Comments and Opinions

Stroke Treatment Academic Industry Roundtable (STAIR) Recommendations for Maximizing the Use of Intravenous Thrombolytics and Expanding Treatment Options With Intra-arterial and Neuroprotective Therapies

Gregory W. Albers, MD; Larry B. Goldstein, MD; David C. Hess, MD; Lawrence R. Wechsler, MD; Karen L. Furie, MD; Philip B. Gorelick, MD; Patty Hurn, PhD; David S. Liebeskind, MD; Raul G. Nogueira, MD; Jeffrey L. Saver, MD; for the STAIR VII Consortium*

Background and Purpose—The goal of the Stroke Treatment Academic Industry Roundtable (STAIR) meetings is to advance the development of acute and restorative stroke therapies.

Summary of Review—At the STAIR VII recommendations for strategies to maximize the use of intravenous thrombolytics through targeting public education, and the refinement of current treatment exclusion criteria were proposed. Increased utilization of mechanical devices for intra-arterial recanalization can be achieved by obtaining more definitive evidence of efficacy in randomized clinical trials, identification of patient characteristics associated with treatment efficacy, optimization of technical approaches, clarification of effective time windows, and development of approaches to limit complications. Neuroprotective strategies remain viable; recommendations for further study of these agents include an emphasis on rapid administration, consideration of the systemic effects of ischemic stroke, prevention of complications associated with early reperfusion, a focus on agents with multiple mechanisms of action, and consideration of possible interactions between neuroprotective and thrombolytic therapies.

Conclusions—Extending intravenous thrombolysis to a broader patient population, clarifying the risk and benefits of intra-arterial reperfusion therapies, and further development of neuroprotective therapies were the key recommendations from STAIR VII. *(Stroke. 2011;42:2645-2650.)*

Key Words: acute stroke ■ basic science ■ drug trials ■ neuroprotection ■ thrombolysis

The Stroke Treatment Academic Industry Roundtable (STAIR) meetings bring together academic physicians, industry representatives, and regulators to discuss ways to enhance the development of acute and restorative stroke therapies. The first 6 STAIR meetings produced recommendations for the preclinical evaluation of stroke therapies, Phase II and Phase III trial design, enhancing trial implementation and completion, novel approaches for measuring outcome, and regulatory considerations. Despite major advances in the understanding of the pathophysiology of brain ischemia and considerable investment in therapeutic trials, currently only a small fraction of patients with ischemic stroke receive acute treatment. The goals of STAIR VII were to propose strategies to maximize the use of intravenous (IV) thrombolytics and to suggest research priorities for the assessment of mechanical devices and neuroprotective therapies. This report is based on expert opinion distilled from discussions and workshops at the STAIR VII meeting held on September 11 and 12, 2010, in Washington, DC.

Maximizing the Use of IV Tissue-Type Plasminogen Activator Within 4.5 Hours of Symptom Onset

Although the benefit is greatest with the shortest possible symptom onset-to-treatment interval, significant IV tissue-type plasminogen activator (tPA)-related functional improvements are found when the drug is administered up to approximately 4.5 hours after symptom onset. Given the available data, placebo-controlled trials for patients who qualify and can be treated within this timeframe are no longer appropriate. Placebo-controlled trials evaluating the use of thrombolytic agents in patients selected using advanced neuroimaging technologies in later time windows and trials of new thrombolytic strategies compared with IV tPA within 4.5 hours remain viable.
Currently approved by regulatory agencies for administration within 3 hours after symptom onset, scientific statements now endorse treatment of appropriately selected patients with IV tPA up to 4.5 hours after symptom onset.\(^4\) Despite being in routine clinical use since 1996, it has been estimated that IV tPA is given to only approximately 2% to 3% of patients with ischemic stroke in the United States.\(^5\) A variety of strategies may be used to increase the proportions of patients who are treated with IV tPA (Table 1).

Organized stroke care is associated with an increased frequency in the use of IV tPA.\(^6\) Transport to the hospital by emergency medical services and several organizational features of Primary Stroke Centers are linked to higher IV tPA treatment rates.\(^8\) Although the use of IV tPA has increased among patients arriving at academic medical centers within 2 hours of symptom onset, the numbers reaching hospitals within this timeframe has not appreciably changed.\(^7\) Despite ongoing stroke-related educational programs aimed at the general population and at-risk groups, the public’s knowledge of stroke symptoms and the need to call 911 or the local country emergency ambulance number remains poor. Knowledge can be increased with the use of mass media educational campaigns, but such knowledge is not necessarily associated with the intent to call for emergency assistance when symptoms occur.\(^8\) Public education, however, is critical for increasing the demand for services. Additional social–behavioral research is needed to develop a strategy of public education that translates into appropriate action.

Telemedicine (ie, “telestroke”) services have the potential to increase use of IV thrombolytic therapy and were reviewed at the STAIR V meeting.\(^9\) It remains uncertain, however, whether full telemedicine capabilities lead to more frequent use of IV tPA or better outcomes as compared with telephone consultations.\(^10\) Having neuroimaging readily available on central servers can facilitate both emergent and routine consultations.

### Table 1. Optimizing the Use of Intravenous Thrombolysis

- Given the available data, placebo-controlled trials for patients who qualify and can be treated within 4.5 hours of symptom onset are no longer appropriate.
- Organized stroke care is associated with an increased frequency in the use of IV tPA.
- Additional social–behavioral research is needed to develop a strategy of public education that translates into appropriate action.
- Large, international databases in different stroke populations are now available that may permit an assessment of risks associated with currently listed contraindications.
- Elimination of unsubstantiated contraindications might also increase the proportions of potentially treatable patients.
- Telemedicine (ie, “telestroke”) services are 1 way of providing clinical, stroke-related expertise to underserved areas.
- The incorporation of all Primary Stroke Centers into research networks may increase the pool of patients available to be offered participation in clinical trials.
- Financial incentives should be realigned to include the personnel and infrastructural costs associated with the administration of acute reperfusion therapies.

Table 2. Relative Exclusion Characteristics for Patients With Ischemic Stroke Who Could Be Treated With tPA Within 3 Hours From Symptom Onset*  

<table>
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<td>Seizure at onset with postictal residual neurologic impairments and documentation of an appropriate intracranial occlusion on CT or MR angiography</td>
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<td>Recent gastrointestinal or urinary tract hemorrhage (within previous 21 d)</td>
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| tPA indicates tissue-type plasminogen activator; rtPA, recombinant tissue-type plasminogen activator. |  


Recent experience suggests that under some circumstances—with careful consideration and weighing of risk to benefit—patients may receive fibrinolytic therapy despite ≥1 relative contraindications. Consider the risk to benefit of rtPA administration carefully if any of these relative contraindications is present:

- Arrival outside of the treatment-eligible timeframe is the most frequent reason that patients are not given IV tPA, but patients are also excluded for a variety of other reasons based on current guidelines, most commonly because the patient was judged to have had a “mild” stroke or was clinically improving.\(^11\) “Minor” stroke, however, can have a significant impact on a patient’s health status.\(^12\) Some of the exclusions for treatment between 3 and 4.5 hours after onset are based on regulatory requirements rather than clinical data.\(^3\) Thus, data showing that several of the currently listed contraindications to IV tPA administration actually lead to increased treatment risk are lacking and some exclusions from European labeling such as advanced age and the combination of diabetes and prior stroke appear to be unfounded.\(^13\)\(^,\)\(^14\) Additionally, relative contraindications to treatment based on clinical trial exclusion criteria may not be associated with harm.\(^15\) A list of these “relative contraindications” was recently published in an American Heart Association guideline statement (Table 2).

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Large, international databases in different stroke populations are now available that may permit an assessment of risks associated with other currently listed contraindications. Elimination of unsubstantiated contraindications might increase the proportions of potentially treatable patients. Individual treatment decisions need to consider available resources and clinical circumstances. Strategies to amplify the ability of IV tPA to lyse thrombi are being tested in ongoing trials of sonothrombolysis and combination therapies such as IV tPA in addition to hypothermia.

Financial issues also have the potential to negatively impact the use of IV tPA. Patients may not call 911 for emergency hospital transport because of concern about the associated costs. Hospitals must be appropriately staffed and organized to safely and appropriately administer the drug. Addressing issues related to the costs of accessing emergency care and realigning financial incentives to include the personnel and infrastructural costs associated with the administration of acute reperfusion therapies might address this barrier.
Table 3. Priorities for Mechanical Reperfusion Devices

- Definitive evidence of efficacy is lacking and both conventional and novel clinical trial designs are needed to help clarify which patient populations are most likely to benefit from devices cleared through the FDA 510(k) process.
- Clarification of how to select patients who are likely to benefit from reperfusion therapy is essential.
- Advanced neuroimaging techniques have the potential to provide preliminary evidence regarding whether a differential therapeutic response is likely to occur in specific patient subgroups.
- Standardized imaging techniques and parameters to assess core and penumbra are needed.
- The optimal time window for interventional therapy remains uncertain and needs clarification.
- Technical aspects of intra-arterial procedures and periprocedural management need to be explored.
- Reporting safety data and recanalization/reperfusion data in a standardized manner is essential.
- Communication and coordination among investigators, industry, FDA, and CMS during the trial design process is recommended.

FDA indicates Food and Drug Administration; CMS, Centers for Medicare & Medicaid Services.

Extending Treatment Options With Intra-arterial Therapies

Improvement in the clinical outcome of patients with middle cerebral artery occlusions treated with intra-arterial prouroki-nase within 6 hours of symptom onset was demonstrated (PROlyse in Acute Cerebral Thromboembolism [PROACT 2]). Subsequently, devices designed to remove thrombus from intracranial arteries were developed and have received clearance from the FDA based on comparison of recanalization rates with the control group in PROACT 2. Evidence from multiple studies confirms that recanalization is strongly associated with improved outcomes and the faster and more complete the recanalization, the better the outcome for the patient. At present, 2 devices have been cleared by the FDA for removal of thrombus from intracranial arteries. However, the approval pathway for these first-generation devices did not require randomization in their clinical studies. Therefore, prospective, randomized efficacy data are not yet available and guidelines for treatment of acute stroke give intra-arterial therapy a Class B or Level II rating. The latest guidelines from the FDA pertaining to Class II products (510k) demand greater clinical evidence such as randomized comparisons with currently FDA-cleared therapies.

In addition to the need for randomized studies, 1 of the most important issues that must be addressed to move the field of intra-arterial therapy forward is clarification of patient selection criteria to identify those likely to benefit from reperfusion therapy and to exclude those most likely to be harmed (Table 3). Patients with fluctuating or minor symptoms traditionally have been excluded from thrombolysis, yet recent data suggest that these patients may subsequently experience debilitating neurological deficits. Relatively mild deficits at presentation may reflect robust collateral flow with subsequent collateral failure associated with a large vessel occlusion. Further studies are warranted to address revascularization when only minor or fluctuating stroke symptoms are present.

Multimodal CT or MRI, including noninvasive angiography and perfusion imaging, may identify reversibly ischemic brain or penumbra as well as established infarction or ischemic core. However, standardized imaging techniques and parameters to assess core and penumbra are needed. Although many studies emphasize identification of penumbra, some believe that the size of core is the more important parameter. Rather than excluding patients from treatment based on severity of deficit or time from stroke onset, treatment might be best determined by demonstration of a limited area of established infarction.

The maximum time window for intra-arterial therapy remains uncertain. Incorporation of appropriate neuroimaging may shift the emphasis to penumbra or the presence of a small core of infarction rather than a fixed time window. Regardless of the chosen time window for patient selection, the sooner an artery is opened, the greater the potential for benefit. Future studies should incorporate time limits for process issues to increase the probability that reperfusion will result in tissue salvage. Time from door-to-groin puncture, device placement, and deployment should be closely monitored and targeted. Although time for deployment of devices may vary depending on unforeseen factors such as tortuosity of proximal vessels, limiting door-to-groin puncture time to <90 minutes is a reasonable goal in most circumstances.

Technical aspects of interventional procedures may also influence outcome. Retrospective data suggest that conscious sedation is at least as safe and may lead to better outcomes as compared with general anesthesia, but confirmatory studies are needed. Many other aspects of periprocedural management that may influence clinical outcomes remain unexplored. For example, hemodynamic strategies before, during, and after endovascular therapy should be studied because they may directly influence perfusion status in the affected territory. Potential contributors to poor outcomes, including reocclusion, hyperperfusion, and air embolism, should be investigated.

Establishing safety is vital for determining the risk-to-benefit ratio of reperfusion therapy. The incidence of procedural complications, including arterial perforation and dissection, must be documented. Distal embolization is a risk associated with thrombus removal, and the rate of reocclusion is important to document and may vary depending on the device. Hemorrhage definitions should conform to those established in prior trials and hemorrhage rates should be tracked carefully in all interventional trials. Reports should include multiple definitions to allow comparison with previous thrombolytic studies. Separate radiological and clinical definitions should be included. Withdrawal of care should be monitored because it may limit the ability to measure some short- and long-term outcomes, especially among patients with severe stroke deficits.

Future interventional studies should include both a measure of arterial recanalization and reperfusion of the distal arterial territory. The arterial occlusive lesion method for measuring recanalization and the Thrombolysis In Cerebral Infarction classification of reperfusion are recommended.
Clinical outcome at 90 days measured by the modified Rankin Scale allows comparison with known standards from thrombolytic and control groups in previous trials. Earlier time points such as 30 days from stroke onset may reduce variability in outcomes introduced by medical complications unrelated to interventional therapy. The field may benefit from exploration of alternative outcomes, including imaging parameters such as infarct size. The development of comprehensive predictive models that incorporate variables routinely available in current data sets may identify key predictors of outcome and potential avenues for novel therapeutic approaches.

To establish efficacy, it is necessary to perform randomized trials comparing interventional therapy with best medical therapy. For patients within 4.5 hours of symptom onset, the comparison should be with an active therapy of proven efficacy (IV tPA) and randomization to a placebo is not appropriate unless IV tPA is contraindicated. For patients beyond 4.5 hours of symptom onset, the control group should ideally be placebo. However, many major stroke centers currently treat patients with an interventional approach in this time window, and at least some interventionalists may no longer feel that equipoise exists. Most would likely agree that there is equipoise for certain subgroups such as patients with unknown time of onset or relatively late presentation times. Randomization ratios of 2:1 or 3:1 might encourage recruitment as well as increase operator experience with devices; however, study power is related to the size of the smallest treatment group. Currently enrolling trials, including Intervventional Management of Stroke (IMS) III and MR and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE), should be supported and rapidly completed to guide the next generation of interventional stroke trials.

Nonrandomized registries cannot prove efficacy but can supplement randomized trials by contributing data regarding safety and generalizability. Although randomized trials are in progress, patients not entered into the trial should be monitored through a registry mechanism. Consecutive patients should be included in the registry and enrollment should always occur before the procedure rather than after completion of the case.

A balance must be achieved between the scientific goals of investigators and the regulatory requirements of device manufacturers to design a valid study. Industry partners expect a reasonable return on investment in the form of study results that can be used for FDA approval or clearance. Single device trials may be optimal for industry, but a large consortia focused on stroke treatment could test multiple devices in a single clinical trial and provide adequate data for each device for their manufacturers. Cooperation between industry and academia in designing clinical trials is critical and requires communication with government agencies, including the FDA and the Centers for Medicare & Medicaid Services. Lack of coordination between these agencies can cause conflicts between optimal trial design and achievable results. Greater discussion is warranted between all stakeholders in the trial design process to develop efficacy standards that do not lead to clinical trial enrollment barriers or discourage technological innovation.

Table 4. Priorities for Research on Neuroprotective/Adjuvant Therapies

- When designing a trial of neuroprotective strategies, it is important to consider that the time window for acute neuroprotection is brief; treatments will be most effective if delivered before ischemia onset or within the first few hours. However, depending on the mechanism of action, some therapies may be effective for hours to even days.
- A focus on drugs/devices/treatments with multiple mechanisms of action and that target multiple pathways is recommended (eg, hypothermia); multifunctional agents that target the network modules of integrated signaling pathways that subserve stress tolerance (including ischemic tolerance) are attractive options.
- Further development of methods in humans for determining the impact of reperfusion injury as well as therapies to ameliorate these effects is needed.
- Selective cerebral delivery (catheter-based intra-arterial delivery) of neuroprotection agents is a promising strategy to maximize local neuroprotection and minimize systemic toxicity.
- Systems outside of the brain, including the immune and cardiovascular systems, may impact neuroprotective and repair mechanisms and should be considered.
- Selective induction of cerebral hypothermia deserves further study.

Expanding Treatment Options With Neuroprotective/Adjunctive Therapies

The success of hypothermia for global hypoxic/ischemic brain injury both in adults (postcardiac arrest) and children (neonatal asphyxia) suggests that neuroprotection for focal ischemia may be achievable. The failure of “neuroprotection” as a treatment for acute stroke to date may be related to both an imperfect clinical trial design (especially delayed time to treatment) and the choice of agents with insufficient preclinical data to support a rational clinical trial design. When designing neuroprotective trials, it is important to consider that the same time window constraints may exist as for thrombolysis, although some tissue injury mechanisms such as apoptosis and inflammation may allow longer windows for intervention.

In addition, acute neuroprotectives are more likely to slow, rather than permanently avert, the progression of injury in ischemic tissue and therefore might be most effective when given with concomitant reperfusion therapy rather than as standalone interventions (Table 4).

Because cerebral ischemia involves a cascade of injury pathways, it may be preferable to focus on drugs/devices/treatments with multiple mechanisms of action and that target multiple pathways. Historically, the simplest approach is to use a drug with multiple targets. More novel approaches should be evaluated, for example, combinations of single target agents within or across cell death/recovery pathways. Because each agent would need to be tested individually to determine safety and efficacy according to FDA standards, a factorial and/or adaptive design would likely be needed. An approach that takes into account stroke biocomplexity is to target processes within the dynamic network that activate ensembles to promote maintenance of homeostasis under stress. Application of high-throughput systems biology approaches to natural and induced forms of tolerance to ischemia may help to identify control points for such targets.
Given the expansion of the IV tPA time window to 4.5 hours, it will be increasingly difficult to test a neuroprotective agent alone, so most neuroprotective agents will be tested in “combination” with reperfusion therapies, that is, on a background of IV tPA as a standard care. The FDA requires in vitro assays to ensure that the investigational agent does not interfere with the fibrinolytic activity of tPA.

The strategy of delivering neuroprotective therapies before reperfusion treatments to extend penumbra survival is attractive and could potentiate the benefit of early reperfusion therapy and expand the time window for late reperfusion interventions. These agents ideally might be given in the field soon after ischemia onset. Reperfusion injury and no reflow phenomenon are established in animal models. With the further dissemination in practice of IV tPA therapy within 3 hours of symptom onset, the extension of the IV tPA window to 4.5 hours, and the increasing use of endovascular recanalization at even later time points, an increasing population of patients with cerebral ischemia are experiencing early recanalization and exposure to potential reperfusion injury. Further development of methods in humans for determining the impact of reperfusion injury should be pursued.

Selective cerebral delivery of neuroprotection interventions is a promising strategy to maximize local neuroprotection and minimize systemic toxicity. Catheter-based, intra-arterial delivery permits infusion of neuroprotective agents directly into ischemic or recently reperfused fields. Selective cerebral induction of hypothermia has been achieved with cooling helmets in neonates and intranasal cooling systems in humans with global brain ischemia after cardiac arrest. Because time to treatment is the most critical factor in neuroprotection, efforts should be continued to moving clinical trials into the prehospital “field setting.” Prehospital trials in ischemic stroke have developed techniques for prehospital stroke identification, informed consent, deficit severity rating, and pre-encounter randomization. In the first Phase 3 prehospital neuroprotective trial, with >1100 patients enrolled, 73% have had treatment started within the first 60 minutes after stroke symptom onset, the timeframe in which neuroprotection is most effective in animal models. Although current prehospital trials are studying “repurposed” safe drugs, prehospital development programs for more novel agents should be strongly considered. Agents appropriate for prehospital testing should have evidence of safety in preclinical hemorrhagic stroke models, systemic safety, adequate stability for drug storage on the ambulance, and a formulation permitting initial delivery by oral, sublingual, intramuscular, IV bolus, or gravity-controlled IV sets. Organ systems outside of the brain may impact neuroprotective and repair mechanisms.

There is evidence that stroke is a systemic disease that affects the cardiovascular and peripheral immune systems in humans and animals partly through activation of the sympathetic nervous system. For example, experimental stroke is associated with activation of lymphoid organs such as the spleen and thymus with subsequent mobilization of monocytes and B and T lymphocytes to the brain. In addition, transiently inducing ischemia in the limbs may stimulate endogenous neuroprotective systems that protect all body organs, including the brain. There is an opportunity to collaborate with experts in immunology, hematology, and systemic ischemic conditioning to develop improved therapies.

The goals of STAIR VII were to build on the foundation of the previous STAIR recommendations to advance the field of acute stroke research. Both drugs and devices currently play an important role in stroke research. Extending intravenous thrombolysis to a broader patient population, clarifying the risk and benefits of intra-arterial reperfusion therapies, and further development of neuroprotective therapies were identified as priorities. Enhanced communication among academics, regulators, and industry was also strongly endorsed.

**Appendix**


**Acknowledgments**

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