extracted data. In addition, dose and type of antiplatelet treatments, duration of follow-up, and the number of defined outcome events were also recorded. Published and unpublished data, which were collected by the ATT, were used. The remaining data were extracted independently by the same 2 reviewers and cross-checked.

The following subgroup analyses were planned in advance: presenting disease, age (≥65 versus >65 years), sex, history of ischemic heart disease, dose of dipyridamole, methodological quality, and type of cerebral ischemia (large-vessel versus small-vessel disease). Separate analyses on the use of dipyridamole in the presence and absence of other antiplatelet drugs were performed. The data were analyzed according to the intention-to-treat principle. If outcome data on some randomized patients were lacking, both best- and worst-case scenarios were planned: the best-case scenario (with regard to treatment) assumed that none of the patients excluded from the reference group had the outcome of interest while all those excluded from the reference group did, with the reverse assumed for the worst-case analysis. RR reductions were calculated by means of the statistical software provided by the Cochrane Collaboration (RevMan). Fixed effects models were used. The figures are obtained from the statistical software provided by the Cochrane Collaboration (RevMan).

Results

Twenty-six randomized controlled trials were included, which studied 39 comparisons of treatments, with a total of 19,842 patients, among whom 1399 vascular deaths and 3085 vascular events (fatal and nonfatal) occurred during follow-up. The mean follow-up duration of the trials ranged from 1 month to 7 years. Data from 2 trials were not published, and data from 2 other trials were not used in the meta-analysis of the ATT. One trial is ongoing: the European/Australian Stroke Prevention in Reversible Ischemia Trial (ESPRIT) (aspirin 30 to 325 mg daily versus aspirin plus modified-release dipyridamole 200 mg twice daily). Fourteen trials were performed in Europe, 7 in North America, 2 in both Europe and North America, 1 in Australia, 1 in the Middle East, and 1 in Asia. The mean age of the patients ranged from 47 to 67 years. More details of the trials included are available in the full version in the Cochrane Library.

In 12 studies the patients presented with a cardiac disease, 7 with (transient) cerebral ischemia, and 4 with arterial peripheral vascular diseases; in 2 studies patients on hemodialysis were included, and in 1 study patients with diabetic retinopathy were included. Daily dipyridamole doses varied between 150 and 800 mg: 4 trials used 150 mg/d, 16 trials 200 to 300 mg/d, and 6 trials ≥400 mg/d, of which 1 trial partly used 800 mg/d. One trial used a modified-release (retard) preparation of dipyridamole. Other antiplatelet drugs were aspirin and sulfipyrazone.

Not all trials had vascular events as a primary outcome. However, most of these trials published additional data about vascular death or vascular events. Primary published data were used, but missing data were compiled from the publication of the ATT, which published additional data not available in the original publications.

All 26 trials were stated to be randomized, but the method of concealment was unclear in 16 trials. In 7 trials baseline data were not sufficiently described to conclude whether there was good baseline comparability between treatment groups. All trials, except 3, were stated to be double-blind studies. For 15 trials we could not determine whether intention-to-treat analysis was performed or might be reconstructed from the published data. In 8 trials the number of lost or excluded patients was not described. Fifteen studies did not describe (exactly) the method of monitoring of the compli-
ance, and in 11 trials nothing was reported on the compliance of the patients. All trials defined criteria for the inclusion of patients; 8 trials did not contain any information about exclusion criteria.

The 26 included trials mostly did not separately report on all types of outcome measures. In some trials the number of patients with a "stroke" during follow-up was described, but no further information could be

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| Figure 1. Dipyridamole vs control (in the presence or absence of other identical antiplatelet drugs): dose of dipyridamole.
Figure 2. Dipyridamole vs control (in the presence or absence of other identical antiplatelet drugs): presenting disease.
found on whether this number included hemorrhagic strokes. Additionally, it was often unclear whether the fatal strokes were calculated as separate outcome events or included in this number of reported strokes.

The outcome data extracted from the original publications did not always match exactly the data from the ATT, which used individual patient data at the end of scheduled follow-up, obtained from the trial investigators. Since most of our defined outcome events could not be extracted from the original publications, we pragmatically decided to analyze 2 outcome measures: vascular death and vascular events. The definition of vascular events, according to the ATT, is “vascular death or any death from unknown cause, nonfatal stroke, or nonfatal myocardial infarction.” The safety measure was, according to the ATT, the combination of all major extracranial bleeding complications plus all fatal extracranial bleeds. For the analyses we assumed that the published outcome events could be used in an intention-to-treat model in all trials and that no patient was lost if no loss to follow-up was reported. Since not many patients were described as lost, no worst- or best-case scenario was performed.

Dipyridamole Versus Control

Compared with control, there was no evidence that, in patients who presented with an arterial vascular disease, dipyridamole, in the presence or absence of other antiplatelet drugs, had any effect on vascular death (RR, 1.02; 95% CI, 0.90 to 1.17) in 18 trials (20 comparisons). This result was not influenced by the dose of dipyridamole (Figure 1) or by the type of presenting vascular disease (Figure 2). However, there was a reduction in the risk of vascular events (RR, 0.90; 95% CI, 0.83 to 0.98). This result reached statistical significance largely because of the data from a single large trial (6602 patients) in patients presenting after cerebral ischemia, who were randomly allocated to receive modified-release dipyridamole 400 mg plus aspirin 50 mg or aspirin 50 mg alone. Figure 3 shows that there were slightly more major extracranial and fatal extracranial bleeding complications in patients allocated to dipyridamole compared with controls, but the difference was not statistically significant (RR, 1.22; 95% CI, 0.82 to 1.82).

Dipyridamole Plus Aspirin Versus Aspirin

As shown in Figure 4, there was no evidence of an effect of the combination of dipyridamole plus aspirin compared with aspirin on vascular death (RR, 1.03; 95% CI, 0.87 to 1.22). On the basis of data from 11 trials, there was a significant reduction in vascular events (RR, 0.90; 95% CI, 0.80 to 1.00). With exclusion of the data from the ESPS-2 study, the RR for vascular death in 10 trials was 1.07 (95% CI, 0.85 to 1.35), and that for vascular events was 0.99 (95% CI, 0.85 to 1.16).

The combination treatment had an RR of 1.52 (95% CI, 0.93 to 2.94) for bleeding complications (all major extracranial plus fatal extracranial bleeding complications).

Dipyridamole Plus Aspirin Versus Placebo

As shown in Figure 5, combination treatment of dipyridamole and aspirin compared with placebo had an RR of 0.89 (95% CI, 0.79 to 0.91) for vascular death and an RR of 0.74 (95% CI, 0.68 to 0.80) for vascular events in 15 trials.

Dipyridamole Versus Other Antiplatelet Drugs

As shown in Figure 6, there was no evidence of a difference between dipyridamole and aspirin in the avoidance of vascular death (RR, 1.07; 95% CI, 0.84 to 1.36) or the prevention of vascular events (RR, 1.02; 95% CI, 0.88 to 1.18). These data originated from 3 trials, in which ESPS-2 contributed 98% of the information. One small trial compared the combination of dipyridamole with aspirin versus sulfinpyrazone.

Discussion

Inclusion of Trials

The aim of this meta-analysis was to include all randomized long-term secondary prevention trials on patients presenting...
with an arterial vascular disease (excluding presumed embolism from the heart). We included trials of patients presenting with a cardiac disease but excluded those that accepted patients after a major vascular intervention, eg, coronary bypass grafting, because of procedure-related side effects. In the trials of patients with cerebral ischemia, it was not always clear whether a cardiac source of embolism was used as an exclusion criterion.10,15,18,19 Trials with hemodialysis patients were included because the cause of nephropathy in a large group of patients is of atherosclerotic origin and all hemodialysis patients are prone to develop atherosclerosis.

Quality of Trials
All included trials were randomized and controlled. Not all trials published information about the method of concealment, monitoring of treatments and compliance, number of patients lost to follow-up, and whether intention-to-treat analysis was possible. However, these deficiencies were confined mainly to the smaller trials. There was no significant heterogeneity.

Outcome Events
The type of outcome events varied greatly between the included randomized controlled trials. Some studies did not have the primary intention to investigate vascular end points.13b,14,20,28 Therefore, we decided to reduce the number of outcome measures in this meta-analysis to those that were extractable from most of the original publications or from the data collected by the ATT: vascular death and vascular events. As a measure for safety, we used the combination of major extracranial bleeding complication (according to the definition of the original investigator) plus fatal extracranial...
bleeding complication, according to the ATT. Separate analyses on bleeding complications were not possible because not all trials published data on bleeding complications. The ATT and ESPS-2 showed that the addition of dipyridamole to aspirin did not have any effect on the secondary prevention of nonfatal coronary events.1,9

**Dose of Dipyridamole**

Different doses of dipyridamole were used, and therefore subgroup analyses were performed in which 3 dosage groups were chosen. One trial compared dipyridamole in the presence of different doses of aspirin in the treatment and control group (150 versus 300 mg).13 However, in the Dutch TIA trial, no influence on the number of outcome events was observed between such differences in aspirin dose. 8

We present effect estimates for 3 groups of dipyridamole doses. Such indirect comparisons of treatment effect do not provide a very reliable assessment of the effects of different doses.1 However, we were unable to identify any trials directly comparing one dose of dipyridamole with another. The CIs of the effect estimates for the 3 different dipyridamole dosage strata overlap considerably. Therefore, no firm conclusions can be drawn about an optimal dose, if any, given the modest overall effect (RR=0.90 for vascular events). It should be noted that the large trial with the largest effect used a modified-release preparation.9 The modified-release form of dipyridamole has been studied in this clinical trial only; moreover, a ratio of dipyridamole versus aspirin of 8 was used. It is predictably bioavailable and inhibits platelet function ex vivo.29 Replication of this finding with similar formulations is warranted before any conclusive inference on the type of preparation is possible and to refute a chance finding in ESPS-2.

**Presenting Disease**

The 5 different high-risk groups were analyzed separately. Approximately three quarters of all information originated from patients with cerebrovascular disease, and approximately one fifth originated from patients with ischemic heart disease. There was a benefit of dipyridamole in the absence or presence of another antiplatelet drug only in patients presenting with cerebral ischemia in the secondary prevention of vascular events (as found in previously published reviews30,31) and not in the prevention of vascular death. These previously published reviews differ somewhat from our review: one review restricted itself to studies with patients after cerebral ischemia,30 whereas the other included studies with patients after a major vascular intervention (which were
The quantity of data is minute regarding patients with arterial peripheral vascular disease, patients with diabetic retinopathy, or patients needing hemodialysis.

Conclusions
This review found that, for patients who presented with arterial vascular disease, there was no evidence that dipyridamole, in the presence or absence of another antiplatelet drug (chiefly aspirin), reduced the risk of vascular death, although it may reduce the risk of further vascular events. However, this benefit was found only in a single large trial and only in patients presenting after cerebral ischemia. There was no evidence that dipyridamole alone was more effective than aspirin alone.

We found no evidence to support the routine use of dipyridamole alone as first-line antiplatelet treatment in all patients at high risk of vascular events. We found no evidence to justify routine use of dipyridamole alone in preference to aspirin alone. The review provides some evidence that, among patients presenting with ischemic stroke or TIA, the combination of dipyridamole plus aspirin is associated with a lower risk of further vascular events than aspirin alone.

Further trials are needed to provide more reliable evidence on whether or not the combination of dipyridamole plus aspirin is more effective than aspirin alone. The ongoing trial ESPRIT will probably provide further data on this question in patients with cerebral ischemia of atherosclerotic origin. More trials are needed in other high-risk groups of patients, such as those with arterial peripheral vascular disease, those with diabetic retinopathy, and those undergoing hemodialysis, to determine the role of dipyridamole in secondary prevention.

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References
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