Editorial

Single Studies and Overview Analyses: Is Aspirin of Value in Cerebral Ischemia?

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Stroke is responsible for more than 200,000 deaths each year in North America[1]; 40% of stroke cases die within 1 month of having a stroke,[1] and the survivors remain at very high risk of cerebral infarction, myocardial infarction, or vascular death.[2,3] Secondary prevention has traditionally been based in part on surgery and on oral anticoagulants, but the efficacy of either of these has never been established.[4] Since most disabling and fatal strokes are thromboembolic[2,5] and many of them are preceded by less significant or transient ischemic events,[6] and given the established role of platelets in arterial thrombosis, it is not surprising that there have been several reported randomized trials of platelet-inhibiting drugs such as acetylsalicylic acid (ASA),[7-16] dipyridamole,[17] and sulfinpyrazone[8,13,18-20] in patients with transient ischemic attacks (TIAs) or minor strokes. From these completed studies, there is no persuasive evidence that either dipyridamole or sulfinpyrazone modify the clinical course of patients with TIAs or mild stroke, and while ASA is now an approved drug in North America for men with this indication, there are some who still question its true benefit. In addition, ASA at the dose recommended has significant side effects and is not well tolerated by many patients.[21]

The last issue of *Stroke* included a report by the Swedish Cooperative Study Group[22] on a study of ASA in patients who had survived an ischemic stroke. This is a somewhat different population of patients from those in previous related reports, and it is reasonable to ask where we now stand with regard to the efficacy of ASA in cerebral ischemia. The authors noted that there was no observed prophylactic effect of high-dose ASA (1.5 g daily) after cerebral infarction in their own study, but then carried out a compilation of the results from available related studies from which they concluded that a prophylactic effect of ASA after TIA and/or stroke is probable but remains to be proved.

The Swedish study, as well as the overview analysis, raises a number of methodologic and operational concerns that require elaboration. It is, therefore, pertinent to review the standards expected in the design, execution, and analysis of individual clinical trials, as well as the requirements for validity in carrying out pooled analyses of independent studies.

Before dealing with these issues, however, one needs to ask whether the question being addressed by the Swedish Cooperative Study Group is an important one; the answer is a resounding "yes" for the following reasons. Firstly, only about 20% of thromboembolic strokes are preceded by TIAs[3] and, hence, only a part of the problem of cerebral ischemia has been addressed in most previous studies. Secondly, it does not necessarily follow that ASA will be of benefit in patients with moderate or severe ischemic stroke, even if it is of benefit in patients with TIAs or mild stroke. Finally, the prognosis of patients surviving an acute ischemic stroke is poor, with an expected incidence of further stroke, myocardial infarction, or vascular death of about 25% over the next 2 years.[3]

The key issues relating to experimental design in this clinical setting include the type of patient to be studied; the intervention to be evaluated and the choice of control treatment; the method of allocating patients to their respective treatment groups; the selection, assessment, and ranking of appropriate outcome events; the number of patients being studied; and the duration of follow-up.

The Swedish Cooperative Study Group provided a brief rationale for evaluating 1.5 g of ASA daily in patients surviving an atherothrombotic stroke, and while this dose is somewhat on the high side in terms of today's understanding of the mechanism of action of ASA, it was not unreasonable at the time their study started. Since there is no intervention known to be of benefit in this patient population, the choice of a placebo control is appropriate and ethical and necessary for minimizing potential bias in the execution of the study. Allocation of patients to their respective treatment groups according to a prescribed randomized arrangement is also essential for avoiding bias.

The outcomes chosen for their primary analysis by the Swedish group were stroke recurrence or death from any cause; the occurrence of myocardial infarction and TIA were classified as secondary outcome events. While this primary cluster is reasonable, one could argue that a more relevant cluster would be recurrence of stroke, occurrence of myocardial infarction, or vascular death. This latter cluster has the advantage of adding a major clinical outcome,

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myocardial infarction, and excluding a possibly irrelevant one, nonvascular death. Myocardial infarction is relatively common among stroke patients and is likely to be modifiable by ASA, whereas nonvascular death is unlikely to be influenced by ASA and its inclusion in the primary cluster of outcomes would tend to make it more difficult to demonstrate a true benefit of treatment. Hence, the risk of important clinical outcomes in the control group and the likelihood of response to ASA could both be increased, and this would have a marked influence on reducing sample size requirements.

Sample size is a particularly important consideration in this clinical setting where large numbers of patients need to be studied to have a high probability of detecting important clinical benefits. The Swedish group postulated an expected rate of 20% for stroke or death over a 2-year follow-up and estimated that they would require 400 patients in total to have an 80% chance of finding a statistically significant difference, at $p = 0.05$, between the observed rates in the two treatment groups if the true benefit of ASA was to reduce the relative risk of stroke or death by 40%. This estimated sample size was scaled up to 500, arbitrarily but reasonably, to allow for those patients who would not complete the protocol as planned. (There is an unfortunate arithmetic error in these calculations, as the correct required number of patients is 516 and not 400 as stated.) Some would consider a 40% risk reduction too much to expect, although such a reduction has been reported with ASA in both cerebral ischemia[9] and in coronary artery disease,[23] and that a 30% risk reduction, say, is more likely and yet still very important. The Swedish study, as planned, would have only a 50% chance of detecting a true risk reduction of 30%. It is for this reason that the ongoing Canadian-American Ticlopidine Study (CATS)[24] has recruited about 1,050 eligible patients with ischemic stroke, which ensures a 90% chance of detecting a true risk reduction of 30% in the primary outcome cluster of stroke, myocardial infarction, or vascular death. In fairness to the Swedish Cooperative Study Group, they clearly recognized the limitations of the size of their study, even though it is the largest randomized trial yet reported in patients with completed stroke.

It is clearly difficult to overcome major flaws in the design of any clinical trial, but even when trials are well designed, they still need to be carried out with considerable care and discipline if they are to yield valid results. In laying out an organizational and operational plan for any study, it is important to avoid the common error of confusing execution and analysis. The sole concern in the execution of a clinical trial is to maximize adherence to the protocol at all times by both patients and investigators, consistent with ethical requirements relating to patient care and patient freedom. How one deals later with patients who deviate from the protocol is a separate matter of analysis.

Hence, one should avoid terms such as *drop-outs* and *withdrawals* to signify patients who discontinue study medication. With the exception of those who die, patients should continue to be followed and assessed as per protocol, unless the patient is unwilling, whatever the reason for discontinuing study drugs. If a patient has a severe adverse reaction attributable to a study treatment, the treatment should be stopped but the patient should remain in the study. If patients stop medication for other reasons, such as mild side effects or because they have some other intervention to deal with an acute comorbid condition or for loss of interest, etc., they should be restarted on study drugs as soon as possible whenever it is appropriate. Since we often do not know the optimal dose of an experimental drug, it may also be better to have a patient taking a reduced dose rather than none at all; this is certainly true of ASA. For these reasons, the operational rules of the Swedish study relating to "withdrawals" are not appropriate — particularly when they switched their analysis strategy from an efficacy analysis to an intention-to-treat one (see later).

Some markers of quality of execution include the proportion of truly eligible patients in the study, the proportion of cases who completed the study as per protocol, the maintenance of blinding, the objective and standardized assessment of outcomes, and the accounting of all patients at the end of the study. The Swedish study scored high on these last 3 criteria in that the code was not broken until all data had been collected and validated; all outcomes were assessed centrally and without knowledge of treatment, although the criteria reported were not very specific; and the vital status of all patients was known at the end of the study.

However, there were more serious problems with respect to the first 2 criteria. There is a key role for a central adjudication committee to play in this type of study, not only to assess and decide on the validity of reported outcome events but also to check on the eligibility of patients entered into the study. There is no evidence of independent review of patient eligibility in the Swedish study, and a major concern is that of the 66 deaths included in the primary assessment of efficacy, 17 (26%) were directly attributed to the qualifying stroke! Since ASA cannot be expected to influence these deaths, their inclusion makes it much more difficult to show a benefit of ASA overall. These deaths also raise serious questions about the study sample, particularly since the authors claim that they tried ". . . to avoid including patients with a very bad early prognosis."[22]

Reference has already been made to the policies and procedures relating to cases who did not complete the protocol as planned. In the Swedish study, 31% were withdrawn from study treatment before the end of the study for reasons other than outcome events. This is due only in part to study policy, and most of it is a reflection of the inherent difficulty of maintaining patients on study medications for long periods of time, for the reasons discussed earlier. Some comparable rates of patients permanently discontinuing study medications in other studies of cerebral ischemia are 32%,[3] 35%,[9] and 43%[16] over similar periods of follow-

up. This is an area that requires attention by those of us who are involved in the execution of long-term trials. We need to recognize the magnitude of the problem and its potential impact on the sensitivity and validity of the resulting findings and work harder at maintaining patients on study medications, except where it is clearly inappropriate.

Protocol deviations in the form of ineligible patients or patients who discontinue study drugs before their scheduled time or patients who take contaminating treatment (e.g., aspirin-containing drugs) raise a number of methodologic concerns about analysis. The intention-to-treat strategy is one in which, once a patient is randomized, any outcome events in that patient from the time of randomization to the end of the study must be counted in the analysis of effectiveness or safety of the study treatment.[25] The consequences of this policy are that there is no resulting bias but there could be a marked loss in sensitivity in the statistical analysis because of the noise introduced by protocol deviations. This can be overcome only by increasing, quite significantly, the number of patients entered into the study.

An alternative strategy is to carry out an efficacy analysis[26,27] in which only eligible patients and only outcome events observed under specified rules and conditions would be included in the primary assessment of efficacy. These specified rules and conditions should be tailored to the particular study[3,23] and need to be clinically sensible and acceptable and operationally feasible in the sense that the rules can be shown to have been applied in an unbiased way. For example, in secondary prevention studies in cerebral ischemia, ruling out all nonvascular deaths and other outcome events that occur more than, say, 28 days after permanently discontinuing study drugs, both of which are unlikely to be influenced by ASA, could make the statistical assessment of efficacy more sensitive, thus minimizing the required sample size. On the other hand, exclusion of patients or events after randomization does create an opportunity for bias and, hence, both the rules and the results of applying those rules must be fully disclosed in the final report of the study.

If one cannot show a benefit of an intervention using an efficacy analysis, then one would certainly not expect to show a benefit using an intention-to-treat approach. It also follows that if the objective of a study is to show that there is little difference in efficacy between two interventions, then an efficacy analysis is superior to an intention-to-treat analysis since the latter would tend to mask true differences in outcomes. Given this and the lack of any demonstrable difference in outcomes in the Swedish study, it is curious why they should choose to switch to an intention-to-treat analysis from the efficacy analysis planned in the original design.

Within whichever of the two strategies adopted, there are 3 other key issues about analysis in secondary prevention studies in cerebral ischemia to which attention should be drawn briefly; these have to do with life-table analyses, adjustments for imbalances in baseline patient characteristics, and subgroup analyses. The most appropriate analysis of outcomes is a comparison of life-table or survival curves, which takes into account the different periods for which patients might be at risk, as well as the actual times when outcome events occur. This particular comparison can be further enhanced by adjusting for the influence of imbalances in important prognostic patient variables at baseline between the 2 treatment groups; this improves sensitivity and provides the most accurate estimate of treatment benefit. The Swedish Cooperative Study Group made use of neither of these statistical methods and simply reported the percent of cases with various outcomes in the 2 treatment groups.

Finally, the identification of highly responsive and nonresponsive subgroups of patients has important implications for patient management. However, in establishing a difference betwen complementary subgroups, one needs to show that the efficacy within each subgroup differs significantly from the other, as was shown for ASA in men and women in the Canadian Study.[9] Simply showing that a treatment appears to be efficacious in one subgroup but not in another does not establish real differences. In addition, the specific subgroup questions should be specified before looking at the data, and allowance should be made in interpreting the resulting p values for the multiple statistical tests since these increase the chance of spurious significance, as pointed out in the report of the Swedish study.

The report of the Swedish Cooperative Study Group has been used as a reference point and a stimulus to recapitulate on some conceptual and operational aspects of individual long-term clinical trials. In closing the report of their study, the Swedish group very thoughtfully and responsibly reviewed their findings with a compilation of other major trials of ASA in cerebral ischemia. Where relevant, this use of meta-analysis, or overview analysis, should become an essential component of reporting and reviewing the current state of affairs; such developments have been very much stimulated by Richard Peto's overview analysis of ASA in myocardial infarction[28] and subsequent work.

The basic principle in pooling data from several independent randomized trials is to develop a clinically appropriate estimate of efficacy for each trial, e.g., relative risk reduction, and then to combine these across studies in an unbiased fashion. The method is quite robust with respect to tolerating reasonable heterogeneity among the protocols of the various studies in terms of types of patients and variations in dosage.

The Swedish group based their compilation of results on the reports of 6 studies[7-9,14,15,22] and estimated that the overall results suggest a risk reduction of 11% in stroke or death among patients treated with ASA; this risk reduction is not statistically significant. Peto and his colleagues at Oxford have recently given some early results of a more comprehensive overview analysis of ASA, including all known studies in cerebral ischemia, based on the raw data provided by the principal investigators. Using the composite outcome of stroke, myocardial infarction, or vascular death, it is

estimated that the risk reduction among patients treated with ASA is about 16%, which is both clinically important and statistically significant. This estimated effect is also similar to the reported risk reduction of 21% in reinfarction among myocardial infarction patients treated with ASA.[28]

It would be reasonable to conclude, therefore, that ASA is of benefit to patients with TIAs or mild stroke. However, the patients in the Swedish study all had completed strokes, which is different from all of the other studies with the possible exception of the French study.[14] While we cannot say that ASA is not effective in moderate or severe completed stroke cases, at this time we cannot say with confidence that it is.

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