Trials of Trials in Acute Ischemic Stroke
The Humana Lecture
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A few years ago, a distinguished colleague and expert in stroke told me, “When we have a treatment for stroke, we will know it” (R. Siekert, personal communication). I agree with this insightful comment, but I also wonder how we will know.

Because stroke is a very complex condition with a number of clinical variables that compound care and influence outcome, it is unlikely that any therapy will produce such a dramatic response that the medical community will accept the benefit of any treatment based only on anecdotal, uncontrolled reports. Thus, a carefully organized experimental and clinical research program is needed to adequately examine any promising therapy for ischemic stroke. During the last three decades, a number of studies have examined the possible usefulness of treatments for stroke, but their results are inconclusive. Unfortunately, some of these studies suffered from problems in design that may, in part, partially explain the negative results. Having been actively involved in the development of several clinical research studies in stroke and having made more than my fair share of mistakes, I wish to share some ideas that might help all of us in our future research endeavors. Some recommendations may be controversial, but they might serve as a springboard for future discussion. These comments supplement previous suggestions, The goal should be to avoid problems in design and conduct that would hamper the trial’s ability to adequately test the intervention.

Recently, Wardlaw and Warlow stated that “Acute stroke treatment research is rejecting compounds thought to have therapeutic response as fast as they can be invented, but with remarkably little good evidence to do so, and this must stop.” I agree but, regretfully, this statement has limitations. The relatively small community of clinical researchers in stroke does not have the resources (money, patients, investigators) to test every drug that might be effective. We should resist testing several drugs that have equivalent mechanisms of action and presumed corresponding usefulness in stroke care. Rather, research should focus on a limited number of compounds that either have special attributes or are representative of a class of drugs that holds the most promise. For example, efforts should be directed at one or two calcium channel blocking drugs or low molecular weight heparins or heparinoids instead of testing several compounds. Our primary goal should be to test the most promising interventions that might improve stroke care, not to meet proprietary interests.

While a randomized clinical trial is the only definitive way to test any intervention for acute ischemic stroke, such an expensive project should not be launched unless there is strong evidence from experimental and pilot clinical studies that there is a reasonable chance for success. The therapy to be tested should make biologic sense. Data from experimental studies should unequivocally positive. The pharmacological and pharmaco-dynamic properties of any drug should be known; the most promising treatments will be those that have an immediate effect. Future trials that examine any therapy aimed at reversing the acute ischemic process will not have the luxury of testing a drug or regimen that may not act for 24 to 48 hours. For example, the lag of up to 48 hours after treatment initiation before the desired reductions in hematocrit were achieved may explain the failure of hypervolemic hemodilution therapy to improve outcomes of patients with acute ischemic stroke.

For an intervention to have widespread clinical applicability, it must be easy to administer and monitor. For example, although intra-arterial infusions of thrombolytic drugs might be useful, it is likely that such treatment will be available to only a limited number of persons with stroke. What is needed is a practical and easy route of administration that can be used by physicians in an emergency room or by emergency medical personnel. A drug that requires a complex regimen, invasive route of administration, sophisticated and special monitoring equipment, or intensive ancillary care will have limited acceptance. Any drug that might be successful in care needs a clear and acceptable margin of safety. A drug that is accompanied by a high risk for major or life-threatening complications such as anaphylaxis, hypotension, serious cardiac arrhythmias, seizures, coma, psychosis, brain edema, or intracranial bleeding may not be widely used by physicians even if it is effective. Such a drug may be efficacious, but it will not be useful.

Issues of safety and possible efficacy are best addressed by pilot clinical studies. They are a critical first step in providing information to justify a large randomized trial. Even though a drug may be safe in healthy young volunteers, its safety profile may differ in a population of elderly, acutely ill persons with stroke.

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The primary emphasis of a pilot study is determination of the frequency and severity of adverse experiences that can be attributed to the drug. The type and severity of observed side effects also facilitate refinement of inclusion and exclusion criteria to be used in the subsequent randomized trial. For example, two hemorrhagic events in the pilot studies of Org 10172 led to changes in two exclusion criteria.6 The upper limit for an acceptable blood pressure was lowered from 140 mm Hg to 130 mm Hg, and patients who had evidence of shift of midline structures on a baseline CT examination were excluded.

Pilot studies can also determine the best regimen, dosage, and duration of therapy. One aim should be to achieve desired therapeutic effects of the drug as rapidly as possible. Thus, issues such as the need for a loading dose and maintenance treatment can be resolved in the pilot study. Establishing the optimal dose is often difficult, as attested by the recent controversies about the ideal dose of aspirin or warfarin to prevent stroke.7,8 Still, a pilot study should determine the dose to be used in the randomized trial. The usual paradigm is a dose-escalation regimen with increasing doses tested among subsequently enrolled patients as safety is demonstrated at lower doses. When side effects begin to occur at an unacceptable rate, the dose is assumed to be too high. The intent is to achieve a dose sufficiently high to ensure that the drug will not miss any dose-related benefit but not so high that dose-related adverse experiences occur at an unacceptable rate. Thus, the "optimal" dose that is selected to be tested in a randomized trial is the largest dose not associated with high rates of adverse effects.

Some pilot studies enroll persons who do not receive active therapy. Such a design avoids comparison with historical controls and also allows monitoring of the vehicle (placebo) for side effects. Thus, a pilot controlled study might give a hint about efficacy. However, most pilot studies are small (fewer than 100 patients), and any differences must be dramatic to provide a trend for efficacy. Conversely, weaknesses are inherent in a controlled pilot study. Actual experience with the active drug is less because a sizeable portion of the patients do not receive treatment. This increases the likelihood of missing uncommon but potentially important side effects. In addition, because of the small size, any data on efficacy may be misleading. Because of the vulnerability of a small controlled trial to the incongruities in patient populations, the data may be falsely positive or negative. In particular, a small pilot study can lead to the conclusion that an intervention is not effective, a scenario that has occurred too frequently. In addition, a small, controlled dose-escalation study, in which very few persons are treated at each level, is susceptible to misleading information about a dose relationship to efficacy. Before investigators commence a small, controlled pilot study, they should review the many pitfalls of this approach. In particular, the data should not be used to determine efficacy or lack of efficacy of the treatment.

K.I.S.S.

If the results of the pilot studies are promising, a definitive trial to test the usefulness of the treatment should be organized. The biggest danger to success is the urge to make the project too elaborate. A large, multicenter randomized trial is inherently complicated, but Candelise11 correctly concluded that simplicity strengthens such a project. Organizers of any trial should resist their own desires to answer every possible question and pressures from sponsors or regulators to create an exceedingly complex trial or to collect a great deal of extraneous information. The more intricate the trial becomes, the more likely there will be mistakes and administrative problems. Investigators should also forego temptations to add spin-off projects. A clinical trial is not the venue to test theories far removed from the primary purpose of the trial. For example, a clinical trial is not the proper forum to validate new diagnostic techniques. Ancillary epidemiological projects should also be avoided because a clinical trial, by its nature, is not completely representative of the universal population of persons with stroke. Only a small fraction of screened patients will subsequently be enrolled. For example, an inclusion criterion that restricts entry to only those persons first encountered within 90 minutes of onset of stroke creates a study population that may differ considerably from persons first seen 24 to 48 hours later.

Unfortunately, clinical trials in stroke often have not described their hypotheses, and readers are left to inferences. The primary hypothesis is the foundation for the entire trial; it should be logical and straightforward. It usually takes the form of a statement such as, "The outcomes of patients treated with conventional medical care and drug X are superior to those of patients treated only with conventional therapy." Although a series of secondary hypotheses and null hypotheses can also be included, the primary hypothesis will be used to calculate the number of patients required to test this postulate (sample size). This calculation is also influenced by the anticipated degree of improvement with treatment and the expected rate of desired outcomes among controls. The trial should recruit an adequate (large) number of patients to avoid statistical errors. Previous trials often have not registered a sufficient number of subjects to avoid a type II (false-negative) error. A large number of patients is also needed to compensate for the diversity of clinical variables, such as the severity or nature of the neurological signs or the etiologies of stroke, that might influence outcome. A large number of patients is also indispensable in order to avoid inconsistencies in baseline characteristics between the two arms. For example, the negative results of one recent small, randomized clinical trial may, in part, be explained by the poorer baseline neurological condition among actively treated patients than among the controls.

To follow the K.I.S.S. ("keep it simple, stupid") dictum, investigators should keep the protocol, treatment regimen, timing of assessments, and data collection forms as clear as possible. Candelise11 rightly concluded that time spent on carefully crafting the protocol will be recouped many times over during the actual conduct of the trial. An operations manual that defines the components of the protocol, treatment regimen, and data collection forms also greatly facilitates conduct of the trial.

Experimental research strongly backs the concept of very early treatment, and modern clinical trials should replicate this approach. A goal of modern stroke care is to shorten or eliminate delays in recognition, transport,
diagnosis, and therapy; a clinical trial should strongly encourage early initiation of treatment. A trial cannot hamper early care by requiring an exhaustive battery of time-consuming baseline tests. Because computed tomography (CT) rapidly eliminates hemorrhage as the cause of stroke, it will be a required baseline test for many trials. However, requiring completion of studies such as arteriography or echocardiography before entry into a trial defeats the goal of early treatment. Ancillary diagnostic studies, if needed, can be performed after treatment has commenced.

By its very nature, a clinical trial cannot enlist patients who represent the entire spectrum of stroke. However, in an attempt to replicate clinical practice as much as possible, it should have broad entry criteria. In general, exclusion criteria should be limited to conditions that contraindicate the use of the study drug. A study that enters a small subset of persons with stroke may have little relevance to clinical practice. For example, restricting enrollment to persons with specific neurological deficits or stroke segregated to one vascular territory greatly limits the utility of a trial’s results. Confining enrollment to only patients with certain subtype of stroke, such as cardioembolism, should also be avoided. It presumes that investigators already know the circumstances in which the treatment does or does not work and it defeats the chief purposes of the trial, which are to test the intervention in stroke and to answer questions about the patients who are most likely to respond.

Entering all patients with stroke, regardless of etiology, best replicates care that patients will likely receive in an emergency room. In addition, categorization of subtypes of ischemic stroke is difficult because clinical features often overlap and imaging is nonspecific.\(^{13,14}\) Excluding a subtype necessitates extensive baseline studies, which will postpone treatment; even when the results of several diagnostic studies are known, physicians often disagree about the most likely etiology.\(^{14}\) As a result, misrandomizations will take place despite the best efforts of the investigators; ineligible patients will inadvertently be entered and eligible patients will be excluded. Overall, the complexity of the trial will be unnecessarily increased and recruitment will be critically hampered because of the uncertainties in subtype diagnosis.

Another problem for investigators is the selection of interventions that can be allowed in conjunction with the study drug. Ancillary care should be as uniform as possible so that differences in outcomes can be attributed to the agent being tested. Provisions for supportive care, rehabilitation, and control of complications should be included in the protocol. Poststroke rehabilitation should be encouraged. Data about auxiliary measures prescribed during the acute treatment and follow-up phases of the study should be recorded. Several medical or surgical measures (aspirin, ticlopidine, warfarin, carotid endarterectomy) are of proven usefulness in preventing stroke among high-risk patients.\(^{7,15,16}\) These therapies, selected on a case-by-case basis, should be administered upon completion of the acute treatment regimen.

Investigators should exercise care in the selection of drugs that are dispensed during the acute treatment period. While no treatment is of proven usefulness in reversing or halting the neurological consequences of acute ischemic stroke, adjunctive use of drugs that are potentially effective should be prohibited. In particular, concomitant use of heparin should be avoided. Trials are presently testing the value of antithrombotic drugs, including heparin, in improving outcome among persons with acute ischemic stroke.\(^{13,20}\) Heparin is of unproven value in improving outcomes or preventing early recurrences in patients with acute stroke, including patients with cardioembolic stroke.\(^{21-23}\) Researchers should resist using the drug to forestall critics ascribing any favorable responses to heparin. Subcutaneous heparin can also be avoided because there are measures, including early mobilization and pneumatic compression devices, that are effective in preventing deep-vein thrombosis or pulmonary embolism. A trial should take advantage of these alternatives to avoid any confusion about the influence of heparin in the rates of favorable outcomes.

Because stroke is a complicated process, it is likely that future treatment will involve a combination of therapies that improve circulation and are cytoprotective. However, researchers should not initially test a “cocktail” of several drugs that each might contribute to improving outcome after stroke. If the combination is beneficial, knowledge about which agent contributes to this effect is lost, and unnecessary and ineffective drugs subsequently may be prescribed to a large population of unsuspecting patients. Conversely, a safe and potentially efficacious drug may be judged incorrectly as not being useful if a concoction of therapies is found to be dangerous. The simple approach of first examining each drug independently before testing a combination of several compounds remains the best.

At present, no therapy is of proven utility in reversing the neurological consequences of acute ischemic stroke. Therefore, patients in the control group should receive placebo; this is the only scientifically and ethically correct approach. An active treatment-controlled trial creates confusion and its results will not conclusively determine whether the new intervention is truly useful or not. There are insufficient data to support any drug as an “active” control. In my experience, physicians are more disinclined by the concept of a placebo-controlled trial than are patients. Physicians must overcome bias and the urge to “do something” by resisting comparison of the intervention to any traditional therapy, including heparin. Once a drug is established as beneficial, clinical trials can move to a non–placebo-controlled design, a sequence that has been successfully used in testing medical intervention to prevent stroke in high-risk patients.\(^{16,18}\)

Blinding to the trial protocol of patients and all treating and rating physicians is a difficult but necessary component of any trial because the results of an unblinded study will immediately be suspect due to concerns about bias. Although a design that includes unblinded treating physicians and a rating physician who is unaware of treatment allocation is necessary in a trial comparing a surgical to a medical therapy, this halfway measure is unacceptable for a trial of a medical intervention. The perception that knowledge of treatment allocation influences adjunctive care or the reporting of complications by physicians managing care greatly weakens the results of a trial. For example, a physician...
in a trial of an antithrombotic drug, such as a low molecular weight heparinoid, may be more worried about the hemorrhagic transformation of an infarction detected by CT in a patient who is receiving the active drug than in a patient who is known to be receiving the control. In such circumstances, the drug may be prematurely and unnecessarily discontinued. There is no way that an independent rater blinded to the trial protocol can compensate for such judgments.

There are several well-described ways to assure blinding of treating personnel. If a parenteral drug is given, a similar appearing placebo likewise can be administered. The same guidelines can be applied to a trial of an oral therapy. To promote patient safety, some drugs will require monitoring levels of the drug or of a biologic response, such as a partial thromboplastin time in a patient receiving heparin. In such circumstances, a trial can enlist a local unblinded “safety” physician, who is otherwise not involved in the care of enrolled patients, to receive the results of any monitoring tests and to recommend adjustments in doses of active therapy. To avoid clues to treatment allocation, the trial would also provide the safety physician with a schedule of “dose adjustments” in randomly selected patients in the control group. This methodology was successfully used in one of the recently completed trials of oral anticoagulants in patients with atrial fibrillation, and it greatly strengthened the trial’s conclusions. The time, expense, and hassle of conducting a truly blinded clinical trial will ultimately pay great dividends in increased credibility. The ongoing Trial of Org 10172 in Acute Stroke Treatment (TOAST) has adapted the methodology described by Ezekowitz et al to its study of the low molecular weight heparinoid in stroke.

**Stroke Scales**

Clinical recovery is the primary way to ascertain a response to treatment; the real goal of patient care is improving the rate of favorable outcomes. Measuring treatment effects using criteria such as differences in the size of brain lesions on CT or the rates of recanalization of arteries are not as medically significant as dissimilarities in obvious responses such as disability or neurological impairment. Physicians and the public primarily want to know whether the drug reduces mortality and improves the quality of life among survivors. This should be the goal of any trial. Because patients spontaneously recover after stroke, any early improvement in the patients’ neurological condition should be sustained and followed by a high rate of favorable outcomes. A short-term dramatic response that is not maintained is not the final measure of efficacy. Assessments should be extended beyond the acute treatment period to permit measurement of any delayed complications of the stroke or treatment. A follow-up examination at 3 to 6 months allows for the effects of the natural recovery after stroke to be incorporated, and this assessment should be the primary outcome determination. For results of the trial to be accurate, this follow-up examination should be performed in all subjects.

Investigators should overcome the inclination to develop a new stroke scale. There are already too many scales, and it is unlikely that any new scale will be significantly better than those already in existence. There are only so many ways to quantify the neurological impairments in persons with stroke. Creating and validating a stroke scale is a time-consuming endeavor that impedes the actual performance of the trial. Because trials involve examinations of patients at several centers, researchers should use scales that are valid and reliable and have good levels of interrater agreement. Any stroke outcome scale should also be immune to influences of gender, age, culture, language, geography, education, social class, or occupation. A good scale is one that is unambiguously and easy to use.

The best scales detect clinically important differences and avoid inflation of minimal changes that are of dubious significance. For example, a two-point difference between groups based on a 100-point scale might be statistically significant and clinically meaningless. The simple categorization of outcomes recommended by van Gijn and Warlow has merit, for these are the real measures of efficacy. The outcome measures developed for the International Stroke Trial differentiate clinically important differences (1, alive and fully recovered; 2, alive and independent but with residual symptoms; 3, alive but dependent; and 4, dead) that can be ascertained by examination or telephone interview. A scale should not combine neurological impairments, disabilities, and epidemiologic variables. The following scales are among the best current measures for recovery from stroke: for global outcome, the Rankin Scale or Glasgow Outcome Scale; for disability, the Barthel Index; and for neurological impairment, the National Institutes of Health Stroke Scale or the Canadian Scale.

**Organization**

A multicenter trial is expensive. A large number of patients will be recruited at several sites scattered across a continent or around the world. A huge amount of data will be generated. Because of the need for meticulous documentation of the administration of the study drug, adverse experiences, and ancillary care, study coordinators are key members of the research team. These individuals, who need to be medically sophisticated, collate the large volumes of required data and assist physician-investigators in the overall conduct of the trial. Preferably, the trial should support full-time coordinators at each center. The trial should also pay for required diagnostic studies and compensate the investigators for their time and effort. Although the fiscal support for each center cannot be lavish, the large number of centers means the overall costs for the trial still will be high.

One way to curb expenditures is to limit the number of centers. Selection of the participating centers is a critical preliminary step. Many physicians have already demonstrated enthusiasm and expertise in clinical stroke research; they are obvious choices for collaboration in future studies. Both academic and private-practice settings can be selected; the most important qualifications are the ability and willingness to enter patients and collect data in an effective and timely manner. Although most trials will use a screening process that documents the center’s ability to recruit an adequate number of patients, many centers have trouble meeting recruitment projections. The trial should work on the following assumptions: (1) centers will actually recruit approximately one third the number of patients.
predicted; (2) approximately one third of the centers will actually reach recruitment goals; and (3) approximately one third of the centers will perform far below expectations. Because the initial selection process is not foolproof, there should be ways to reward prolific centers and to punish nonproductive ones. An effective way to support productivity in recruitment is to fund reimbursement on a per-case basis. Contingency plans to add centers and close problem centers should also be ready. The principal investigator should be aware that some of the disciplinary actions may create bruised feelings among colleagues.

The coordinating center is a critical component because it supervises all the participating centers, oversees changes in the protocol and data collection instruments, and manages interactions with funding sources and regulators. It ensures the trial's integrity and independence. The coordinating center and principal investigator should enroll and treat patients; they should not ask collaborating centers to perform duties that they are not also doing. For example, the principal investigator should be willing to admit patients at 2 AM and to travel some distances to do the follow-up examinations. The support personnel at the coordinating center are also key; they should be available to answer questions, thoughtful, tough when necessary, and thorough in their review of compiled data. Quality-control measures to ensure accuracy of all collected information are also the responsibility of the coordinating center.

Researchers should expect that the time required to actually start the trial will be longer than estimated. The actual time to finalize the protocol; to complete negotiations with participating institutions, regulators, and the pharmaceutical company; and to resolve issues with institutional review boards will be approximately three times that originally predicted. The whole process, which also includes finalizing budgets, obtaining letters of indemnification, and certifying investigators and laboratories, is extraordinarily obtuse. Investigators should persevere because this byzantine administrative process will become more streamlined as the trial progresses.

Conclusions

Any clinical trial is a trial. It is not only a trial of the intervention being tested, it is a trial of the scientific method being applied to the art and inexact science of patient care. It is also a trial of the investigators' ability to design and operate a large clinical research program. In addition, it is a trial of everyone's stamina, patience, and goodwill.

Yet, these are exciting times for clinical research in stroke. A number of promising therapies are being tested, and it is likely that one or more of them will be demonstrated as useful. We should learn from past mistakes and build on past and future successes. Even if the results of a well-designed trial are negative, such a study is important. It may halt research on a treatment that truly is ineffective, and resources can then be directed toward testing other interventions. A well-designed trial also serves as the foundation for future clinical research. Testing exciting and promising treatments through the use of modern clinical trial methods should allow us to soon state, “We have a treatment for acute ischemic stroke and we know it.”

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