Dipyridamole plus aspirin versus aspirin alone in secondary prevention after TIA or stroke: a meta-analysis by risk

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ABSTRACT

Objectives: To study the effect of combination therapy with aspirin and dipyridamole (A+D) over aspirin alone (ASA) in secondary prevention after transient ischaemic attack (TIA) or minor stroke of presumed arterial origin and to perform subgroup analyses to identify patients that might benefit most from secondary prevention with A+D.

Data sources: The previously published meta-analysis of individual patient data was updated with data from ESPRIT (n = 2,738); trials without data on the comparison of A+D versus ASA were excluded.

Review methods: A meta-analysis was performed using Cox regression, including several subgroup analyses and following baseline risk stratification.

Results: A total of 7612 patients (five trials) were included in the analyses, 3800 allocated to A+D and 3812 to ASA alone. The trial-adjusted hazard ratio (HR) for the composite event of vascular death, non-fatal myocardial infarction and non-fatal stroke was 0.82 (95% confidence interval (CI) 0.72 to 0.92). HRs did not differ in subgroup analyses based on age, sex, qualifying event, hypertension, diabetes, previous stroke, ischaemic heart disease, aspirin dose, type of vessel disease and dipyridamole formulation, nor across baseline risk strata as assessed with two different risk scores. A+D were also more effective than ASA alone in preventing recurrent stroke; HR 0.78 (95% CI 0.68 to 0.90).

Conclusion: The combination of aspirin and dipyridamole is more effective than aspirin alone in patients with TIA or ischaemic stroke of presumed arterial origin in the secondary prevention of stroke and other vascular events. This superiority was found in all subgroups and was independent of baseline risk.

After a transient ischaemic attack (TIA) or stroke of presumed arterial origin, patients have an annual risk of a serious vascular event (recurrent stroke, myocardial infarction or death from vascular cause) of 9% in population-based studies.1 Treatment with aspirin, at a dose of between 30 and 300 mg daily, reduces this risk by 13–22%.2–4 In one study, treatment with dipyridamole alone was found to reduce the risk by a similar amount.5 Although clopidogrel was marginally superior to aspirin in the CAPRIE trial, no statistically significant difference was seen in the subset of patients with previous ischaemic stroke (average event rate per year 7.15% for clopidogrel versus 7.71% for aspirin, relative-risk reduction of 7.3% (95% confidence interval (CI) 5.7 to 18.7).6 Furthermore, there is no indication for an additional benefit of combining aspirin and clopidogrel compared with either drug alone,7–8 or for anti-coagulation treatment with any International Normalised Ratio range.9–10 The combination of aspirin and dipyridamole (A+D) has been tested in several trials, although early results did not show any beneficial effect over aspirin alone.11–17 In contrast, the “Second European Stroke Prevention Study” (ESPS2) found that the addition of dipyridamole (extended release 200 mg twice daily) to aspirin (50 mg daily) reduced serious vascular events by 22% (95% CI 9% to 33%) in comparison with aspirin alone (ASA).3–5 The positive results of two meta-analyses on this comparison were based mainly on the results of ESPS2, which was by far the largest trial included.18–20 Subsequently, the European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT)21 confirmed the results of ESPS2, the hazard ratio (HR) for the primary outcome event (vascular death, recurrent stroke, myocardial infarction or major bleeding complication) was 0.80 (95% CI 0.66 to 0.98).21 We have updated the earlier meta-analysis based on individual patient data (IPD)20 with the inclusion of ESPRIT and aimed to identify patients who may benefit most from the combination of aspirin and dipyridamole. In particular, we wished to assess whether a patient’s baseline risk would modify the efficacy of combination therapy.

METHODS

Searching and selection

The search strategy to identify all eligible randomised controlled trials on the effectiveness of dipyridamole in the secondary prevention after TIA or minor stroke of arterial origin has been described previously.22 We selected trials that compared, at a minimum, the combination therapy of A+D with ASA. The principal investigators of each included trial shared IPD for use in the current analysis.

Data abstraction

Data from the different trials were merged into a single data set for analysis. This database contained information on demography (age, sex), qualifying event (TIA or stroke, clinical features of the event, findings on brain imaging), vascular risk profile (history of hypertension, diabetes, ischaemic heart disease or stroke and blood pressure at baseline), prescribed trial medication (dose of aspirin and formulation of dipyridamole) and the occurrence of serious events (vascular)
Study characteristics

The primary outcome event was the composite of death from all vascular causes, non-fatal stroke and non-fatal myocardial infarction. Secondary outcome events were the composite of death from all vascular causes or non-fatal stroke, all death, death from vascular causes, fatal and non-fatal stroke, and fatal and non-fatal myocardial infarction.

Prespecified subgroup analyses for the primary outcome event were performed according to age (<65 years vs. ≥65 years), sex (male vs. female), qualifying event (TIA vs. stroke), type of vessel disease in qualifying event (small vs. large), dose of aspirin (<75 mg vs. ≥75 mg), formulation of dipyridamole (immediate vs. extended release), time between qualifying event and randomisation (<1 week vs. 1 week to 1 month vs. 1–6 months) and history of hypertension, diabetes, stroke or ischaemic heart disease.

In addition, we performed a subgroup analysis according to baseline risk, as assessed with two different risk models. The first model used three risk factors: age 65 years or older, stroke as a qualifying event and a history of hypertension; the risk of stroke increased with an increasing number of risk factors (0–3) in the previous IPD meta-analysis. The area under the receiver operator characteristics curve (AUC-ROC) for this model in the current data set was 0.59 (95% CI 0.57 to 0.60). The second model was developed with data from the Dutch TIA Trial (DTT), a secondary stroke prevention trial with a factorial design comparing two doses of aspirin, and atenolol, with placebo. We used those characteristics identified previously to be associated with new vascular events and that were available in the present dataset, resulting in a risk score: 0.532*sex (0: female, 1: male) + 0.037*age (years) + 0.757*diabetes (0: no, 1: yes) + 0.385*history of ischaemic heart disease (0: no, 1: yes) + 0.007*systolic blood pressure (mmHg); its AUC-ROC was 0.62 (95% CI 0.60 to 0.64). Based on this risk score, patients were divided into five risk-quintiles. Subgroup analyses were performed based on the different risk groups from these two models. The numbers needed to treat (NNTs) were calculated for each subgroup. In table 1, a cross-tabulation for the risk scores from the two models is shown to give an impression of the agreement of risk between the models.

Table 1 Cross-tabulation for the risk scores from the two models used (both scores known for 5967 patients)

| Risk score quintiles* | Risk score based on 3 risk factors; n of factors present | 0 | 1 | 2 | 3 |
|----------------------|---------------------------------------------------------|---|---|---|---|
| 1                    |                                                         | 237| 594| 365| 2 |
| 2                    |                                                         | 116| 392| 521| 164|
| 3                    |                                                         | 58 | 273| 556| 310|
| 4                    |                                                         | 15 | 180| 547| 449|
| 5                    |                                                         | 2  | 81 | 469| 636|

*Quintiles based on risk score calculated with formula: 0.532*sex (0: female, 1: male) + 0.037*age (years) + 0.757*diabetes (0: no, 1: yes) + 0.385*history of ischaemic heart disease (0: no, 1: yes) + 0.007*systolic blood pressure (mmHg).

Quantitative data synthesis

Data were analysed according to the intention-to-treat principle. The occurrence of outcome events was compared between patients allocated to combined aspirin and dipyridamole versus patients allocated to aspirin (HR, with 95% CI), calculated with Cox proportional hazard modelling. To adjust for a possible heterogeneity between the trials, we stratified the Cox model with trial as the stratification factor. All analyses were performed in duplicate, independently, by two investigators (PHAH, LJG).

Analyses were performed with Stata version 8 and SPSS version 12.0.02.

RESULTS

Trial flow and study characteristics

Five randomised controlled trials comparing the combination of A+D with ASA in the secondary prevention after cerebral ischaemia of arterial origin were identified (fig 1). In two trials, randomisation was only carried out between combination therapy and ASA, whereas the other trials also compared combination therapy with placebo.

The dose of aspirin was fixed in four trials: 25 mg twice daily, 300 mg three times daily, 325 mg three times daily, or 350 mg three times daily. In ESPRIT, the dose of aspirin was left to the discretion of the treating physician, provided it was between 30 and 325 mg daily. The dose of dipyridamole was 50 mg three times daily, 75 mg three times daily, or four times daily or 200 mg twice daily.

In three trials, all patients used the immediate-release formulation of dipyridamole, and in one trial all patients used the extended-release formulation. In ESPRIT, the majority of patients (83%) used the extended-release formulation and the remaining patients used the immediate-release formulation. One trial only included patients with a TIA, the others also included patients with a minor stroke. The five trials included 3800 patients allocated to combined A+D, and 3812 patients allocated to ASA. Table 2 shows the baseline characteristics for the different trials and for the combined data. Apart from the differences mentioned above (dose of aspirin, formulation of dipyridamole and type of qualifying event), the main difference between the samples was that the mean age was higher in ESPS2 (mean age 67 years versus 62–63 years in the other trials) and the fact that, in the Toulouse trial, there were more males included (more than 80% versus less than 70% in the others). In total, almost two-thirds of patients were male, with a mean age of 65 years. In the majority, the qualifying event was a stroke. There were no major differences in the prevalence of vascular risk factors between the different trials. The mean length of follow-up was 2.6 years (range 0–8.21 years).
Quantitative data synthesis

In the combined A+D group, 475 patients (12.5%) had a primary outcome event, compared with 579 patients (15.2%) in the ASA group, resulting in an adjusted HR of 0.82 (95% CI 0.72 to 0.92) (table 5). The adjusted HR for the composite event of death from vascular cause or non-fatal stroke was 0.81 (95% CI 0.72 to 0.92), that for vascular death 0.96 (95% CI 0.78 to 1.18) and for recurrent stroke 0.78 (95% CI 0.68 to 0.90). The NNT (1/absolute risk reduction*100) with A+D instead of ASA to prevent one serious vascular event happening is 100 per year. Figure 2 shows the time-to-event curve for the primary outcome event.

Figure 2 shows the results of the subgroup analyses according to age, sex, qualifying event, hypertension, diabetes, stroke, ischaemic heart disease, dose of aspirin, type of vessel disease, formulation of dipyridamole, and interval between qualifying event and randomisation for the primary outcome event. No major differences between the subgroups were found (smallest p value for interaction 0.14). The only slight differences in the estimated HRs for the subgroups confirm the superior efficacy of A+D in all groups. Figure 4 shows the subgroup analyses according to the number of risk factors present at baseline (known for 7302 patients, panel A) and according to the risk score derived from the DTT-risk model (known for 5989 patients, panel B). The HRs were broadly similar in all risk groups and not different from the overall HR (smallest p value for interaction 0.11). The NNT with A+D instead of ASA to prevent one major vascular event per year are also shown; no major differences were found here either.

**DISCUSSION**

This individual patient data meta-analysis confirms that the combination of A+D is more effective than ASA in secondary vascular prevention after TIA or minor stroke from arterial origin. From figure 2, we can conclude that the advantage of the combination therapy of A+D starts early on and remains present over time. Importantly, analyses in prognostic subgroups, including age, sex and vascular history, found no differential effects between groups of patients, whereas currently there may be a selection of patients who receive dipyridamole in addition to aspirin. Quantitatively, combined A+D reduce vascular events by 18%, and stroke by 22%, compared with ASA, results which do not differ materially from earlier meta-analyses. In contrast, dual antiplatelet therapy had no advantage over aspirin in preventing total death, vascular death or myocardial infarction; importantly, the combination of A+D did not increase the incidence of myocardial infarction.

The NNT found in this meta-analysis is 100 per year, which is about the same as the NNT for aspirin versus placebo. Whether this NNT is cost-effective for A+D should be formally assessed in a cost-effectiveness analysis.

The risk models we used did not have a strong discriminatory ability with regards to prediction of major vascular events, as is obvious from the AU ROCs (0.59 and 0.62, respectively). Unfortunately, there are no stronger prediction models for vascular events after a TIA or minor stroke. Moreover, we could only use those variables that were available in the included trials.

Previous subgroup analyses in ESPS2 suggested that the relative efficacy for combination therapy was greater in patients at high risk of recurrence than those at lower risk. In our larger individual patient data meta-analysis, in contrast, we found that relative efficacy for vascular events was not related to the estimated baseline risk. Moreover, the NNT varied.
between the different risk groups, but there was no indication that these numbers were higher in low-risk patients. The independence of relative risk reduction from baseline risk is important as the risk of recurrence has fallen with time in patients randomised to aspirin (overall, 6.1% per year versus 4.3% per year in ESPRIT), this presumably reflecting improved non-antiplatelet prophylaxis.

The main difference between the five trials was the prescribed trial medication. Aspirin doses varied, reflecting historical and geographical variations in practice. As lower doses of aspirin (30–75 mg daily) are no less effective at preventing vascular recurrence than higher doses,2 24 this variation is unlikely to have influenced the results. Similarly, the dose and formulation of dipyridamole varied between the trials; older studies used short-acting (immediate-release) dipyridamole given 3–4 times per day,14–16 whereas all patients in ESPS2 and most (83%) in ESPRIT received extended-release dipyridamole twice daily.5 21 This difference might explain, in part, the difference seen in efficacy between older and newer trials with dipyridamole. However, our subgroup analyses do not show any differences in efficacy of aspirin and dipyridamole between different doses of aspirin or different formulations of dipyridamole.

### Table 3 Occurrence of outcome events, according to treatment

|                          | A+D n = 3800 | ASA n = 3812 | HR   | 95% CI       |
|--------------------------|--------------|--------------|------|-------------|
| Person-years of observation | 9441         | 9396         |      |             |
| Vascular death, non-fatal stroke or non-fatal myocardial infarction | 475 (12.5%)  | 579 (15.2%)  | 0.82 | 0.72–0.92   |
| Vascular death or non-fatal stroke | 434         | 528          | 0.81 | 0.72–0.92   |
| All death                | 358          | 360          | 1.01 | 0.87–1.17   |
| Vascular death           | 175          | 187          | 0.96 | 0.78–1.18   |
| Recurrent stroke         | 341          | 429          | 0.78 | 0.68–0.90   |
| Myocardial infarction    | 81           | 87           | 0.94 | 0.69–1.27   |

A+D, aspirin and dipyridamole; ASA alone, aspirin; HR, hazard ratio, adjusted for trial.

### Figure 3 Subgroup analyses according to risk factors

- **Age**: < 65 years, ≥ 65 years
- **Sex**: male, female
- **Qualifying event**: TIA, stroke
- **Hypertension**: no, yes
- **Diabetes**: no, yes
- **Stroke**
  - yes
- **IHD**
  - yes
- **Aspirin dose**: < 75 mg, ≥ 75 mg
- **Formulation**: immediate
- **Dipyridamole**: extended
- **Type of vessel**: small, large
- **Interval QE**
  - < 1 week
- **Randomisation**
  - 1 week–1 month, 1–6 months

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Figure 4 Subgroup analyses based on risk groups. (A) Risk groups based on presence of three risk factors; (B) groups based on DTT-risk model. *Risk of a major vascular event (vascular death, nonfatal stroke or nonfatal myocardial infarction) per year; HR, hazard ratio; NNT, numbers needed to treat with aspirin and dipyridamole instead of with aspirin alone to prevent one major vascular event per year.

The results of meta-analyses may be confounded if data from unpublished trials are not available for inclusion; notably, these trials are more likely to be neutral or negative in outcome, leading to publication bias. Missing trials have never been reported to us following our previous meta-analyses, so it is unlikely that any medium-sized to large trials are missing here. However, data on risk factors were not available for all five trials, so the subgroup analyses involve fewer patients for some analyses. Nevertheless, meta-analysis allows the total evidence to be assessed and the use of individual patient data, as here, is superior to the use of summary group data.

The superiority of combination A+D over ASA in secondary vascular prevention after TIA or stroke is now well supported. The HR found in this individual patient data meta-analysis is consistent with the two largest clinical trials and does not appear to differ in subgroups of patients. Combination therapy with A+D should be preferred over ASA in all patients after a TIA or minor stroke of presumed arterial origin, as supported by several national guidelines.

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