Endovascular Clot Retrieval Therapy
Implications for the Organization of Stroke Systems of Care in North America

Eric E. Smith, MD, MPH; Lee H. Schwamm, MD

Abstract—Endovascular acute ischemic stroke therapy is now proven by randomized controlled trials to produce large, clinically meaningful benefits. In response, stroke systems of care must change to increase timely and equitable access to this therapy. In this review, we provide a North American perspective on implications for stroke systems, focusing on the United States and Canada, accompanied by initial recommendations for changes. Most urgently, every community must create access to a hospital that can safely and quickly provide intravenous tissue-type plasminogen activator and immediately transfer appropriate patients onward to a more capable center as required. Safe and effective therapy in the community setting will be ensured by certification programs, performance measurement, and data entry into registries. (Stroke. 2015;46:00-00. DOI: 10.1161/STROKEAHA.115.008385.)

Key Words: quality improvement • stroke

Five recent randomized controlled trials provide compelling evidence that endovascular clot retrieval improves outcomes after acute ischemic stroke.1-4 In response, stroke systems of care will need to adapt to facilitate patient’s access to this therapy in a timely, equitable, and safe fashion. Although the trials differed in important aspects related to entry criteria, imaging selection and outcomes, all patients who were eligible for intravenous alteplase (recombinant human tissue plasminogen activator) received this first, received it rapidly after hospital arrival, and many were transferred to another facility for thrombectomy. These data do not imply that every community must develop a comprehensive stroke center (CSC); rather these data support the strengthening of ties between hospitals of increasing capabilities, from the basic receiving hospital that can only diagnose and stabilize stroke patients, to the acute stroke ready hospital (ASRH) that can provide intravenous tissue-type plasminogen activator (tPA) but has no stroke unit, to the primary stroke center (PSC) that has a full stroke unit but not the full range of services for complex ischemic and hemorrhagic stroke patients, to the CSC. Every community must create access to a hospital that can safely and quickly provide intravenous tPA and immediately transfer appropriate patients onward to a more capable center as required.

In this review, we discuss the implications of this new era of endovascular therapy with regard to organization of stroke systems of care, suggest principles that should guide the adaptation of such systems and provide preliminary recommendations for change (Table 1). Our review is informed by the 6 principles of quality care in the framework proposed by the Institute of Medicine in their seminal report, Crossing the Quality Chasm: effectiveness, patient-centeredness, timeliness, equity, safety, and efficiency.6

Effectiveness
The 5 recent randomized controlled trials provide consistent evidence for the efficacy of endovascular thrombectomy. Details of these trials are reviewed elsewhere in this issue of Stroke. Importantly, the therapy was consistently effective overall and among important prespecified patient subgroups of sex, age, and stroke severity.1-4

In light of the overwhelming evidence for effectiveness, we recommend that stroke systems of care be modified to provide access to thrombectomy equitably to all eligible patients. To facilitate appropriate implementation of these therapies, we recommend review by professional societies, revision of existing acute stroke guidelines (in North America, published by the American Stroke Association and Canadian Stroke Best Practice Recommendations, as well as by Emergency Medicine organizations), review by policy makers and generation of performance measures by professional societies and government agencies.
The large treatment effect on the modified Rankin scale, which discriminates between different patient-valued health outcome states, validates endovascular thrombectomy as a treatment that improves patient-centered outcomes. We recommend further analysis of the trial data to explore other patient-centered outcomes, including quality of life, mood, cognition and function, including the ability to live independently in a private residence (also termed home time).

Given the large differences in patient-centered disability outcomes, we recommend that physicians should proceed without delay to thrombectomy in cases where the patient is without capacity for informed consent and no legally authorized representative is available. Hospitals and other healthcare organizations should establish protocols that explicitly recommend that the physician act under the doctrine of implied consent, based on what a reasonable patient would choose in this scenario, much as would be expected for a patient with acute coronary syndrome or cardiac arrest.7

**Patient-Centeredness**

The large treatment effect on the modified Rankin scale, which discriminates between different patient-valued health outcome states, validates endovascular thrombectomy as a treatment that improves patient-centered outcomes. We recommend further analysis of the trial data to explore other patient-centered outcomes, including quality of life, mood, cognition and function, including the ability to live independently in a private residence (also termed home time).

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**Table 1. Recommendations**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Rationale</th>
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<tr>
<td>1. Updates to professional guidelines</td>
<td>New, clear evidence of effectiveness with important systems implications</td>
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<tr>
<td>2. Develop, or revise, EMS and interhospital referral patterns</td>
<td>To ensure that patients with ischemic stroke can be diagnosed, rapidly treated with alteplase if eligible, and then have access to thrombectomy. EMS policies will need to be revised to determine the appropriate destination for patients when &gt;1 level of stroke care is available in a community, balancing time, distance, and likely eligibility</td>
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<tr>
<td>3. Implementation of CT-angiography at PSCs and CSCs</td>
<td>Needed to determine eligibility for thrombectomy</td>
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<tr>
<td>4. Programs to facilitate rapid administration of alteplase should be maintained and strengthened</td>
<td>All eligible patients should receive alteplase first</td>
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<tr>
<td>5. Participation in registries</td>
<td>Need to demonstrate similar effectiveness in community practice as in trials and to identify disparities by age, race, sex, and geography</td>
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<tr>
<td>6. Feedback on quality of care using standardized performance measures</td>
<td>To facilitate local, regional, and national quality improvement programs. Feedback should be given to both prehospital and hospital providers</td>
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<tr>
<td>7. Certification programs for thrombectomy-capable centers</td>
<td>Unregulated proliferation of CSCs may produce many low-volume, relatively inexperienced operators, and less desirable outcomes</td>
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CT indicates computed tomography; CSCs, comprehensive stroke center; EMS, emergency medical services; and PSCs, primary stroke center.

**Timeliness**

Analyses show that the effectiveness of endovascular thrombectomy decreases with increasing time from symptom onset,8 mandating a systems emphasis on rapid assessment and treatment. Patients with suspected proximal arterial occlusion should be identified rapidly, transported to the nearest appropriate medical facility, diagnosed and treated with intravenous alteplase if eligible, then receive evaluation for endovascular therapy onsite or at a thrombectomy-capable hospital. Standard national emergency medical services (EMS) protocols for stroke recognition should be used by dispatchers and EMS personnel. As described in recent recommendations,5 EMS agencies will need to modify or create point-of-entry criteria to determine the most appropriate destination for patients when >1 level of stroke care is available in a community, balancing time, distance, and likely eligibility into the decision.

All hospitals receiving patients with stroke via EMS, except those in remote regions, should be able to diagnose ischemic stroke and assess the intracerebral vessels to identify proximal arterial occlusion. For certified PSCs and CSCs, we recommend that all stroke patients with potentially disabling stroke deficits and symptom onset <6 hours, and optionally <12 hours, before arrival should undergo computed tomography angiography (CTA) of the head and neck to identify proximal vascular occlusion amenable to thrombectomy. However, CTA should not delay administration of intravenous alteplase, which can be given on the CT table before advanced imaging. Because many PSCs do not currently provide CTA around the clock, extra resources will be required. However, by implementing CTA imaging at all PSCs thrombectomy-eligible patients can be more rapidly identified for transfer to CSCs. We do not recommend proceeding to angiography without CTA information, as was performed in the Interventional Management of Stroke 3 trial (IMS3; which had negative results),9 because this approach exposes some patients without occlusions to the risk of a conventional invasive angiogram. Although all of the trials excluded posterior circulation stroke, we think that CTA is warranted in all patients with ischemic stroke because the history and clinical examination are not highly specific for thrombus location, and many CSCs would offer endovascular treatment of basilar artery occlusion.

For patients being evaluated at a PSC that does not yet have CTA capability, or at an ASRH or equivalent, it is reasonable to transfer all patients with National Institutes of Health Stroke Scale (NIHSS) ≥9 or who have a hyperdense vessel sign in the middle cerebral artery to a thrombectomy-capable center after starting intravenous tPA in eligible patients. An NIHSS of ≥9 is 75% sensitive and 74% specific for the presence of a proximal vascular occlusion, with a positive predictive value of 80%90 but a negative predictive value of 68%, meaning that 32% of patients with NIHSS <9 still have a proximal vascular occlusion. The trial evidence is inconclusive about whether more advanced imaging beyond CTA is needed for patient selection. CT perfusion or multiphase CTA with collateral scoring was used in 3 trials, but in the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial no additional imaging criteria, beyond the need to demonstrate a proximal arterial occlusion, was used. It is reasonable to refer all patients with a proximal middle cerebral artery or basilar artery occlusion to a CSC for consideration for endovascular thrombectomy, with or without more advanced imaging, if the patient meets other criteria for treatment.

We recommend that existing systems for rapid provision of intravenous thrombolysis be supported and leveraged...
to also facilitate rapid access to endovascular thrombectomy. This includes institutional thrombolysis protocols, as well as quality improvement programs, such as the American Heart Association’s Target: Stroke initiative.\textsuperscript{11} Patients who are eligible for alteplase, as well as endovascular thrombectomy, should always first receive alteplase. Reasons to continue to provide alteplase to patients with proximal artery occlusion include increasing the chances of recanalization with intravenous therapy alone or with rescue thrombectomy and for the 10% to 30% of cases where endovascular thrombectomy is unsuccessful. Systems changes that support rapid alteplase therapy should also shorten times to endovascular therapy. Protocols should support activation of the endovascular team in parallel with initiation of alteplase therapy to reduce time to treatment.

An ideal stroke system of care should ensure equitable access to the fastest possible endovascular thrombectomy. In practice, this principle must be considered in light of the number and distribution of CSCs within a given system (please see the section on Equity for more discussion on disparities related to the nationwide distribution of CSCs).

A major question is whether EMS transporting an acute stroke patient with symptom duration <6 hours or <12 hours should bypass a local ASRH or PSC for a more distant CSC. If the transport times between the CSC and PSC/ASRH are similar, then the chance of a good outcome would be improved by transporting directly to the CSC, assuming the CSC has favorable door to treatment time intervals. When the CSC is much farther than the PSC, alteplase should be accompanied in parallel by steps to initiate immediate transfer to the CSC because alteplase recalculates only about 20% to 40% of proximal arterial clots and rescue thrombectomy is usually required.\textsuperscript{12}

The need for evaluation and treatment at CSCs must be balanced against the current capacity of such centers to handle the expected patient load. In many jurisdictions, EMS is regulated by local health authorities to bypass hospitals incapable of providing alteplase to transport stroke patients with symptoms <3 or 4.5 hours to PSCs or CSCs. According to time of onset data from the Get With The Guidelines registry, 25% of patients present within 3 hours and 36% present within 8 hours.\textsuperscript{13} Therefore, extending the bypass criterion from 0 to 3 hours up to 6 to 12 hours could potentially increase the number of EMS bypass cases ≥50%, with increased case volume at PSCs and CSCs. If bypass is extended to PSCs, such that these patients are taken only to CSCs, the increase in case volume at the CSCs could be substantial and potentially detrimental. To mitigate these effects, it is reasonable to exclude from thrombectomy-based triage patients with preexisting disability who are unlikely to benefit, such as those with modified prestroke Rankin score of >2. Certain communities may benefit from alternative strategies, such as mobile stroke units, or use of telemedicine-enabled vascular neurology consultation into the EMS vehicle.

We recommend that public health agencies, such as departments of public health and provincial and regional health authorities, establish regulations about stroke patient transfer that are appropriate for the resources available in their local settings with a deliberate effort to encourage 30 minute access to ASRH and PSC for all citizens and strategically placed CSC to leverage this network of care.

Equity

Endovascular acute ischemic stroke therapy has large treatment effects across subgroups of age, sex, and stroke severity, and so it should be provided without restrictions based on these characteristics, geography, or socioeconomic status. Equitable access to care should be a guiding principle underlying stroke system reorganization. New stroke systems solutions should be data driven and transparent and designed to achieve what is in the patient’s best interest.

The largest, most comprehensive analysis of endovascular acute ischemic stroke therapy use in North America comes from the US nationwide Get With The Guidelines-Stroke (GWTG-Stroke) Registry.\textsuperscript{14} This analysis showed that before the publication of the pivotal trials in 2014–2015, endovascular therapy was used uncommonly and inconsistently, with disparities according to age, sex, and race/ethnicity. It was used less frequently in older patients, black patients, and women.\textsuperscript{14} Only 99 of 1509 participating hospitals (9.6%) provided endovascular therapy continuously throughout their duration of participation in the GWTG-Stroke registry; however, by 2013, 23.4% of hospitals were providing this therapy. Among the hospitals providing endovascular therapy, only 1.6% of patients with ischemic stroke were treated with endovascular therapy even though 8.0% received intravenous tPA.\textsuperscript{14} In a US nationally representative 2009 analysis, only 0.6% of ischemic stroke discharges underwent thrombectomy.\textsuperscript{15} Systematic data collection in registries will be useful to detect disparities and support QI initiatives to address them.

One of the biggest challenges to improving patient access to therapy may be the limitations imposed by the geographic distribution of CSCs (Figure). Using 2011 data, it was estimated that 56% of the US population lived within 1 hour of a thrombectomy-capable hospital, with the largest gaps in coverage in the Midwest (Figure I in the online-only Data Supplement).\textsuperscript{16} Recent geospatial modeling data suggest that even under optimal configuration, many US residents would be >60 minutes’ drive from a CSC, underscoring the need for a distributed, 3-tiered stroke system of care.\textsuperscript{17}

CSCs must offer endovascular therapy 24 hours per day, 7 days per week. To sustainably provide this 24-hour coverage, 2 to 3 neurointerventionists are usually needed per service. Although the overall number of current neurointerventionists and neurointerventionists-in-training seems adequate,\textsuperscript{18} it is likely that local shortages will arise. Systems of care will need to adapt locally to address mismatches between supply and demand when they arise, and strategies that promote cross-disciplinary training or interinstitutional coverage may be cost-effective. Wherever thrombectomy is offered, a stroke unit must also be present for appropriate evidence-based care for the remainder of the hospitalization. In regions that lack a CSC, a thrombectomy-capable PSC may be a reasonable option but this must be carefully monitored and regulated to ensure that the expected outcomes are achieved.

Safety

The recent trial data show good safety outcomes for endovascular therapy, without an increase in rates of symptomatic intracranial hemorrhage despite the use of intravenous...
alteplase in both arms for most patients. We recommend capturing safety outcomes in real world practice using registries to ensure that endovascular therapy in community practice is as safe as in the trials, as was previously documented for alteplase. We recommend that safety outcomes include symptomatic intracranial hemorrhage and the rate of major disability at 90 days. We strongly recommend participation in certification programs which ensure adequate resources to provide endovascular acute ischemic stroke therapy, as well as excellent general stroke unit care. Certification should be based on the Brain Attack Coalition19 criteria for CSCs.

One component of maintenance of site certification should be participation in a registry and review of one’s own performance and outcomes. Performance measure definitions for endovascular acute ischemic stroke therapy are provided by the American Heart Association/American Stroke Association,20 Joint Commission,21 and by a multisociety consensus group (Table 2).22 Reporting of data and outcomes to regional regulatory bodies should be considered to ensure that expected outcomes are achieved.

Table 2. Performance Measures and Benchmarks Offered by Professional Societies

<table>
<thead>
<tr>
<th>Measure Title</th>
<th>Additional Description</th>
</tr>
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<tbody>
<tr>
<td>Percentage of ischemic stroke patients seen within 6 h who have endovascular recanalization performed or was considered not to be appropriate</td>
<td>A reason should be documented if an endovascular procedure was not performed</td>
</tr>
<tr>
<td>Median time from arrival to start of treatment</td>
<td></td>
</tr>
<tr>
<td>Percentage who develop SICH within 36 h of treatment</td>
<td>SICH defined as hemorrhage on CT or MRI in association with clinical deterioration without other cause</td>
</tr>
<tr>
<td>Percentage for whom there is documentation of a 90-day mRS score</td>
<td></td>
</tr>
<tr>
<td>The Joint Commission Comprehensive Stroke Center Program21</td>
<td></td>
</tr>
<tr>
<td>Median time to revascularization</td>
<td>Revascularization defined as time of first infusion of lytic or first pass of mechanical device</td>
</tr>
<tr>
<td>TICI post-treatment reperfusion grade</td>
<td></td>
</tr>
<tr>
<td>Multisociety Consensus Quality Improvement Guidelines for Intra-Arterial Therapy22</td>
<td></td>
</tr>
<tr>
<td>Indication for treatment</td>
<td>≥90% should meet institutional selection criteria</td>
</tr>
<tr>
<td>Door to puncture</td>
<td>≥75% should have door-to-puncture time ≤2 h</td>
</tr>
<tr>
<td>Puncture time to start of revascularization</td>
<td>≥50% with time from puncture to start of lytic or first pass of mechanical device &lt;45 min</td>
</tr>
<tr>
<td>Puncture time to revascularization</td>
<td>≥50% with TIMI grade 2 or TICI grade 2a within 90 min</td>
</tr>
<tr>
<td>Recanalization/reperfusion</td>
<td>≥60% with TIMI grade 2 or TICI grade 2/3 within 90 min</td>
</tr>
<tr>
<td>Post-procedure CT/MR</td>
<td>≥90% should have brain CT or MR imaging within 36 h after procedure</td>
</tr>
<tr>
<td>SICH</td>
<td>≤12% should have SICH</td>
</tr>
<tr>
<td>Clinical outcome</td>
<td>≥30% should have mRS 0–2 at 90 days</td>
</tr>
</tbody>
</table>

CT indicates computed tomography; MRI, magnetic resonance imaging; mRS, modified Rankin scale; SICH, symptomatic intracranial hemorrhage; TICI, Thrombolysis in Cerebral Infarction; and TIMI, Thrombolysis in Myocardial Infarction.

For many medical procedures, there is a relationship between higher case volume and better outcomes. This is likely to be true for endovascular acute stroke therapy as well. Endovascular acute stroke therapy procedures should be performed by neurointerventionists with adequate training23 and yearly case experience, and in hospitals with established written protocols for management of endovascular-treated patients, including provision of stroke unit care after thrombectomy. An unregulated proliferation of CSCs may dilute the pool of patients across too many centers and produce many low volume, relatively inexperienced operators, and less desirable outcomes.

However, training and maintenance of endovascular therapy skills will be challenging because of low case volumes at
many hospitals. In GWTG-Stroke, half of hospitals providing endovascular therapy treated 6 or fewer patients with ischemic stroke per year.24 Similarly, a study using data from the Nationwide Inpatient Sample found that in 2008 only 27 of 1038 hospitals (2.6%) performed ≥10 acute ischemic stroke endovascular cases per year.24 Although annual case volumes will grow as endovascular therapy is applied more widely and equitably, they are likely to remain modest compared with other neurointerventional procedures, such as carotid stenting or aneurysm coiling. To increase operator experience, stroke systems could centralize endovascular acute ischemic stroke therapy in larger centers. However, the benefits of centralizing care must be weighed against the risks related to longer transport times for patients. Decisions on the optimal distribution of CSCs, taking into account both transport times and the need to maintain adequate case load at each center, would be facilitated by more registry-based research on the relationship between good outcomes and the critical variables of time from onset to treatment, and hospital and operator experience. Telemedicine-enabled supervision or mentoring of less experienced operators by expert centers is a strategy that might increase favorable outcomes and should be considered for low volume centers or geographically dispersed populations.

Efficiency

In strained healthcare systems with finite resources, there is increasing emphasis on achieving greater value, which has been defined simply as quality divided by cost. We consider it likely that investments in systems of care for endovascular therapy will be money well spent, with appropriately large benefits to patient health. The trial data suggest that many treated patients will have large reductions in disability, expected to result in overall cost savings to the system for these patients. We recommend that health economics analyses be conducted based on the trial data to calculate costs per quality-adjusted life years saved by endovascular therapy. Such data will be useful to policy makers and health administrators to justify expenditures on reorganizing stroke systems of care. Equitably treating all eligible patients will maximize the return on initial investments to build capacity, but this cost must be shared across payers so that those who bear the increased upfront costs will benefit from some of the downstream savings.

Conclusions

Endovascular therapy is now proven to produce large, clinically meaningful improvements in outcomes from acute ischemic stroke. Stroke systems of care must be modified to promote timely and equitable access to this therapy. Most urgently, this requires regional stroke systems to implement emergency medical systems and interfacility referral policies to transport patients with acute ischemic stroke to centers where rapid vessel imaging can be used to identify proximal arterial occlusion followed by access to a neurointerventional service for endovascular therapy. The optimal transport policies and distribution of CSCs is uncertain, hard to verify objectively, and will depend on local resource constraints. Research on the relationship between treatment effect and time will help to determine optimal transport times, and research on stroke center volume and outcomes will help determine optimal case loads and centralization of centers. To promote good outcomes and patient safety, stroke centers providing endovascular therapy should be certified, should record their outcomes in a registry, and should evaluate their own performance using accepted, standardized measures.

Disclosures

Dr Smith is a member of the Get With The Guidelines (GWTG) Steering Committee, AHA Scientific Oversight Committee and co-Chair of the Canadian Stroke Best Practice Recommendations. Dr Schwamm is chair of the GWTG Stroke Clinical Workgroup, PI of the National Institutes of Health and Genentech-funded MR WITNESS phase 2 safety trial of extended window alteplase, a member of the DIAS-3 and 4 international steering committee (Lundbeck), the Data Safety Monitoring Board of the Penumbra 3D Separator Trial (Penumbra), and a stroke systems consultant to the Massachusetts Department of Public Health.

References


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SUPPLEMENTAL MATERIAL

Supplemental Figure I.

Travel times to endovascular capable facilities by ambulance or helicopter, according to a previously published analysis of 2011 Medicare files.\textsuperscript{1} Endovascular-capable hospitals were identified by procedure billing codes. Ambulance response times were estimated using arc-Geographic Information System’s network analyst and helicopter transport times were estimated using validated models. By ground, 56% of patients had access to an endovascular-capable hospital within 60 minutes. By air, 85% had access to an endovascular-capable hospital within 60 minutes.