Trials of Thrombolysis in Acute Ischemic Stroke
Does the Choice of Primary Outcome Measure Really Matter?

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Background and Purpose—Controversy regarding the risks and benefits of thrombolysis has not been helped by the perception that some trials were “positive” and others “negative” on their primary outcome measure of either “good” or “poor” functional outcome. We wondered whether the definition of good or poor functional outcome might have contributed to this perception, and what effect altering the definition might have on the individual trials and on the systematic review of all the trials combined.

Methods—We analyzed data on functional outcome, extracted from the randomized trials of thrombolysis in acute ischemic stroke, according to good (modified Rankin scale scores of 0 to 1 versus 2 to 6) and poor (modified Rankin 0 to 2 versus 3 to 6) functional outcome, to determine the effects of thrombolysis.

Results—Twelve trials (4342 patients, treated up to 6 hours after stroke) contributed to this analysis. Overall, there was no difference in the estimate of treatment effect between the 2 definitions (modified Rankin 0 to 2 versus 3 to 6, and 0 to 1 versus 2 to 6 [ORs 0.83 and 0.79, respectively]). However, the apparent “success” of several individual trials did alter.

Conclusions—We should not place undue emphasis on the results of individual trials, when a change of a single point on the Rankin scale can make the difference between “success” and “failure.” Overall, by either analysis, there was a significant benefit in patients treated with thrombolysis up to 6 hours after stroke. (Stroke. 2000;31:1133-1135.)

Key Words: cerebral infarction ■ meta-analysis ■ stroke, acute ■ thrombolytic therapy ■ treatment outcome

If a new treatment is tested in 1 or more trials which then provide evidence of a statistically and clinically significant benefit, it is likely that the new treatment licensing process will be swift and treatment will be adopted rapidly in routine medical practice. For example, recombinant tissue plasminogen activator (rtPA) has been licensed in the United States on the basis of 2 small trials (one statistically significant, the other not) of 624 patients in total.1 On the other hand, the reaction to trials that do not achieve a statistically significant positive result, but for which the size of the clinical benefit is approximately similar to a trial that did, may be equally pronounced but quite different: licensing will be difficult, uptake of the drug into routine medical practice will be negligible, and numerous hypotheses to explain why the trial was “negative” may be generated (it was the wrong drug, the wrong dose, the wrong patient population, or the wrong doctors performing the trial). But is this view necessarily correct?

In the case of thrombolysis in acute ischemic stroke, all trials used functional outcome as the primary measure. Total deaths and intracranial hemorrhage were secondary outcomes. Functional outcome in some trials was measured as “poor functional outcome,” ie, dead or dependent (modified Rankin scale score of 3 to 6),2 and others measured “good outcome,” ie, complete or almost-complete recovery (modified Rankin score 0 or 1). However, in all trials, data were collected on the number of patients in each individual Rankin group. It is therefore possible to analyze the data from each trial using the different definitions of “good” or “bad” functional outcome (apart from the PROACT3 and ATLANTIS A4 studies, for which data for only 1 Rankin dichotomization have so far been published). We therefore explored whether the choice of definition altered the conclusions of each individual trial or the overall estimate of treatment effect in a meta-analysis of all the available randomized data.5

This meta-analysis shows that the overall estimate of primary treatment effect is remarkably similar. Whichever of the 2 definitions is chosen (ie, poor outcome defined as Rankin 2 to 6 or as 3 to 6), the summary ORs in the meta-analysis are virtually identical (Figure). Changes in the choice of definition make minor quantitative, but not qualitative, changes in the estimate of treatment effect (ie, not from clearly beneficial to clearly harmful). However, some individual trials change from having a statistically significant primary outcome result to a nonsignificantly positive result, including ECASS II,6 ECASS,7 PROACT II,8 and the patients...
in MAST-I\textsuperscript{9} who received streptokinase versus control in the absence of aspirin.

Perhaps we are wrong to place undue emphasis on an analysis based on just one particular definition, when a change of a single point on the Rankin scale (widely used in stroke trials), can make the difference between apparent success and failure to a substantial proportion of the trials (one third in this case). Overly rigid, prespecified analysis plans required by a licensing body may obscure the fact that, overall, the treatment in question (thrombolysis) is clearly having a beneficial effect on functional outcome.\textsuperscript{5} All of these trials were relatively small, and thus their results are subject to the play of chance.\textsuperscript{10} It makes more sense to be pragmatic and analyze outcome from more than 1 point of view. In the case of thrombolysis for stroke, the choice of functional outcome definition does not make a material difference to the overall conclusion of the meta-analysis: there is a statistically and clinically significant benefit in patients treated up to 6 hours after stroke, no matter which analysis is chosen. However, either way, the confidence intervals remain wide and thus the estimate of the size of the benefit is imprecise (between 6\% and 27\% relative reduction in poor outcomes in patients treated up to 6 hours after stroke, with the present trial data). This benefit of improved functional outcome has occurred despite the increase in total mortality of 37 per 1000 in patients treated up to 6 hours after stroke, no matter which analysis is chosen. However, either way, the confidence intervals remain wide and the estimate of the size of the benefit is imprecise (between 6\% and 27\% relative reduction in poor outcomes in patients treated up to 6 hours after stroke, with the present trial data).

The interpretation of these data are a matter for debate and personal opinion, but failure to recognize the play of chance in trials with small sample sizes,\textsuperscript{10} or the fact that there appears to be overall benefit,\textsuperscript{5} could result in patients being denied effective treatments through lack of a license. Although rtPA is licensed in the United States and Canada, it is only for patients who can be treated within 3 hours of stroke and who meet fairly stringent criteria (as yet, there is no European license). The uptake of rtPA in the United States since licensing has been disappointing.\textsuperscript{11} Yet the data suggest that the benefit is large and extends beyond 3 hours. Granting a license on the present evidence (granting it at all in Europe or extending it beyond 3 hours in the United States) might increase patient access to this treatment. However, the dilemma for the individual clinicians, managers, family doctors, public health doctors, and health services is that the size of the benefit and the types of patients most likely to benefit need further definition. In particular, the existing trials provide little data on thrombolysis in elderly patients or those with CT infarct signs, when to start aspirin, the effect of stroke severity, and the time window beyond which there is unlikely to be any benefit. The latest time window may depend on individual patient characteristics, perhaps detectable by brain imaging, rather than an arbitrary value of 3 or 6 hours for all patients. These issues should be addressed in further trials, which in the case of thrombolysis need to be much larger (ie, approximately 6000 patients) to provide a more precise estimate of the treatment effect and clearer definition of which patients are most likely to benefit. This information will certainly be required to convince healthcare providers that the benefit of thrombolysis is worth its risk, the expense, and the work involved in restructuring acute stroke services to enable the safe delivery of thrombolysis.
References

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