NINDS-Sponsored Clinical Trials in Stroke: Past, Present, and Future

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For the past 25 years, the National Institute of Neurological Disorders and Stroke (NINDS) has been encouraging and supporting major multicenter, randomized, controlled clinical trials evaluating medical and surgical interventions to prevent and to treat stroke. More than a score of trials involving more than 20,000 participants have assessed antplatelet agents, anticoagulants, thrombolysis, carotid endarterectomy, hormone replacement, and psychosocial interventions (Figure). Since 1977, the NINDS has spent more than $200 million on clinical trials in stroke, the bulk during the past decade. This large investment of public research dollars is justified by the huge public health burden due to stroke, amounting to billions of dollars yearly in the United States, and the savings in health care dollars garnered to date by the results of NINDS-sponsored clinical trials, which have paid their way and more.

NINDS-sponsored clinical trials are flagship studies in many areas of stroke, influencing treatment decisions daily in clinics throughout the world. When is carotid endarterectomy indicated for patients with cervical carotid stenosis? The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the Asymptomatic Carotid Atherosclerosis Study (ACAS). What antithrombotic therapy should be given to prevent stroke in patients with atrial fibrillation? The Stroke Prevention in Atrial Fibrillation (SPAF) I, II, and III trials. How should thrombolytic therapy be used in acute ischemic stroke? The NINDS rt-PA Stroke Trial.

We are equally proud to have supported definitive “negative” trials that have importantly influenced medical practice by limiting the use of interventions proven to be ineffective. The EC/IC (Extracranial/Intracranial) Bypass trial showed by limiting the use of interventions proven to be ineffective. The EC/IC (Extracranial/Intracranial) Bypass trial showed that anastomosis of the superficial temporal artery to the middle cerebral artery does not reduce subsequent stroke for most patients with occlusion of the carotid artery. This result was a surprise to many and made clear the need to test all major interventions in well-designed randomized clinical trials. This trial answered one specific question and established much of the methodology used in later NINDS-sponsored clinical trials. As successive trials have been done, methodology has been advanced based on the community’s experience. The recently funded Carotid Occlusion Surgery Study (COSS) will take another look at the EC-IC procedure in specially selected patients.

In the 1980s the NINDS established the Master Agreement for Cerebrovascular Research. This program was designed to develop the capability to get appropriate preliminary data necessary for successful peer review of investigator-initiated clinical trial applications. More than 30 centers were prequalified to do stroke research in the program. Although many did not perform NINDS-sponsored studies under the Agreement, many centers became successful participants and leaders in pharmaceutical industry stroke trials. The Master Agreement studies applied phase 1 and phase 2 methodology to the field of stroke. Three NINDS-sponsored clinical trials were a direct result of the pilot studies done under the Master Agreement: the Trial of Org 10172 in Acute Stroke Treatment (TOAST), the Nicardpine for Subarachnoid Hemorrhage (NICSAl) study, and the NINDS rt-PA Stroke Study. NICSAl evaluated the use of nicardpine for the prevention of vasospasm following subarachnoid hemorrhage, and TOAST provided the most serious challenge yet to the routine use of anticoagulation in the treatment of acute stroke.

Later, the Warfarin Aspirin Recurrent Stroke Study (WARSS) would carry the challenge onward in the first NINDS trial using double blinding for oral anticoagulants in the secondary prevention of stroke.

Stroke results from several common and multiple uncommon etiologies, and clinical trials have increasingly and appropriately focused on specific pathophysiologic subtypes: large artery atherosclerosis (NASCET, ACAS, WASID [Warfarin vs Aspirin for Symptomatic Intracranial Disease], EC-IC Bypass, CREST [Carotid Revascularization Endarterectomy vs Stenting Trial]), cardiogenic embolism (SPAF I, II and III, WARCEF), and cryptogenic stroke (WARSS). African-Americans have a particularly high risk of stroke; investigation of optimal antplatelet prophylaxis is ongoing in the African-American Antiplatelet Stroke Prevention Trial (AAASPS), while the WASID trial is testing antithrombotic management of intracranial stenosis, especially common in blacks. The Vitamin Intervention for Stroke Prevention (VISP) trial is evaluating patients with elevated levels of homocyst(e)ine. Pilot studies are under way for evaluation of prevention strategies for other stroke subtypes. The SP3 pilot study is looking at cerebral small artery disease.

NINDS-sponsored clinical trials in stroke have set high standards for scientific design, ethical conduct, study execution, and reporting of results. Attention to inclusion of women and minorities, as well as focus on relevant gender and minority issues in stroke, are salient features. Each trial is overseen by an independent Performance and Safety Monitoring Board whose primary responsibility is to protect the
safety and interests of trial participants. Double-blinding of interventions can be challenging and expensive, but it provides the hardest scientific evidence. With evidence-based effective therapies now available in many situations, future trials must compare new treatments to established therapies (for example, carotid stenting versus endarterectomy in CREST), requiring larger, more complex trials—an ironic measure of our success.

Recently introduced programs include pilot clinical trial grants (see Table), planning grants, allowing investigators to develop the data and the organization, leading to better, more efficient phase III clinical trials. NINDS staff have taken a more active role in working with investigators prior to submission of clinical trial grant applications to identify deficiencies. Clinical trials are but one facet of NINDS-sponsored stroke research activities, which include other clinical and epidemiologic studies and basic research—the underpinnings of trials testing interventions. We are committed to translational research in stroke, bridging basic science and clinical trials (eg, the recent Special Program of Translational Research in Acute Stroke).

New directions are on the horizon. Primary prevention trials involving people at special risk that assess not only stroke prevention but also the cognitive decline that frequently accompanies vascular disease (ie, vascular dementia) must complement efforts at secondary prevention. Large "simple" trials with restricted goals must be balanced with more complicated (and expensive) trial designs that include study of the disease process. Clinical trials have often taken several years to complete recruitment, a situation difficult to justify given the huge numbers of patients with cerebrovascular diseases. A clinical trial investigator network and infrastructure, to include community-based physicians similar to those used successfully in oncology and cardiology, could potentially address this problem. Novel design strategies to make trials more efficient and economical will be encouraged.

The NINDS has also taken on the challenge of educating the public and professionals about the results of NINDS-sponsored trials. Stroke recognition, stroke prevention strategies, and the need for rapid diagnosis and treatment are themes of an increasing public and professional information program led by NINDS and exemplified by NINDS participation in the Brain Attack Coalition.

Stroke clinical trials have an exciting future at NINDS, building on the conspicuous successes of the past 25 years. We invite young investigators and physicians to join the effort and be a part of the next generation of landmark clinical trials aimed at decreasing the neurological burden of cerebrovascular disease.

Pilot Studies in Stroke Currently Funded by NINDS

- Human Albumin Therapy-Treatment of Acute Ischemic Stroke
- Pilot Study of TNK-tPA in Acute Ischemic Stroke
- Angioplasty in Aneurysmal Subarachnoid Hemorrhage
- Secondary Prevention in Small Subcortical Strokes (SPS3)
- Interventional Management of Stroke (IMS) Study
- New MRI Techniques Prior to tPA Therapy After Stroke
- Coronary Artery Bypass Endarterectomy Staging Trial
- Hemicraniectomy for Swelling From Cerebral Infarction

Major clinical trials funded by the National Institute of Neurological Disorders and Stroke. For trials not yet completed, number of patients is projected sample size. The total number of patients randomized in all of these trials will be 34,056 when complete. For years after 2001, the number of funded trials may increase. The EXCITE Trial is funded largely by the National Institute of Child Health and Human Development.
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