Entry Criteria and Baseline Characteristics Predict Outcome in Acute Stroke Trials

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Background and Purpose—We sought to study the range of entry criteria and baseline characteristics in acute stroke trials and to understand their effects on patient outcomes.

Methods—Randomized, placebo-controlled therapeutic trials in patients with acute ischemic stroke were identified. Entry criteria, baseline clinical characteristics, and outcome were extracted for the placebo group of each trial. The relationship between key variables was then determined.

Results—Across 90 placebo groups identified, there was great variation in entry criteria and outcome measures. This was associated with divergent outcomes; for example, in some studies most placebo group patients died, while in other studies nearly all had no disability. Entry criteria were significantly correlated with outcome; for example, higher age cutoff for study entry correlated with 3-month mortality. Entry criteria also predicted baseline clinical characteristics; for example, wider time window for study entry correlated directly with time to treatment and inversely with stroke severity (initial National Institutes of Health Stroke Scale score). Baseline characteristics predicted outcome. Greater stroke severity predicted higher 3-month mortality rate; despite this, successful thrombolytic trials have enrolled more severe strokes than most trials. The mean age of enrollees also predicted 3-month mortality and was inversely related to percentage of patients with 3-month Barthel Index score ≥95. The strongest predictors of 3-month mortality were obtained with multivariate models.

Conclusions—Acute stroke studies vary widely in entry criteria and outcome measures. Across multiple studies, differences in entry criteria, and the baseline clinical characteristics they predict, influence patient outcomes along a continuum. In some studies, enrolling a specific subset of patients may have improved the chances of identifying a treatment-related effect, while in others, such chances may have been reduced. These findings may be useful in the design of future stroke therapeutic trials. (Stroke. 2001;32:909-916.)

Key Words: clinical trials ■ outcome ■ stroke, acute

A number of reasons have been advanced to explain the paucity of successful human stroke trials.1,2 Trial design may also be important because it influences the population under study and thus the likelihood of identifying a difference between treatment and placebo groups.

Several aspects of trial design may be important to interpreting results of previous stroke studies. Stroke study entry criteria result in enrollment of patients who are not representative of the stroke population in general.3,4 Selectively enrolling a particular subpopulation of stroke patients could affect study outcome, and therefore there is a need to better understand how changes in entry criteria influence the specific population under study. Differences in baseline patient characteristics can also influence study group outcomes. In stroke studies using a single cohort of patients, a number of clinical characteristics have been shown to influence final clinical status. For example, age,5 stroke severity,6 and stroke subtype7 each influence mortality rate.

A recent study noted the lack of consensus on acute stroke trial outcome measures.8 There has been limited study of the range of entry criteria used and the baseline characteristics measured in acute stroke trials. These issues were explored in the present study. Furthermore, the effect that variation in entry criteria and baseline clinical characteristics has on clinical outcome has received limited attention. This study addressed this issue by exploring the hypothesis that the clinical outcome of patients randomized to placebo group has been very different across studies and that some of these differences can be accounted for on the basis of variation in entry criteria and baseline characteristics across studies.

Methods

Randomized, placebo-controlled, therapeutic trials of human patients with acute ischemic stroke were identified by searching the Cochrane Controlled Trials Register with the terms stroke, acute, and therapy. Additional trials were identified through a MEDLINE search with the keywords ischemic, stroke, acute, therapy, and trials. Secondary
references and review articles were also used to identify relevant studies. Studies published in abstract form, having no placebo group, or enrolling patients >72 hours after stroke were excluded. When treatment subgroups were prespecified and placebo group data were reported separately, each subgroup was evaluated separately. Data from intention-to-treat analyses were used whenever possible. Entry criteria, baseline characteristics, and outcome measures were identified for the placebo group in each trial.

A wide range of entry criteria was used across stroke studies. Of these, 2 entry criteria appeared most often and were extracted for each study: the maximum age for study entry and the maximum time from stroke onset to study entry (time window). The definition for time of stroke onset varied across studies, ranging from the last time the patient was known to be normal to the first time the patient was found to have neurological abnormalities. The definition for time of study entry also varied across studies and included time to treatment and time to randomization. The minimum time window of 1 hour specified in several trials was not further considered in the present analysis.

A large number of baseline characteristics at study entry were identified. Mean age, mean time from stroke onset to treatment, median National Institutes of Health Stroke Scale (NIHSS) score, and stroke subtype were noted for each study. For the purposes of this analysis, median values were also accepted when mean values were not reported. The definitions for each stroke subtype were determined by the individual studies. As a secondary analysis, the prevalence in placebo group patients was also noted for 8 other baseline characteristics: previous stroke, previous transient ischemic attack, aspirin use, hypertension, diabetes mellitus, coronary artery disease, atrial fibrillation, and tobacco use.

Finally, across the studies, a large number of outcome measures were used. Of these, mortality at 3 months and the percentage of patients with a Barthel Index ≥95 at 3 months were extracted for each study. Data collected at 90 days were not distinguished from data collected at 3 months. A secondary analysis included the mortality rate at 6 months, the percentage of patients with Barthel Index ≥60 at 3 months, and the mean Barthel Index at 3 months. The primary end point used by each trial was also noted.

The bivariate relationships between entry criteria and outcome measures, between baseline characteristics and outcome measures, and between entry criteria and baseline characteristics were evaluated with Spearman rank-order correlation statistic; significance was set at $P<0.05$. We acknowledge that multiple tests may produce an occasional spurious result when there are truly no relationships; however, in the context of this analysis we believe that the consequences of missing an important relationship outweigh those of reporting a spurious one.

Multiple linear regression was used to evaluate multivariate relationships between entry criteria and baseline characteristics in predicting outcome. In addition, because the NIHSS score is known to be a powerful predictor of outcome, entry criteria were used to model NIHSS score. For outcome measures that are proportions (3-month mortality, percentage of patients with Barthel score >95), the arcsine–square root transform was used to stabilize variance. Because studies varied widely in the criteria and outcomes reported, sample sizes available for multiple regression were consistently smaller than the 90 studies surveyed. We considered only regression models in which ≥10 studies reported both dependent and independent variables. Multivariate models were weighted according to placebo group size.

Results

A total of 87 trials that met criteria were identified, published during 1978–2000.11–96 Three of these trials had 2 prespecified placebo subgroups, results for which were reported separately, leading to a total of 90 placebo groups evaluated and 31 919 patients. The trials evaluated a wide range of stroke therapies, including neuroproteictants (29 trials), thrombolytics (15 trials), calcium channel blockers (15 trials), hemodilution (10 trials), anticoagulants (5 trials), and other interventions (16 trials).

Table 1 describes the number of studies reporting each entry criterion, baseline characteristic, and outcome measure for placebo groups. The range of values is also shown, as is the median value for these trial placebo groups.

A broad range of outcome measures was used across the studies (Table 1). As a result, a limited number of studies were available for comparison of each pair of variables. The most common time for assessing clinical outcome was 3 months, followed by 1 month and 6 months after stroke. Several measures were used to assess clinical outcome, including survival, dependence, mobility, infarct volume, cerebral blood flow, as well as the following 12 scales: Barthel Index, NIHSS, Scandinavian Stroke Scale, Toronto Stroke Scale, Canadian Neurological Scale, Glasgow Outcome Scale, modified Rankin Scale, modified Mathew Scale, Orgogozo Scale, Turnhill weighted neurological scale, WHO disability score, and European Stroke Scale.

Bivariate analysis identified several relationships between entry criteria, baseline characteristics, and outcome (Table 2). Across studies performed at many sites in numerous countries across several decades, several variables were powerful predictors of outcome. Entry criteria also predicted placebo group characteristics at study entry. Examples are shown in the Figure. Interestingly, the year of study publication correlated inversely with time window to treatment ($r = -0.47, P < 0.0001$), from a median of 72 hours in 1978 to 9 hours in 2000.

 Few of the baseline characteristics considered in secondary analyses showed a significant relationship with entry criteria or outcome. In addition, none of the entry criteria or baseline characteristics correlated with the 6-month mortality rate, the 3-month median Barthel Index, or the percentage of patients with 3-month Barthel Index ≥60.

In multiple linear regression modeling, weighted by group size, NIHSS score was the single best predictor of observed 3-month mortality, accounting for 91% of the observed variation. Adding mean age further improved the model to account for 95% of the variation in mortality, based on 16 studies reporting all 3 variables. Adding time to treatment instead also improved the model, accounting for 96% of the variation in mortality, based on 12 studies. To summarize, we predict 3-month mortality as follows.

$$M_{\text{obs}} = [\sin(Y)]^2$$

where $Y = 0.049 \times \text{NIHSS} + 0.0048 \times \text{time to treatment} - 0.26$ or $Y = 0.035 \times \text{NIHSS} + 0.011 \times \text{mean age} - 0.76$.

Multivariate modeling did not improve univariate analysis in predicting percentage of patients with Barthel score ≥95. The NIHSS score was well predicted in a model that combined 2 entry criteria. This model accounted for 62% of the observed variation and was based on 11 studies:

$$\text{NIHSS}_{\text{predicted}} = 0.42 \times \text{maximum age} - 0.22 \times \text{time window} - 20.9$$

where maximum age is the age cutoff for study entry (in years) and time window is the maximum time from stroke onset to study entry (in hours).
Discussion

The present study of placebo group patients provides some insight into how entry criteria and patient characteristics influence outcome in acute stroke trials. Previous studies of a single cohort of patients have described a number of predictors of outcome after stroke. Many of these relationships hold true in placebo groups from randomized controlled trials of acute ischemic stroke, despite great variability between trials in the year, site, and conditions of evaluation.

Clinical trials vary widely in the choice of entry criteria. These entry criteria determine which patients are included in the study. Entry criteria also influence patient baseline characteristics, and both influence clinical outcome and thus the likelihood of finding a difference between treatment arms. In particular, enrollment of patients with greater neurological deficits or a smaller proportion of patients with small-artery strokes is associated with higher mortality. Enrollment of younger patients is associated with lower rates of placebo group mortality and disability at 3 months. Patients enrolled many hours after stroke onset have less severe deficits at time of enrollment. Many of these relationships have been established in previous studies examining a single cohort of patients, such as the relationship between early presentation and greater stroke severity, or the influence of age and stroke severity on mortality. The present study confirms the role of these factors in acute stroke trials and furthermore describes the continuum by which these principles are expressed across multiple studies of acute ischemic stroke. Findings are based on data from placebo group patients, but many of the same relationships are likely operative in those patients randomized to active-treatment groups.

Many studies enroll patients whose outcome deviates from studies of historical controls, though the latter may be imperfect for comparison given their own vulnerability to bias. In some instances, enrollment was biased toward patients with better than average outcomes. The mean age of placebo group patients across 77 studies was 68 years. This is somewhat lower than most, but not all, previously published values, typically 73 to 74 years, in population-based studies and stroke data banks. In 8 studies, the mean age was lower, being <64 years; the maximum age for study entry was <80 years in 3 of these studies, while in 4 of these studies no maximum age was used. In 1 study that limited the upper age for study enrollment to 69 years, the mean age of placebo group patients was 58 years. As another example, in
7 studies, the 3-month placebo group mortality rate was <10%, also lower than the value found in most stroke trials and in historical controls. Some stroke studies enroll patients with greater severity of illness. The median value for 6-month mortality rate was 28% among the placebo groups of the 13 studies reporting this measure, with 3 studies having rates >30%. These values are higher than the rates of 21% to 22% reported in unselected historical controls. These variations from historical controls are in part due to choice of entry criteria and study design.

Enrolling patients with a relatively high or low chance of having a good outcome may influence the ability of a study to demonstrate a treatment-related benefit. In some trials, enrolling patients with a poorer prognosis might increase the likelihood of demonstrating a treatment-related benefit. Some successful trials of thrombolytics have enrolled patients with more severe strokes, their median NIHSS scores of 14 to 17 being higher than the value of 12 over all acute stroke studies (Table 1). On the other hand, enrolling patients with a very good prognosis may impede the ability to identify a significant treatment effect. The median value for 3-month Barthel Index among placebo group patients in 10 stroke studies was 67, similar to the value of 69 found in historical controls. In 5 studies, however, the majority of placebo group patients reached a Barthel Index score ≥95. In these studies, identifying a treatment-related effect would be very difficult using this outcome measure. Trials most vulnerable to this effect may be those that enter all patients regardless of stroke subtype, those that use a relatively low age cutoff for study entry, or those with a wide time window.

The results of this study may have value in the design of future trials. The bivariate relationships (Table 2 and Figure) and results of multiple linear regression modeling may be useful for predicting placebo group morbidity and mortality and thus for power calculations. Such predictions may aid in selection of entry criteria as well as target baseline patient characteristics. Studies that include variables most frequently used in previous trials (those with the highest n in Table 1) will best be able to make use of this information. Mortality is a central issue in stroke studies, and its rate correlated strongly with several entry criteria and baseline characteristics. Although 3 disability measures obtained at 3 months after stroke (mean Barthel Index score, percentage of patients with Barthel ≥60, percentage of patients with Barthel ≥95) were used by studies with almost equal frequency (Table 1), only the percentage of patients with Barthel ≥95 correlated with baseline patient characteristics (Table 2). Among the 3, this measure may therefore most reliably reflect differences in clinical status between patients.

Several approaches can be used during study design to ensure that the natural course of enrollees is not so favorable, or unfavorable, as to reduce the likelihood of identifying a possible treatment effect. Stratification, blocking, and other randomization methods can be used to ensure that the proportion of patients with certain characteristics, such as those with small-artery disease or a particular range of NIHSS scores, does not exceed a desired limit. Depending on the drug under study, there may be a need to avoid enrolling a large proportion of patients expected to have a very good outcome, such as those with mild strokes or a young age. In such a case, consideration should be given to setting the

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**TABLE 2. Bivariate Relationships Between Entry Criteria, Baseline Characteristics, and Outcome Measures**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Response</th>
<th>n</th>
<th>r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry criteria predicting outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum age</td>
<td>3-mo mortality</td>
<td>20</td>
<td>0.52</td>
<td>0.018</td>
</tr>
<tr>
<td>Time window (among studies with time window ≤24 hs)</td>
<td>3-mo mortality</td>
<td>35</td>
<td>-0.41</td>
<td>0.014</td>
</tr>
<tr>
<td>Baseline characteristics predicting outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age</td>
<td>3-mo mortality</td>
<td>45</td>
<td>0.49</td>
<td>0.0007</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>3-mo mortality</td>
<td>16</td>
<td>0.89</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% patients with small-artery disease</td>
<td>3-mo mortality</td>
<td>15</td>
<td>-0.80</td>
<td>0.0004</td>
</tr>
<tr>
<td>% patients with large-artery disease</td>
<td>3-mo mortality</td>
<td>6</td>
<td>0.83</td>
<td>0.042</td>
</tr>
<tr>
<td>% patients with coronary artery disease</td>
<td>3-mo mortality</td>
<td>5</td>
<td>0.90</td>
<td>0.0374</td>
</tr>
<tr>
<td>% patients with atrial fibrillation</td>
<td>3-mo mortality</td>
<td>22</td>
<td>0.52</td>
<td>0.014</td>
</tr>
<tr>
<td>% patients using tobacco</td>
<td>% patients with 3-mo Barthel ≥95</td>
<td>7</td>
<td>0.86</td>
<td>0.014</td>
</tr>
<tr>
<td>Entry criteria predicting baseline measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum age</td>
<td>Mean age</td>
<td>30</td>
<td>0.54</td>
<td>0.002</td>
</tr>
<tr>
<td>Time window</td>
<td>Time to treatment</td>
<td>47</td>
<td>0.96</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% patients with hypertension</td>
<td>Baseline NIHSS score</td>
<td>22</td>
<td>-0.54</td>
<td>0.009</td>
</tr>
<tr>
<td>% patients with small-artery disease</td>
<td>22</td>
<td>0.48</td>
<td>0.024</td>
<td></td>
</tr>
</tbody>
</table>

For each row, n is the number of studies reporting both variables; r is Spearman’s ρ. Note that the time window did not correlate significantly (0.05 < P < 0.1) with 3-month mortality when evaluated across all studies, but a significant relationship was found among studies with time window ≤24 hours.
maximum age for study entry to ≥80 years and to using a time window for study entry ≤12 hours. Some studies, such as Stroke Treatment with Acrod (STAT), Prolyse in Acute Cerebral Thromboembolism (PROACT II), and part 2 of the National Institute of Neurological Disorders and Stroke tissue plasminogen activator (tPA) trial, specified a minimum score on neurological testing as an entry criterion to specifically exclude patients with mild neurological deficits. Enrolling a selected population may, however, limit the extent to which results can be generalized to all stroke patients.

Divergent entry criteria and outcome measures have been used during the decades of acute stroke studies. As a result, most of the statistical evaluations described in this report are based on a limited number of comparisons. A wide range of measures was used to assess outcome, including mortality, radiological measures, physiological assessments, and combinations of 12 different neurological scales. Studies also varied widely in choice of entry criteria. The number of different entry criteria and outcome measures used in these trials in part reflects the heterogeneity of the trials reviewed and also highlights the nonuniformity of primary end points in stroke therapeutic trials. This variability limits the ability to make direct comparisons across studies and increases the likelihood of a type I error in the present analyses.
The present analysis of clinical trials, restricted to patients enrolled within 72 hours of stroke onset, confirms the findings of Duncan et al.4 who analyzed a broader set of stroke trials and found a lack of consensus on choice and timing of clinical end points. In the present study a wide range of values was also found for entry criteria and baseline characteristics. Entry criteria, as well as the baseline patient characteristics they predict, are significantly related to clinical outcome when evaluated across multiple stroke trials. These resulting effects on placebo group outcomes may influence the likelihood of demonstrating therapeutic efficacy. The present results provide some insight into how entry criteria and baseline characteristics influence outcome measures in acute stroke trials and may be of utility in the design of future trials.

Acknowledgments
Dr Cramer is supported by grants from the National Institute of Child Health and Human Development and the American Heart Association, Northwest Affiliate (to Dr Cramer).

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Stroke. 2001;32:909-916
doi: 10.1161/01.STR.32.4.909

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