The Ideal Antiplatelet Drug for Stroke Prevention—Still Elusive

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See related article, pages 1358–1363.

Since the publication of the Antiplatelet Trialists Collaboration meta-analyses well over a decade ago showing a relative risk reduction of 25% from aspirin for all secondary vascular ischemic events in patients presenting with a variety of vascular disorders, there have been numerous attempts to improve on these modest benefits. Reducing the dose of aspirin reduced the risks of bleeding while maintaining therapeutic effectiveness, but using other antiplatelet drugs with different pharmacological actions such as ticlopidine, clopidogrel, or dipyrimadole have so far not produced any impressive differences from those early data.

The many attempts to pool the results of tens of thousands of patients using meta-analyses from the accumulating data of all these antiplatelet trials have also proven contentious. The problem with any meta-analysis is that the investigator must be selective, so introducing bias, but clearly should not include trials with obvious outdated methodology, incomplete data sets or where the patient cohort is so selective it can be generalized only to a minority of patients.

This issue of Stroke includes a fresh attempt at an extensive meta-analysis of results from trials of the combination of aspirin and dipyrimadole in preventing further vascular events after stroke or transient ischemic attacks (TIAs). The authors examined published and unpublished studies, as well as those using immediate and extended-release dipyrimadole formulations. Their analysis was stringent, and only 6 randomized studies out of over 70 met their inclusion criteria for subsequent analysis. They concluded that the combination of aspirin plus dipyrimadole is more effective than aspirin alone in preventing stroke and other serious vascular events in patients with minor stroke or TIA; but is this correct?

In their rigorous attempt to avoid bias they included trial data of the immediate release dipyrimadole formulation of over 20 years ago, with trials of far too few patients and at a time when our knowledge of the underlying pathogenesis and outcome of cerebrovascular disease was incomplete. It was all part of a necessary learning curve but most of those data are no longer valid. For instance, the older trials allowed trial entry as long as 6 months after TIA or stroke, long after the immediate and serious threat of further cerebrovascular episodes had passed. New data from recent studies clearly demonstrating that the crucial period for new cerebrovascular events after TIA is within days or at most, weeks, has revolutionised trial design. For instance, in the recent FASTER trial, patients were randomized to an antiplatelet drug within 24 hours after the initial TIA or minor stroke.

Paradoxically, the authors gave less weight to the ESPRIT study which used far superior and modern methodology than the early French studies. In addition, any meta-analysis including the ESPS-2 study cannot avoid incorporating the number weighting bias of that study, with its huge patient cohort of nearly 7000 patients. In ESPS-2, with four arms (placebo, aspirin, dipyrimadole and combination), only non-fatal stroke was significantly reduced (37%) by combination therapy, but strangely, this beneficial effect was not reflected in the death rate. Also, the incidence of myocardial ischemia and vascular death were unaffected, though the explanation may be that stroke has more protean causes than the more uniform pathology of coronary artery disease. Again, about 25% of patients were withdrawn due to headache or gastro-intestinal upset from dipyrimadole or its combination, a serious drawback to uniform prescribing.

In this present meta-analysis, a lower weighting was given to the ESPRIT study than the others because it was ‘open label’, though this trial is arguably superior in methodology, and avoided a placebo group as in ESPS-2. Also, although treatment in the two ESPRIT groups (aspirin with and without dipyrimadole) was ‘open label’, auditing was blinded. After 3.5 years of mean follow-up the trialists concluded that “combined with the results of previous trials, there was sufficient evidence to prefer the combination over aspirin alone”. However, there are some other interesting and disturbing findings in this study. Both the primary end points and the overall vascular events were significantly different in the 2 groups at the end of the study apparently favoring the combination (authors’ Figure 2) but the 2 curves completely merge at 2 years, then diverge significantly at the end. Does this imply that there is no therapeutic effect for the first 2 years? Furthermore, the ‘intention to treat’ group paradoxically fare better than the ‘on treatment’ group (authors’ Table 3). Similar to the ESPS-2 study there was a high discontinuation rate in the dipyrimadole arm of 34% due mainly to headache. Therefore, presumably patients in the ‘intention to treat’ group took an alternative antiplatelet drug, most likely clopidogrel, which could explain this discrepancy.

The authors of this present meta-analysis infer that there is a ‘robust benefit’ from the aspirin and dipyrimadole combination compared to aspirin alone, in stroke prevention. There may be an absolute risk benefit (as opposed to relative risk) of about 1% of aspirin-dipyrimadole combination over aspirin...
rin alone, but considering the 40 times difference in cost and the discrepancies noted above, such benefit is uncertain and, judging by the data, far from robust.

Finally, there is increasing concern worldwide regarding the relationships between the pharmaceutical industry and physicians. Even though this relationship is necessary and symbiotic, any relationship however minor, may influence physicians opinions. All 3 authors have received unrestricted funding from the sponsor, as well as other fees, though their data collection and analysis were conducted independently. This in no way impugns their honesty or credibility, but a group of investigators independent of the pharmaceutical sponsor would have ensured neutrality without further question.

Disclosures
None.

References

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