Trends in Acute Ischemic Stroke Trials Through the 20th Century

Chelsea S. Kidwell, MD; David S. Liebeskind, MD; Sidney Starkman, MD; Jeffrey L. Saver, MD

Background and Purpose—The advent of controlled clinical trials revolutionized clinical medicine over the course of the 20th century. The objective of this study was to quantitatively characterize developments in clinical trial methodology over time in the field of acute ischemic stroke.

Methods—All controlled trials targeting acute ischemic stroke with a final report in English were identified through MEDLINE and international trial registries. Data regarding trial design, implementation, and results were extracted. A formal 100-point scale was used to rate trial quality.

Results—A total of 178 controlled acute stroke trials were identified, encompassing 73,949 patients. Eighty-eight trials involved neuroprotective agents, 59 rheological/antithrombotic agents, 26 agents with both neuroprotective and rheological/antithrombotic effects, and 5 a nonpharmacological intervention. Only 3 trials met conventional criteria for a positive outcome. Between the 1950s and 1990s, the number of trials per decade increased from 3 to 99, and mean trial sample size increased from 38 (median, 26) to 661 (median, 113). During 1980–1999, median time window allowed for enrollment decreased per half decade from 48 to 12 hours. Reported pharmaceutical sponsorship increased substantially over time, from 38% before 1970 to 68% in the 1990s. Trial quality improved substantially from a median score of 12 in the 1950s to 72 in the 1990s.

Conclusions—Accelerating trends in acute stroke controlled trials include growth in number, sample size, and quality, and reduction in entry time window. These changes reflect an increased understanding of the pathophysiology of acute stroke, the imperative for treatment initiation within a critical time window, and more sophisticated trial design. (Stroke. 2001;32:1349-1359.)

Key Words: cerebral ischemia ■ clinical trials ■ stroke, acute ■ stroke, ischemic ■ stroke management

The rise of the controlled clinical trial in the last 50 years constitutes a scientific revolution that has reshaped modern medicine as much as contemporaneous discoveries in molecular biology, neuroscience, immunology, and other basic sciences. Clinical trials have a long, even ancient, history.1–3 Lind’s demonstration in 1747 of the beneficial effects of lemons and oranges in treating scurvy among British seamen is perhaps the most well-known precursor of the modern clinical trial. However, viewed from the perspective of the end of the millennium, it may be seen that in number and in sophistication, the controlled clinical trial is primarily a phenomenon, in many ways a defining hallmark, of medical investigation of the second half of the 20th century. The close of the millennium provides a convenient demarcation point. From this vantage, many aspects of the rise of clinical trials may be delineated comprehensively and systematically, including the exponential increase in the number of clinical trials, temporal trends in scientific targets for clinical trial investigation, and progress in the sophistication of clinical trial methodology.

The advent of the controlled clinical trial in medicine is well illustrated by its application in the field of acute ischemic stroke. As the third leading cause of death and the leading cause of adult disability in the United States, stroke is a major public health concern. At the fundamental science level, remarkable advances occurred in the field of cerebrovascular disease in the latter part of the 20th century, including increased understanding of the basic pathophysiology of intricate regulatory systems for vascular hemostasis and cellular energetic homeostasis that are disrupted in ischemia. These advances generated a multitude of promising therapeutic agents for clinical investigators to evaluate. One set of clinical trials led to the widespread acceptance of intravenous tissue plasminogen activator (tPA) as the first proven, effective treatment for acute ischemic stroke.4 In contrast, there has been persistent failure of human trials targeted at neuroprotective agents for acute ischemic stroke.
To characterize general and domain-specific trends in the conduct of controlled clinical trials, we undertook a systematic and comprehensive analysis of treatment trials for acute ischemic stroke. We hypothesized that, over time, significant changes have occurred in clinical trial design characteristics, time windows from symptom onset allowed for enrollment, choice of outcome measures, and overall trial quality. Moreover, we expected that these trends would afford a contextual framework for understanding both the successes and failures of prior trials and for identifying areas of ongoing deficiency.

Methods

Search Strategy

Controlled acute ischemic stroke clinical treatment trials reported in the English language through December 31, 1999, were identified by search of the following sources: MEDLINE database (1966–1999), Ottawa Stroke Trials Registry, Cochrane Controlled Trials Register (CCTR), all published Cochrane Stroke Group reviews, and the reference sections of retrieved articles. The following search strategy was used to search MEDLINE: the terms stroke, acute stroke, cerebral infarct, cerebral infarction, ischemia, and cerebrovascular disease were cross-referenced with the terms trial, randomized, controlled, treatment, anticoagulant, antiplatelet, thrombolytic, fibrinolytic, neuroprotective, and hemorrhoid. The CCTR was searched with the terms stroke, acute stroke, and cerebrovascular disease. The CCTR incorporates MEDLINE 1966–1999, EMBASE 1974–1999, BIOSYS 1969–1999, DERWENT Drug File 1983–1999, SCISEARCH 1974–1999, multiple conference proceedings in the 1980s–1990s, and hand searches of individual journals beginning as early as 1948. Potentially relevant articles cited in bibliographies of retrieved articles were also reviewed back to 1900.

Reports that met the following criteria were included for detailed analysis: (1) study was a controlled clinical trial, (2) study treatment was initiated within 15 days of symptom onset, (3) target disease was ischemic or both ischemic and hemorrhagic, single target stroke mechanism (cardioembolic, lacunar, large-vessel atherosclerosis, or other), randomizedization (yes, no), blinding (none, single, double), control group (placebo, other active agent, or standard care), number of agents tested, minimum and maximum time windows allowed for enrollment, and study phase (2, 2/3, 3, not specified). A trial was categorized as phase 2 if a surrogate outcome measure was used as the primary end point or if any of the following terms were used: pilot, phase 2, exploratory, dose escalation, dose comparison. A trial was categorized as phase 2/3 if the authors stated that the trial was primarily testing both safety and efficacy and was categorized as phase 3 if the authors stated that the trial was primarily testing efficacy or directly stated that the study was a phase 3 trial. Phase 2 trials were further divided into those that were primarily pilot trials with clinical outcome measures, those that primarily involved surrogate outcome measures, and those that were primarily dose-ranging studies.

Outcome data abstracted from each report included the type of outcome measures used (clinical or surrogate), the time point at which the final outcome measures were assessed (measured in days), and whether the study prespecified a single primary outcome measure. Clinical outcome measures were further categorized into nonvalidated versus validated rating scales (eg, National Institutes of Health Stroke Scale [NIHSS], Barthel Index). Rating scales were considered validated if there was published evidence for their validity and reliability.

Classification of Trial Results

For all studies, the following classification scheme was used to record the authors’ final judgment of trial findings regarding drug efficacy: beneficial, trend beneficial, neutral with a subgroup beneficial, neutral, neutral with a subgroup harmful, trend harmful, harmful, or dose escalation/safety/surrogate trial. Author judgment of beneficial was assigned if anywhere in the article, abstract, or text the authors used the words positive, efficacious, beneficial, better than placebo, effective, useful, or similar terms to describe trial results. Author judgment of trend beneficial was assigned if the authors used the words trend positive, encouraging, suggestive, beneficial trend, or like terms. Author judgment of subgroup positive was assigned if the authors explicitly discussed a subgroup finding as positive, showing benefit or efficacy, or significantly better than placebo. Neutral was assigned if the authors concluded that the trial had no net positive or negative effects overall or in subgroup analyses. Harmful, trend harmful, and subgroup harmful were assigned in a manner analogous to the beneficial categories.

All trials were reviewed to identify those that had a positive result by conventional criteria, defined as a trial identifying one primary prespecified efficacy outcome measure and demonstrating a beneficial effect of study treatment on that measure with a reported P value <0.05. Also accepted were trials with >1 primary prespecified outcome measure if (1) statistical criteria for success were prospectively tightened to adjust for testing of >1 hypothesis and (2) results showed a statistically significant beneficial effect of study treatment on a primary end point.

Trial Design and Quality

Trial design and report quality were assessed for all studies excluding abstracts with a 100-point quality scale (higher score represents better quality) adapted specifically for stroke trials from a previously reported treatment trial quality checklist. The scale addresses the following 5 aspects of trial design and reporting: randomization, outcome, inclusion/exclusion criteria, description of therapeutic regimen(s), and statistical analyses. This scale was chosen because, in a previous study, it demonstrated good interrater reliability and good concordant and superior discriminant validity compared with 2 alternative instruments. Additional data abstracted from each report included the dates the study was performed (if provided), year of publication, and how the trial was funded (nonprofit/governmental, pharmaceutical, both nonprofit/governmental and pharmaceutical, not reported).
Data Extraction Reliability and Statistical Methods

Data from each report were abstracted by 1 neurologist-reviewer (either C.S.K. or D.S.L.). Trial quality scale ratings were performed by 3 independent neurologist-reviewers (C.S.K., D.S.L., J.L.S.) on a representative sample of 10 trials. Once analysis of this sample showed good interrater reliability ($r$ ranged from 0.91 to 0.97 between raters), the remaining trials were rated by 1 neurologist-reviewer (C.S.K. or D.S.L.). When a reviewer encountered an ambiguity or difficulty in abstracting data from a report, the study was reviewed by the second reviewer, and joint consensus was achieved.

Because trends over time are best communicated visually, multiple graphs are used to illustrate study findings. For many analyses, inferential statistics are not used because the study encompasses the entire population of relevant trials rather than a representative sample. Quantitative differences over time are instead presented directly. Spearman correlation coefficients were calculated to characterize the degree of change over time for select variables.

**Results**

**General**

A total of 178 controlled clinical trials of acute ischemic stroke, encompassing 73,949 patients, were reported in the English language through December 31, 1999. Two megatrials, the International Stroke Trial (IST) and the Chinese Acute Stroke Trial (CAST), accounted for more than one half of these patients (40,541 patients for the 2 trials combined).13,14 Eighty-eight trials involved neuroprotective agents (24% of patients), 59 rheological/antithrombotic agents (71% of patients), 26 agents with both neuroprotective and rheological/antithrombotic effects (5% of all patients enrolled), and 5 trials tested a nonpharmacological strategy (0.4% of all patients enrolled). Nine studies enrolled patients with both ischemic stroke and intracerebral hemorrhage (intracerebral hemorrhage patients accounted for only 269 of the total 73,949 patients). A total of 75 agents or interventions were tested, including 37 neuroprotective agents, 22 rheological/antithrombotic agents, 12 agents with both neuroprotective and rheological/antithrombotic properties, and 4 nonpharmacological interventions. One hundred forty-seven trials were reported as full-length articles, 12 as brief reports, and 19 in abstract format only. Of the 19 trials reported in abstract format only, 16 were published before 1998.

The total number of trials (Figure 1) and total number of patients enrolled progressively increased over time, with a total of 113 patients enrolled in 3 trials during 1955–1959 and 56,888 patients enrolled in 59 trials during 1995–1999. While growth in the number of trials has been similar for agents with rheological/antithrombotic and neuroprotective mechanisms of action, the total number of patients enrolled in rheological/antithrombotic trials is twice that in neuroprotective trials, primarily because of the 2 recent megatrials, IST and CAST.

Figure 2 delineates shifting trends in neuroprotective trials by subclass, demonstrating a proliferation of antiedema agent trials in the 1970s, modulators of calcium influx in the 1980s and 1990s, and modulators of excitatory amino acids in the 1990s. Overall, modulators of excitatory amino acids, antiedema agents, and modulators of calcium influx were the most common neuroprotective target mechanisms of action. Figure 3 demonstrates the temporal trends of rheological/antithrombotic trials by subclass, indicating the increase in anticoagulant and fibrinolytic trials in the 1980s and 1990s. Table 1 shows the total number of patients enrolled in each class and subclass of trials.

**Trial Design**

Details of overall trial design are provided in Table 2. The proportion of trials that were randomized, double-blind, placebo-controlled, and multicenter steadily increased over time (Figure 4). The proportion of trials designated as phase
2 has increased over the last 20 years. Of the phase 2 trials, 27 were dose escalation/optimization studies, and 16 primarily involved surrogate outcome measures (2 were both dose escalation and surrogate outcome trials combined). Only 3 trials specified a target stroke mechanism (2 embolic, 1 small-vessel lacunar), while 62 trials specified a target stroke territory (including 19 hemispheric/supratentorial, 18 carotid, and 20 middle cerebral artery).

**Trial Sample Size**

For the 178 studies as a whole, the mean sample size per trial was 415 patients (median, 73). If the 2 megatrails, IST and CAST, are excluded, mean sample size was 190 (median, 72). The mean and median sample sizes for the various types of trials (phase 2, 2/3, 3, and not specified) are provided in Table 2. For neuroprotective trials, mean sample size was 186 (median, 69), and for rheologic/antithrombotic trials, mean

---

**Figure 2.** Temporal trends in number of neuroprotective trials by subclass. The overall number of trials increased over time. Trials of antiedema agents predominated in the 1970s, trials of modulators of calcium influx grew in the 1980s and 1990s, and trials of modulators of excitatory amino acids expanded in the 1990s.

**Figure 3.** Temporal trends in number of rheological/antithrombotic trials by subclass. Trials of anticoagulant and fibrinolytic agents increased in number in the 1980s and the 1990s.
The sample size was 656 (183 if IST and CAST are excluded) (median, 71). Trial sample size progressively increased over time from a mean of 38 (median, 26) in the 1950s to a mean of 661 (median, 113) in the 1990s, including IST and CAST. This trend was evident for both rheological/antithrombotic and neuroprotective agents. If only self-designated efficacy trials (phase 2/3 and phase 3) are considered, sample size increased from a mean of 34 (median, 35) in 1975–1979 to a mean of 1820 (median, 561) in 1995–1999.

To place in perspective the statistical power afforded by the sample sizes of reported trials, the following general calculation was performed: the sample size required to demonstrate a clinically relevant 5% absolute reduction in the number of patients dead or disabled at 6 months (reduction from 60% to 55%) with 80% power and $\alpha=0.05$ is 3148, and the sample size required to demonstrate a clinically relevant 10% absolute reduction in the number of patients dead or disabled at 6 months (reduction from 60% to 50%) with 80% power and $\alpha=0.05$ is 816. Compared with these cut points, the sample sizes of reported trials were substantially smaller.

### Table 1. Total Number of Patients Enrolled in Trials by Agent Class*

<table>
<thead>
<tr>
<th>No. of Patients Enrolled</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroprotective agents</td>
<td></td>
</tr>
<tr>
<td>Modulators of excitatory amino acids</td>
<td>6209</td>
</tr>
<tr>
<td>Modulators of calcium influx</td>
<td>5749</td>
</tr>
<tr>
<td>Free radical scavengers</td>
<td>2108</td>
</tr>
<tr>
<td>Promoters of membrane repair</td>
<td>2062</td>
</tr>
<tr>
<td>Antiedema agents</td>
<td>1885</td>
</tr>
<tr>
<td>Metabolic activators</td>
<td>943</td>
</tr>
<tr>
<td>Agents of other or unknown mechanism</td>
<td>799</td>
</tr>
<tr>
<td>Rheological/antithrombotic agents</td>
<td></td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td>41,530</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>22,197</td>
</tr>
<tr>
<td>Agents affecting viscosity/blood flow</td>
<td>7043</td>
</tr>
<tr>
<td>Thrombolytic/fibrinolytic agents</td>
<td>5052</td>
</tr>
</tbody>
</table>

*Trials of agents having both neuroprotective and rheological/antithrombotic mechanisms of action were included in both neuroprotective and rheological/antithrombotic subanalyses. Patients in factorial arm trials were counted under categories of all treatments among which they were randomized.

### Table 2. Aspects of Trial Design

<table>
<thead>
<tr>
<th>No. of Trials (Percent)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>166 (93%)</td>
</tr>
<tr>
<td>Blinding</td>
<td></td>
</tr>
<tr>
<td>Unblinded</td>
<td>46 (26%)</td>
</tr>
<tr>
<td>Single-blinded</td>
<td>6 (3%)</td>
</tr>
<tr>
<td>Double-blinded</td>
<td>126 (71%)</td>
</tr>
<tr>
<td>Placebo-controlled</td>
<td>139 (78%)</td>
</tr>
<tr>
<td>Phase</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>62 (35%)</td>
</tr>
<tr>
<td>2/3</td>
<td>26 (15%)</td>
</tr>
<tr>
<td>3</td>
<td>32 (18%)</td>
</tr>
<tr>
<td>Not specified</td>
<td>60 (34%)</td>
</tr>
<tr>
<td>More than 1 agent tested</td>
<td>24 (13%)</td>
</tr>
<tr>
<td>Center design</td>
<td></td>
</tr>
<tr>
<td>Single-center</td>
<td>93 (52%)</td>
</tr>
<tr>
<td>Multicenter</td>
<td>85 (48%)</td>
</tr>
<tr>
<td>Single target stroke mechanism (e.g., cardioembolic, lacunar, large-vessel atherosclerosis)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Single target vascular territory (e.g., hemispheric, carotid, middle cerebral artery)</td>
<td>62 (35%)</td>
</tr>
</tbody>
</table>

Figure 4. Temporal trends in trial design characteristics including randomization, blinding, trial location (single-center vs multicenter), and use of a placebo control.
points, only 2% of the 118 reported non–phase 2 trials were powered to demonstrate a clinically relevant 5% benefit, and only 7% were powered to demonstrate a more substantial 10% benefit.

**Time Window and Time to Treatment**

Of the 178 trials, 8 studies did not report a maximum time window permitted for patient enrollment but did provide sufficient data to indicate that the enrollment period was considered to be in the acute phase and <15 days from symptom onset. For the remaining 170 trials, the median time window for enrollment was 24 hours (range, 3 to 360 hours). Three trials limited enrollment to patients under 3 hours, 29 trials under 6 hours, 50 trials under 12 hours, and 86 trials under 24 hours. For all trials, the duration of time window allowed for enrollment has shown a progressive decrease over the last 20 years (Figure 5). Seventy-three trials reported average (generally mean) actual time from symptom to enrollment. Trends to decrease in time window and actual time to enrollment were similar for both neuroprotective and rheological/antithrombotic trials. Nevertheless, even in the most recent 1995–1999 epoch, the median time window for neuroprotective trials was 12 hours (range, 4 to 288 hours) (median time to actual treatment, 14.3 hours), and for rheological/antithrombotic trials the median time window was 12.0 hours (range, 3 to 288 hours) (median time to actual treatment, 5.2 hours).

In the 20 trials that identified a minimum time that deficits had to be present before a patient could be enrolled, this period varied from 0.5 to 96 hours (mean, 26.8 hours; median, 24 hours).

**Outcome Measures**

Figure 6 shows the authors’ judgment of trial outcomes, excluding dose escalation and surrogate outcome trials. Thirty-two trials were considered beneficial in the authors’ opinion. However, according to the generally accepted definition of positive (eg, a single prespecified primary outcome measure with \( P \) value <0.05), only 3 trials were positive.15–17 The percentage of trials with beneficial, neutral, and harmful outcomes has not significantly changed over time. None of the 19 trials appearing only in abstract format met our strict criteria for a positive outcome.

For all 178 trials, the latest outcome time point ranged from 2 to 400 days after symptom onset (mean, 85 days; median, 90 days) and increased from 11 days in the 1950s to 90 days from symptom onset in the 1990s. Forty-seven percent of trials reported using at least 1 validated outcome measure,
and this number increased from 0% of trials in the 1950s to 95% in the 1990s.

Quality of Trial Design and Reporting
Trial quality assessed with a formal 100-point scale was generally modest, with a median score of 63 for the 159 full-length reports. However, trial quality steadily increased over time, from a median score of 12 in the 1950s to 72 in the 1990s (Figure 7). Since the Consolidated Standards of Reporting Trials (CONSORT) guidelines for clinical trials were published in 1996, 34 full-length reports of acute stroke clinical trials have been published, 9 of these appearing in journals adhering to CONSORT guidelines and 25 appearing in journals not adhering to CONSORT guidelines. Mean quality score for the 9 articles appearing in CONSORT journals was 88.3, substantially higher than the mean of 71.2 for the 25 articles appearing in non-CONSORT journals.

Sponsorship
Of the 178 trials, some type of pharmaceutical sponsorship was reported in 102, nonprofit/governmental sponsorship was reported in 42 (22 of these had pharmaceutical sponsorship as well), and 56 trials did not report funding sources. The percentage of trials reporting pharmaceutical sponsorship steadily increased over time, from 38% before the 1970s to 68% in the 1990s, while the percentage of trials reporting nonprofit/governmental sponsorship decreased from 36% to 16% for the same time periods. Sixty-six percent (58/88) of neuroprotective trials reported some type of pharmaceutical or commercial sponsorship, compared with 58% (34/59) of rheological/antithrombotic trials, 38% (10/26) of trials of agents with both rheological/antithrombotic and neuroprotective effects, and 0% (0/5) of nonpharmacological trials.

Discussion
General Trends
This systematic analysis of all controlled clinical trials in the field of acute ischemic stroke published in English to the year 2000 documents and quantifies many important aspects of the evolution of clinical trial design in the 20th century. While a few prior reports have described changes over time in individual elements of clinical trial design and reporting, to our knowledge no prior investigation has quantitatively documented the evolution of so broad a range of clinical trial features. Our data provide an overview of both general trends in clinical trial methodology, as reflected in the illustrative condition of acute stroke, and domain-specific developments in trial design dictated by a growing understanding of the underlying pathophysiology of acute cerebral ischemia.

Many trends in our data reflect growing awareness and sophistication of clinical trial methodology. Our data demonstrate a dramatic rise in the number of reported clinical trials and in the total number of patients participating in clinical trials over the course of the last 50 years. When we compare the first and last 5-year intervals with reported trials in our survey (1955–1959 versus 1995–1999), the number of reported acute ischemic stroke clinical trials increased 20-fold,

<table>
<thead>
<tr>
<th>Phase</th>
<th>Mean</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not specified</td>
<td>107</td>
<td>65.5</td>
</tr>
<tr>
<td>Phase 2</td>
<td>91</td>
<td>58</td>
</tr>
<tr>
<td>Phase 2/3</td>
<td>390</td>
<td>325</td>
</tr>
<tr>
<td>Phase 3</td>
<td>1623*</td>
<td>304</td>
</tr>
</tbody>
</table>

*380 excluding IST and CAST.
and the total number of patients enrolled increased 500-fold. This growth reflects advances in basic science yielding ever-increasing numbers of promising agents for clinical testing, growing recognition by the clinical investigative community and regulatory agencies of clinical trials as the gold standard for demonstrating treatment efficacy, and the general remarkable growth in the scale of medical research in the late 20th century.

The substantial growth in trial sample size, particularly for phase 2/3 and phase 3 trials, is noteworthy. Clinical investigators in stroke and other conditions were slow to appreciate the full scope of the problem of type II statistical error (failing to detect a difference between treatments because studies are underpowered). Particularly large sample sizes are required to demonstrate efficacy of agents that provide only a modest benefit. In fact, we calculated that only 2% of the 118 non-phase 2 trials in our analysis were powered to demonstrate a clinically relevant 5% absolute reduction in the number of patients dead or disabled at 6 months, and only 7% were powered to detect a more substantial 10% absolute reduction. The first appearance of “megatrials” in the final years of our data set highlights this observation. The combined results of 2 aspirin megatrials (IST and CAST), enrolling >40,000 patients, were required to demonstrate a very modest benefit from aspirin for acute ischemic stroke. Other agents studied in acute ischemic stroke may also have similar small, but clinically worthwhile, treatment effects that could only be determined by trials of this magnitude.23 Yet, acute stroke clinical trials have generally had sample sizes 100-fold less than those in these 2 megatrials.

We found, in accord with Bath and colleagues,19 steadily progressive improvement in trial quality over time as measured by a formal quality rating scale assessing trial design and reporting. However, our data demonstrate that the quality of acute stroke clinical trial design and reporting remains suboptimal, a finding similar to that in many other fields of medicine.24,25 These persisting deficiencies led to the CONSORT initiative to provide guidelines to improve the quality of reporting of randomized clinical trials.18 We found that more than one half of all trials reported some type of pharmaceutical sponsorship, with the proportion steadily increasing over time. These findings are in accord with those of Dorman and colleagues26; however, we additionally found that the percentage of trials reporting nonprofit/government sponsorship steadily decreased over time. While advantages of pharmaceutical sponsorship include increased funding for both basic science and clinical trial research, disadvantages include potential for bias in agent selection, data analysis and interpretation, and reporting and publication of results.27–29 The growing predominance of pharmaceutical sponsorship, as well as the concomitant decline in the proportion of countervailing nonprofit and governmental support, suggests a greater vulnerability in stroke clinical research to these biases.

We found an increasing trend toward prespecification of a primary end point by which to judge trial success or failure. Yet, only 17% of all trials and 36% of 1995–1999 trials used such a measure. This failure reflects suboptimal understanding of clinical trial methodology and renders interpretation of trial results subject to bias by increasing the risk of a type I statistical error.

**Stroke-Specific Trends**

Perhaps most important of the stroke domain–specific trends in clinical trials that we identified is the decrease in both the time windows permitted for enrollment and the actual time to enrollment. This development reflects fundamental changes in the understanding of the pathophysiology of acute cerebral ischemia during the 20th century, including the concept that the duration of the ischemic penumbra is brief. While disagreement about the optimal time window for enrollment persists,30 a general consensus has emerged that thrombolytic and neuroprotective interventions will only be effective if delivered early after stroke onset, optimally within the first 3 to 6 hours.31–33 Enrollment of patients beyond the critical time window for rescuing salvageable tissue will lead to a dilution of true treatment effects. This more sophisticated understanding of the pathophysiological target of acute stroke therapy is reflected in the decreasing enrollment windows used by clinical trials. It is notable, however, that use of extended enrollment time windows persists. Even in the most recent 1995–1999 epoch, the median permitted entry window in neuroprotective trials was 12 hours, and the median reported time to entry was 14.3 hours.

Our analysis documents the emergence of validated outcome clinical trial rating scales to assess functional end points. Over time, validated scales assessing the degree of neurological deficit, such as the NIHSS, functional activities of daily living, and global disability, have increasingly displaced the poorly specified global judgments or ad hoc scales used by early investigators. Consistent and reproducible scales provide readers with a context for interpretation of clinical results and allow comparison of outcomes across different trials.

Our data also demonstrate an evolution in the times at which final outcome end points have been assessed in acute stroke clinical trials. While initial stroke trials tended to measure treatment efficacy at very early time points (2 to 14 days), later trials tend to have settled on 3 months as the most common outcome time point. This choice optimizes potential for ongoing recovery and neural plasticity within the first months after a stroke, minimizes chances of new or recurrent events that would confound interpretation of effects at very late time points (6 to 12 months), and allows assessment of the performance of the individual in real life, in terms of activities of daily living and independence. Our findings are in accord with and extend those of Duncan and colleagues,34 who analyzed outcome measures in a substantially smaller set of acute stroke trials and did not examine trends over time.

It has been suggested that many acute stroke therapies may only be effective for a particular subtype or mechanism...
because of variations in underlying pathophysiological processes. Rheological/antithrombotic therapies, in particular, may have differential effects on ischemia due to large-vessel atherosclerosis versus cardioembolism versus small-vessel lacunar disease. For example, in the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) trial, no benefit was demonstrated from the low-molecular-weight heparinoid danaparoid, yet a secondary analysis suggested a benefit in patients with large-vessel atherosclerosis. Our analysis, however, suggests that the approach of targeting specific stroke mechanisms has not yet been translated into changes in clinical trial design. We found that only 3 of the 178 trials targeted a specific stroke mechanism.

Our analysis of authors’ opinions of trial outcomes provides one explanation for the large variations in what is considered routine clinical practice in the treatment of acute ischemic stroke. Only tPA and aspirin are accepted by expert panels as proven acute stroke therapies, and there remains some dispute even about these. However, 32 trials from our review were reported by their authors as beneficial, 23 as showing a beneficial trend, and 14 as showing a beneficial outcome in a subgroup of patients. While these trials are not widely accepted as definitive by the stroke research community because of flaws in clinical trial design and small sample size, many have influenced clinical practice to some degree.

The aforementioned observations, taken together, may provide important insights into the success and failure of various acute stroke clinical trials performed to date. For example, our analysis suggests that many trials may have been handicapped in their ability to show agent efficacy because of inadequate sample size, inappropriate time windows permitted for patient enrollment, inappropriate choice of outcome time points, or failure to target a specific stroke mechanism. The success of the National Institute of Neurological Disorders and Stroke (NINDS) trial leading to Food and Drug Administration approval of tPA as the first effective treatment for acute stroke can be attributed, in part, to progress in understanding the pathophysiology of acute cerebral ischemia, combined with a growing appreciation for rigorous clinical trial methodology. Conversely, the persistent failure of trials testing neuroprotective strategies may be attributed, in part, to inappropriate trial design, including inadequate sample size and lengthy time windows allowed for patient enrollment. These observations indicate the crucial and evolving role of appropriate clinical trial design in identifying effective treatments for acute stroke.

In some respects, this systematic review of controlled clinical trials for acute ischemic stroke documents a remarkable record of futility. Of 75 different therapeutic strategies that have been tested in acute stroke clinical trials, only 2 (3%) have been widely accepted as of proven benefit (tPA on the basis of the NINDS trials and aspirin on the basis of the combined results of IST and CAST). While disappointing, nonefficacious trials are of some value. Nonefficacious trials help to identify agents that should not be introduced into or should be used less often in routine clinical practice, protecting patients from expensive and potentially harmful interventions that may have otherwise become established elements of care. Observations in the control arms of nonefficacious trials better delineate the natural history of acute ischemic stroke, allowing iterative improvements in clinical trial design. Analysis of the reasons for failure in nonefficacious trials may provide insights that can be used to generate new avenues for basic research and development of more promising agents. Finally, meta-analysis of several individually nonefficacious trials may sometimes permit identification of subtle beneficial effects of agents.

The generally dismal record of clinical trials in the domain of acute stroke treatment is a departure from the norm in clinical medicine. In a review of 1041 randomized controlled clinical trials for a variety of medical conditions, Chalmers et al found that 55% of reported trials showed a positive result, with a documented $P$ value $<0.05$. This contrasts with 23% of non–phase 2 trials with a positive result in the reporting authors’ opinion and 3% of non–phase 2 trials with a positive result on a prespecified primary end point with a documented $P$ value $<0.05$ among the acute ischemic stroke trials we reviewed. Moreover, the statistical significance of the 3 positive trials must be interpreted with caution given the possibility that 1 in 20 trials will be positive by chance. This analysis suggests that acute ischemic stroke, biologically, may be more refractory to therapy than many other medical conditions. The field of acute stroke provides several formidable challenges, including the narrow time window of viability of the ischemic brain, complex pathophysiological processes that depend on a variety of underlying mechanisms (eg, thromboembolism versus hemodynamic ischemia), and dilemmas in diagnosis (a multitude of clinical presentations and the need to differentiate ischemia from hemorrhage).

Our analysis is limited by several factors. In rating trial quality, good interrater reliability was established at the beginning of the study but not formally rechecked at intervals during data abstraction, raising the possibility of coder drift. The joint working of the reviewers when ambiguous or difficult abstractions arose helped to diminish this possibility. We incorporated only trials with a final report appearing in the English language. Our database therefore underrepresents clinical trial methodology and therapies used in countries less likely to publish their results in English-language journals. In addition, an unknown number of unpublished trials were not included in our analysis. There is a recognized need to gather data from unreported trials because these studies may also provide important lessons to other researchers.

In conclusion, our analysis demonstrated several accelerating trends in acute stroke clinical trial design in the last century, including increased sample size, decreased time windows for enrollment, and improvement in clinical trial methodology/reporting over time. These trends have reflected 2 important themes: (1) emerging understanding of the pathophysiology of cerebral ischemia and the imperative for treatment initiation within a critical time window and (2) increasing awareness of the importance of sound trial design. These findings afford important lessons to clinical trialists in the 21st century, including the need to calculate and recruit adequate sample sizes, the use of appropriate time windows, the importance of rigorous clinical trial design and
reporting, and the need to develop comprehensive registries of all ongoing trials.

Acknowledgments
This work was supported in part by grants K23 NS 02088-01 (Dr Kidwell) and K24 NS 02092-01 (Dr Saver) from the NINDS and a fellowship grant from the National Stroke Association (Dr Liebeskind). The authors thank Barbara Vickrey, MD, MPH, and Stanley Cohen, MD, for thoughtful review of the manuscript. Dr Kidwell has participated as a co-investigator in acute stroke clinical trials sponsored by the following companies: Parke Davis, Baker Norton, Interneuron Pharmaceuticals, Sanofi, Glaxo Wellcome, Upjohn Pharmacria, Boehringer Ingelheim, Astra Zeneca, and Lilly. Dr Saver has participated as a co-investigator in acute stroke clinical trials sponsored by the following companies: Parke Davis, Baker Norton, Interneuron Pharmaceuticals, Sanofi, Glaxo Wellcome, Upjohn Pharmacria, Boehringer Ingelheim, Astra, Lilly, Genentech, Ciba-Geigy, Knoll, and Syntax. Dr Saver has received lecture honoraria or served on the speaker’s bureau for Genentech and Boehringer Ingelheim and has served on the scientific advisory board for the following companies: Boehringer Ingelheim, Astra Zeneca, and Glaxo Wellcome. Dr Starkman has participated as a co-investigator in acute stroke clinical trials sponsored by the following companies: Parke Davis, Interneuron Pharmaceuticals, Glaxo Wellcome, Upjohn Pharmacria, Boehringer Ingelheim, Astra Zeneca, Lilly, Genentech, and ICOS. Dr Starkman has served on the speaker’s bureau for Genentech and has served on the scientific advisory board for the following companies: Parke Davis, Genentech, Astra Zeneca, Upjohn Pharmacria, and Jansen. Dr Liebeskind has participated as a co-investigator in acute stroke clinical trials sponsored by the following companies: Interneuron Pharmaceuticals and Astra Zeneca. A list of all acute ischemic stroke trials included in this study is available upon request. Three supplemental figures have been filed with the National Auxiliary Publication Service, illustrating the following: (1) neuroprotective trials grouped by mechanism of action, displaying the number of trials and authors’ judgments of study results in each category; (2) rheological/antithrombotic trials grouped by mechanism of action, displaying the number of trials and authors’ judgments of study results in each category; and (3) temporal trends in average trial sample size. These are available for a nominal fee by writing to ASIS/NAPS, c/o Burrows Systems, 248 Hempstead Turnpike, West Hempstead, NY 11552-2664.

References


Trends in Acute Ischemic Stroke Trials Through the 20th Century
Chelsea S. Kidwell, David S. Liebeskind, Sidney Starkman and Jeffrey L. Saver

Stroke. 2001;32:1349-1359
doi: 10.1161/01.STR.32.6.1349
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/32/6/1349

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/