Clinical trials of stroke prevention in patients at high risk are based on, at best, a few hundred outcome events. Therefore, the conclusions of single trials are necessarily subject to random error. The Ticlopidine Aspirin Stroke Study (TASS) trial, which directly compared ticlopidine with aspirin, is no exception: the 3-year event rate for stroke or death (all causes) was 17% for ticlopidine and 19% for aspirin, corresponding with a marginally nonsignificant risk reduction of 12% (95% confidence interval [CI], −2% to 26%). This tendency in favor of ticlopidine diminishes if stroke and vascular death, instead of stroke and total mortality, are counted in the analysis (risk reduction, 10%; 95% CI, −4% to 22%). Nonvascular deaths occurred less often in the ticlopidine group, but it is usual to exclude such an “effect” because it is biologically implausible, at least with antiplatelet agents. Myocardial infarction was not analyzed in the original report of the TASS study but occurred more often in the ticlopidine group. If myocardial infarction is included in the analysis together with stroke and vascular death, the risk reduction is only a 6% advantage in favor of ticlopidine (95% CI, −7% to 17%). In summary, ticlopidine seems approximately as effective as aspirin in the prevention of stroke or other vascular complications, while its potential side effects are more serious.

Of course, some degree of uncertainty remains about the relative efficacy of ticlopidine and aspirin in either direction. A possible way of narrowing the confidence interval of the point estimate is to perform an overview analysis of all trials in which ticlopidine and aspirin have been directly compared. In the second cycle of the Antiplatelet Trialists' Collaboration, which has just appeared in print, there was no doubt that ticlopidine was more effective than placebo, with similar degrees of risk reduction (for the combined outcome event of stroke, myocardial infarction, or vascular death) in different kinds of arterial disease, including cerebrovascular, coronary, or peripheral arterial disease (risk reduction, 31%; 95% CI, 20% to 40%). The overview of direct comparisons between ticlopidine and aspirin included three trials. Apart from TASS there were two smaller trials, one also in patients with a preceding stroke or transient ischemic attack (TIA), the other in patients after intermittent claudication. The outcome event was again composite: stroke, myocardial infarction, or vascular death, whichever occurred first. The total risk reduction favoring ticlopidine was 8% (95% CI, −4% to 19%). In other words, as far as all available evidence from clinical trials goes, any advantage of ticlopidine over aspirin could well be the result of chance.

The least appropriate way of coming to grips with the existing uncertainty, at least from a scientific point of view, is to conduct not an overview but a “miniview,” singling out certain subgroups in terms of either baseline characteristics or outcome events. In subgroups the vagaries of random error are even more capricious than for single trials. By chance alone one can expect 5% of all comparisons to yield a statistically significant result. The danger of data dredging with subgroups is plain enough when applied to astrological birth signs, but the results of such “fishing expeditions” may briefly look respectable when the characteristic is some biological variable. Yet the result can be equally misleading, as attested to by the question of aspirin in women, a one-time controversy settled long ago by the first cycle of the Antiplatelet Trialists' Collaboration and one that most neurologists now prefer to forget. “Subgroups kill people” is how British statistician Richard Peto has put it. Belief in the results of subgroup analysis should be strictly limited to analyses that are biologically plausible, defined in advance, and reproducible. An example of relevant, predefined, and reproducible subgroup analysis is that of the two well-known clinical trials of carotid endarterectomy, according to the degree of stenosis. But in the case of single trials the results of subgroup analysis should be interpreted with great caution, regardless of whether these results are positive or negative.

For the TASS trial these precautions have not been heeded. The study has been dissected into a large number of subgroups in one report, and separate communications have claimed superiority of ticlopidine over aspirin, to a greater degree than in the main study, in patients with minor stroke, in blacks, and in patients with diabetes. We might as well have read reports about ticlopidine in patients who smoke, wear glasses, or whose surname begins with K to Z. Suffice it to point out the corollary, namely, that ticlopidine is relatively less effective in patients with TIAs, patients who are white, and patients who are not diabetic. A different kind of “data torturing” is to include minor outcome events. The October 1993 issue of Stroke contained a subsidiary analysis of all trial patients according to the occurrence of reversible events (temporary analysis) or even attacks of less than 24 hours (an afterthought). Perhaps not unexpectedly for the wary reader, ticlopidine came out best. But of course tran-
sient outcome events are ephemeral and hardly affect the patient's quality of life. In addition, the diagnosis of TIsAs is fraught with interobserver variation, particularly in a multicenter study. Daily drug treatment, with potential side effects, is warranted only for the prevention of serious events.

The latest installment of the TASS saga appears in this issue. A model developed in a study by Oster et al,17 based on the technique of decision analysis, leads the authors to conclude that for patients aged 65 years with a TIA, the cost-effectiveness of ticlopidine compares favorably with that of aspirin and to suggest that the indications for ticlopidine as approved by the US Food and Drug Administration are too restrictive. The present recommendations of this body are that ticlopidine be reserved for patients with threatened stroke who cannot tolerate aspirin.

The model as presented by Oster et al suffers from some of the methodological ailments outlined above. First, the only outcome event considered in the model is stroke (fatal or nonfatal), for which the TASS trial showed a 21% advantage in favor of ticlopidine.1 Death from other causes was not taken into account, contrary to the primary analysis chosen by the investigators of the TASS trial themselves. And that was for good reason, heart disease being by far the most common cause of death in any trial of this kind.2 TASS included. Dying from heart disease is an undesirable way to avoid stroke, for which reason exclusion of such deaths from the analysis should be viewed with great reserve, to put it mildly. A second problem with the model of Oster et al is its instability, in view of the wide confidence interval in the comparison between ticlopidine and aspirin, even for the subordinate outcome event of stroke alone (4% to 38%). As indicated in the section on sensitivity analysis, this factor causes the cost-effectiveness of ticlopidine to vary from $306,000 per quality-adjusted year of life gained at the lower limit of efficacy to $18,300 at the upper limit. Paradoxically, the emphasis in the sensitivity analysis is on the utility of life after nonfatal stroke, a much smaller source of variation. We feel this is an unbalanced appraisal of hazards, rather like weighing the pros and cons of seat belts in inebriated drivers.

Decision analysis can be a useful tool in quantifying the options in medical dilemmas,18 including those in neurology.19 Yet the credibility of the conclusions depends on the stability of the underlying assumptions. If this happens to be a clinical trial, the basis for calculations should be all randomized patients and not subgroups, all outcome events included in the primary analysis and not just some, and confidence intervals of the most relevant and not the most stylish variable.20 Neurologists should beware of being penny-wise and pound-foolish. Why not simply await the results of the ongoing Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study, a meticulously executed clinical trial in which the successor of ticlopidine, clopidogrel, is compared with aspirin in approximately 15,000 patients, including 5000 with ischemic stroke.

References


Key Words • aspirin • clinical trials • confidence intervals • decision analysis • ticlopidine
Ticlopidine, trials, and torture.
J van Gijn and A Algra

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