Trial Design and Reporting Standards for Intra-Arterial Cerebral Thrombolysis for Acute Ischemic Stroke

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Background and Purpose—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 well-designed 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 studies, intra-arterial studies, and combinations of both, as well as use of mechanical devices for removal of thromboemboli and of neuroprotectant drugs, alone or in combination with thrombolytic therapy. At this time, the only therapy demonstrated to improve outcomes from an 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 between 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, in particular, 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 <3 hours for intravenous tissue plasminogen activator and <6 hours for intra-arterial 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. 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 in particular, to predict the development of intracerebral hemorrhage, with and without clinical deterioration. It is not clear to assume that achieving immediate flow restoration due to thrombolytic therapy implies clinical success and improved outcome. There is no simple correlation between recanalization and observed clinical benefit in all ischemic stroke patients, because other interactive variables, such as collateral circulation, the ischemic penumbra, lesion location and extent, time to treatment, and hemorrhagic conversion, are all interrelated to outcome.

Methods—This article was written under the auspices of the Technology Assessment Committees for both 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 of trials of intra-arterial cerebral thrombolysis in acute ischemic stroke. It serves as a background for the intra-arterial 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 intra-arterial thrombolysis in acute stroke. Included in this guidance document are suggestions for uniform reporting standards for such trials. 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 the NIH Stroke Scale score, imaging evaluation, occlusion sites, perfusion grades, follow-up imaging studies, and

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

This article also seeks to standardize patient selection for treatment based on neurologic condition at presentation, baseline imaging studies, and utilization 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 both primary and secondary variable analysis. A discussion on techniques for angiography, intra-arterial thrombolysis, anticoagulation, adjuvant therapy, and patient management after therapy is given, as well as recommendations for posttreatment evaluation, duration of follow-up, and reporting of disability outcomes.

Imaging assessment before and after treatment is given. In the past, noncontrast CT brain scans were used as the initial screening examination of choice to exclude cerebral hemorrhage. However, it is now possible to quantify the volume of early infarct by using contiguous, discrete (nonhelical) images of 5 mm. In addition, CT angiography by helical scanning and 100 mL of intravenous contrast agent can be used expeditiously to obtain excellent vascular anatomy, define the occlusion site, obtain 2D and 3D reformatted vascular images, grade collateral blood flow, and perform tissue-perfusion studies to define transit times of a contrast 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 MR brain studies at baseline in addition to, or instead of, CT scans. MRI 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 pathology noninvasively. Case series have demonstrated and characterized the early detection of intraparenchymal hemorrhage and subarachnoid hemorrhage by MRI. Echo planar images, used for diffusion MRI and, in particular, perfusion MRI are inherently sensitive for the susceptibility changes caused by intraparenchymal blood products. Consequently, MRI has replaced CT to rule out acute hemorrhage in some centers. The rationale and the potential uses of MR scanning 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, a better patient stratification might be possible if CT and/or MRI brain scans are used not only as exclusion criteria but also to provide individual inclusion and exclusion criteria based on tissue physiology. Imaging techniques might also be used as a surrogate outcome measure in future thrombolytic trials. The context of a controlled study is the best environment 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 their relation to treatment groups. Recommendations are made regarding comparing treatment groups, randomization and blinding, intention-to-treat analysis, quality-of-life analysis, and efficacy analysis.

This document concludes with an analysis of general costs associated with therapy, a discussion regarding entry criteria, outcome measures, and the variability of assessment of the different stroke scales currently used in the literature is also featured.

Conclusion—In summary, this article serves to provide a more uniform set of criteria for clinical trials and reporting outcomes used in designing stroke trials involving intra-arterial thrombolytic agents, either alone or in combination with other therapies. It is anticipated that by having a more uniform set of reporting standards, more meaningful analysis of the data and the literature will be able to be achieved.

Key Words: stroke, ischemic ■ thrombolysis ■ trial design