The 2005 Feinberg Lecture

NINDS Clinical Trials in Stroke
Lessons Learned and Future Directions

John R. Marler, MD

Abstract—Since 1977 the National Institute of Neurological Disorders and Stroke (NINDS) at the National Institutes of Health (NIH) has sponsored 28 phase 3 trials to evaluate treatments of stroke, which when all completed will have randomized a total of 44,862 patients in the United States and other countries. NINDS stroke clinical trials have been successful in finding beneficial and cost-effective treatments for cerebrovascular disease. Future trials are likely to be larger and have simpler designs which allow for the inclusion of more patients and which collect less data for each patient. In addition, measures of cognitive outcomes, particularly timed tests of executive function, disability scales, and quality-of-life outcomes will become more common. The stroke research community can take pride in the solid base of evidence that has been built over the past 2 decades. If we continue to follow the discoveries of science, continue to create new trial methodology, and increase participation in clinical trials, significant advances in the treatment of cerebrovascular disease will continue. (Stroke. 2007;38:3302-3307.)

Key Words: clinical trials ■ stroke

Since 1977 the National Institute of Neurological Disorders and Stroke (NINDS) at the National Institutes of Health (NIH) has sponsored 28 phase 3 trials to evaluate treatments of stroke, which when all completed will have randomized a total of 44,862 patients (Figure 1). The average number of patients in each trial is 1602. The trials were designed to test drugs, devices, surgery, and behavioral intervention in stroke prevention, acute treatment, and rehabilitation. Trials require months of planning, extensive national and international organization, years of effort from physicians and nurses, and hundreds, even thousands, of patient volunteers, voluminous data reports, and extensive documentation of compliance with governmental regulations. Most trials supported by NINDS are based on proposals from independent investigators that are given high scores during extensive review by independent panels of experts in stroke and clinical trial design. Each trial has established its own network of centers, developed its own data management systems, and had an independent NINDS-appointed data safety monitoring committee. As such, each has been seen by its investigators as a free-standing project. However, for the purposes of this review and from the point of view of the stroke clinical research community, the trials can be placed in sequential groups that reflect an evolution in the methodology or type of clinical problem being addressed. Each trial has also had its own name, usually an acronym. (These acronyms are spelled out in Figure 1, which also contains references to trials that have published their primary results.)

Getting Started: Tackling Difficult Problems
The trial that started it all was the Extracranial-Intracranial (EC/IC) bypass trial, which began in 1977, led by Henry Barnett.1 This 7-year endeavor established that the stroke community could tackle very difficult questions and get answers that would be put into practice. Conventional wisdom at the time of the trial was that restoring blood flow downstream from a completely occluded carotid artery would prevent future strokes. The EC/IC bypass procedure was already being performed by numerous neurosurgeons and recommended by neurologists before it had been evaluated in a clinical trial. The EC/IC bypass trial surprised many by showing that the risk of the procedure was not balanced by any long-term benefit. The conduct of the study set high standards for future trials—particularly in regard to virtually complete follow-up on all randomized patients and inclusion of all randomized patients in the analysis whether or not they received the intended treatment. The trial collected evidence that the EC/IC procedure did increase blood flow as intended; however, this increased blood flow did not reduce the future incidence of stroke.
While the EC/IC trial was finishing up, Peter Safar and Norm Abramson were starting the first of a series of trials in acute intervention to prevent brain injury after cardiac arrest. Based on extensive laboratory testing, the Brain Resuscitation Clinical Trials (BRCT) established principles in the conduct of emergency research, although no effective treatment for global ischemia after cardiac arrest was identified.2–4 Waiver of consent for unconscious cardiac arrest patients was developed initially in these trials as “deferred consent.” These pioneering trials also emphasized emergency intervention on the scene to administer the study drug.

### Three Landmark Positive Trials

Drawing inspiration from the EC/IC trial success, clinical trials sought to resolve other uncertainties about treatments to prevent stroke.

The Asymptomatic Carotid Atherosclerosis Study (ACAS) and North American Carotid Endarterectomy (NASCET) trials studied carotid endarterectomy.5,6 The surprising failure of EC/IC bypass surgery to prevent stroke had increased growing uncertainty about the benefits of carotid endarterectomy, in both symptomatic patients (transient ischemic attack or mild stroke) and asymptomatic patients with no history of stroke symptoms.

An astonishing benefit for endarterectomy in patients with severe (>70%) carotid stenosis lead to an early conclusion of the high stenosis part of the NASCET trial, which continued to evaluate patients with <70% symptomatic stenosis. When completed, patients with symptoms and 50% to 70% stenosis also benefited from carotid endarterectomy. The ACAS trials established conventions for measuring stenosis and national standards for carotid ultrasound. Patients with >60% asymptomatic stenosis had fewer strokes after CEA, a result surprising many, but confirmed by the MRC Asymptomatic Carotid Surgery Trial (ACST).7

At the same time NASCET and ACAS were starting up, Stroke Prevention in Atrial Fibrillation (SPAF) I, the first of 3 NINDS stroke prevention in atrial fibrillation trials, began recruiting patients to compare aspirin or warfarin to placebo in patients with chronic nonvalvular atrial fibrillation.8 At the time neither aspirin nor warfarin was commonly used to prevent stroke in patients with nonvalvular atrial fibrillation. The placebo arm in the first SPAF trial was stopped early when it became evident that both aspirin and warfarin were time neither aspirin nor warfarin was commonly used to prevent stroke in patients with nonvalvular atrial fibrillation. The placebo arm in the first SPAF trial was stopped early when it became evident that both aspirin and warfarin were much better than placebo. Subsequent trials, SPAF II and SPAF III, continued to define the relative benefits from aspirin and warfarin for atrial fibrillation patients with different risk factors.7,8

Following the precedents of the EC/IC trial, NASCET, SPAF, and ACAS attained high rates of complete patient follow-up (>95%). The responsibility to evaluate stroke treatments using clinical trials was reinforced by the demonstration that it was possible and that the results were convincing, and lead to significant improvements in the ability of physicians to prevent stroke.

### Phase 1, 2, Then 3: Use the Right Dose

Several clinical trials were based on dose and safety determination studies done by centers in the NINDS Master

![Figure 1. Major phase 3 clinical trials in stroke 1977 to 2007.](image-url)
Agreement for Cerebrovascular Research. Seven pilot studies of different stroke treatments led to results significant enough to warrant 3 major randomized trials: Nicardipine for Subarachnoid Hemorrhage (NICS AH), Trial of ORG 10172 in Acute Stroke Treatment (TOAST), and NINDS tPA (tissue plasminogen activator). NICS AH tried the calcium-channel blocker nicardipine for prevention of vasospasm after subarachnoid hemorrhage. TOAST continued evaluation of the heparinoid ORG-10172 for use in acute ischemic stroke. Neither of these trials identified a positive treatment effect. However, the third trial, the NINDS tPA Stroke Study, was positive. The NINDS tPA trial demonstrated that tPA was an effective treatment for acute stroke if given within 3 hours of stroke symptom onset.

Many were surprised by the results of these 3 trials. Heparin had been given for years to acute stroke patients, despite minimal evidence to support its effectiveness. The failure of a more selective intravascular anticoagulant to have any significant impact was unexpected. Many hoped a safer form of heparin would work as well or better than standard heparin. With the effectiveness of nimodipine already accepted by many, the benefits of nicardipine were expected to be as much or better. The failure of previous thrombolysis trials led many to doubt that tPA would work in acute stroke. At first, many found it difficult to implement a treatment that required such a major change in the way acute stroke was treated. The success of tPA energized both the clinical and laboratory research communities.

The success of these trials established the importance of doing necessary pilot studies to help select appropriate doses and determine adverse effects while also helping to determine at the same time whether or not a large trial should be done.

**Adaptive Design**

The Randomized Trial of Hirulog in Acute Stroke patients (RANTTAS) trial tested Hirulog, basically an antioxidant, in a creative adaptive trial design that allowed for early stopping of the trial if criteria predicting successful treatment of acute stroke were not met. RANTTAS was stopped early, saving the expense of a large trial.

**Second Wave of Secondary Prevention**

Warfarin-Antiplatelet Recurrent Stroke Study (WARSS),

Women’s Estrogen for Stroke Trial (WEST),

Aspirin and Carotid Endarterectomy (ACE) carefully evaluated aspirin/warfarin, estrogen, and different doses of aspirin for stroke prevention in patients who had a transient ischemic attack or minor stroke.

WARSS was a double-blind trial of warfarin compared with aspirin for secondary prevention of stroke in patients with no apparent cause of their first stroke. Patients with a significant carotid stenosis or atrial fibrillation were not included because best medical therapy had already been determined for them in previous trials. WEST treated postmenopausal females who had a stroke with unopposed estrogen to see whether further strokes could be prevented. ACE compared different doses of aspirin preceding carotid endarterectomy in patients that previously had a minor or transient stroke. None of the trials showed the hoped-for outcome. Despite a great deal of supportive epidemiological evidence, unopposed estrogen failed to prevent stroke and may have actually worsened outcomes in women in the WEST trial. These results were confirmed by other trials of estrogen to treat cardiovascular disease. The ACE trial failed to demonstrate the benefit of higher preoperative doses of aspirin in patients undergoing endarterectomy. This had been predicted in a secondary analysis of data from the NASCET trial. The biggest surprise came from WARSS. This trial showed no benefit over aspirin of the expensive and complex widely practiced regime of oral anticoagulation to prevent a second stroke in patients without atrial fibrillation or severe carotid stenosis. Based on the expected outcomes, these trials were “negative.” However, the WARSS, WEST, and ACE trials had significant impact on medical strategies to reduce the incidence of second strokes. Aspirin is hard to beat.

The WARSS trial advanced stroke trial methodology by developing successful methods to do effective double-blindin trials comparing warfarin to aspirin. WARSS was one of the first trials with separately funded independent ancillary studies. One of them, the PFO in Cryptogenic Stroke Study (PICSS) trial, tested for patent foramen ovale (PFO) in a subgroup of WARSS participants. This ancillary study was a formal and separately funded prospective secondary analysis. The results were that patients with PFO had no more strokes than those without PFO regardless of whether they were treated with aspirin or warfarin. This finding has had a significant impact on the level of evidence being required for acceptance of the efficacy of any device to close a PFO. Antiphospholipid Anitbodies in Stroke Study (APASS) and Hemolytic System Activation Study (HAS) measured antiphospholipid antibodies and prothrombin fragment F1.2.

**New Directions for Stroke Prevention and Treatment**

Some physicians had started to use some treatments because of epidemiological data or a retrospective analysis of data from a previous trial. The NINDS sponsored trials to determine whether these treatments were truly effective. Based on a secondary analysis of industry-sponsored trials of ticlopidine, the African American Antiplatelet Stroke Prevention Study (AAASPS) trial set out to compare ticlopidine to aspirin in blacks. Data from a previous trial suggested that ticlopidine might be more effective than aspirin in blacks compared with other ethnic groups. The Vitamin Intervention for Stroke Prevention (VISP) trial evaluated folate and several B vitamins in patients with recent strokes and high homocysteine levels. Epidemiological evidence from the Framingham and other studies predicted a higher second stroke incidence in these patients. Warfarin versus Aspirin for Symptomatic Intracranial Disease (WASID) compared aspirin to warfarin in stroke patients with intracranial stenosis for prevention of a second stroke. Intraoperative hypothermia during surgery to clip ruptured intracranial aneurysms was evaluated in Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST). Hypothermia had been increasingly used by surgeons despite the lack of clinical trial evidence. The 4 trials all met their recruitment goals and had a high rate
of follow-up but failed to establish new treatment strategies. Important ancillary studies included the availability of blood for genetic analysis from the VISP participants and the successful minority recruitment methods of the AAASPS trial.

Progress in stroke trials continues. Building on the experience gained in prior trials, the stroke community is addressing even more difficult problems.

Secondary Prevention Continues
After the conclusion of the WARSS trial, efforts to find better methods for secondary stroke prevention continued. The ongoing Carotid Revascularization Endarterectomy versus Stenting (CREST), Warfarin versus Aspirin in Reduced Ejection Fraction (WARCEF), Carotid Occlusion Surgery Study (COSS), Secondary Prevention of Small Subcortical Strokes (SPS3), and Insulin Resistance Intervention After Stroke (IRIS) trials are each looking at different secondary prevention measures.

WARCEF is evaluating warfarin versus aspirin to prevent stroke in patients with heart failure. The COSS trial is seeking to determine whether patients with symptomatic carotid occlusion and increased oxygen extraction fraction will benefit from the EC-IC bypass procedure—essentially a repeat of the EC-IC bypass trial on a select subgroup to see whether PET scanning will identify patients who will benefit significantly from the surgical procedure. A pilot trial tested the special PET scanning procedures that it is hoped will identify patients who can benefit from the procedure. Even with the best medical management, patients with symptomatic carotid occlusion remain at very high risk of stroke.

The CREST trial is also a follow-up on previous NINDS trials. CREST is evaluating whether carotid stenting and angioplasty is as good as endarterectomy, previously proven beneficial in the ACAS and NASCET trials. The SPS3 trial is looking at 2 treatments in patients with recent nondisabling lacunar stroke. A large proportion of these patients will be Hispanic because of the association with lacunar stroke and diabetes which is more prevalent in this subpopulation. The treatments are aggressive treatment of blood pressure and clopidogrel added to the standard medical care, aspirin.

IRIS is looking at piaglitazone to prevent a second stroke in patients with evidence of the metabolic syndrome.

The recently started A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA) trial will compare medical care to more invasive procedures in individuals with unruptured brain arteriovenous malformations over 5 years.

Rapid Treatment
Acute ischemic stroke interventions are the target of several ongoing trials. A wide variety of clinical problems are being addressed. The Field Administration of Stroke Therapy-Magnesium (FAST-MAG) trial is testing prehospital administration of magnesium sulfate. Albumin in Acute Stroke (ALIAS) is looking at albumin given acutely to reduce disability. International Stroke Trial (IST)-3 is looking to see whether intraarterial tPA will improve outcomes compared with intravenous tPA in patients who do not initially respond to an intravenous dose.

Rehabilitation
NINDS has funded 3 trials in stroke rehabilitation over the years. Families In Recovery From Stroke Trial (FIRST) compared 2 strategies for improving recovery from stroke.17 Usual poststroke care was compared with usual care plus a psychosocial intervention that engaged families in stroke patient care. Families, not patients, were recruited. No difference in the treatments was identified. The Extremity Constraint Induced Therapy Evaluation (EXCITE) trial was cofunded by the NINDS and the Rehabilitation Medicine Center at the National Institute of Child Health. EXCITE has been completed and reported the effectiveness of constraint therapy in patients in rehabilitation after stroke.22 The recently funded Locomotor Experience Applied Post-Stroke (LEAPS) trial will evaluate weight-supported gait training for patients recovering from stroke.

Discussion
The outcomes of NINDS-sponsored clinical trials have often been surprising, adding new knowledge and influencing important treatment decisions.24 It seems reasonable to assume that more trials will continue to reduce the burden of cerebrovascular disease. However, the research community still struggles to complete trials in a reasonable amount of time and at a reasonable cost. The difficulty will increase in the future. Trials that compare one treatment to an existing effective treatment require larger numbers of participants than placebo-controlled trials. Trials with less restrictive selection criteria will be more likely to change practice. More extensive networks will have a larger number of recruiting sites—hundreds rather than dozens. In addition, more trials will focus on outcomes in every participant. An estimate of brain health in every patient will give a better estimate of the overall effect of a treatment. Cognitive function testing has been limited in most NINDS stroke trials. Future studies are likely to contain short but reliable measures of cognition, particularly measures that assess many domains, particularly executive function. Timed tests of executive function can be performed quickly and reliably in the setting of a clinical trial. A disability rating scale like the Rankin test and a measure of life quality are also likely outcomes to be determined in all participants in future trials. Many NINDS stroke trials have benefited from the participation of Canadian and other international centers. Future trials will be completed more quickly with increased international participation, simplified selection criteria, and outcome assessments in every participant. Expect the stroke clinical research community and attendance at the International Stroke meeting to continue to grow (Figure 2).

After a clinical trial, extensive analysis of the data often yields apparently important differences between subgroups of patients. Often, without further testing, physicians may base treatment decisions on these “retrospective subgroup analyses.” Several NINDS trials tested subgroup analyses from previous trials. The results surprised many by showing that the subgroup analyses were misleading. For example ACE
showed that the higher doses of aspirin were no more effective than lower doses—contrary to what a subgroup analysis of the NASCET trial data had shown. AAASPS was another trial based on a retrospective subgroup analysis of the results from a previous trial. AAASPS data did not find the predicted benefits of ticlopidine for secondary prevention of stroke in blacks.

NINDS stroke clinical trials have been successful in finding beneficial and cost-effective treatments for cerebrovascular disease. Part of this success is due to the often slow and arduous process of peer review. The trials that succeed in this process are often “win-win” trials—important knowledge is gained regardless of the outcome. Not only are the trials showing that some treatments are effective, they are also showing that other treatments, even those used widely for decades, are not effective. Definitely negative clinical trials can have health benefits equal to positive clinical trials. As stroke clinicians have gained experience, the methodology of trials has evolved and the community has learned how to interpret and apply the results. Several of the trials have established methodology that set precedents across trials in all diseases. These new methodologies included those for doing a randomized trial with warfarin (WARSS) and the use of global outcome measures (the NINDS tPA study trials). Peer review also emphasizes the importance of having a scientific basis for the treatments that are tested.

Several NINDS-supported trials have been proposed and led by investigative teams from Canada. Canadian centers have been significant contributors to the majority of NINDS stroke trials. Centers from Europe and Australia have made significant contributions to accrual in many of the trials, including EC/IC, ACAS, NASCET, and WARCEF. Japanese investigators were part of the EC/IC trial. In the future, increased international participation in trials is desirable to speed trial completion and increase the patient population to which the results apply.

In summary, the stroke research community can take pride in the solid base of evidence that has been built over the past 2 decades. If we continue to follow the discoveries of science, continue to create new trial methodology, and increase participation in clinical trials, significant advances in the treatment of cerebrovascular disease are likely. Stroke research can be enjoyable—it provides intellectual stimulation and a creative and energetic community enjoying open discussion and debate as well as the satisfaction of improving the health of millions of people. While clinical trials often require us to challenge long-held practices and theories, they also give us confidence in the information we provide to our patients.

Acknowledgments
I wish to acknowledge Michael D. Walker, MD, who led the NINDS Division of Stroke and Trauma for many of the past 20 years, fellow staff members at NINDS, and the efforts of all the participants, data safety monitoring committee volunteers, and investigators and coordinators who make NINDS clinical trials in stroke possible. Scott Janis, PhD, and Marian Emr and her staff at NINDS helped prepare the slides for the presentation at the AHA in New Orleans, February 4, 2005.

Disclosures
None.

References

Figure 2. Attendance at the International Stroke Meeting 1986 to 2005.


NINDS Clinical Trials in Stroke: Lessons Learned and Future Directions
John R. Marler

*Stroke*. 2007;38:3302-3307; originally published online October 25, 2007;
doi: 10.1161/STROKEAHA.107.485144
*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 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/38/12/3302

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/