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Stroke Treatment Academic Industry Roundtable Research Priorities in the Assessment of Neurothrombectomy Devices

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Abstract

Background and Purpose—The goal of the Stroke Treatment Academic Industry Roundtable (STAIR) meetings is to advance the development of stroke therapies. At STAIR VIII, consensus recommendations were developed for clinical trial strategies to demonstrate the benefit of endovascular reperfusion therapies for acute ischemic stroke.

Summary of Review—Prospects for success with forthcoming endovascular trials are robust, because new neurothrombectomy devices have superior reperfusion efficacy compared with earlier-generation interventions. Specific recommendations are provided for trial designs in 3 populations: (1) patients undergoing intravenous fibrinolysis, (2) early patients ineligible for or having failed intravenous fibrinolysis, and (3) wake-up and other late-presenting patients. Among intravenous fibrinolysis–eligible patients, key principles are that CT or MRI confirmation of target arterial occlusions should precede randomization; endovascular intervention should be pursued with the greatest rapidity possible; and combined intravenous and neurothrombectomy therapy is more promising than neurothrombectomy alone. Among patients ineligible for or having failed intravenous fibrinolysis, scientific equipoise was affirmed and the need to randomize all eligible patients emphasized. Vessel imaging to confirm occlusion is mandatory, and infarct core and penumbral imaging is desirable in later time windows. Additional STAIR VIII recommendations include approaches to test multiple devices in a single trial, utility weighting of disability end points, and adaptive designs to delineate time and tissue injury thresholds at which benefits from intervention no longer accrue.

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Conclusions—Endovascular research priorities in acute ischemic stroke are to perform trials testing new, highly effective neurothrombectomy devices rapidly deployed in patients confirmed to have target vessel occlusions.

Keywords

endovascular recanalization; ischemic; reperfusion; stroke

The Stroke Treatment Academic Industry Roundtable (STAIR) meetings bring together academic physicians, industry representatives, and regulators biannually to discuss approaches to enhance the development of stroke therapies. The first 7 STAIR meetings produced recommendations for the pre-clinical evaluation of stroke therapies, pilot and pivotal clinical trial design, enhancing trial implementation and completion, novel approaches for measuring outcome, and regulatory considerations. Major advances in understanding the pathophysiology of acute brain ischemia, the use of thrombolytic stroke therapy, and the creation of effective regional systems of acute stroke care have characterized the STAIR era; nonetheless, currently, only a fraction of patients with ischemic stroke receive targeted therapies of proven benefit. The STAIR VIII meeting had 3 goals—to suggest research priorities for (1) the assessment of neurothrombectomy devices, (2) prevention therapy with direct oral anticoagulants, and (3) neuroimaging outcome measures. This report addresses the first goal: research priorities for the assessment of neurothrombectomy devices.

This report is based on expert opinion distilled from discussions and workshops at the STAIR VIII meeting held on March 9 and 10, 2013, in Washington, DC. The meeting occurred at an important juncture in neurothrombectomy research, immediately after the disappointing reports of the failure of the first 3 randomized trials of first-generation neurothrombectomy devices to demonstrate benefit of intervention^{1–3} and the countervailing promising reports of several trials of newer-generation neurothrombectomy devices showing superiority to first-generation interventions.^{4,5}

Three somewhat distinctive candidate populations for neurothrombectomy device treatment exist: (1) patients presenting in the first 3 to 4.5 hours after last known well who are fully eligible for or currently undergoing treatment with intravenous tissue plasminogen activator (IV tPA) according to national guidelines or regulatory approvals; (2) patients presenting in the first 6 to 8 hours after last known well who are ineligible for IV tPA or who have already failed IV tPA; and (3) patients presenting with late strokes, including wake-up strokes, beyond 6 to 8 hours after last known well. Clinical trial designs need to take into account the distinctive character of these patient populations.

Neurothrombectomy Trials in Patients Eligible for or Currently Undergoing IV Fibrinolysis

Although IV tPA is an effective therapy for acute cerebral ischemia due to large artery occlusion, the benefits that it confers do not accrue to all treated patients. In the IV tPA arm of the Interventional Management of Stroke 3 (IMS 3) trial, among patients with presumed

large artery occlusion, only 27% achieved excellent outcome (modified Rankin Scale 0–1) after IV fibrinolytic treatment.¹ Lack of reperfusion efficacy is the chief draw-back of IV tPA (with hemorrhagic transformation risk a real, but less frequent, concern). tPA achieves early recanalization of only \approx 40% of intracranial arterial occlusions, with greatest efficacy for distal arterial occlusions with small clot burdens and least efficiency for proximal intracranial internal carotid obstructions containing large volumes of thrombotic material to digest.^{6–9} Because neurothrombectomy devices are able to achieve much higher recanalization rates, 80% to 95% with newer, stent-retriever devices,^{4,5} endovascular treatment has the potential to substantially improve the clinical yield of reperfusion therapy.¹⁰

The first strategic issue in clinical trial design for neurothrombectomy studies in patients eligible for IV tPA is whether the novel intervention to be tested against the current standard (IV tPA alone) should be neurothrombectomy alone or IV tPA combined with neurothrombectomy. Considerations of the speed of infarct progression and the lack of increased complications from dual therapy risk suggest that combined IV tPA plus neurothrombectomy is likely to be a more efficacious treatment approach than neurothrombectomy alone. Soon after stroke onset, every minute of ischemia, until reperfusion is achieved, brings substantial additional irreversible brain injury.¹¹ Early treatment initiation is associated with markedly better outcomes for both IV tPA and endovascular reperfusion.^{12–14} IV tPA can be initiated sooner than endovascular thrombectomy, as demonstrated in recent randomized trials. In the IMS 3 trial, onset to needle time for IV tPA was 122 minutes, whereas onset to treatment time for endovascular therapy was 249 minutes (2 hours and 7 minutes longer); similarly, in the SYNTHESIS trial, onset to needle time for IV tPA was 165 minutes, whereas onset to treatment time for endovascular therapy was 225 minutes (1 hour longer).^{1,2} Moreover, combining IV tPA with neurothrombectomy does not substantially increase the risk of symptomatic intracerebral hemorrhage or other complications compared with neurothrombectomy alone.^{4,5,15,16} Consequently, adding IV tPA to neurothrombectomy is an attractive option. The combination offers the possibility, albeit by no means certain, of achieving early via the lytic drug, without delaying or increasing the risk of the more definitive endovascular reperfusion intervention.

The absolute imperative to hasten reperfusion dictates several additional constraints on the design of trials performed in patients eligible for or currently receiving IV tPA. In the emergency stroke setting, it is preferable to not delay the start of IV tPA in order to conduct a prolonged research informed consent process. In studies in which all enrolled patients are to receive IV tPA (eg, neurothrombectomy and IV tPA combined versus IV tPA alone), the IV tPA can be started promptly in all patients using standard clinical consent processes. Once it is infusing, a separate research consent for the second therapy stage options can be pursued. In studies that require some patients to forego IV tPA (eg, head-to-head neurothrombectomy versus IV tPA), novel approaches to consent are required. Options include using exception from informed consent in emergency circumstances,¹⁷ prearrival consent obtained in the ambulance,^{18,19} or short form consent on arrival in the emergency department.¹⁹

An additional consequence of the tremendous time urgency in acute brain ischemia is that neurothrombectomy interventions should be pursued with the greatest rapidity possible. Trialists should monitor key procedure time intervals, including emergency department arrival to brain imaging (door to imaging), brain imaging to arterial puncture (imaging to puncture, or picture to puncture), arterial puncture to microcatheter at the target thrombus (puncture to clot), and arrival at thrombus to achievement of reperfusion (clot to reperfusion).^{20,21} Feedback about site performance and quality improvement programs should be put in place to reduce door to reperfusion time to be as short as possible. In trials that test combined IV tPA and neurothrombectomy, the start of endovascular intervention should not be delayed. The combined therapy should not be handicapped by a requirement that the endovascular procedure be delayed until some arbitrary definition of IV tPA failure has been reached. Moving the patient to angiography, shaving and sterilizing the puncture site, placement of a bladder catheter, placement of arterial sheath, performance of diagnostic injection of the target vessel, navigation of neurothrombectomy device to the target lesion, and retrieval, aspiration, or other endovascular intervention should optimally take place while IV tPA is still running. Continued presence of clot by the time the target artery is accessed by the microcatheter is adequate demonstration of fibrinolytic failure. More importantly, the intervention being tested is not IV tPA with delayed neurothrombectomy rescue, but rather IV tPA and neurothrombectomy combined as the upfront, initial strategy. A policy of conscious sedation by default, with general anesthesia reserved for special circumstances, is likely to foster better outcomes than a policy of general anesthesia for all cases, because general anesthesia delays the start of the procedure and has also been associated with hypotension and less favorable outcomes in multiple series.^{22,23}

Using imaging to improve patient selection is a critical need for neurothrombectomy trials in IV tPA-eligible patients. Using stroke deficit severity alone to identify patients who are likely to harbor large artery occlusions was unavoidable in the past because multimodal imaging was not widely available, but resulted in enrollment of heterogeneous patient populations, with occlusions at diverse locations and some with no large artery occlusions at all.^{1,2} At minimum, all patients should undergo CT angiography or MR angiography to confirm the presence of large artery occlusion. Often, it is appropriate to restrict entry criteria to just anterior circulation or just posterior circulation occlusions so as to increase population homogeneity. An additional option will be to include only patients with vessel imaging showing occlusions likely to not be responsive to IV tPA. For example, a trial may enroll only more proximal occlusions, such as intracranial internal carotid artery and M1 middle cerebral artery stem lesions, and exclude more distal M2 middle cerebral artery lesions, or only enroll the subset of M1 middle cerebral artery lesions with substantial clot length visualized on thin-section noncontrast CT.⁸ By excluding patients with higher response rate to IV tPA from the trial, these vessel selection strategies ensure that enrolled patients will be informed regarding the benefits of neurothrombectomy, but these increase trial complexity and reduce trial generalizability.

The benefit of using sophisticated parenchymal imaging to select subjects among patients undergoing IV tPA therapy is uncertain. Advanced imaging always entails an information-tissue tradeoff. More time is needed to acquire and process advanced penumbral imaging: Is the value of information gained worth the tissue lost to infarct progression during this

interval? In the very early time window after onset, preliminary data suggest that only $\approx 10\%$ of tPA-eligible patients will have an unfavorable penumbral pattern.²⁴ Therefore, among patients being imaged within the first 3 hours after last known well, a vast majority of patients harboring a large artery occlusion on vessel imaging will have a favorable penumbral profile and could proceed directly to randomization without need for additional imaging analyses. Imaging advances, such as more rapid acquisition and automated processing of perfusion scans, have the potential to limit the time required for penumbral imaging to an additional 10 to 15 minutes, provided advanced imaging is performed concurrently and using the same modality (CT or MR), as routine pretreatment imaging.

Neurothrombectomy Trials in Early Patients Ineligible for or Having Failed IV Fibrinolysis

The population presenting within 6 to 8 hours after onset and not eligible for or having failed IV tPA comprises 3 distinct subgroups: (1) patients presenting before 8 hours but beyond the 3- to 4.5-hour treatment window (2–3.5-hour emergency department arrival) for IV tPA; (2) patients presenting within the first 3 to 4.5 hours with a contraindication to IV tPA but not to endovascular therapy (such as being on warfarin with a therapeutic international normalized ratio); and (3) patients with vascular occlusion visualized on CT angiography or MR angiography or transcranial Doppler imaging >1 hour after start of IV tPA—typically drip-and-ship patients arriving at an endovascular facility after receiving IV tPA at a frontline hospital. Collectively, these patients account for a substantial proportion of patients seen at tertiary academic medical centers. For example, in 2 recent endovascular trials, patients ineligible for IV tPA accounted for 47% to 53% of enrollees.^{4,5}

In the past, reluctance to randomize these patients slowed their enrollment in randomized trials with a medical therapy control arm. For patients ineligible for IV tPA, control medical therapy generally consisted of aspirin and supportive medical care without any active reperfusion intervention, and stroke physicians, especially interventionalists, were reluctant to have patients have no chance at vessel reopening. The randomized trial evidence favoring vessel reopening in these patients is modest, not definitive, and arises from studies of intra-arterial administration of fibrinolysis, not mechanical thrombectomy. The evidence base includes a single positive trial of intra-arterial administration of prourokinase, an agent not available for clinical use, which was judged insufficiently convincing by regulatory agencies for drug approval,²⁵ and supportive data from several other smaller trials, none individually positive.²⁶ In the face of this suggestive, but not definitive, evidence, community equipoise with regard to benefit of neurothrombectomy in IV tPA–ineligible or –failed patients clearly existed, but personal equipoise was often lacking. Although the recent negative randomized controlled trials of neurothrombectomy were performed largely in IV tPA–eligible patients, the neutral results have increased personal equipoise among stroke physicians. Performance and timely completion of a large, pivotal randomized trial in the IV tPA–ineligible or –failed patient population is now viewed both as entirely ethical and as much more feasible.²⁷

Vessel imaging, and core and penumbral imaging potentially, is certainly important in trials of neurothrombectomy among ineligible/failed IV tPA patients. Vessel imaging is needed to confirm an appropriate large artery occlusion target for endovascular therapy. In this patient

population, more distal and lower clot burden occlusions can still be included, in addition to more proximal occlusions, as long as the vessel is accessible by the device(s) under study, given that the target lesion will not be treated with, or has already failed to respond to, IV tPA.

Penumbral imaging should be helpful because, among patients presenting after 3 but before 8 hours, a substantial proportion, perhaps 20% to 40%, will have already completed their infarct or have a malignant infarct pattern and be unlikely to benefit from reperfusion, as demonstrated in Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) 1 and 2, and Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) studies.^{28–30} Caution regarding use of penumbral selection is suggested by the failure of the MR and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) pilot trial to show a differential benefit of endovascular intervention among favorable penumbral pattern patients.³ The MR RESCUE trial results provide an important reminder that observations comparing recanalizers and nonrecanalizers in single-arm intervention studies detect association, not causation, and are subject to the confound that patients more likely to recanalize may also be the patients more likely to do well whether they recanalize or not. However, MR RESCUE is by no means definitive, given its small sample size, large core lesions at baseline, and modest rate of substantial recanalization achieved with endovascular therapy. An alternative to full-scale penumbral imaging is core imaging. Instead of seeking to define both the already established core infarction and the still-at-risk penumbral tissue, this strategy seeks only to delineate the size of the core. The great preponderance of <8-hour patients with small to moderate cores and substantial neurological deficits (clinical mismatch), or small to moderate cores and large artery occlusions (vessel mismatch), harbor substantial penumbral tissue and may benefit from intervention. Core imaging can be performed using simple CT and MR acquisitions (noncontrast CT or CT angiography source images with Alberta Stroke Program Early CT score [ASPECTS]; diffusion MRI) or abbreviated perfusion CT imaging analysis. CT angiography source imaging and perfusion CT imaging for core infarct delineation are technique dependent, and require further standardization and investigation for optimal use.^{31,32}

Neurothrombectomy Trials in Wake-Up and Other Late-Presenting Patients

Patients presenting after 6 to 8 hours and within 12 to 24 hours of last known well, including those who woke up from sleep with a new deficit, constitute an attractive target population for randomized trials of neurothrombectomy. Clinical equipoise regarding potential benefit of neurothrombectomy in these patients is well established because pivotal registration trials of neurothrombectomy devices did not include >8-hour patients, and no randomized trial of any recanalization intervention has shown benefit at this late time point. Besides vessel imaging to confirm large artery occlusion, full-scale penumbral imaging is desirable for patient selection in the 8-to-24-hour timeframe, given the high proportion of patients with already completed infarcts.

Additional Priorities in Endovascular Trial Design

In addition to the broad frameworks discussed above, several other priorities and developments in endovascular trial design are noteworthy.

It is attractive to test >1 device in a single trial. Promising devices are legion. However, endovascular stroke trials are expensive and time-consuming; the number of sites with extensive interventionalist experience is limited; and achievable throughput of stroke patients in stroke trials is quite modest. As a result, stroke trialists cannot interrogate the universe of promising devices for cerebral reperfusion nearly as rapidly or efficiently as cardiac trialists can for cardiac reperfusion. Accordingly, it is desirable that the industry and governmental sponsors and clinical trialists avoid mounting several competing trials of individual devices, each slow to enroll, if a single trial of multiple devices could be performed more efficiently. However, multiple device trials create challenges for regulators, because device-specific data may be underpowered to confirm efficacy and safety although combined device data in total may demonstrate benefit.

Rigorous approaches to evaluating device-specific performance in multidevice trials need to be developed. The simplest technique is a shared control group.³³ For example, patients could be randomized among 4 arms (eg, device A, device B, device C, and medical control) in a single trial, rather than among 2 arms in 3 separate trials (device A versus control, device B versus control, device C versus control). The 4 arm–1 trial approach would reduce overall sample size by 33% compared with the 2 arm–3 trial approach, reducing costs for study sponsors and early trial completion. Another more complex approach is to have patients randomized between a control medical arm and an endovascular interventional arm in which the proceduralist could select from among 2 alternative devices. Approval of each device in the trial would be based on: (1) overall benefit of the general device arm versus medical therapy, and (2) consistency of effect of each study device with the effect seen in the entire trial. Statistical criteria for regulatory approval would be set at trial start for the minimum proportion of cases in which a device would need to be used for demonstration of absence of heterogeneity of its safety and efficacy performance compared with the overall trial. Though challenging, collaboration among competing industry sponsors, academic investigators, and regulatory agencies to define these criteria is desirable to advance patient care.

Reimbursement of endovascular procedures in clinical practice has complex effects on performance of clinical trials. The availability of reimbursement promotes hospital investment in the capital and labor infrastructure needed to perform endovascular therapy and attainment and maintenance of expertise by interventionalists. It also permits costs of interventions in the neurothrombectomy arm of trials to be covered by clinical revenues as a conventional care option rather than requiring coverage by research funds. However, clinical reimbursement also provides a financial incentive to treat patients outside of randomized trials, rather than enroll them in a trial with a control medical arm. In the wake of neutral results of randomized trials of first-generation devices, some payers are beginning to restrict clinical reimbursement for neurothrombectomy procedures. Retaining reimbursement at least for patients enrolled in a randomized trial would be an optimal approach for payers to

proceed to rapidly determine the most cost-effective treatment option for acute ischemic stroke patients. In addition, there is a consensus among STAIR clinicians that it would be ethically problematic to not have endovascular therapy available and reimbursed for <3-hour patients who are ineligible for IV tPA.³⁴ The SYNTHESIS trial showed that endovascular thrombectomy yielded similar outcomes as IV tPA in this time window, suggesting indirectly that endovascular thrombectomy is better than supportive care in tPA-ineligible patients < 3 hours of onset.²

With regard to clinical end point analysis in neurothrombectomy acute stroke trials, the consensus against crudely dichotomizing outcome scales and discarding important end point information has deepened.³⁵ An important advance in analysis over ranks, taking into account all possible health state outcomes, is the development of utilities and disability weights for each level of the widely used modified Rankin Scale of global disability.^{36,37} The use of utility-weighted Rankin Scale would permit a trial to capture all the effects a treatment can have on a patient to the degree each effect is important to the patient and society, which is the fundamental goal of regulatory agencies. A related desideratum is the need to develop a sliding dichotomy approach to the modified Rankin Scale that calibrates expected prognosis based on core size, vessel occlusion location, and other imaging findings in addition to clinical deficits and demographic information. Incorporating imaging prognosis predictors would improve precision and power when trials use prognosis-adjusted end point analysis.

Adaptive trial design techniques may be helpful with the emerging issue in endovascular clinical trials of subgroups of patients with hypothesized, substantially enhanced treatment benefit and delineating the thresholds at which benefits fade.³⁸ Several biomarkers have been identified that are hypothesized to identify patients with substantially increased benefit from neurothrombectomy. One example is clot location. IV tPA-eligible patients with intracranial internal carotid artery occlusion are suggested to especially benefit from neurothrombectomy, given their low recanalization rate with IV tPA and dismal prognosis without recanalization. This subgroup showed signals of increased benefit in the IMS 3 trial.¹ Another example is degree of mismatch. tPA-ineligible patients in the 3 to 8 hour window with extreme mismatch (small cores and large areas of penumbra) are thought to be most likely to benefit from intervention. Both Bayesian and frequentist adaptive trial design techniques can permit information gained about subgroups in the course of the trial to modify enrollment criteria as the study progresses. The core volume threshold at which benefit no longer accrues, if one exists, is likely to be most efficiently identified by using adaptive modification of trial entry criteria.

The goals of STAIR VIII were to build on the foundation of the previous STAIR recommendations to advance the field of acute and prevention stroke research. Applying lessons learned from initial endovascular trials to test the new generation of more effective devices and gather definitive evidence of benefit against medical control was identified as a priority. Specific approaches for 3 distinct acute ischemic stroke patient populations were outlined. Continued collaboration between academics, regulators, and industry was also strongly endorsed.

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