Special Report

Stroke Treatment Academic Industry Roundtable
The Next Generation of Endovascular Trials

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Background and Purpose—The STAIR (Stroke Treatment Academic Industry Roundtable) meeting aims to advance acute stroke therapy development through collaboration between academia, industry, and regulatory institutions. In pursuit of this goal and building on recently available level I evidence of benefit from endovascular therapy (ET) in large vessel occlusion stroke, STAIR IX consensus recommendations were developed that outline priorities for future research in ET.

Methods—Three key directions for advancing the field were identified: (1) development of systems of care for ET in large vessel occlusion stroke, (2) development of therapeutic approaches adjunctive to ET, and (3) exploring clinical benefit of ET in patient population insufficiently studied in recent trials. Methodological issues such as optimal trial design and outcome measures have also been addressed.

Results—Development of systems of care strategies should be geared both toward ensuring broad access to ET for eligible patients and toward shortening time to reperfusion to the minimum possible. Adjunctive therapy development includes neuroprotective approaches, adjuvant microcirculatory/collateral enhancing strategies, and periprocedural management. Future research priorities seeking to expand the eligible patient population are to determine benefit of ET in patients presenting beyond conventional time windows, in patients with large baseline ischemic core lesions, and in other important subgroups.

Conclusions—Research priorities in ET for large vessel occlusion stroke are to improve systems of care, investigate effective adjuvant therapies, and explore whether patient eligibility could be expanded.

Key Words: consensus ■ goals ■ microcirculation ■ reperfusion ■ stroke

The STAIR (Stroke Treatment Academic Industry Roundtable) IX meeting, gathered expert opinion generated through lectures, plenary discussions and workshops held during the STAIR IX meeting in Bethesda, MD, on October 4 and 5, 2015 and focused on establishing research priorities in 3 main areas: (1) next generation of endovascular trials, (2) neuroimaging, and (3) pooling of data from multiple randomized trials. This report summarizes recommendations about the next generation of endovascular trials.

The meeting occurred in the wake of a landmark moment for the field of acute stroke treatment defined by the recent publication of 5 prospective randomized trials, unequivocally demonstrating benefit of endovascular therapy (ET) compared with best medical therapy (which in most cases included intravenous tissue-type plasminogen activator [tPA]) in patients with proximal large vessel occlusion (LVO) stroke in the anterior circulation.[1–5] Thus, given the established proof of benefit of ET in acute stroke, focus on discussions related to the next generation of endovascular stroke trials has shifted toward strategies aimed at enhancing access to this therapy, exploring potential benefit in the patient population not included in previous trials, and evaluating approaches to improve procedural and periprocedural aspects of the therapy.

Given the suboptimal absolute rates of favorable outcome currently achieved with ET for acute stroke, the need to further refine this treatment modality is clearly recognized. At least 50% of patients do not achieve functional independence, despite undergoing ET, and ≈15% of these patients do not survive. Furthermore, data from the United States and European registries obtained before the publication of positive trials indicate that <5% of patients with ischemic stroke currently receive this highly beneficial therapy.[6,7]Although utilization

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rates of ET are likely to have increased, after evidence of benefit became available, the lack of widespread vascular imaging (computer tomography angiography, magnetic resonance angiography) in patients with acute stroke as a matter of routine care, geographical disparities in access to ET and insufficiently developed stroke systems of care for patients with LVO are some of the factors based on which it is reasonable to conclude that ET is currently being underutilized even in those patient population for which class one evidence of benefit is available. Therefore, further research is critical to establish more effective approaches that will not only lead to more patients treated but also result in higher rates of favorable outcomes than those hitherto reported. Although at the first glance these 2 goals may seem to be potentially counteracting, improving access to endovascular centers for large segments of the population with LVO in the timeliest possible manner after stroke onset constitute strategies that are likely to achieve both goals.

Three distinctive directions for future stroke research in ET for stroke have been recognized: (1) refinement of stroke systems of care to incorporate the new evidence supporting ET, (2) development of adjunctive therapeutic approaches in conjunction with ET, and (3) assessment of potential clinical benefit in the patient population insufficiently studied by recent trials.

Development of Systems of Care for ET in LVO Stroke

The need to improve current stroke systems of care as a research priority stems from 2 widely acknowledged facts are (1) the time-dependent nature of the treatment effect associated with reperfusion therapy[8] and (2) substantial underutilization of thrombectomy relative to the number of potentially eligible patients (Table 1).[6] Revisions to systems of care should ensure timely access to safe and effective, patient-centered endovascular stroke therapy while reducing or eliminating race, sex, and geographical disparities, at a reasonable cost.[9]

Analogous to systemic thrombolytic treatment, thrombectomy, particularly when performed in patients not selected by more advanced imaging methods, results in clinical outcomes that are profoundly dependent on time to reperfusion. Khatri et al[8] reported that in the cohort of patients undergoing intra-arterial thrombolysis in IMS3, every 30 minute delay in the time from symptom onset to reperfusion is associated with a 10% decreased chance of achieving an independent level of functioning. Given such dramatic differences in clinical outcomes according to time to reperfusion, it is imperative that profound changes in stroke-related systems of care are implemented. These changes need to address the 3 main settings where initial care occurs in patients who may ultimately be candidates for endovascular reperfusion: the prehospital setting, the initial hospital if it is only capable of intravenous thrombolysis, and the intrahospital setting of the endovascular capable center. Development of systems of care addressing these locations will not only lead to timely prehospital or interhospital transportation of patients with LVO to an endovascular capable center, but also ensure the optimization of patient workflow at every step from endovascular center arrival to successful reperfusion.

Improvement of systems of care should include all steps from the first medical contact to access site puncture. The scarcity of available data on transportation, delivery pathways, and time expenditure at each step from the first medical contact to access site puncture has been recognized as a major impediment in the implementation of any potential initiatives aimed to streamline the process of optimal delivery in patients with LVO. We recommend capturing these data in a nationwide comprehensive registry or national database. We suggest this database be housed by an organization with adequate experience and infrastructure, such as the American Heart Association or other large national or international professional organization. ET-specific metrics are already being incorporated into the Get With The Guidelines-Stroke database while prehospital care registries, such as the Mission Lifeline Stroke are in advanced planning stages. Other potential registry options include the NEMSIS Prehospital Database. Central to the concept of streamlining data collection into a national registry database is real-time collection not only of demographic data and vital signs but also of all time intervals relevant to the transportation of patients with LVO from the first point of contact to endovascular center and linkage of these time intervals to clinical outcomes. Support was expressed for the development of innovative registry formats that include not just abstracted metrics, but the actual source data from imaging and angiography acquired in cases treated with ET.

Another important concept pertaining to systems of care is triage and delivery of patients with stroke to the most appropriate medical facility according to the specific needs of each individual patient. Current paradigms are typically focused only on timely intravenous tPA delivery regardless of stroke mechanism and are not geared toward recognition and preferential triage and transportation of patients with LVO to an endovascular capable center. The STAIR working group was in unanimous agreement that the current triage and transportation paradigms that result in patient delivery to the geographically nearest hospital may be detrimental to care of patients with LVO because of the substantial time delays associated with many current drip and ship models. Indeed, data from SWIFT PRIME (Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment), a trial whose prespecified secondary analysis included an assessment of outcomes in patients treated according to the drip and ship paradigm versus primary endovascular center presentation revealed that outcomes were significantly worse in those patients who were transferred to the study site after receiving intravenous tPA at an outside hospital.[3] It is, thus, imperative that new paradigms are created to preferentially triage patients with high likelihood of harboring LVO directly to endovascular capable centers based on tools available in the prehospital arena or, at the minimum, to substantially reduce the door-in-door out delays at the first receiving hospital. This process requires appropriate identification of patients that are likely to have LVO, public reporting of median door-in-door out times by all stroke centers, and addressing overcrowding at large ET-capable stroke centers that can produce intrahospital delays.

Several approaches to early identification of LVO in the field have been proposed. These range from simple approaches, such

Table 1. Stroke Systems of Care

Research Question	Optimal Study Design	Alternative Study Design	Optimal Primary Outcome Measure	Alternative Primary Outcome Measure/ Secondary Outcome Measure
Prehospital				
Stroke recognition accuracy by 911 operator	Prospective Registry	Retrospective study	% recognized as stroke	N/A
Prehospital work flow (time from call to EMS arrival, time from EMS arrival to hospital arrival, time from referring hospital arrival to treating hospital arrival, time from referring hospital arrival to referring hospital departure [DIDO], and time from imaging at referring hospital to access site puncture picture to puncture)	Prospective Registry	Retrospective data collection from prospective national registries	Descriptive statistics	N/A
Inflection point (in terms of time to endovascular center beyond which transport of patients with suspected LVO at primary center is beneficial over direct transport to endovascular center	Randomized trial	Prospective national registry	Clinical outcomes (ordinal mRS)	% treated with reperfusion tx (intravenous or IA)
				Cost of direct transport to endovascular center compared with endovascular center
Accuracy of large vessel stroke diagnosis in the field	Prospective Registry	Retrospective data collection from prospective national registries	% recognized as ischemic stroke; % recognized as proximal LVO (ICA, M1)	Time required to perform assessment
			Comparison between different clinical scales and different approaches	Cost
				Interrater reliability
				Training requirements
				Feasibility
				Yield—IA thrombolysis treatment per population unit
Prehospital scales				
Prehospital telemedicine				
Mobile Stroke Unit				
Delivery site—direct transfer to endovascular center vs local hospital	Randomized trial	Prospective Registry	Clinical efficacy (ordinal mRS)	% patients undergoing endovascular therapy
		Randomized trial within registry	Safety (mortality and siCH) in all patients with suspected LVO	Time to IA reperfusion
				Recanalization rates at 24 h
Intrahospital				
Intrahospital work flow (time from hospital arrival to imaging, time from hospital arrival to intravenous tPA, time from imaging to access site puncture, time from access site puncture to base catheter placement, time from access site puncture to reperfusion, number of passes, time from hospital arrival to access site puncture, and time from symptoms onset to reperfusion)	Prospective Registry	Retrospective data collection from prospective national registries	Descriptive statistics	

(*Continued*)

Table 1. Continued

Research Question	Optimal Study Design	Alternative Study Design	Optimal Primary Outcome Measure	Alternative Primary Outcome Measure/ Secondary Outcome Measure
CT vs advanced imaging	Randomized trial—needs to also include patients excluded by advanced imaging who would have been treated with CT only based selection	Prospective registry	Clinical outcomes (ordinal mRS); Safety (sICH, mortality)	Time to treatment (door to groin)
		Cluster randomization		Cost
				Availability/feasibility
				Training requirements for imaging interpretation
				Yield—IA thrombolysis rates per population unit
Imaging in angiosuite	Prospective Registry	Retrospective	Time from door to puncture	Cost
			Time from door to reperfusion	Yield (% of patients treated with endovascular therapy relative to all patients with LVO presenting at endovascular center)
			Safety (sICH, mortality)	
			Clinical outcomes	
Alternative access (carotid, radial)	Randomized trial	Prospective Registry	Clinical outcomes	Time from door to reperfusion
			Safety (access site complications)	
Direct IA vs intravenous/IA (for patients presenting to endovascular capable center within intravenous tPA time window)	Randomized trial	No other option	Clinical outcomes (ordinal mRS)	Cost effectiveness
			Safety (sICH, mortality)	

CT indicates computed tomography; DIDO, door-in-door out; EMS, Emergency Medical Services; IA, intra-arterial; ICA, internal carotid artery; IV, intravenous; LVO, large vessel occlusion; mRS, modified Rankin scale; sICH, symptomatic intracerebral hemorrhage; and tPA, tissue-type plasminogen activator.

as in field recognition of LVO stroke by Emergency Medical Service providers through specifically designed prehospital scales (LAMS [Los Angeles Motor Scale],[10] RACE [The Rapid Arterial Occlusion Evaluation],[11] CPSS [Cincinnati Prehospital Stroke Scale],[12] etc), to technologically advanced modalities, such as Mobile Stroke Units. Telemedicine technologies used in the field constitute another approach with significant potential.[13] A more in-depth analysis of the advantages and disadvantages in terms of triage accuracy, ease of implementation, and cost effectiveness of each of these approaches is best accomplished through incorporation of these data into prospective registries. Once a method of identifying LVO in the field with desirable receiver–operator curve characteristics has been established, the fundamental question of benefit from direct transportation to an endovascular capable center versus transportation to the closest hospital for the entire population identified as likely to harbor LVO can be more objectively addressed. Although the STAIR group believes that direct transfer to endovascular sites is likely to yield improved clinical outcomes, variations in available local prehospital and hospital resources and their governance may make large-scale and standardized implementation of this paradigm difficult without definitive proof of benefit from randomized trials.

An important point to be considered is how to approach triage in locations that are remote from endovascular capable centers. Even when LVO stroke is appropriately recognized, it is necessary to establish the time-based inflection point for patients who cannot be transported to an endovascular center in a timely manner. In these remote locations, early intravenous tPA administration at the geographically closest hospital may lead to better outcomes than delayed ET. However, transfer to an endovascular center after intravenous tPA administration should occur as soon as possible and transfer pathways should be developed around obtaining shortest possible door-in-door-out times.

Intrahospital workflow improvement is another system of care setting recognized as a quality improvement and research priority. Initiatives can be emulated from the intravenous tPA experience where impressive reductions in door to needle times have been accomplished through process improvement

efforts, such as the Target Stroke initiative resulting in significant reductions of door-to-needle times nationally. In addition, much has been learned with respect to workflow and its impact on clinical outcomes from the recently completed endovascular trials. In these studies, prospective recording of the most relevant time intervals, from hospital arrival to reperfusion and continuous feedback processes aimed at shortening door to reperfusion times to the minimum have provided valuable insights. Time intervals between ER arrival and ET have varied substantially between studies and between participating centers within a study. Even in the efficient systems, intrahospital patient throughput for patients with endovascular stroke is substantially slower than for the treatment of ST-segment–elevation myocardial infarction. The median door to puncture time was 96 minutes in ESCAPE (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times; the most workflow efficient endovascular stroke study) and ranged from 103 to 116 minutes in SWIFT PRIME and REVASCAT (Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours), respectively. These times do not compare favorably to door to balloon times of around 60 minutes that are routinely achieved in ST-segment–elevation myocardial infarction centers. These dramatic differences in workflow reflect, in part, the more inherently time-consuming steps necessary to perform a standard initial emergency department evaluation of acute stroke compared with ST-segment–elevation myocardial infarction patients (including imaging, need for neurological evaluation, etc.) but also a different hospital wide culture about the urgency of ST-segment–elevation myocardial infarction care compared with acute stroke care, the former being a more mature process that builds on decades of accumulating experience on ways to maximize workflow efficiency. Therefore, drawing on the cardiology experience, national initiatives with clearly outlined goals and implementation strategies are necessary in endovascular stroke care to substantially reduce currently achieved workflow times. Improvements in workflow design and process engineering with parallel activation and processing are likely to represent means through which time delays can be mitigated.

Technological advances in angiographic equipment may enable obtaining some of the physiological information necessary for patient selection directly in the angiography suite, which may result in bypassing time-consuming transportation steps to and from scanners. In patients in whom femoral access is associated with long times from puncture to reperfusion (aortofemoral occlusion or severe stenosis, difficult aortic arch anatomy, etc.), alternative potentially faster access routes (direct carotid puncture, radial or brachial access) should be explored. Whether these novel approaches can replace currently used workflow pathways remains to be established by future studies. Time stamps for every key procedure and interval (Emergency Department arrival, first imaging, endovascular suite arrival, arterial puncture, first pass of ET device, reperfusion, or cessation of reperfusion attempts if recanalization is not achieved) should be established and key consensus measures developed including time from ED arrival to brain imaging (door to imaging), brain imaging to arterial puncture (picture to puncture), arterial puncture to arrival of microcatheter at the target thrombus (puncture to clot), and arrival at thrombus to the achievement of reperfusion (clot to reperfusion), as well as the aggregate times of door to access site (reflecting the throughput efficiency of the endovascular center), door to reperfusion, and qualifying imaging to reperfusion (an important predictor of clinical outcome). All future endovascular acute stroke trials should capture these important consensus metrics, and national registries are necessary to provide the data required for improvement through continuous feedback processes.

Adjuvant Approaches to ET

Several potential approaches have been proposed to further enhance the results of neurothrombectomy (Table 2). These approaches include collateral therapeutics, neuroprotectant strategies, improvement of microcirculation, and periprocedural management. Collateral therapeutic strategies[14] recognize the pivotal impact of collateral status on the time course and outcome of patients with stroke, seeking to leverage collateral pathophysiology in concert with ET. Microcirculatory disturbances because of microthrombosis, sludging, no reflow phenomenon, and endothelial dysfunction have been recognized as factors with potential deleterious effects on outcomes after ET for LVO. Potential approaches to improve microcirculation include argatroban (a compound that also has neuroprotectant properties) and GP IIb/IIIa inhibitors.[15] Small case series attesting to the safety and feasibility of these approaches have been published. Randomized trials should further clarify the benefit of these approaches in patients treated with ET with or without previous tPA administration.

Despite promising results in preclinical studies, neuroprotectants have failed to show benefit when tested in humans. However, major methodological shortcomings of human trials have been recognized. These trials have enrolled heterogeneous groups of stroke patients with respect to stroke severity, stroke location, and vessel patency, mostly in late time windows and without controlling for reperfusion, the most powerful determinant of outcome in large vessel stroke. With the advent of proof of benefit for mechanical thrombectomy in LVO stroke, a reappraisal of neuroprotection's role in conjunction with ET is justified. The advantages of studying a combined approach include enrolling a more homogeneous patient population with respect to vessel occlusion site, a high likelihood of salvageable brain tissue and high reperfusion rates. Important unanswered questions related to trials testing the efficacy of a combined neuroprotectant/ET approach include safety aspects, optimal time windows, extent to which more advanced imaging techniques are required as selection tools and timing of neuroprotectant administration relative to reperfusion.

After LVO, growth of the ischemic core at the expense of the penumbra occurs with different speeds in different individuals.[16] Factors that specifically drive this difference in core growth rates are poorly understood but collaterals play a critical role. Neuroprotectant agents with potential to delay the progression of the ischemic process resulting in the transformation of fast progressors into slow progressors

Table 2. Adjuvant Therapy

Treatment	Optimal Trial Design	Alternative Design	Key Outcome Measure	Surrogate/Secondary Outcome
Microcirculation, collateral and periprocedural management				
Argatroban with/without tPA	Randomized prospective clinical trial	None	Clinical (ordinal 90-d mRS) Safety(sICH and systemic bleeding)	Infarct volume, early (5- to 7-d mRS), early (24- to 48-h NIHSS)
GP IIb/IIIa inhibitors (Eptifibatide)	Randomized trial	None	Clinical (ordinal 90-d mRS) Safety (sICH and systemic bleeding)	Infarct volume, early (5- to 7-d mRS), early (24–48 h NIHSS)
Collateral enhancing tx (body position, fluids, BP management pre- and postintervention)	Registry	Cluster randomization	Clinical (descriptive 90-d mRS) Safety—sICH and medical complications	Imaging (CBF/collaterals measurement pre- and postintervention)
Intubation/General anesthesia	Randomized trial	Cluster randomization	Clinical (descriptive 90-d mRS) Safety—medical complications and procedural complications (perforation)	Cost Hospital/ICU length of stay
Antiplatelet agents postintervention	Registry (randomized trial not practical because of large required sample size)	Cluster randomization	Reocclusion at 24 h Safety (sICH)	Clinical (90-d mRS)
Neuroprotectant agents				
NA-1	Randomized trial	None	Clinical (ordinal 90-d mRS) Safety (sICH, mortality, and medical complications)	Infarct volume, early (5- to 7-d mRS), early (24- to 48-h NIHSS), quality of life, cognition
Uric acid	Randomized trial	None	Clinical (ordinal 90-d mRS) Safety (sICH and mortality, medical complications)	Infarct volume, early (5- to 7-d mRS), early (24- to 48-h NIHSS), quality of life, cognition
Glyburide	Randomized trial	Single arm, phase 2	Clinical (ordinal 90-d mRS) Safety (sICH, mortality, and medical complications including hypoglycemia)	Infarct volume, early (5- to 7-d mRS), early (24- to 48-h NIHSS), quality of life, cognition
Activated protein C	Randomized trial	None	Clinical (ordinal 90-d mRS) Safety (sICH, mortality, and medical complications)	Infarct volume, early (5- to 7-d mRS), early (24- to 48-h NIHSS), quality of life, cognition
Hypothermia	Randomized trial	Single arm, phase 2	Clinical (ordinal 90-d mRS) Safety (sICH, mortality, and medical complications including pneumonia)	Infarct volume, early (5- to 7-d mRS), early (24- to 48-h NIHSS), quality of life, cognition
Neuroprotectant/neurorecovery agents				
IA stem cells	Phase 2 randomized	Single arm, phase 2	Clinical (ordinal 90-d mRS) Safety (medical complications)	Infarct volume, early (5- to 7-d mRS), early (24- to 48-h NIHSS), quality of life, cognition

BP indicates blood pressure; CBF, cerebral blood flow; IA, intra-arterial; ICU, intensive care unit; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; sICH, symptomatic intracerebral hemorrhage; and tPA, tissue-type plasminogen activator.

could represent an important advancement in acute stroke treatment. If administered in the prehospital setting, penumbral preservation could result in many more patients eligible for ET. Ultra-early administration of neuroprotectant agents within the first hour of symptoms onset in the field has been recently shown to be feasible.[17] Several agents with neuroprotectant properties, such as NA-1,[18] uric acid,[19] glyburide,[20] argatroban,[15] and activated protein C,[21] have recently been found to yield signals of potential benefit in phase II human studies with no associated major safety concerns. These encouraging preliminary results support randomized studies testing their benefit in conjunction with ET compared with ET alone. Autologous and allogenic stem cell therapy is thought to have both neuroprotectant and recovery enhancing properties. The intra-arterial route of administration has recently shown promising safety results in humans.[22] Human phase 2 trials are necessary to consolidate the observed safety data and to assess for signals of clinical benefit.

Hypothermia, considered to potentially be the most powerful neuroprotectant, has been found to improve outcomes in cardiac arrest and neonatal hypoxemia.[23] The use of hypothermia in stroke is backed by animal data attesting to its

strong neuroprotectant effect[23]; however, efficacy data in humans are needed. Human data investigating the role of hypothermia in conjunction with thrombolytic treatments (intravenous and endovascular) suggest that this approach is feasible and overall safe, although a higher incidence of pneumonia has been consistently observed. Therefore, while a randomized trial investigating the benefit of hypothermia in conjunction with ET is a goal worth pursuing, the lack of prospective data demonstrating safety and feasibility of this approach along with lack of evidence of benefit in humans suggest that a phase 2 study before a randomized study is advisable.

There are numerous unanswered questions related to periprocedural management of ET. These include blood pressure management before and after reperfusion, the use of general anesthesia, optimal postprocedural antithrombotic regimen, optimal blood glucose management, and optimal collateral augmentation strategies (body position, blood pressure, fluid status, etc). While ideally, randomized trials should answer these questions, pragmatic considerations suggest that registries represent a more likely means to advance knowledge in these areas. The development of infrastructure for randomized registry trials could, in the future, allow for cost-effective randomized trials of periprocedural management embedded within large national or international registries.[24]

Exploring Clinical Benefit in Insufficiently Studied Patient Population

Exploring venues to expand the patient population that may benefit from ET is a high priority (Table 3). To maximize the chance of showing benefit, most of the recent randomized trials included the highly selected patient population with respect to likelihood of treatment response, which may explain the strong treatment effects observed. Although this approach was necessary to establish proof of efficacy, concerns remain that certain patient populations who may also derive benefit, albeit of lesser magnitude, were excluded.

A small core in the presence of a large territory at risk characterizes the concept of mismatch, which represents the underlying pathophysiological rationale for reperfusion therapy and has been shown to predict clinical response after ET.[25] Since it is now well recognized that a significant proportion of patients with LVO present with small baseline core and significant mismatch in later time windows (beyond 6 hours) and that treatment in this time window is feasible and safe,[26] a priority for the field of ET research best answered through randomized trials is to determine whether there is benefit from treatment beyond the 6-hour time window.

Because patients with large baseline ischemic core lesion (ASPECTS [Alberta Stroke Program Early CT Score] of <5) or ischemic core volume >70 mL were excluded from enrollment in nearly all of the recent randomized trials, the question of potential benefit or harm in this patient population still remains to be answered. Addressing this question is important because if benefit or lack of harm in patients with large baseline infarction is demonstrated, it may become unnecessary to perform time-consuming imaging studies that are currently performed solely to exclude patients who do not benefit or are harmed by treatment. In case harm or futility is demonstrated, it is important to establish clinical and imaging predictors thereof (age, core thresholds, medical comorbidities, pre-existing disability level, etc.). The computed tomography and magnetic resonance imaging core volume thresholds at which benefit no longer accrues, if one exists, is likely to be most efficiently identified by using adaptive modification of trial entry criteria.

Even within the currently accepted time windows and utilizing currently accepted ischemic core thresholds for selection, several patient populations were either not included in recent randomized trials or the trials were underpowered to detect benefit in these subgroups. While pooled analyses will address some of these gaps, further research is necessary to more conclusively establish benefit in subgroups, such as patients with basilar occlusion, distal middle cerebral artery segment occlusion, LVO with low NIHSS (National Institutes of Health Stroke Scale) at presentation, and patients with preexisting significant disability.

Other Unanswered Questions

While superior compared with previous treatment methods, the current generation of thrombectomy devices, primarily represented by stent retrievers, is still suboptimal. This is evidenced by the effective reperfusion rates (defined as TICI [Thrombolysis in Cerebral Ischemia] 2b) of 60% to 90% and median times of 35 to 45 minutes from access site to reperfusion in recent randomized trials,[3–5] suggesting significant potential for further improvements. It is important to recognize that, at present, level I evidence of benefit exists only when ET is performed with stent retrievers. Thus, stent retrievers constitute the benchmark against which other devices or approaches should be measured. Although trials comparing safety and efficacy of devices across different technologies should include clinical efficacy end points, pragmatic considerations dictate that the rates of effective reperfusion and speed of achieving reperfusion are the preferred primary outcome measures. Although evidence suggests that the use of stent retrievers is associated with better outcomes when performed in conjunction with aspiration, future studies should clarify whether aspiration through a balloon guide catheter versus through an aspiration catheter located at target lesion yields superior results with respect to recanalization rates, speed of recanalization, rates of distal embolization and hemorrhagic complications. Aspiration as a primary thrombectomy modality has been shown in single-arm case series to yield procedural results comparable to stent retrievers. However, consistent proof of clinical efficacy of aspiration compared with stent retrievers is lacking and therefore randomized trials would be preferred to establish primary aspiration as equivalent treatment modality. Data from several randomized trials suggest that tandem extracranial carotid occlusion/intracranial occlusions represent the condition possibly associated with strongest treatment effect when ET is compared with medical therapy.[1,4,5] Yet, because a multitude of approaches with respect to the management of the extracranial occlusion were used, many questions remain unanswered. Research in this area is further compounded by the significant regulatory restrictions associated with concomitant

Table 3. Assessment of Clinical Benefit in Insufficiently Studied Patient Populations

Patient Population	Optimal Trial Design	Alternative Design	Key Outcome Measure	Surrogate/Secondary Outcome
Anterior circulation beyond 6 h	Randomized, ongoing (DAWN, DEFUSE 3, POSITIVE)	Clustered randomization	Clinical—ordinal 90-d mRS, weighted mRS adaptive design Safety (sICH and mortality)	Infarct volume/Infarct growth, early (5- to 7-d mRS), early (24- to 48-h NIHSS), quality of life, cognition, and cost effectiveness
Distal occlusions	Randomized	Cluster randomization, Prospective Registry	Clinical—ordinal 90-d mRS	Infarct volume/Infarct growth, early (5- to 7-d mRS), early (24- to 48-h NIHSS), quality of life, cognition, and cost effectiveness
M2 MCA, ACA, PCA			Safety (sICH and mortality)	
Proximal occlusion	Randomized	Cluster randomization, Prospective Registry	Clinical—dichotomized 90-day mRS 0–1	Infarct volume/Infarct growth, early (5- to 7-d mRS), early (24- to 48-h NIHSS), quality of life, cognition, and cost effectiveness
Mild deficit (NIHSS<6)			Safety (sICH and mortality)	
Large core early time window (0–6 h); ASPECTS 0–5/ Core>70 mL	Randomized	Adaptive modification	Clinical, ordinal 90-day mRS or dichotomized mRS 0–3 Safety (sICH and mortality)	Infarct volume/Infarct growth, early (5- to 7-d mRS), early (24- to 48-h NIHSS), quality of life, cognition, and cost effectiveness
Intravenous tPA, noneligible within intravenous tPA time window	Prospective registry (randomized unlikely due loss of equipoise)	Retrospective analysis from prospective registry	Clinical (90-day ordinal compared with historical controls)	Infarct volume (compared with historical controls)
Basilar occlusion	Randomized, ongoing (BASICS)	Clustered randomization	Clinical(90-day mRS—(ordinal or dichotomized 0–3 or 0–4) Safety (sICH and mortality)	Cognition, quality of life, and cost effectiveness
Extracranial non tandem ICA occlusion	Phase 2 feasibility and safety	Randomized, clustered randomization, and adaptive modification	Clinical (ordinal 90-d mRS or dichotomized 0–1) Safety (sICH, mortality, and feasibility)	Infarct volume/Infarct growth, early (5- to 7-d mRS), early (24- to 48-h NIHSS), quality of life, cognition, and cost effectiveness

ACA indicates anterior cerebral artery; DAWN, DWI/PWI and CTP assessment in the triage of wake-up and late presenting strokes undergoing neurointervention; DEFUSE 3, endovascular therapy following imaging evaluation for ischemic stroke 3; IV, intravenous; mRS, modified Rankin scale; PCA, posterior cerebral artery; sICH, symptomatic intracerebral hemorrhage; and tPA, tissue-type plasminogen activator.

treatment of extracranial and intracranial occlusions. Acute or subacute extracranial internal carotid occlusions without associated intracranial occlusions are known to be amenable to revascularization in a high proportion of cases. However, the safety and clinical benefit of this approach compared with standard medical therapy needs to be proven in randomized trials. Another important unanswered question constitutes the treatment of occlusions when the underlying lesion is a ruptured atherosclerotic plaque rather than an embolus. Similar to acute coronary syndromes, this condition, highly prevalent in Asian and black populations, may be optimally treated with primary stenting or angioplasty and further studies are needed to clarify optimal treatment strategies.

Methodological Issues

While widely considered to be the standard clinical end point in neurothrombectomy acute stroke trials, the modified Rankin Scale (mRS) at 90 days is not without limitations. The 90-day lag in primary end point adjudication introduces the possibility of contamination by nonindex stroke-related morbidity in this medically complex patient population. In addition, suboptimal inter-rater reliability and potential for lack of blinding continue to constitute shortcomings, justifying exploration of alternative approaches. Various assessment time points have been proposed and each has advantages and disadvantages (eg, assessment at 24 hours may miss important later evolution of ischemic damage, including brain swelling and secondary ischemia, or hemorrhagic transformation, but later time points may be confounded by loss of patients because of early mortality or medical instability). Several clinical outcome measures such as the 24-hour NIHSS and 7-day mRS have been shown to strongly correlate with the 90-day mRS and could conceivably replace it as primary outcome measure in future trials. Follow-up infarct volume on brain imaging is

emerging as a powerful predictor of 90-day mRS and may be incorporated into outcome prediction scores that improve precision and power. Another important outcome measure relates to the adjudication of symptomatic intracerebral hemorrhage, which continues to suffer from the lack of standardization across trials.

Because reperfusion correlates closely with clinical outcome measures, it may be regarded as surrogate marker when used for specific questions, such as a comparison between effectiveness of various thrombectomy devices. Potential limitations of currently used reperfusion assessment methods include inter-rater variability. This may, in part, explain the widely discrepant rates of effective reperfusion observed in the recent endovascular trials, despite the use of similar technologies, and suggests that centralized and possibly automated perfusion assessment paradigms should be explored. Technological advances have made thrombectomy increasingly more effective. As such, high rates of reperfusion of the nearly entire territory at risk are being routinely observed. Therefore, a reappraisal of the effective reperfusion concept from the current definition of >1/2 at risk territory to >2/3 at risk territory (according to original criteria) is necessary.

Ordinal analysis of the mRS has now largely replaced dichotomized approaches, and new advances have been made particularly with regard to more patient-centered outcome analysis through the development of utilities and disability weights for each level of the modified Rankin Scale.[27]

An issue of critical importance for conducting endovascular trials is the process of informed consent recognized as an important bottleneck of acute endovascular stroke trials. Consenting as currently applied in most endovascular acute stroke trials entails signed informed consent by a legally authorized representative. This paradigm represents a major impediment in the timely and scientifically valid execution of trials because it not only significantly hinders enrollment but also restricts participation to certain patient population (those with available proxies, those whose proxies are willing to consent on their behalf, and those whose proxies can present to the hospital in time to sign consent), thus potentially rendering trial results not applicable to the general population of patients with stroke. In addition, through time delays that can critically influence outcomes in the endovascular arm and that are not consistent with routine clinical practice, current consenting paradigms may not only bias results in favor of the control group whose outcomes are not affected by consenting, but may also be detrimental to patient care. Nonetheless, informed consent constitutes a fundamental principle for the respect for autonomy of the person in human research. Therefore, solving the conundrum of satisfying the appropriate steps to ensure the proper conduct of human research within the particular circumstances of acute interventional stroke trials remains a formidable challenge. Not only are patients frequently unable to make decisions for themselves and are dependent on others whose decisions may not necessarily reflect their own beliefs, but because of the critically time-sensitive nature of the treatment being tested, the time required for the consenting process has the potential to negatively affect outcomes. Potential solutions to this problem include phone, telemedicine, or electronic consent, which can help address the issue of time but not that of proxy availability and thus have limitations. In the absence of available family members, Exception of Informed Consent (EFIC) represents a viable solution to the many problems posed by consenting in acute endovascular trials that could lead to a dramatic increase in enrollment and thus offer this patient population the potential for improved outcomes. An ongoing dialogue is necessary with all parties involved in informed consent decisions including Institutional Review Board's physician communities and the community at large to find optimal solutions to the consenting dilemma facing endovascular acute stroke trials.

Conclusions

Recent advances in the treatment of acute ischemic stroke, realized by the success of randomized controlled trials of ET, herald novel opportunities to extend such benefit to broader populations of patients with stroke worldwide. Research priorities in ET for LVO stroke are to improve systems of care, investigate effective adjuvant therapies, and explore clinical benefit in insufficiently studied patient population.

Disclosures

Dr Jovin has consulted for Codman Neurovascular and Neuravi, holds stock in Silk Road, Blockade Medical, Anaconda and Remedy Pharmaceuticals, has acted as an unpaid consultant to Stryker as PI of the DAWN trial, and served as an unpaid member of a Medtronic Advisory Board. Dr Albers has consulted for iSchemaView, Covidien, and Lundbeck and has equity interest in iSchemaView. Dr Liebeskind is a consultant to Stryker (modest) and Covidien (modest) and employed by the University of California (UC), which holds a patent on retriever devices for stroke.

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Appendix: STAIR IX Writing Committee Members

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