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EDITORIAL

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## Secondary prevention after cerebral ischaemia of presumed arterial origin: is aspirin still the touchstone?

Patients who have had a transient ischaemic attack or non-disabling ischaemic stroke of presumed arterial origin have an annual risk of death from all vascular causes, non-fatal stroke, or non-fatal myocardial infarction that ranges between 4% and 11% without treatment.<sup>1,2</sup> In the secondary prevention of these vascular complications the use of aspirin has been the standard treatment for the past two decades. Discussions about the dose of aspirin have dominated the issue for some time, although there is no convincing evidence for any difference in effectiveness in the dose range of 30-1300 mg/day.<sup>2,3</sup> A far greater problem is the limited degree of protection offered by aspirin: the accumulative evidence from trials with aspirin alone and only for cerebrovascular disease of presumed arterial origin as qualifying event indicates that a dose of aspirin of at least 30 mg/day prevents only 13% of serious vascular complications.<sup>1,2</sup> In this commentary we use the AntiPlatelet Trialists' (APT) composite outcome event—death from all vascular causes, non-fatal stroke, or non-fatal myocardial infarction—unless otherwise stated. An outcome event that takes the entire vascular burden into account is most relevant from the perspective of a patient. In other words 87% of the major arterial complications are not avoided with aspirin. The question therefore is: Do we have something "stronger"?

Until recently the only alternative drug was ticlopidine. A direct comparison with aspirin was made in the Ticlopidine Aspirin Stroke Study (TASS).<sup>4</sup> A total of 3069 patients with transient or non-disabling cerebral ischaemia were randomised between ticlopidine (250 mg twice daily) or aspirin (650 mg twice daily). The occurrence of non-fatal myocardial infarction was not reported in the original document,<sup>4</sup> but data on the APT composite event were reported later.<sup>1</sup> The relative risk reduction (RRR) was a 6% advantage in favour of ticlopidine, but the 95% confidence interval (95%CI) was compatible with no difference at all (-7 to 17%).<sup>5</sup> Thus ticlopidine is about as effective as aspirin. A major disadvantage is, however, that it is definitely more toxic. Diarrhoea and skin rashes were reported in up to 20 and 14%, respectively, and neutropenia in about 1%.<sup>4</sup>

In the past 2 years three trials in patients with cerebral ischaemia of presumed arterial origin also tried to find a more efficacious treatment than aspirin, in different ways.<sup>6-9</sup>

### CAPRIE

CAPRIE<sup>6</sup> was a randomised, blinded, international trial designed to assess the relative efficacy of clopidogrel (75

mg daily) and aspirin (325 mg daily) in reducing the risk of the composite outcome event vascular death, non-fatal stroke, or non-fatal myocardial infarction.<sup>6</sup> Clopidogrel is a new thienopyridine derivative, chemically related to ticlopidine. Patients from three diagnostic strata participated: ischaemic stroke (6431), myocardial infarction (6302), and peripheral arterial disease (6452). The overall RRR by clopidogrel versus aspirin was 8.7% (95% CI 0.3-16.5). The trialists based the design of the trial on the assumption that the three presentations of arterial disease are all expressions of a single underlying disease—atherosclerosis. Their data, however, do not necessarily support the quantitative implications of such a view. The RRRs differed significantly ( $p=0.042$ ) between the strata: 7.3% for ischaemic stroke, -3.7% for myocardial infarction, and 23.8% for peripheral arterial disease. The RRRs (for the APT standard outcome) reported by the APT Collaboration (mainly based on aspirin trials) also differ according to indication: unstable angina 35%, acute myocardial infarction 25%, previous myocardial infarction 22%, and cerebral ischaemia 18%. Thus the magnitude of the risk reduction conferred by drug treatment may depend on the type of arterial disease.<sup>1</sup> For the stroke subgroup in CAPRIE, the point estimate of the RRR is a modest 7.3%: the absolute risk reduction is 0.56%/year, and the number needed to be treated with clopidogrel for 1 year instead of aspirin to avoid one vascular event is therefore about 200. Furthermore, the 95% CI in the stroke stratum is wider than for all patients (-5.7 to 18.7) and includes the interpretation that clopidogrel is not better than aspirin at all. The modest advantage of clopidogrel over aspirin after stroke is similar to that obtained with ticlopidine compared with aspirin (6%). On the other hand, clopidogrel does not have the toxic side effects of ticlopidine which necessitated haematological monitoring. Because of the small advantage of clopidogrel, both in the stroke stratum and overall, and the high cost of the drug (wholesale price about \$1000/year in the United States), clopidogrel is not attractive as a drug of first choice in patients after cerebral ischaemia, but may be used as a safe second line alternative.

### ESPS-2

The second European Stroke Prevention Study (ESPS-2)<sup>7,8</sup> was a randomised, placebo controlled, double blind trial comparing the effects of low dose aspirin (50 mg daily), modified release dipyridamole (400 mg daily), and the combination of both drugs with that of placebo in 6602

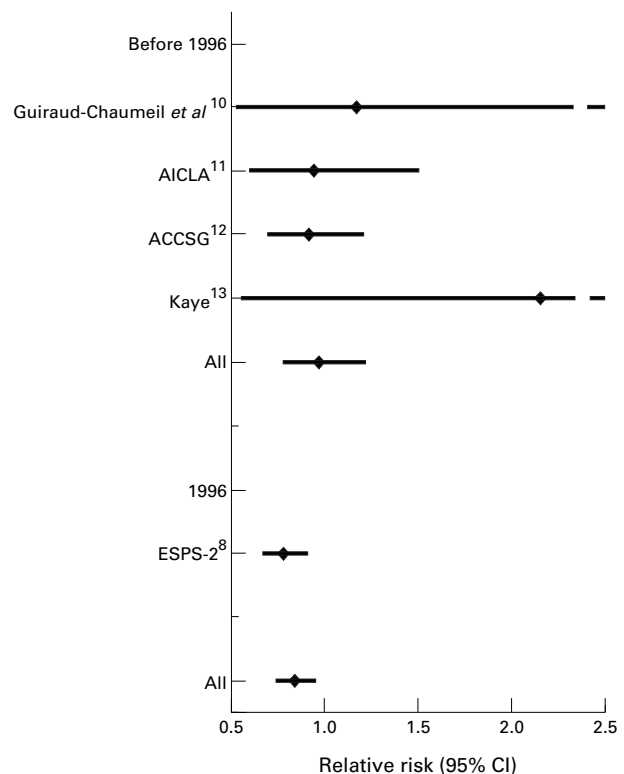
patients with a previous ischaemic stroke or transient ischaemic attack.<sup>7</sup> Primary outcome events were stroke, death, and stroke and death together. The trial showed a benefit for the combination therapy in comparison with aspirin alone for the occurrence of stroke (relative risk (RR) 0.76; 95% CI 0.63 - 0.93), a marginally statistically significant difference for the combination of stroke and death (RR 0.87; 95% CI 0.75-1.00), and no difference for total mortality (RR 1.02; 95% CI 0.84-1.23).

The main paper does not report on the APT standard outcome event, but in a more recent publication these data were given: the RR of aspirin plus dipyridamole versus aspirin only was 0.78 (95% CI 0.67-0.91).<sup>8</sup>

The RR of aspirin versus placebo for (APT) vascular events was 0.87 (95% CI 0.76-1.00).<sup>8</sup> Some might interpret the protective effect of 13% with 50 mg of aspirin as evidence that this is too low a dose, given that this effect is less than the 24% risk reduction generally attributed to aspirin, in any dose and for any indication.<sup>1</sup> However, we pointed out above that for the prevention of stroke alone risk reductions with aspirin have always been in this order of magnitude and were already known at the start of ESPS-2.<sup>2</sup> Therefore, the relevant question considered by ESPS-2 was whether aspirin plus dipyridamole was more efficacious than aspirin alone.

Four earlier studies compared the efficacy of combination therapy and aspirin alone<sup>10-13</sup>; data on these studies have been listed in an appendix of the report on the second cycle of the APT Collaboration.<sup>1</sup> The unpublished and therefore often forgotten study by Kaye enrolled stroke patients and studied deep venous thrombosis as primary outcome and vascular events as secondary outcomes.<sup>13</sup> A systematic review of these four studies for the composite outcome event vascular death, stroke, or myocardial infarction yields a Mantel-Haenszel RR of 0.97 (95% CI 0.78-1.22; figure). This is strikingly—although not significantly—different from the result obtained in ESPS-2, also if Kaye's small study is omitted (cumulative RR 0.95; 95% CI 0.75-1.19). A similar discrepancy exists between the ESPS-2 primary outcome measure “stroke or death” RR of 0.87 (95% CI 0.75-1.00) for ESPS-2 and 1.01 (95% CI 0.82-1.25) for the four earlier studies taken together. If the results of all five trials are combined, despite the discrepancy described above, the overall RRR is 16% (95% CI 5-26%) (figure). For total deaths, the comparison of the combination of aspirin and dipyridamole versus aspirin alone showed no benefit (RR=1.02) nor for vascular death (RR=0.99; 95% CI 0.77-1.27).<sup>8</sup> This suggests that any beneficial effect of the combination may apply, especially to non-fatal events.

A Bayesian approach to the interpretation of ESPS-2 may be as follows.<sup>14 15</sup> Firstly, assume one was (as we were) sceptical about the possible efficacy of the combination of aspirin and dipyridamole (a priori opinion).<sup>10-13 16</sup> Then the ESPS-2 results show a statistically significant reduction in RR of 22% for major vascular events in favour of the combination of aspirin and dipyridamole versus aspirin alone. Finally, the a posteriori opinion is to be less sceptical and wonder whether there might after all be a true benefit of the combination therapy above aspirin alone. To be convinced one will seek confirmation by another Bayesian update of opinion—that is, by the results of a new clinical trial. Clearly, for those clinicians who were less sceptical from the outset the ESPS-2 data will be convincing in their own right. However, even in that situation the costs of addition of dipyridamole to aspirin should be weighed against the perceived clinical benefits.



Relative risks with 95% CIs for all trials on the comparison of aspirin plus dipyridamole versus aspirin alone, before 1996, in 1996, and their combined results for the outcome event “vascular event”.

## SPIRIT

The aim of SPIRIT (Stroke Prevention In Reversible Ischemia Trial)<sup>9</sup> was to compare the efficacy and safety of oral anticoagulants (INR 3.0-4.5) and 30 mg aspirin daily. Patients referred to a neurologist because of a transient ischaemic attack or minor ischaemic stroke (Rankin grade ≤ 3) were eligible. The primary measure of outcome was the composite event “death from all vascular causes, stroke, myocardial infarction, or major bleeding complication”. The trial was stopped at the first interim analysis, when a total of 1316 patients were enrolled; their mean follow up was 14 months. There was an excess of the primary outcome event in the anticoagulant group (81/651) versus 36/665 in the aspirin group (hazard ratio 2.3, 95% CI 1.6-3.5).<sup>9</sup> This excess could be attributed to 53 major bleeding complications (27 intracranial; 17 fatal) during anticoagulant therapy versus six on aspirin (three intracranial; one fatal). The annual bleeding incidence was 7% overall, but it increased sharply with the achieved INR-value. The efficacy of a lower intensity of anticoagulation is currently assessed in two trials: WARSS and ESPRIT.<sup>17 18</sup>

The striking difference in incidence of intracerebral bleeding complications between SPIRIT (3.7%/year in patients with cerebral ischaemia of presumed arterial origin, mean achieved INR 3.3, mean age 63 years) and the EAFT (0.4%/year in patients with cerebral ischaemia and atrial fibrillation, mean achieved INR 2.9, mean age 71 years)<sup>19 20</sup> confirms the notion that not all vascular disease is the same in its response to treatment. Therefore specific therapy should be given for specific vascular indications.

## New drugs or combinations of drugs

Glycoprotein IIb/IIIa (GP-IIb/IIIa) receptor blockers, or GP-IIb/IIIa antagonists, block the final common pathway of platelet aggregation by binding of fibrinogen to the GP-IIb/IIIa receptor. Hence these drugs inhibit platelet

activation irrespective of the metabolic pathway that leads to platelet aggregation. In patients after PTCA the monoclonal antibody to the GP-IIb/IIIa receptor c7E3 was found to be promising.<sup>21</sup> The most important side effect was gingival bleeding. After the placement of coronary artery stents the combination of ticlopidine and aspirin was more effective than conventional anticoagulant therapy with regard to the occurrence of both cardiac events and haemorrhagic and vascular complications.<sup>22</sup> The safety and efficacy of these new drugs or combinations have still to be established in patients with cerebrovascular disease and indeed several such studies are being planned.

### Conclusions

- Aspirin alone (in any dose of at least 30 mg daily) confers a relative risk reduction of death from all vascular causes, non-fatal stroke, or non-fatal myocardial infarction of 13% relative to placebo treatment.
- The combination of aspirin and dipyridamole may give an RRR of 16% (95% CI 5–26%) compared with aspirin alone if one is prepared to overlook the striking (although not statistically significant) disparity of ESPS-2 with four previous studies. Another large trial comparing the combination of aspirin plus dipyridamole and aspirin alone seems called for.
- Clopidogrel may give a reduction in RR of 7–9% compared with aspirin treatment, but is not an attractive drug because the costs are considerably higher than those of aspirin. The drug, however, has a more favourable safety profile than ticlopidine.
- Anticoagulation with INR 2.0–4.0 is highly effective for secondary prevention in atrial fibrillation, but anticoagulation with INR 3.0–4.5 is not safe in the secondary prevention after cerebral ischaemia of presumed arterial origin. The efficacy and safety of mild anticoagulation (INR 2–3) needs further study.
- The efficacy of new antiplatelet drugs such as GP-IIb/IIIa receptor blockers will be studied in the years to come.
- Combinations other than aspirin and dipyridamole deserve to be investigated—for example, the combination of a low dose of aspirin and clopidogrel.
- Not all atherosclerotic vascular disease is necessarily the same: the therapeutic effect may be modified by the presenting disease.

We have received fees and expenses from the producers of dipyridamole (Boehringer Ingelheim) and clopidogrel (Sanofi), but we have no permanent links with these companies (such as shares or consultancies).

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