

STROKE TREATMENT ACADEMIC INDUSTRY ROUNDTABLE - RESEARCH PRIORITIES IN THE ASSESSMENT
OF NEUROTHROMBECTOMY DEVICES

Jeffrey L. Saver, MD;¹ Tudor G. Jovin, MD;² Wade S. Smith, MD;³ Gregory W. Albers, MD;⁴ for the STAIR
VIII Consortium

¹Stroke Center and Department of Neurology, David Geffen School of Medicine at the University of
California, Los Angeles

²Department of Neurology, University of Pittsburgh Medical Center Stroke Institute, University of
Pittsburgh Medical Center

³Department of Neurology, University of California, San Francisco

⁴Stroke Center and Department of Neurology, Stanford University School of Medicine

Address for Correspondence:

Jeffrey L. Saver, MD
UCLA Stroke Center
710 Westwood Plaza
Los Angeles, CA 90095
Tel 310-794-6379
Email: jsaver@mednet.ucla.edu

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, as new neurothrombectomy devices have superior reperfusion efficacy compared with earlier generation interventions. Specific recommendations are provided for trial designs in three populations: 1) patients undergoing intravenous fibrinolysis, 2) early patients ineligible for or having failed intravenous fibrinolysis, and 3) wakeup and other late-presenting patients. Among intravenous fibrinolysis-eligible patients, key principles are that CT or MR imaging 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 desirable in later time windows. Additional STAIR VIII recommendations include approaches to test multiple devices in a single trial, utility-weighting of disability endpoints, and adaptive designs to delineate time and tissue injury thresholds at which benefits from intervention no longer accrue.

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.

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 preclinical 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 three 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 – 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 three 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 3-4.5 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 and/or regulatory approvals, 2) patients presenting in the first 6-8 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 6-8 hours after last known well time. Clinical trial designs need to take into account the distinctive character of these patient populations.

Neurothrombectomy Trials in Patients Eligible for or Currently Undergoing Intravenous Fibrinolysis

While intravenous tissue plasminogen activator is an effective therapy for acute cerebral ischemia due to large artery occlusion, the benefits it confers are only modest. 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 drawback of intravenous TPA (with hemorrhagic transformation risk a real, but less frequent concern). TPA achieves early recanalization of only about 40% of intracranial arterial occlusions, with greatest efficacy for distal arterial occlusions with small clot burdens and least for proximal intracranial internal carotid obstructions containing large volumes of thrombotic material to digest.^{6,7,8,9} As neurothrombectomy devices achieve much higher recanalization rates, 80-95% with newer, stent retriever devices,^{4,5} endovascular treatment has the potential to substantially improve the clinical yield of reperfusion therapy.¹⁰

The first clinical trial design strategic issue for neurothrombectomy studies in patients eligible for IV tPA is whether the novel intervention to be tested against the current standard of IV tPA alone should be neurothrombectomy alone or IV tPA combined with neurothrombectomy. Time urgency and absence of increased risk suggest that combined IV tPA plus neurothrombectomy is likely to be a more efficacious treatment approach than neurothrombectomy alone. Early after stroke onset, every minute of ischemia until the reperfusion is achieved brings substantial additional irreversible brain injury.^{11,12} IV tPA can be initiated much sooner than endovascular thrombectomy, as demonstrated in the recent randomized trials. In the IMS 3 trial, onset to needle time for IV tPA was 122 minutes while 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 while the 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 over that of neurothrombectomy alone.^{4, 5, 13, 14} Consequently, adding IV tPA to neurothrombectomy is an attractive option, offering the possibility, albeit by no means certain, of hyperacute reperfusion, without delaying or increasing the risk of the more definitive endovascular reperfusion intervention.

The absolute imperative to hasten reperfusion dictates several additional constraints upon 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 will be receiving IV tPA (such as combined neurothrombectomy plus IV tPA versus IV tPA alone designs), 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 would require some patients to forego IV tPA (such as head to head neurothrombectomy versus IV tPA designs), novel approaches to consent are required. Options include using exception from informed consent in emergency circumstances,¹⁵ pre-arrival consent obtained by cell phone discussion in the ambulance,^{16, 17} or short form consent on arrival in the Emergency Department.¹⁷

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 from ED arrival to brain imaging (door to imaging), brain imaging to arterial puncture (imaging to puncture or picture to puncture), arterial puncture to arrival of microcatheter at the target thrombus (puncture to clot), and arrival at thrombus

to achievement of reperfusion (clot to reperfusion).^{18, 19} Feedback to sites about their performance and continuous quality improvement programs should be put in place to reduce door to reperfusion times to briefest span attainable. In trials testing combined IV tPA plus neurothrombectomy, start of the endovascular intervention should not be delayed by the administration of the tPA. The combined therapy intervention 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 the arterial sheath, performance of the diagnostic injection of the target vessel, navigation of the neurothrombectomy device to the target lesion, and performance of the retrieval, aspiration, or other endovascular intervention all optimally would take place while the 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 combined IV tPA plus neurothrombectomy 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 also has been associated with hypotension and less favorable outcomes in multiple series.^{20, 21}

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 likely harboring large artery occlusions was unavoidable in the past when multimodal imaging was not widely available, but resulted in enrollment of heterogeneous patient populations, with occlusions at diverse locations and even some with no large artery occlusions at all.^{1, 2} At a minimum, all patients should undergo computed tomography angiography (CTA) or magnetic resonance angiography (MRA) 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 to increase population homogeneity. An additional option is 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 from the trial patients with a high response rate to IV tPA, these vessel selection strategies ensure that enrolled patients will be informative regarding the benefits of neurothrombectomy, but increase trial complexity and reduce trial generalizability.

The value of using sophisticated parenchymal imaging to select trial subjects among patients undergoing IV tPA therapy is uncertain. Advanced imaging always entails an information – tissue tradeoff. Extra time is needed to acquire and process advanced penumbral imaging: is the value of the 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 about 10% of tPA eligible patients will have an unfavorable penumbral pattern.²² Therefore, among patients being imaged within the first 3 hours after last known well, the 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 delay 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 10-15 minutes, provided the advanced imaging is performed concurrently, and using the same modality (CT or MRI), as the routine pre-treatment imaging.

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

The population presenting within 6-8 hours after onset and not eligible for or having failed IV tPA is comprised of three distinct subgroups: 1) patients presenting under 8 hours but beyond the 3-4.5

hour treatment window (2-3.5 hour ED arrival window) for IV tPA; 2) patients presenting within the first 3-4.5 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 CTA, MRA or transcranial Doppler imaging more than 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 two recent endovascular trials, patients ineligible for IV tPA accounted for 47-53% 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 consists 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 re-opening. The randomized trial evidence favoring vessel reopening in these patients is of modest, not definitive, weight, 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 pro-urokinase, an agent not available for clinical use, that was judged insufficiently convincing by regulatory agencies for drug approval;²³ and supportive data from several other smaller trials, none individually positive.²⁴ 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.²⁵

Vessel imaging is certainly, and core and penumbral imaging potentially, 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 may be helpful as, among patients presenting beyond 3 but under 8 hours, a substantial proportion, perhaps 20-40%, will have already completed their infarct or have a malignant infarct pattern and be unlikely to benefit from reperfusion, as demonstrated in the DEFUSE 1 and 2 and EPITHET studies.²⁶⁻²⁸ 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 non-recanalizers in single-arm intervention studies detect association, not causation, and are subject to the confound that the 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 under 8 hour patients with small to moderate cores and substantial neurologic 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 CTA source images with ASPECTS scoring, diffusion MRI) or abbreviated perfusion CT

imaging analysis. CTA source imaging and perfusion CT imaging for core infarct delineation are technique dependent, and require further standardization and investigation for optimal use.^{29 30}

Neurothrombectomy Trials in Wakeup and Other Late-Presenting Patients

Patients presenting beyond 6-8 hours and within 12-24 hours of last known well, including those who awaken 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 as pivotal registration trials of neurothrombectomy devices did not include greater than 8 hour patients and no randomized trial of any recanalization intervention has shown benefit at this late timepoint. In addition to vessel imaging to confirm large artery occlusion, full-scale penumbral imaging is desirable for patient selection in the 8-24 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.³¹

It is desirable to be able to test more than one 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 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 one or a few trials of multiple devices could be performed more efficiently. However, multiple device trials create challenges

for regulators, as device-specific data may be underpowered to confirm efficacy and safety even though 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.³¹ For example, patients could be randomized among four arms, device A, device B, device C, and medical control, in a single trial, rather than among 2 arms in three 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 speeding trial completion. Another, more complex approach is to have patients be randomized between a control medical arm and an endovascular interventional arm in which the proceduralist could select from among two or more alternative devices. Approval of each device in the trial would be based on: 1) overall benefit of the general device arm vs medical therapy, and 2) consistency of effect of each study device with the effect seen in the entire trial. Statistical criteria for regulatory approvability 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 to enroll them in a trial with a control medical arm. In the wake of the neutral results of randomized trials of first generation devices, some payors 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 payors to pursue 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 under 3 hour patients who are ineligible for IV tPA.³² The SYNTHESIS trial showed that endovascular thrombectomy yielded similar benefits as IV tPA in this time window.²

With regard to clinical endpoint analysis in neurothrombectomy acute stroke trials, the consensus against crudely dichotomizing outcome scales and discarding important endpoint information has deepened.³³ 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 employed modified Rankin Scale of global disability.^{34, 35} Use of a utility-weighted Rankin Scale permits 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 endpoint 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.³⁶ 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 3-8 hour window with extreme mismatch – very small cores and very 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 three distinct acute ischemic stroke patient populations were outlined. Continued close collaboration between academics, regulators, and industry was also strongly endorsed.

Disclosures

The University of California, Regents receive funding for Dr Saver's services as a scientific consultant regarding trial design and conduct to Covidien, CoAxia, BrainsGate, Genervon, and Grifols. Dr Saver has served as an unpaid site investigator in multicenter trials run by Lundbeck and Covidien for which the UC Regents received payments on the basis of clinical trial contracts for the number of subjects enrolled.

Dr. Smith is a consultant to Stryker. Dr. Albers has served as a consultant / steering committee member for Covidien, Codman, Lundbeck, and Genentech, was the Chair of the Data and Safety Monitoring Board for Thrombectomy Revascularization of large Vessel Occlusions 2 (Concentric) and has equity interest in iSchemaView. Dr. Jovin has served as a consultant and has equity interest in Silk Road Medical.

Appendix

STAIR VIII writing committee members: Jean-Claude Baron , Johannes Boltze, Joseph P Broderick, Lisa A. Davis, Andrew M. Demchuk, Salvatore DeSena, Jens Fiehler, Philip B Gorelick, Werner Hacke, Bill Holt. Reza Jahan, Hui Jing, Chelsea S. Kidwell, Kennedy R Lees, Michael H Lev, David S Liebeskind, Marie Luby, Patrick Lyden, J Thomas Megerian, J Mocco, Keith W Muir, Howard A Rowley, Richard M. Ruedy, Sean I Savitz, Samuel K. Shimp III, Lawrence R Wechsler, Max Wintermark, Ona Wu, Albert J Yoo

References

1. Broderick JP, Palesch YY, Demchuk AM, Yeatts SD, Khatri P, Hill MD, et al. Endovascular therapy after intravenous t-pa versus t-pa alone for stroke. *N Engl J Med*. 2013;368:893-903
2. Ciccone A, Valvassori L, Nichelatti M, Sgoifo A, Ponzio M, Sterzi R, et al. Endovascular treatment for acute ischemic stroke. *N Engl J Med*. 2013;368:904-913
3. Kidwell CS, Jahan R, Gornbein J, Alger JR, Nenov V, Ajani Z, et al. A trial of imaging selection and endovascular treatment for ischemic stroke. *N Engl J Med*. 2013;368:914-923
4. Saver JL, Jahan R, Levy EI, Jovin TG, Baxter B, Nogueira RG, et al. Solitaire flow restoration device versus the merci retriever in patients with acute ischaemic stroke (swift): A randomised, parallel-group, non-inferiority trial. *Lancet*. 2012
5. Nogueira RG, Lutsep HL, Gupta R, Jovin TG, Albers GW, Walker GA, et al. Trevo versus merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (trevo 2): A randomised trial. *Lancet*. 2012;380:1231-1240
6. del Zoppo GJ, Poeck K, Pessin MS, Wolpert SM, Furlan AJ, Ferbert A, et al. Recombinant tissue plasminogen activator in acute thrombotic and embolic stroke. *Ann Neurol*. 1992;32:78-86
7. Alexandrov AV, Demchuk AM, Burgin WS, Robinson DJ, Grotta JC. Ultrasound-enhanced thrombolysis for acute ischemic stroke: Phase i. Findings of the clotbust trial. *J Neuroimaging*. 2004;14:113-117
8. Riedel CH, Zimmermann P, Jensen-Kondering U, Stingele R, Deuschl G, Jansen O. The importance of size: Successful recanalization by intravenous thrombolysis in acute anterior stroke depends on thrombus length. *Stroke*. 2011;42:1775-1777
9. Bhatia R, Hill MD, Shobha N, Menon B, Bal S, Kochar P, et al. Low rates of acute recanalization with intravenous recombinant tissue plasminogen activator in ischemic stroke: Real-world experience and a call for action. *Stroke*. 2010;41:2254-2258
10. Saver JL. Improving reperfusion therapy for acute ischaemic stroke. *J Thromb Haemost*. 2011;9 Suppl 1:333-343
11. Lees KR, Bluhmki E, von Kummer R, Brott TG, Toni D, Grotta JC, et al. Time to treatment with intravenous alteplase and outcome in stroke: An updated pooled analysis of ecass, atlantis, ninds, and epithet trials. *Lancet*. 2010;375:1695-1703
12. Saver JL. Time is brain--quantified. *Stroke*. 2006;37:263-266
13. Shi ZS, Loh Y, Walker G, Duckwiler GR. Endovascular thrombectomy for acute ischemic stroke in failed intravenous tissue plasminogen activator versus non-intravenous tissue plasminogen activator patients: Revascularization and outcomes stratified by the site of arterial occlusions. *Stroke*. 2010;41:1185-1192
14. The Penumbra Pivotal Stroke Trial I. The penumbra pivotal stroke trial: Safety and effectiveness of a new generation of mechanical devices for clot removal in intracranial large vessel occlusive disease. *Stroke*. 2009;40:2761-2768
15. Kasner SE, Baren JM, Le Roux PD, Nathanson PG, Lamond K, Rosenberg SL, et al. Community views on neurologic emergency treatment trials. *Annals of Emergency Medicine*. 2011;57:346-354.e346
16. Sanossian N, Starkman S, Liebeskind DS, Ali LK, Restrepo L, Hamilton S, et al. Simultaneous ring, voice-over-internet phone system enables rapid physician elicitation of informed consent in prehospital stroke trials (abstract). *Stroke* 2008;39:708
17. Enama ME, Hu Z, Gordon I, Costner P, Ledgerwood JE, Grady C. Randomization to standard and concise informed consent forms: Development of evidence-based consent practices. *Contemporary Clinical Trials*. 2012;33:895-902

18. Menon BK, Goyal M. A systems approach towards intra-arterial management of acute ischemic stroke: Need for novel outcome measures and a focus on sequence rather than steps. *Interv Neuroradiol.* 2011;17:296-298
19. Almekhlafi MA, Eesa M, Menon BK, Demchuk AM, Goyal M. Ultrashort imaging to reperfusion time interval arrests core expansion in endovascular therapy for acute ischemic stroke. *J Neurointerv Surg.* 2012
20. Abou-Chebl A, Lin R, Hussain MS, Jovin TG, Levy EI, Liebeskind DS, et al. Conscious sedation versus general anesthesia during endovascular therapy for acute anterior circulation stroke: Preliminary results from a retrospective, multicenter study. *Stroke.* 2010;41:1175-1179
21. Jumaa MA, Zhang F, Ruiz-Ares G, Gelzinis T, Malik AM, Aleu A, et al. Comparison of safety and clinical and radiographic outcomes in endovascular acute stroke therapy for proximal middle cerebral artery occlusion with intubation and general anesthesia versus the nonintubated state. *Stroke.* 2010;41:1180-1184
22. Inoue M, Mlynash M, Straka M, Lansberg MG, Zaharchuk G, Bammer R, et al. Patients with the malignant profile within 3 hours of symptom onset have very poor outcomes after intravenous tissue-type plasminogen activator therapy. *Stroke.* 2012;43:2494-2496
23. Furlan A, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, et al. Intra-arterial prourokinase for acute ischemic stroke. The proact ii study: A randomized controlled trial. Prollyse in acute cerebral thromboembolism. *JAMA.* 1999;282:2003-2011
24. Lee M, Hong KS, Saver JL. Efficacy of intra-arterial fibrinolysis for acute ischemic stroke: Meta-analysis of randomized controlled trials. *Stroke.* 2010;41:932-937
25. Lyden PD, Meyer BC, Hemmen TM, Rapp KS. An ethical hierarchy for decision making during medical emergencies. *Ann Neurol.* 2010;67:434-440
26. Albers GW, Thijs VN, Wechsler L, Kemp S, Schlaug G, Skalabrin E, et al. Magnetic resonance imaging profiles predict clinical response to early reperfusion: The diffusion and perfusion imaging evaluation for understanding stroke evolution (defuse) study. *Ann Neurol.* 2006;60:508-517
27. Lansberg MG, Straka M, Kemp S, Mlynash M, Wechsler LR, Jovin TG, et al. Mri profile and response to endovascular reperfusion after stroke (defuse 2): A prospective cohort study. *Lancet Neurol.* 2012;11:860-867
28. Davis SM, Donnan GA, Parsons MW, Levi C, Butcher KS, Peeters A, et al. Effects of alteplase beyond 3 h after stroke in the echoplanar imaging thrombolytic evaluation trial (epithet): A placebo-controlled randomised trial. *Lancet Neurol.* 2008;7:299-309
29. Pulli B, Schaefer PW, Hakimelahi R, Chaudhry ZA, Lev MH, Hirsch JA, et al. Acute ischemic stroke: Infarct core estimation on ct angiography source images depends on ct angiography protocol. *Radiology.* 2012;262:593-604
30. Kamalian S, Maas MB, Goldmacher GV, Payabvash S, Akbar A, Schaefer PW, et al. Ct cerebral blood flow maps optimally correlate with admission diffusion-weighted imaging in acute stroke but thresholds vary by postprocessing platform. *Stroke.* 2011;42:1923-1928
31. Wason J, Magirr D, Law M, Jaki T. Some recommendations for multi-arm multi-stage trials. *Statistical Methods in Medical Research.* 2012
32. Broderick JP, Tomsick TA, ftIMoSIIEC. Reimbursement for thrombectomy devices in patients who are in-eligible for iv t-pa. *Stroke.* In Press
33. Bath PM, Lees KR, Schellinger PD, Altman H, Bland M, Hogg C, et al. Statistical analysis of the primary outcome in acute stroke trials. *Stroke.* 2012;43:1171-1178
34. Rivero-Arias O, Ouellet M, Gray A, Wolstenholme J, Rothwell PM, Luengo-Fernandez R. Mapping the modified rankin scale (mrs) measurement into the generic euroqol (eq-5d) health outcome. *Med Decis Making.* 2010;30:341-354

35. Hong KS, Saver JL. Quantifying the value of stroke disability outcomes: Who global burden of disease project disability weights for each level of the modified rankin scale. *Stroke*. 2009;40:3828-3833
36. Kairalla JA, Coffey CS, Thomann MA, Muller KE. Adaptive trial designs: A review of barriers and opportunities. *Trials*. 2012;13:145