

Trial Design and Reporting Standards for Intraarterial Cerebral Thrombolysis for Acute Ischemic Stroke

The Technology Assessment Committees of the American Society of Interventional and Therapeutic Neuroradiology and the Society of Interventional Radiology

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THE National Institutes of Health (NIH) estimates that stroke costs now exceed \$45 billion per year. Stroke is the third leading cause of death, and one of the leading causes of adult disability, in North America, Europe, and Asia. A number of randomized stroke trials and case series have now been reported in the literature to evaluate the safety and efficacy of thrombolytic therapy for the treatment of acute ischemic stroke. These stroke trials have included intravenous (IV) studies, intraarterial (IA) studies, and combinations of both, as well as use of mechanical devices for removal of

thromboemboli and use of neuroprotectant drugs alone or in combination with thrombolytic therapy. At this time, the only therapy demonstrated to improve outcomes in acute stroke is thrombolysis of the clot responsible for the ischemic event.

There is room for improvement in stroke lysis studies. Divergent criteria, with disparate reporting standards and definitions, have made direct comparisons with stroke trials difficult to compare and contrast in terms of overall patient outcomes and efficacy of treatment. There is a need for more uniform definitions of multiple variables such as collateral flow, degree of recanalization, assessment of perfusion, and infarct size.

In addition, there are multiple unanswered questions that require further investigation, particularly questions as to which patients are best treated with thrombolysis. One of the most important predictors of clinical success is time to treatment, with early treatment of less than 3 hours for IV tissue plasminogen activator (tPA) and less than 6 hours for IA thrombolysis demonstrating significant improvement in terms of 90-day clinical outcome and reduced cerebral hemorrhage. It is possible that improved imaging that identifies the ischemic penumbra and distinguishes it from irreversibly infarcted tissue will more accurately select patients for therapy than duration of symptoms would. There are additional problems in the assessment of patients eligible for thrombolysis. These include being

able to predict whether a particular site of occlusion can be successfully revascularized, predict an individual patient's prognosis and outcome after revascularization, and, particularly, predict the development of intracerebral hemorrhage with and without clinical deterioration. It is not clear to assume that achieving immediate flow restoration with thrombolytic therapy implies clinical success and improved outcome. There is no simple correlation between recanalization and observed clinical benefit in all patients with ischemic stroke because other interactive variables such as collateral circulation, the ischemic penumbra, lesion location and extent, time to treatment, and hemorrhagic conversion are all related to outcome.

This paper was written under the auspices of the technology assessment committees of the American Society of Interventional and Therapeutic Neuroradiology and the Society of Interventional Radiology. The purpose of this document is to provide guidance for the ongoing study design for trials of IA cerebral thrombolysis in acute ischemic stroke. It serves as a background for the IA thrombolytic trials in North America and Europe, discusses limitations of thrombolytic therapy, defines predictors for success, and offers the rationale for the different considerations that might be important during the design of a clinical trial for IA thrombolysis in acute stroke. Included in this guidance document are suggestions for uniform reporting standards for such trials.

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These definitions and standards are mainly intended for research trials; however, they should also be helpful in clinical practice and applicable to all publications.

This article serves to standardize reporting terminology and includes pretreatment assessment, neurologic evaluation with use of the NIH Stroke Scale (NIHSS) score, imaging evaluation, occlusion sites, perfusion grades, follow-up imaging studies, and neurologic assessments.

Moreover, previously used and established definitions for patient selection, outcome assessment, and data analysis are provided with some possible variations on specific endpoints. This document is therefore targeted to help an investigator to critically review the scales and scores used previously in stroke trials.

This article seeks to standardize patient selection for treatment based on neurologic condition at presentation, baseline imaging studies, and use of standardized inclusion/exclusion criteria. It defines outcomes from therapy in Phase I, II, and III studies. Statistical approaches are presented for analyzing outcomes from prospective, randomized trials with primary and secondary variable analysis. A discussion on techniques for angiography, IA thrombolysis, anticoagulation, adjuvant therapy, and patient management after therapy is given, as are recommendations for posttreatment evaluation and duration of follow-up and reporting of disability outcomes.

Imaging assessment before and after treatment is given. In the past, non-contrast computed tomography (CT) was used as the initial screening examination of choice to exclude cerebral hemorrhage. However, it is now possible to quantify the volume of early infarction with use of contiguous discrete (nonhelical) images of 5 mm. In

addition, CT angiography by helical scanning and the use of 100 cm³ of IV contrast material can be used expeditiously to obtain excellent depiction of vascular anatomy, define the occlusion site, obtain two- and three-dimensional reformatted vascular images, grade collateral blood flow, and perform tissue perfusion studies to define transit times of a contrast material bolus through specific tissue beds and regions of interest in the brain. Dynamic CT perfusion scans to assess the whole dynamics of a contrast agent transit curve can now be routinely obtained at many hospitals involved in these studies. The rationale, current status of this technology, and potential use in future clinical trials are given.

Many hospitals are also performing magnetic resonance (MR) brain studies at baseline in addition to or instead of CT. MR imaging has a high sensitivity and specificity for the diagnosis of ischemic stroke in the first several hours from symptom onset, identifies arterial occlusions, and characterizes ischemic disease noninvasively. Case series have demonstrated and characterized the early detection of intraparenchymal hemorrhage and subarachnoid hemorrhage by MR imaging. Echo-planar images used for diffusion, and particularly perfusion MR imaging, are inherently sensitive for the susceptibility changes caused by intraparenchymal blood products. Consequently, MR imaging has replaced CT to rule out acute hemorrhage in some centers. The rationale and potential uses of MR imaging are provided.

In addition to established criteria, technology is continuously evolving, and imaging techniques have been introduced that offer new insights into the pathophysiology of acute ischemic stroke. For example, better patient stratification may be possible if CT and/or MR brain scans are not only

used as exclusion criteria, but are also used to provide individual inclusion and exclusion criteria based on tissue physiology. Imaging techniques may also be used as a surrogate outcome measure in future thrombolytic trials. The context of a controlled study is the best environment in which to validate emerging imaging and treatment techniques.

The final section details reporting standards for complications and adverse outcomes, defines serious adverse events, adverse events, and unanticipated adverse events, and describes severity of complications and relationship to treatment groups. Recommendations are made regarding comparing treatment groups, randomization and blinding, intent-to-treat (ITT) analysis, quality-of-life analysis, and efficacy analysis.

This document concludes with an analysis of general costs associated with therapy and a discussion regarding entry criteria, outcomes measurement, and the variability of assessment of the different stroke scales used in the literature.

In summary, this paper serves to provide a more uniform set of criteria for clinical trials and reporting outcomes used in designing stroke trials involving IA thrombolytic agents alone or in combination with other therapies. It is anticipated that, by having a more uniform set of reporting standards, more meaningful analyses of data and literature will be able to be made.

Web Site Feature

The full-length article can be found on the World Wide Web at <http://www.jvir.org>