8th Annual Lawrence M. Brass Stroke Symposium: Partnerships for Best Practice

October 1, 2015
LEARNING OBJECTIVES
This course will enable participants to:

- Perform an emergent diagnostic evaluation and design a treatment plan for patients presenting with a suspect stroke/TIA
- Interpret the pathology, imaging and treatment options for patients with an ischemic or hemorrhagic stroke
- Summarize the endovascular study results from recently published clinical trials
- Identify different rehabilitation strategies for stroke recovery
- Describe the secondary prevention algorithms following ischemic and hemorrhagic strokes

ACCREDITATION STATEMENT
The Yale School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

DESIGNATION STATEMENT
The Yale School of Medicine designates this live activity for a maximum of 7 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.
# Schedule

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>7:00am</td>
<td>Registration and Continental Breakfast</td>
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<tr>
<td>7:45 am</td>
<td>Welcome and Introductions</td>
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<tr>
<td></td>
<td>Karin V. Nystrom MSN, APRN, FAHA</td>
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<tr>
<td>8:00 am</td>
<td>It's a New Day: Mechanical Thrombectomy in Acute Stroke</td>
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<tr>
<td></td>
<td>Ketan R. Bulsara MD</td>
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<tr>
<td>8:30 am</td>
<td>Imaging Selection for Neuro-endovascular Cases</td>
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<tr>
<td></td>
<td>Michele H. Johnson MD</td>
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<tr>
<td>9:00 am</td>
<td>Let's Get Technical; Devices in Neuro-endovascular Procedures</td>
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<tr>
<td></td>
<td>Charles C. Matouk MD</td>
</tr>
<tr>
<td>9:40 am</td>
<td>Systems of Care for Optimizing Acute Stroke Treatment Options</td>
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<tr>
<td></td>
<td>David M. Greer MD, MA, FCCM, FAHA</td>
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<tr>
<td></td>
<td>and Karin V. Nystrom MSN, APRN, FAHA</td>
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<tr>
<td>10:00 am</td>
<td>Panel Discussion: Audience Questions- Intervention</td>
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<tr>
<td>10:15 am</td>
<td>Refreshment Break</td>
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<tr>
<td>10:35 am</td>
<td>ICU Management of Malignant Stroke</td>
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<td></td>
<td>Kevin N. Sheth MD, FAHA, FCCM, FNCS, FAAN, FANA</td>
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<tr>
<td>11:05 am</td>
<td>Case Study</td>
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<tr>
<td></td>
<td>Jennifer L. Dearborn-Tomazos MD, MPH</td>
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<tr>
<td>11:25 am</td>
<td>Making Head-way: Hemorrhagic Stroke</td>
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<td>Lauren Sansing MD, MSTR</td>
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<tr>
<td>11:55 am</td>
<td>Lunch</td>
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<tr>
<td>1:00 pm</td>
<td>Back to the Basics: Stroke Prevention</td>
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<tr>
<td></td>
<td>Walter Kernan MD</td>
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<tr>
<td>1:45 pm</td>
<td>AFIB Monitoring: You Don’t Know What You Are Missing</td>
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<tr>
<td></td>
<td>Nimrod Lavi MD</td>
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</tbody>
</table>
2:15 pm  Case Study
   Jason J. Sico MD, FACP

2:35 pm  Carotid Endarterectomy: Old But Good
   Timur P. Sarac MD

3:00 pm  Refreshment Break

3:15 pm  Carotid Stenting: Look How Far We Have Come...
   Carlos Mena MD, FACC

3:40 pm  Update on Novel Anti-coagulants
   Alfred I. Lee MD, PhD

4:10 pm  Case Study
   Hardik P. Amin MD

4:30 pm  Closing Remarks & Adjourn
   Joseph L. Schindler MD
Faculty

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Yale School of Medicine
Clinical Director,
Yale-New Haven Stroke Center

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Firm Chief, Inpatient Hematology, Yale Cancer Center  
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Traditional Internal Medicine Residency Program

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Chief of Vascular and Endovascular Surgery,  
Co-Director of Heart and Vascular Center

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Division Chief, Neurocritical Care and Emergency Neurology  
Director, Neuroscience ICU  
Chief, Clinical Research, Department of Neurology

Jason J. Sico MD, FACP  
Assistant Professor of Neurology  
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Director, Stroke Care VA Connecticut Healthcare System
8th Annual Lawrence M. Brass Stroke Symposium  
*Partnerships for Best Practice*  
Thursday, October 1, 2016

**DISCLOSURE SUMMARY**

It is the policy of Yale University School of Medicine, through its Center for Continuing Medical Education, to ensure balance, independence, objectivity, and scientific rigor in all its educational programs. All faculty participating in this symposium are required to disclose to the program audience (orally or with slide): any relevant financial relationship(s) they (or spouse/partner) have with a commercial interest that benefits the individual in any financial amount that has occurred within the past 12 months; and the opportunity to affect the content of CME about the products or services of the commercial interest. The Center for Continuing Medical Education will ensure that any conflicts of interest are resolved before the educational activity occurs.

The following indicates participants' responses to disclosure policy:

<table>
<thead>
<tr>
<th>Name</th>
<th>Nothing to Disclose</th>
<th>Speaker (and/or spouse/partner) has significant corporate relationship(s) with:</th>
<th>Role of service/financial relationship</th>
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<tbody>
<tr>
<td>Hardik P. Amin MD</td>
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<tr>
<td>Ketan R. Bulsara MD</td>
<td>X</td>
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<tr>
<td>Jennifer L. Dearborn-Tomazos MD, MPH</td>
<td>Alexion Pharmaceuticals</td>
<td></td>
<td>Husband is employed</td>
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<tr>
<td>Deborah S. Dunn</td>
<td>X</td>
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<tr>
<td>David M. Greer MD, MA, FCCM, FAHA</td>
<td>Bard, Inc.</td>
<td></td>
<td>Consulting</td>
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<tr>
<td>Michele H. Johnson MD</td>
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<td>Walter Kernan MD</td>
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<td>Nimrod Lavi MD</td>
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<td>Charles C. Matouk MD</td>
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<tr>
<td>Carlos Mena MD, FACC</td>
<td>Abbott, Bard CR, Gore, Pathway Medical</td>
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<td>Speaker</td>
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<tr>
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<tr>
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<tr>
<td>Kevin N. Sheth MD, FAHA, FCCM, FNCS, FAAN, FANA</td>
<td>Remedy Pharmaceuticals</td>
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<td>Speaker</td>
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<tr>
<td>Joseph L. Schindler MD</td>
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<tr>
<td>Jason J. Sico MD, FACP</td>
<td>VA Health Services, Acorda</td>
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<td>Grant Support Advisory Council</td>
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After review by the Course Directors, it has been determined there are no conflicts of interest.
8th Annual Lawrence M. Brass Stroke Symposium
Partnerships for Best Practice
Thursday, October 1, 2015

This conference is supported by educational grants from

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We are grateful for their support
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THANK YOU
The views of the speakers do not necessarily reflect the views of the Yale School of Medicine

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Recording of this session by attendees is strictly prohibited
It’s a New Day: Mechanical Thrombectomy in Acute Stroke

Ketan R. Bulsara M.D
Associate Professor
Yale Department of Neurosurgery
Director Neuroendovascular and Skull Base Surgery

Clinical Trials to know: Mechanical Thrombectomy as Standard of Care for Acute Ischemic Stroke

<table>
<thead>
<tr>
<th>Factor</th>
<th>MR CLEAN</th>
<th>ESCAPE</th>
<th>EXTEND IA</th>
<th>SWIFT PRIME</th>
<th>REVASCAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centers</td>
<td>16 in Netherlands</td>
<td>22 mostly N America</td>
<td>10 in Australia/M2</td>
<td>39 in US + Europe</td>
<td>4 in Spain</td>
</tr>
<tr>
<td>Age</td>
<td>18+</td>
<td>18+</td>
<td>18+</td>
<td>18-80</td>
<td>18-85</td>
</tr>
<tr>
<td>NIHSS</td>
<td>2 or higher</td>
<td>6 or higher</td>
<td>No requirement</td>
<td>8-29</td>
<td>6 or higher</td>
</tr>
<tr>
<td>Location of ELVO</td>
<td>ICA, M1, M2, A1 or A2</td>
<td>ICA, M1, or 2 M2s</td>
<td>Anterior circulation</td>
<td>ICA, M1 or both</td>
<td>ICA, M1 or both</td>
</tr>
<tr>
<td>Time from Onset</td>
<td>groin puncture within 6 hrs</td>
<td>8-12 hours</td>
<td>groin puncture within 6 hrs</td>
<td>0-6 hours</td>
<td>0-8 hours</td>
</tr>
<tr>
<td>IV TPA</td>
<td>No requirement</td>
<td>No requirement</td>
<td>All pts received within 4.5 hrs</td>
<td>All pts received within 4.5 hrs</td>
<td>Ineligible or received without improvement</td>
</tr>
<tr>
<td>Imaging Criteria</td>
<td>ELVO only</td>
<td>ASPECTS 6-10; &lt;1/3 territory infarct</td>
<td>Perfusion mismatch</td>
<td>ASPECTS 6-10; &lt;1/3 territory infarct</td>
<td>ASPECTS 7-10;</td>
</tr>
<tr>
<td>Patients in IA arm</td>
<td>223</td>
<td>165</td>
<td>35</td>
<td>98</td>
<td>103</td>
</tr>
<tr>
<td>Medical Patients</td>
<td>267</td>
<td>195</td>
<td>35</td>
<td>98</td>
<td>103</td>
</tr>
<tr>
<td>Treatment Device</td>
<td>Stentriever in 190 of 195 treated with IAT</td>
<td>Stentriever +/- aspiration</td>
<td>Solitaire + aspiration</td>
<td>Solitaire</td>
<td>Solitaire</td>
</tr>
<tr>
<td>Primary Outcome (p-value/CI)</td>
<td>mRS shift at 90 days (CI 1.2-2.3)</td>
<td>mRS shift at 90 days (&lt;0.001)</td>
<td>Reperfusion at 24h; NIHSS &lt;1/3 pts at 3days (P&lt;0.001)</td>
<td>mRS shift at 90 days (&gt; 0.001)</td>
<td>mRS shift at 90 days (CI 1.05-2.8)</td>
</tr>
<tr>
<td>IA: mRS of 0-2 at 90d</td>
<td>13%</td>
<td>53%</td>
<td>71%</td>
<td>60%</td>
<td>44%</td>
</tr>
<tr>
<td>Medical: mRS of 0-2 at 90d</td>
<td>19%</td>
<td>29%</td>
<td>40%</td>
<td>35%</td>
<td>20%</td>
</tr>
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</table>
Purpose—The aim of this guideline is to provide a focused update of the current recommendations for the endovascular treatment of acute ischemic stroke. When there is overlap, the recommendations made here supersede those of previous guidelines.

Methods—This focused update analyzes results from 8 randomized, clinical trials of endovascular treatment and other relevant data published since 2013. It is not intended to be a complete literature review from the date of the previous guideline publication but rather to include pivotal new evidence that justifies changes in current recommendations. Members of the writing committee were appointed by the American Heart Association/American Stroke Association Stroke Council’s Scientific Statement Oversight Committee and the American Heart Association/American Stroke Association Manuscript Oversight Committee. Strict adherence to the American Heart Association conflict of interest policy was maintained throughout the consensus process. Recommendations follow the American Heart Association/American Stroke Association methods of classifying the level of certainty of the treatment effect and the class of evidence. Prerelease review of the draft guideline was performed by 6 expert peer reviewers and by the members of the Stroke Council Scientific Statement Oversight Committee and Stroke Council Leadership Committee.
Results—Evidence-based guidelines are presented for the selection of patients with acute ischemic stroke for endovascular treatment, for the endovascular procedural, and for systems of care to facilitate endovascular treatment.

Conclusions—Certain endovascular procedures have been demonstrated to provide clinical benefit in selected patients with acute ischemic stroke. Systems of care should be organized to facilitate the delivery of this care. (Stroke. 2015;46:3024-3039. DOI: 10.1161/STR.0000000000000074.)

Key Words: AHA Scientific Statements ▪ endovascular procedures ▪ infusions, intra-arterial ▪ neuroimaging ▪ stents ▪ stroke ▪ therapeutics

Since the publication of the most recent “Guidelines for the Early Management of Patients With Acute Ischemic Stroke” in 2013, substantial new high-quality evidence on the clinical efficacy of endovascular treatments of acute ischemic stroke has become available. This focused update on endovascular treatment of acute ischemic stroke analyzes results from 8 randomized, clinical trials of endovascular treatment and other relevant data published since 2013 while taking into account the previous evidence summarized in the 2013 guidelines. This focused update is not intended to be based on a complete literature review from the date of the previous guideline publication but rather to include pivotal new evidence that justifies changes in current recommendations. When there is overlap, the recommendations made here supersede those of previous guidelines.

Members of the writing committee were appointed by the American Heart Association (AHA)/American Stroke Association Stroke Council’s Scientific Statement Oversight Committee and the AHA/American Stroke Association Manuscript Oversight Committee, representing various areas of medical expertise. Strict adherence to the AHA conflict of interest policy was maintained throughout the consensus process. Panel members were assigned topics relevant to their areas of expertise, reviewed the stroke literature with emphasis on publications since the prior guidelines, and drafted recommendations in accordance with the American College of Cardiology/AHA’s Level of Evidence grading algorithm (Table 1). All recommendations were unanimously approved by the members of the writing group.

Treatment With Intravenous Recombinant Tissue-Type Plasminogen Activator

Rapid administration of intravenous recombinant tissue-type plasminogen activator (r-tPA) to appropriate patients remains the mainstay of early treatment of acute ischemic stroke. Timely restoration of blood flow in ischemic stroke patients is effective in reducing long-term morbidity. For patients who meet national and international eligibility guidelines, intravenous r-tPA improves functional outcomes at 3 to 6 months when given within 4.5 hours of ischemic stroke onset and should be administered. Every effort should be made to shorten any delays in the initiation of treatment because earlier treatments are associated with increased benefits. If patients who are eligible for intravenous r-tPA do not have intracranial vascular imaging as part of their initial evaluation, they should begin receiving intravenous r-tPA before being transported for additional imaging and before being transferred for endovascular treatment. This approach will help minimize onset-to-treatment times, a key driver of efficacy for r-tPA.1-6

New Randomized, Clinical Trials of Endovascular Stroke Treatment

Studies With Primarily Intra-Arterial Fibrinolysis or First-Generation Mechanical Embolectomy Devices

Three randomized controlled trials of endovascular treatment of acute ischemic stroke with primarily intra-arterial fibrinolysis and/or first-generation mechanical embolectomy devices were carried out from 2004 to 2012 (Tables 2–4). Intra-arterial Versus Systemic Thrombolysis for Acute Ischemic Stroke (SYNTHESIS Expansion) was a prospective, randomized, open-label, blinded-end-point (PROBE), 2-arm superiority trial that enrolled 362 patients with ischemic stroke who were eligible for intravenous r-tPA within 4.5 hours of onset and for whom endovascular treatment was possible within 6 hours. No imaging other than nonenhanced computed tomography (CT) was required. The patients were randomized 1:1 to standard-dose intravenous r-tPA 0.9 mg/kg or endovascular therapy (intra-arterial r-tPA, mechanical clot disruption or retrieval, or a combination of these approaches). Only 8% had posterior circulation strokes. Median onset to treatment time interval was 165 minutes in the intravenous r-tPA group and 225 minutes in the endovascular group. Among the patients who received endovascular treatment, 66% underwent infusion of intra-arterial r-tPA and thrombus fragmentation with a guidewire only; in 34%, a device was also deployed. Stent retrievers were used in 14%. Data on rates and efficacy of recanalization were not published. There was no difference in the primary end point of the percentage with good outcome defined as a modified Rankin Scale (mRS) score of 0 or 1, death at 3 months, or symptomatic intracerebral hemorrhage (sICH) at 7 days. There were no significant differences in outcomes in subgroups, including time to treatment (0–3 or 3–4.5 hours), baseline National Institutes of Health Stroke Scale (NIHSS) score (<11 or ≥11), and age (≤67 years or >67 years).10

The Interventional Management of Stroke Trial III (IMS III) was a PROBE, 2-arm superiority trial that enrolled patients with a major ischemic stroke defined by NIHSS score ≥10 who received intravenous r-tPA within 3 hours and were likely to or known to have occlusion of a major cerebral artery. Those who showed clear hypodensity in greater than one third of the middle cerebral artery (MCA) territory on nonenhanced CT were excluded. No other imaging was required. An amendment midway through the trial allowed screening with CT angiography (CTA) for patients with NIHSS score >8. More than 95% received a clinical diagnosis of anterior circulation stroke. Patients were randomly allocated 1:2 to standard-dose intravenous r-tPA (0.9 mg/kg) or to intravenous...
r-tPA 0.6 mg/kg followed by endovascular therapy with a device and/or intra-arterial r-tPA if occlusion persisted and if the endovascular intervention could be started within 5 hours and completed within 7 hours of onset. In the endovascular group, groin puncture occurred at a mean±SD of 208±47 minutes after stroke onset. Endovascular therapy was administered in 77% randomized to this treatment group. Intra-arterial r-tPA alone was used in 41%, and a device with or without intra-arterial r-tPA was used in 59%; in only 1.5% were stent retrievers used. Recanalization occurred 325±52 minutes after stroke onset, achieving Thrombolysis in Cerebral Infarction (TICI) grade 2b/3 in 41%. The trial was stopped early for futility after 656 of the projected 900 subjects were enrolled. There was no significant difference in outcome between the intravenous r-tPA–only group and the endovascular group for the primary end point of the percentage of patients with a good outcome as measured by an mRS score of 0 to 2 or for death at 90 days. In the endovascular group, there was no difference in...
outcome between those treated <90 minutes and those treated >90 minutes from intravenous r-tPA to groin puncture. The proportion of patients with an mRS score of 0 to 2 at 90 days increased with increasing recanalization.12

MR and Recanlization of Stroke Clots Using Embolectomy (MR RESCUE) was a PROBE, 2-arm superiority trial that enrolled 118 patients with large-artery occlusion and anterior circulation ischemic stroke within 8 hours who were ineligible for intravenous r-tPA or had persistent vessel occlusion after intravenous r-tPA. Patients were divided into 2 subgroups by pretreatment CT or magnetic resonance imaging (MRI) into those with a favorable or those with an unfavorable penumbral pattern with the use of imaging criteria based on a previous study.13 Patients were randomly allocated 1:1 to standard medical care or endovascular therapy (MERCI [Mechanical Embolus Removal in Cerebral Ischemia] or Penumbra device with optional intra-arterial r-tPA). Onset to groin puncture in the endovascular group was 381±74 minutes (mean±SD). TICI grade 2b/3 recanalization was achieved in 25% of the endovascular group. Among all patients, mean mRS scores at 90 days did not differ between endovascular and standard medical care, nor was endovascular therapy superior to standard medical care in patients with a favorable penumbral pattern (mean score, 3.9 versus 3.4; P=0.32) or in patients with an unfavorable penumbral pattern (mean score, 4.0 versus 4.4; P=0.32).

Studies With Primarily Stent Retrievers
Five randomized controlled trials of endovascular treatment of acute ischemic stroke with primarily stent retrievers were carried out from 2010 to 2015 (Tables 2–4). The Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke and Endovascular Treatment...
Acute Ischemic Stroke (MR CLEAN) was a PROBE, 2-arm superiority trial that studied 500 patients with acute ischemic stroke caused by an proximal intracranial occlusion in the anterior circulation (distal intracranial carotid artery, MCA [M1 or M2], or anterior cerebral artery [A1 or A2]) established with CTA, magnetic resonance angiography (MRA), or digital subtraction angiography and a score of ≥2 on the NIHSS. The steering committee recommended that neuroimaging studies to assess vessel patency should preferably be done before or simultaneously with treatment with intravenous r-tPA. Initiation of endovascular treatment within 6 hours of stroke onset had to be possible. There were different specific exclusion criteria for patients with coagulation abnormalities, previous ischemic stroke, ICH, or severe head trauma, depending on whether intra-arterial fibrinolysis was contemplated. Patients who were eligible in agreement with national guidelines received intravenous r-tPA. Those with a nonfavorable response were eligible for inclusion. There was no specified time for observation to determine the response to intravenous r-tPA, nor was there an exact definition of what constituted a nonfavorable response, although recovery to a level that would not result in administration of intravenous r-tPA was suggested. Patients were...
randomly allocated 1:1 to either usual care alone or intra-arterial treatment plus usual care. Intra-arterial treatment consisted of arterial catheterization with a microcatheter to the level of occlusion and delivery of a fibrinolytic agent, mechanical thrombectomy, or both. The method of intra-arterial treatment was left to the discretion of the local interventionist. Sixty-four percent of participants had M1 occlusion alone, and an additional 27% had occlusion of M1 and the internal carotid artery (ICA). Of the 195 patients in the endovascular group of 233 who received endovascular treatment, onset to groin puncture was 260 minutes (interquartile range, 210–313 minutes), a stent retriever was used in 81.5%, and TICI grade 2b/3 recanalization was achieved in 59%. The treatment effect was estimated as an odds ratio (OR), adjusted for prespecified prognostic factors that intra-arterial treatment would lead to lower mRS score at 90 days, compared with usual care alone (shift analysis). The adjusted OR was 1.67 (95% confidence interval [CI], 1.21–2.30) in favor of intervention. There was an absolute difference of 13.5% (95% CI, 5.9–21.2) in the rate of functional independence (mRS score, 0–2) in favor of the intervention (32.6% versus 19.1%). There were no significant differences in mortality or the occurrence of sICH. Most patients (445 of 500) received intravenous r-tPA and showed benefit in subgroup analysis. There were too few patients who did not receive intravenous r-tPA to draw any conclusions.15 In a subsequent presentation at the 2015 International Stroke Conference, the MR CLEAN investigators reported a stroke onset–to–reperfusion time of 332 minutes (interquartile range, 279–394 minutes) and demonstrated a marked decline in clinical benefit with time so that the benefit was no longer statistically significant if reperfusion occurred after 6 hours 19 minutes.16

The Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanализation Times (ESCAPE) was a PROBE, 2-arm superiority trial of 316 patients with disabling acute ischemic stroke (NIHSS score >5) who could be randomized up 12 hours after the onset. Groin puncture had to be possible within 60 minutes of CT/CTA. Nonenhanced CT and CTA (preferably multiphase) were performed rapidly with a target doorto-imaging time of 25 minutes to identify participants with a small infarct core (by Alberta Stroke Program Early CT Score [ASPECTS]6–10 or CT perfusion), an occluded proximal intracranial artery in the anterior circulation (internal carotid, M1 MCA, or ≥2 M2s), and moderate to good collateral circulation defined as “the filling of 50% or more of the middle cerebral artery pial arterial circulation on CTA (preferably on multiphase CTA).” There were no exclusions for coagulopathy, prior stroke, or head trauma. Fifty-eight patients received intravenous r-tPA at a community hospital and then were transferred to an ESCAPE endovascular center. Participants were randomly assigned 1:1 to receive guideline-based care alone or guideline-based care plus endovascular treatment with the use of available thrombectomy devices. The use of retrievable stents and suction through a balloon guide catheter during thrombus retrieval was also recommended. Participants in both groups received intravenous r-tPA within 4.5 hours after onset if they met accepted local guidelines. The primary outcome was the OR that the intervention would lead to lower scores on the mRS at 90 days (shift analysis). After the release of the MR CLEAN results, an interim analysis conducted earlier than planned showed that a stopping criterion based on the prespecified O’Brien-Fleming stopping boundary had been crossed, and the trial was stopped. For the primary end point, the adjusted OR (indicating the odds of improvement of 1 point on the mRS) was 3.1 (95% CI, 2.0–4.7) favoring endovascular intervention. The proportion of patients with an mRS score of 0 to 2 at 90 days was 53.0% in the intervention group and 29.3% in the control group (P<0.001). Mortality at 90 days was 10.4% in the intervention group and 19.0% in the control group (adjusted rate ratio, 0.5; 95% CI, 0.3–0.8). The rate of sICH clinically determined at the study sites was 3.6% in the endovascular intervention group and 2.7% in the control group (adjusted rate ratio, 1.2; 95% CI, 0.3–4.6). Of the 165 participants randomized to endovascular intervention, retrievable stents were used in 130 of the 151 (86.1%) who underwent an endovascular procedure. TICI grade 2b/3 recanalization was observed in 72.4% in the endovascular group. In subgroup analysis, similar benefit was observed in the 235 patients who received intravenous r-tPA (OR, 2.5; 95% CI, 1.6–4.0) and the 76 who did not (OR, 2.6; 95% CI, 1.1–5.9). Only 49 participants (15.5%) underwent randomization ≥26 hours after symptom onset, too few to assess efficacy in the 6- to 12-hour time window.18

Solitaire FR With the Intention for Thrombectomy as Primary Endovascular Treatment of Acute Ischemic Stroke (SWIFT PRIME) was a PROBE-design trial that randomized 196 patients with acute ischemic stroke and NIHSS scores of 8 to 29 who received intravenous r-tPA within 4.5 hours of onset and had CTA or MRA confirmation of intracranial ICA, M1, or carotid terminus occlusion. If CTA or MRA was part of the local standard of care, it was performed at initial evaluation before intravenous r-tPA was started; if not, it was performed after review of the initial imaging and signing of informed consent. Groin puncture had to be possible within 6 hours of stroke onset. There were exclusion criteria for coagulopathies. Initially, CT perfusion or multimodal MRI was required, and enrollment was restricted to patients with the target mismatch profile (as assessed by specialized software19) and defined as follows: The ischemic core lesion measured ≤50 mL; the volume of tissue with a time to maximum delay of >10 seconds was ≤100 mL; the mismatch volume was at least 15 mL; and the mismatch ratio was >1.8. Midway through the trial, the inclusion criteria were modified to accommodate sites with limited perfusion imaging capability. Sites with perfusion imaging were encouraged to continue to use the target mismatch criteria. Sites without perfusion imaging used ASPECTS (ASPECTS >6 was required). A total of 71 patients were enrolled under the initial imaging entry criteria and 125 patients under the revised imaging entry criteria. Perfusion imaging was performed and used for selection in 82.6%. Seventy-three percent of participants had M1 occlusion, and 17% had ICA occlusion. Intravenous r-tPA was administered at an outside hospital in 35%. Participants were randomized 1:1 to treatment with intravenous r-tPA alone or to treatment with intravenous r-tPA followed by neurovascular thrombectomy with the use of a stent retriever. After the results of the MR CLEAN trial and the passing of stopping boundaries in the ESCAPE trial were announced, a decision was made to conduct the first interim efficacy analysis a little earlier than originally planned. The results of this interim efficacy analysis
Table 4. Selected Clinical Outcomes for Recent Randomized, Clinical Trials of Endovascular Treatments for Acute Ischemic Stroke

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary End Point</th>
<th>Death (90 d/3 mo)</th>
<th>Symptomatic ICH</th>
<th>mRS 0 to 2 at 90 d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active, Control, %</td>
<td>Active, Control, %</td>
<td>Active, Control, %</td>
<td>Active, Control, %</td>
</tr>
<tr>
<td>SYNTHESIS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expansion</td>
<td>30.4</td>
<td>34.8</td>
<td>0.71 (0.44 to 1.14)*</td>
<td>14.4</td>
</tr>
<tr>
<td>IMS III</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS 0 to 2 at 90 d</td>
<td>40.8</td>
<td>38.7</td>
<td>1.5 [-6 to 9]†</td>
<td>19.1</td>
</tr>
<tr>
<td>MR RESCUE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean mRS</td>
<td>3.9</td>
<td>3.9</td>
<td>P=0.99</td>
<td>19</td>
</tr>
<tr>
<td>MR CLEAN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improvement in mRS at 90 d (shift analysis)</td>
<td>1.67</td>
<td>21.2 to 2.3)*</td>
<td></td>
<td>90 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESCAPE</td>
<td>Improvement in mRS at 90 d (shift analysis)</td>
<td>3.1 (2.0 to 4.7)*</td>
<td>10.4</td>
<td>19</td>
</tr>
<tr>
<td>SWIFT PRIME</td>
<td>Improvement in mRS at 90 d 5 and 6 combined (shift analysis)</td>
<td>P=0.001</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>EXTEND-IA</td>
<td>Median reperfusion at 24 h</td>
<td>4.7 (2.5 to 9.0)*</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Decrease in NIHSS 8 or NIHSS 0, 1 at 3 d</td>
<td>6.0 (2.0 to 18.0)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>REVASCAT</td>
<td>Improvement in mRS at 90 d 5 and 6 combined (shift analysis)</td>
<td>1.7 (1.05 to 2.8)$</td>
<td>18</td>
<td>16</td>
</tr>
</tbody>
</table>

(Continued)

Demonstrated that the prespecified criteria for stopping the trial at the first interim analysis were met. The 2 simultaneous success criteria used for the primary end point were both in favor of endovascular intervention: improved distribution (shift analysis) of mRS score at 90 days (P<0.001) and increased proportion with mRS score of 0 to 2 at 90 days (60% in the endovascular group and 35% in the nonendovascular group; risk ratio, 1.70; 95% CI, 1.23–2.33). There were no significant differences in death or sICH. TICI grade 2b/3 recanalization was observed in 88% of the endovascular group.20

The Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial (EXTEND-IA) was similar in design to SWIFT PRIME. Seventy participants who were eligible with the use of “standard criteria” to receive intravenous rt-PA within 4.5 hours of stroke onset were randomized in a PROBE design to receive either intravenous rt-PA only or intravenous rt-PA plus endovascular therapy with a stent retriever. groin puncture had to be within 6 hours, and endovascular treatment had to be completed within 8 hours after stroke onset. CT or MRI had to be performed before intravenous rt-PA was started. Occlusion of the ICA, M1, or M2 on CTA was required. In addition, CT or MRI perfusion imaging had to show a mismatch ratio of >1.2, an absolute mismatch volume of >10 mL, and an infarct core lesion volume of <70 mL as assessed with specialized software.19 There were specified exclusion criteria for coagulopathies. Occlusion of the ICA and M1 was present
Table 4. Continued

<table>
<thead>
<tr>
<th>N r-tPA Subgroups</th>
<th>Time Subgroups</th>
<th>ASPECTS Subgroups</th>
<th>NIHSS Subgroups</th>
<th>Age Subgroups</th>
<th>Vessel Subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV r-tPA n Comparison</td>
<td>Time n Comparison</td>
<td>ASPECTS n Comparison</td>
<td>NIHSS n Comparison</td>
<td>Age y n Comparison</td>
<td>Vessel n Comparison</td>
</tr>
<tr>
<td>None</td>
<td>0 to 3 h to treatment</td>
<td>&lt;11</td>
<td>0.79</td>
<td>129</td>
<td>0.57</td>
</tr>
<tr>
<td></td>
<td>3 to 4.5 h</td>
<td>≥11</td>
<td>0.88</td>
<td>233</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>&gt;4.5 h</td>
<td>28</td>
<td>0.28</td>
<td>(0.03 to 22.1)*</td>
<td>(0.4 to 1.92)*</td>
</tr>
<tr>
<td>All</td>
<td>&lt;120 min</td>
<td>345</td>
<td>1.24</td>
<td>(0.68 to 1.74)*</td>
<td>(0.79 to 1.34)*</td>
</tr>
<tr>
<td></td>
<td>&gt;120 min</td>
<td>310</td>
<td>0.88</td>
<td>(0.6 to 1.26)*</td>
<td>(0.67 to 1.87)*</td>
</tr>
<tr>
<td>Yes</td>
<td>445</td>
<td>1.71</td>
<td>(1.22 to 2.40)*</td>
<td>(1.51 to 4.85)*</td>
<td>(1.11 to 2.34)*</td>
</tr>
<tr>
<td>No</td>
<td>55</td>
<td>2.06</td>
<td>(0.69 to 6.13)*</td>
<td>(1.21 to 2.38)*</td>
<td>(0.89 to 4.35)*</td>
</tr>
<tr>
<td></td>
<td>&lt;180 min</td>
<td>449</td>
<td>1.69</td>
<td>(0.69 to 4.6)*</td>
<td>(1.1 to 6.46)*</td>
</tr>
<tr>
<td></td>
<td>&gt;180 min</td>
<td>25</td>
<td>2.6</td>
<td>(1.6 to 4.0)*</td>
<td>(1.5 to 4.5)*</td>
</tr>
<tr>
<td></td>
<td>&gt;8 h</td>
<td>49</td>
<td>1.7</td>
<td>(0.7 to 4.8)</td>
<td>(1.0 to 7.2)*</td>
</tr>
<tr>
<td>All</td>
<td>&lt;180 min</td>
<td>96</td>
<td>1.62</td>
<td>(1.08 to 2.42)**</td>
<td>(1.08 to 2.42)**</td>
</tr>
<tr>
<td></td>
<td>&gt;180 min</td>
<td>94</td>
<td>1.77</td>
<td>(1.0 to 7.1)**</td>
<td>(0.73 to 5.33)**</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>150</td>
<td>1.4</td>
<td>≤4.5 h to randomized</td>
<td>135</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>56</td>
<td>2.7</td>
<td>&gt;4.5 h</td>
<td>71</td>
<td>1.4</td>
</tr>
</tbody>
</table>

(Continued). *Adjusted odds ratio (95% confidence interval [CI]). †Adjusted difference, 95% CI. ‡Relative risk, 99% CI. §Adjusted rate ratio, 95% CI. ¶Odds ratio, 95% CI. ‖Risk ratio, 95% CI. **Relative risk, 95% CI. ††Adjusted risk ratio, 95% CI.

in 31% and 54%, respectively. The coprimary outcomes were reperfusion at 24 hours and early neurological improvement (≥8-point reduction on the NIHSS or a score of 0 or 1 at day 3). The mRS score at 90 days was a secondary outcome. After the release of the MR CLEAN results, an unplanned interim efficacy analysis was implemented on the basis of a Haybittle-Peto stopping rule. The results of the interim analysis showed that the stopping criteria for efficacy were met, and the trial was halted. The percentage of ischemic territory that had undergone reperfusion at 24 hours was greater in the endovascular therapy group than in the intravenous r-tPA–only group (median, 100% versus 37%; P<0.001). Endovascular therapy, initiated at a median of 210 minutes (interquartile range, 166–251 minutes) after the onset of stroke, increased early neurological improvement at 3 days (80% versus 37%; P=0.002). More patients achieved functional independence in the endovascular group (score of 0 to 2 on the mRS, 71% versus 40%; P=0.01). There were no significant differences in rates of death or sICH. Recanalization to TICI grade 2b/3 was achieved in 86% of patients in the endovascular group at a median of 248 minutes (interquartile range, 204–277 minutes) after stroke onset. 21

Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours (REVASCAT) was a PROBE-design trial.
randomizing 206 patients with acute ischemic stroke and an NIHSS score of ≥6 who had intracranial ICA or M1 occlusion by CTA, MRA, or digital subtraction angiography. Patients who had received intravenous r-tPA were eligible if there was no significant neurological improvement (criteria specified in the protocol) at 30 minutes after initiation of the infusion and vascular imaging at this time confirmed an eligible occlusion. Groin puncture had to be possible within 8 hours of stroke onset. There were exclusion criteria for coagulopathies. The main exclusion criteria on imaging were ASPECTS of <7 on nonenhanced CT or <6 on diffusion-weighted imaging–MRI. After the enrollment of 160 patients, the inclusion criteria were modified to include patients up to the age of 85 years (initially, 80 years was maximum allowed) with an ASPECTS of >8. Twenty-six percent had ICA occlusion, and 65% had M1 occlusion. Participants were randomized 1:1 to receive either medical therapy alone or thrombectomy with a stent retriever. Intravenous r-tPA was administered to 73%. When results of other similar trials became known, the Data Safety Monitoring Board recommended the recruitment be stopped because the emerging results showed that equipoise was lost, although the interim results did not reach the prespecified stopping boundaries. The masked steering committee agreed. Because just 1 analysis was performed, adjustment for multiple comparisons was no longer performed, and 95% CIs were reported. The primary outcome analysis showed a common OR of improvement in the distribution of the mRS score (shift analysis) favoring endovascular treatment (adjusted OR, 1.7; 95% CI, 1.05–2.8). The proportion of patients with an mRS score of 0 to 2 at 90 days was 43.7% in the intervention group and 28.2% in the control group (adjusted OR, 2.1; 95% CI, 1.1–4.0). There were no significant differences in death or sICH. Ninety-five percent of those in the endovascular group underwent thrombectomy. TICI grade 2b/3 recanalization was observed in 66% of the endovascular group. Across the prespecified subgroups, there were no significant interactions according to NIHSS score, vessel occlusion site, baseline ASPECTS, administration of intravenous r-tPA, age, or time of randomization, although for time of randomization dichotomized at 4.5 hours; the P value for interaction was 0.9 with the latter group doing worse. No data are given for those who underwent groin puncture after 6 hours.22

Analysis and Conclusions

None of the 3 earlier studies carried out with primarily intra-arterial fibrinolysis or first-generation mechanical embolectomy devices showed a benefit of endovascular treatment over intravenous r-tPA in intravenous r-tPA–eligible patients either as a substitute for initial treatment (SYNTHESIS Expansion) or as subsequent intervention in those with persistent large-artery occlusion after intravenous r-tPA (IMS III and MR RESCUE). MR RESCUE also showed no benefit for other patients treated within 8 hours even if selected by multimodal neuroimaging criteria. These studies, using almost exclusively intra-arterial r-tPA and first-generation endovascular devices alone or in combination, achieved recanalization rates of 27% to 41%. The subsequent trials using stent retrievers almost exclusively demonstrated improved results for both recanalization rates and outcome. Studies have shown that clinical outcome improved with increasing effectiveness of recanalization. Those with partial recanalization (TICI grade 2a) did not do as well as those with nearly complete or complete recanalization (TICI grade 2b/3) reflected as both differences in discharge disposition (41.0% of the TICI grade 2b/3 group discharged home versus 17.4% of the TICI grade 2a group) and functional outcome (34% with a TICI grade of 2a had an mRS score of 0 to 2 at 90 days versus 49% with a TICI grade of 2b/3).12,21 TICI grade 2b/3 recanalization was achieved in 59% to 88% of endovascularly treated subjects in the 5 stent retriever trials, whereas in the previous 3 studies, the rate had been 25% to 41%, as mentioned above. All 5 stent retriever studies showed clinical benefit in the endovascular group.

Of the 5 stent retriever trials, MR CLEAN, ESCAPE, and SWIFT PRIME permitted use of salvage intra-arterial fibrinolytic drugs, whereas EXTEND-IA and REVASCAT did not. These data do not establish the benefit of intra-arterial fibrinolytic salvage, nor can they establish lack of benefit. Such salvage techniques may be reasonable to use in some clinical circumstances.

The MR RESCUE trial enrolled patients up to 8 hours from symptom onset and showed no benefit from endovascular therapy with first-generation devices regardless of penumbral imaging pattern. Three of the 5 stent retriever studies specified a 6-hour window after stroke onset (2 specified 6 hours to groin puncture; the third specified 6 hours to start treatment). Aggregate data from REVASCAT and ESCAPE with treatment permitted out to 8 and 12 hours show a benefit, but ESCAPE enrolled too few patients after 6 hours to provide useful data, and REVASCAT provides no data about patients who underwent groin puncture between 6 and 8 hours. How much the overall positivity in these 2 trials was completely driven by those treated at shorter times is unknown at this time. The only time-dependent data are from the MR CLEAN presentation, which are not consistent with a benefit of treatment beginning after 6 hours. It will take patient-level meta-analyses to sort this out.

Every or nearly every patient in the 5 stent retriever studies first received intravenous r-tPA. Only REVASCAT stipulated the specific guidelines to be used to determine intravenous r-tPA eligibility (“guidelines provided by the European Stroke Organization”). EXTEND-IA refers to “standard criteria,” and the 3 other trials used “national guidelines.” Because it is not the purpose of this update is to address eligibility criteria for intravenous r-tPA, we have used the phrase “guidelines from professional medical societies” to address this issue in our recommendations. Too few data are available from the small number of those who did not receive intravenous r-tPA, for either time-based or non–time-based exclusion criteria, to determine with certainty whether there are characteristics that identify those who benefited from endovascular treatment. Two trials (MR CLEAN and REVASCAT) stipulated waiting for a period of time after beginning the administration of intravenous r-tPA before proceeding to endovascular therapy, whereas 3 trials (ESCAPE, SWIFT PRIME, and EXTEND-IA) did not. On the basis of these data, a waiting period is not necessary to achieve beneficial outcome in these patients.
All of these studies enrolled participants ≥18 years of age. There are no randomized trials of endovascular therapy in patients <18 years of age. Ischemic stroke resulting from large-vessel occlusion is rare in children and young adults relative to older individuals, posing challenges to rigorous study of this clinical scenario. Case reports and case series have documented that high rates of recanalization and favorable outcomes in young patients can be achieved with endovascular therapy.24–26 Ideally, appropriate trials would be done to test the efficacy of endovascular therapy in young patients. Studies in the United States, the United Kingdom, Australia, and Canada have shown median times from onset of symptoms to initial brain imaging for pediatric stroke of 8.8 to 16 hours.27 This problem of diagnostic delay will need to be addressed if trials of endovascular treatment for acute ischemic stroke are to be conducted successfully in this population.

Four stent retriever trials used NIHSS scores as eligibility criteria (>2, >5, 8–29, and >5), and the fifth enrolled patients with a similar distribution of NIHSS scores. From these trials, there are insufficient data in patients with NIHSS scores <6 to determine whether there is an overall net benefit from endovascular therapy in this population. Further randomized trials in patients with low NIHSS scores may be warranted. An NIHSS score of ≥6 was the minimum score used in 2 trials, thus fulfilling the AHA’s Level of Evidence grading algorithm for Level A evidence.

Four of the 5 stent retriever trials used a prestroke function eligibility criterion. REVASCAT and SWIFT PRIME used a prestroke mRS score of 0 to 1; EXTEND-IA used mRS scores of 0 to 2; and ESCAPE used Barthel scores of ≥90 to 100. MR CLEAN did not set a threshold and did not provide data on prestroke function. Thus, there are good data from 4 trials for patients with good baseline function (including 2 that required an mRS score of 0 to 1) and very few data for those without good baseline function.

All 5 stent retriever studies required baseline nonenhanced CT or MRI. MR CLEAN did not use a specific ASPECTS criterion for eligibility; it was the only positive trial that permitted enrollment of patients with ASPECTS <6. Although the treatment effect in that trial favored intervention in all 3 ASPECTS subgroups of 0 to 4 (28 patients), 5 to 7 (92 patients), and 8 to 10 (376 patients), the point estimate in the subgroup with an ASPECTS of 0 to 4 was close to unity with wide CIs (adjusted common OR, 1.09; 95% CI, 0.14–8.46). In the ESCAPE trial secondary analyses based on ASPECTS, the risk ratio favoring intervention was 2.6 (95% CI, 1.7–4.1) for patients with an ASPECTS of 8 to 10 and 2.7 (95% CI, 1.0–7.2) for those with a score of 6 to 8. EXTEND-IA did not report secondary analyses based on ASPECTS. SWIFT PRIME reported similar benefit for those with ASPECTS of 8 to 10 (OR, 1.62; 95% CI, 1.17–2.24) and 6 to 7 (OR, 1.98; 95% CI, 0.73–5.33), although the small number of 43 patients in the latter group produced wide confidence bounds. REVASCAT reported greater benefit for those with ASPECTS ≥8 (OR, 2.2; 95% CI, 1.1–4.4) than for those with ASPECTS <8 (OR, 1.4; 95% CI, 0.7–2.9). On the basis of these data, the benefit from endovascular therapy in patients with ASPECTS <6 is uncertain, and further randomized, controlled trials are warranted. An ASPECTS ≥6 was the minimum score used in 2 trials, thus fulfilling the AHA’s Level of Evidence grading algorithm for Level A evidence.

Each of the 5 stent retriever trials used different strategies of imaging-based selection criterion in addition to nonenhanced CT or MRI. Common to all was required demonstration, usually with a noninvasive vessel imaging study (CTA or MRA), of a large-vessel occlusion before randomization. MR CLEAN and REVASCAT also allowed digital subtraction angiography screening to identify a target occlusion. Two trials required noninvasive imaging to be performed at initial evaluation before intravenous r-tPA was started (combined occurrence of no clot at endovascular intervention in 12 of 200 [6.0%]); a third recommended the same (no clot at endovascular intervention in 8 of 233 [3.4%]); and a fourth stipulated that it be done at all centers for which this was part of local standard of care but otherwise after consent was obtained (no clot at endovascular intervention in 7 of 98 [7.1%]). REVASCAT stipulated that the imaging study must be completed no more than 90 minutes but ideally within 60 minutes before groin puncture, and for patients who received intravenous tPA, an imaging study assessing vessel patency must be obtained at a minimum of 30 minutes after that start of intravenous r-tPA infusion (no clot at endovascular intervention in 5 of 103 [4.9%]). The REVASCAT strategy did not result in a decrease in the number who failed to have a clot present at the time of endovascular intervention compared with the other studies. The goal of intravenous r-tPA and of endovascular therapy is to recanalize the occluded vessel as soon as possible. After the initiation of intravenous r-tPA, some patients will experience successful recanalization, obviating the need to pursue follow-on endovascular therapy.28 However, because recanalization occurs in only a minority of patients with large-vessel occlusion receiving intravenous r-tPA alone (eg, 37.3% in the ESCAPE trial), noninvasive intracranial vascular imaging should proceed without delay before or immediately after initiation of r-tPA to identify the majority of patients who will benefit from follow-on endovascular therapy and to expedite its performance. This approach was explicitly taken by investigators in the ESCAPE trial, helping them achieve a median CT–to–groin puncture time of only 51 minutes.

The ESCAPE, EXTEND-IA, and SWIFT PRIME trials were initially designed with the intent to select and enroll only patients with small regions of ischemic cores and the presence of salvageable brain tissue (SWIFT PRIME and EXTEND-IA) and/or adequate collateral flow (ESCAPE). In ESCAPE, nonenhanced CT and CTA (preferably multiphase) were used to select patients with a target occlusion, small infarct core (ASPECTS 6–10), and moderate to good collateral circulation (filling of ≥50% pial arterial circulation visualized on CTA). EXTEND-IA required demonstration of potentially salvageable brain tissue on perfusion CT (mismatch ratio of >1.2, absolute mismatch volume of >10 mL) and ischemic core <70 mL (relative cerebral blood flow <30% of normal). All images were processed on site with a specialized software package.29 Penumbra tissue was defined as regions with time-to-maximum (Tmax) perfusion values >6 seconds that were
not included in the ischemic core. SWIFT PRIME excluded patients with evidence of frank ischemia in greater than one third of the MCA territory or involving >100 mL of tissue. For the first 71 patients enrolled, an additional inclusion criterion was the presence of target mismatch defined as infarct core ≤50 mL (as assessed by specialized software19) and ischemic penumbra ≥15 mL with a mismatch ratio >1.8. After the enrollment of the first 71 patients, the investigators switched to the criterion to ASPECTS of ≥6 for sites that did not have CT perfusion capability. To date, subgroup analyses with the various imaging criteria have not been published. In these trials, the use of advanced imaging selection criteria had the potential advantage of increasing the likelihood of showing treatment benefit by enhancing the study population with patients most likely to respond to therapy. However, the inherent disadvantage of this study design is the possibility that patients who may have responded to therapy were excluded. In contrast, the MR RESCUE trial was designed specifically to validate imaging biomarkers as a selection tool for endovascular therapy. However, the trial was unable to demonstrate an overall benefit from endovascular therapy with first-generation devices or in the subgroup with a favorable penumbral pattern. None of the 5 stent retriever studies was designed to validate the utility of the advanced imaging selection criteria themselves in either the early or late time windows. Thus, the role of these techniques for patient selection requires further study.

The overwhelming majority of patients in the stent retriever trials had ICA or proximal MCA (M1) occlusion. The number of patients with isolated M2 lesions was small; ESCAPE, REVASCAT, and SWIFT PRIME excluded patients with isolated M2 occlusions, although small numbers of these patients were enrolled in these trials. The distinction of M1 from M2 can be difficult in some patients because of early branches of the M1 such as the anterior temporal branch. Inadequate numbers of patients with occlusion of other vessels, including M3 and anterior cerebral artery occlusions and those in the vertebrobasilar circulation, also were enrolled to allow assessment of clinical efficacy in these territories.

The usefulness of mechanical thrombectomy devices other than stent retrievers is not well established, either for technical efficacy or for clinical benefit. Most of the patients in MR CLEAN and ESCAPE and all of the patients in EXTEND-IA, SWIFT-PRIME, and REVASCAT who underwent an endovascular procedure were treated with a stent retriever (81.5% in MR CLEAN, 86.1% in ESCAPE). These trials were not designed to demonstrate the superiority of stent retrievers over other devices such as snare or suction aspiration systems. Therefore, the recommendation that stent retrievers are preferred over MERCI is unchanged from the previous guidelines based on the SWIFT and TREVO 2 (Trevo Versus Merci Retrievers for Thrombectomy Revascularisation of Large Vessel Occlusions in Acute Ischaemic Stroke) studies.30,31 At the time the present guidelines were written, there were no published randomized, clinical trials demonstrating clinical benefit or comparing the relative effectiveness of other devices versus stent retrievers.

None of these studies specified requirements for the use of a proximal balloon guide catheter, large-bore distal-access catheter, or cervical guide catheter alone or in conjunction with stent retrievers. The concomitant use of distal-access suction catheters during stent retriever mechanical thrombectomy has been described in retrospective case series.32–34 The advantages of the combined stent-aspiration technique include a flexible large-bore catheter in a triaxial technique, which provides stability for the stent-retriever; flow reversal to prevent distal embolization during stent retrieval of the thrombus; and the potential synergistic effect of both techniques of suction aspiration and stent retrieval used simultaneously.32,34 Clinical experience has shown the combination of balloon guide catheters or distal-access/aspiration catheters and stent retrievers to provide rapid, effective, and safe recanalization.35,36

All the stent retriever trials allowed the inclusion of patients with proximal cervical carotid stenosis, and all but 1 trial allowed the inclusion of patients with complete atherosclerotic cervical carotid occlusion (SWIFT PRIME). One difficulty with this exclusion is that differentiating complete cervical carotid occlusion from a distal ICA occlusion is often not possible on CTA or MRA.37 The number of patients with cervical carotid occlusion or stenosis was not consistently reported but was substantial, ranging from 18.6% (REVASCAT) to 32.2% (MR CLEAN). Stenting of the underlying stenosis or occlusion was discouraged in the ESCAPE protocol. Thirty of the 75 patients with carotid stenosis or occlusion in the intervention arm were stented during the thrombectomy procedure in MR CLEAN. Nine of the 19 patients with carotid occlusion in REVASCATs were stented at the time of thrombectomy. The management of the underlying lesion was not reported in the other trials. Outcomes for the subgroup of patients with cervical carotid occlusion were reported in ESCAPE (OR, 8.7; 95% CI, 1.9–39.4) and MR CLEAN (adjusted OR, 1.43; 95% CI, 0.78–2.64). Although thrombectomy for patients with cervical ICA occlusion is clearly indicated by these data, the optimal management of the underlying stenosis is not clear. There are several potential advantages and disadvantages for angioplasty and stenting at the time of thrombectomy. Although immediate revascularization may reduce the risk of recurrent stroke, urgent stenting generally requires antiplatelet prophylaxis, which has been associated with intracranial hemorrhage in this setting. Carotid stenting and intracranial thrombectomy for the treatment of acute stroke resulting from tandem occlusions with aggressive antiplatelet therapy may be associated with a high incidence of intracranial hemorrhage.38,39 In addition, there is some risk for thromboembolic stroke at the time of stenting. Further studies are indicated.

General anesthesia with intubation and conscious sedation are the 2 most frequently used anesthetic approaches for patients with an acute ischemic stroke receiving endovascular therapy.40 No dedicated randomized, controlled, clinical trials have addressed this issue. The MR CLEAN investigators have reported that the outcomes of the 79 patients in the endovascular group who received general anesthesia were not different from the outcomes of the 267 nonendovascular control patients (adjusted OR, 1.09; 95% CI, 0.69–1.71.), whereas the outcomes for the 137 endovascular patients who did not receive general anesthesia were better than the outcomes for
the 267 control patients (adjusted OR, 2.13; 95% CI, 1.46–3.11). Similar data showing worse outcomes in those undergoing general anesthesia compared with conscious sedation for endovascular were reported in a recent meta-analysis of 9 nonrandomized studies comprising 1956 patients (814 received general anesthesia, 1142 received conscious sedation), with the largest study having 1079 patients and the smallest study having 66 patients. In this meta-analysis, compared with conscious sedation, general anesthesia was linked to lower odds of a favorable functional outcome (OR, 0.43; 95% CI, 0.35–0.53; P<0.01), higher odds of mortality (OR, 2.59; 95% CI, 1.87–3.58; P<0.01), and more adverse respiratory events (OR, 2.09; 95% CI, 1.36–3.23; P<0.01). No significant differences in the rates of asymptomatic ICH, sICH, or other vascular complications were seen between the groups. Furthermore, mean time to groin puncture, mean procedure time, and mean time from symptom onset to revascularization were not significantly different between the 2 techniques. There was substantial heterogeneity (I²>50%) across the included studies for the outcomes of functional status (I²=55%), time to revascularization (I²=60%), time to groin puncture (I²=83%), and procedure time (I²=91%). In most of the included studies, patients who received general anesthesia were typically in worse clinical condition at baseline, as reflected by their comparatively higher NIHSS scores. Only 6 of the 9 studies included information on baseline NIHSS score. Adjusting for NIHSS score by the use of meta-regression for the odds of having good functional outcomes yielded an OR of 0.38, which was similar to the unadjusted estimate of 0.43; however, the 95% CI became statistically insignificant (0.12–1.22). Thus, even after adjustment for initial stroke severity, the possibility of selection bias cannot be completely excluded. Patients with more severe strokes or poorer baseline conditioning may have received general anesthesia or may have been intubated before the procedure because of an actual or expected inability to maintain airway patency. Moreover, it is possible that the lower recanalization rates observed with general anesthesia in some studies were attributable to greater numbers of more technically difficult vascular occlusions in those who received general anesthesia. On balance, published data broadly indicate that conscious sedation might be safer and more effective than general anesthesia in the setting of endovascular therapy for acute ischemic stroke. However, specific randomized, controlled trial data are warranted to definitively establish conscious sedation as the preferred anesthetic technique in patients receiving endovascular treatment for acute ischemic stroke. Clinical trials are ongoing (http://www.clinicaltrials.gov; NCT01872884, NCT02317237).

The AHA’s Level of Evidence grading algorithm requires high-quality evidence from >1 randomized, controlled trial for Level of Evidence A. In accordance with this algorithm and the results from the 5 recent studies with stent retrievers summarized above, we concluded that the data supported Class I, Level of Evidence A recommendations but only for a carefully defined group of patients (see Recommendation 2). Subsequent meta-analysis of patient-level data may allow these recommendations to be expanded.

**Recommendations**

**Endovascular Interventions**

1. **Patients eligible for intravenous r-tPA should receive intravenous r-tPA even if endovascular treatments are being considered** (Class I; Level of Evidence A). (Unchanged from the 2013 guideline)

2. **Patients should receive endovascular therapy with a stent retriever if they meet all the following criteria** (Class I; Level of Evidence A). (New recommendation):
   - a. Prestroke mRS score 0 to 1,
   - b. Acute ischemic stroke receiving intravenous r-tPA within 4.5 hours of onset according to guidelines from professional medical societies,
   - c. Causative occlusion of the ICA or proximal MCA (M1),
   - d. Age ≥18 years,
   - e. NIHSS score ≥6,
   - f. ASPECTS of ≥6, and
   - g. Treatment can be initiated (groin puncture) within 6 hours of symptom onset

3. **As with intravenous r-tPA, reduced time from symptom onset to reperfusion with endovascular therapies is highly associated with better clinical outcomes. To ensure benefit, reperfusion to TICI grade 2b/3 should be achieved as early as possible and within 6 hours of stroke onset (Class I; Level of Evidence B-R).** (Revised from the 2013 guideline)

4. **When treatment is initiated beyond 6 hours from symptom onset, the effectiveness of endovascular therapy is uncertain for patients with acute ischemic stroke who have causative occlusion of the ICA or proximal MCA (M1) (Class IIb; Level of Evidence C). Additional randomized trial data are needed.** (New recommendation)

5. **In carefully selected patients with anterior circulation occlusion who have contraindications to intravenous r-tPA, endovascular therapy with stent retrievers completed within 6 hours of stroke onset is reasonable (Class IIa; Level of Evidence C).** Inadequate data are available at this time to determine the clinical efficacy of endovascular therapy with stent retrievers for those patients whose contraindications are time based or not time based (eg, prior stroke, serious head trauma, hemorrhagic coagulopathy, or receiving anticoagulant medications). (New recommendation)

6. **Although the benefits are uncertain, the use of endovascular therapy with stent retrievers may be reasonable for carefully selected patients with acute ischemic stroke in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have causative occlusion of the M2 or M3 portion of the MCAs, anterior cerebral arteries, vertebral arteries, basilar artery, or posterior cerebral arteries (Class IIb; Level of Evidence C).** (New recommendation)

7. **Endovascular therapy with stent retrievers may be reasonable for some patients <18 years of age with acute ischemic stroke who have documented large-vessel occlusion in whom treatment can be initiated (groin puncture) within 6
hours of symptom onset, but the benefits are not established in this age group (Class III; Level of Evidence C). (New recommendation)

8. Although its benefits are uncertain, the use of endovascular therapy with stent retrievers may be reasonable for patients with acute ischemic stroke in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have prestroke mRS score >1, ASPECTS <6, or NIHSS score <6 and causative occlusion of the ICA or proximal MCA (M1) (Class IIb; Level of Evidence B-R). Additional randomized trial data are needed. (New recommendation)

9. Observing patients after intravenous r-tPA to assess for clinical response before pursuing endovascular therapy is not required to achieve beneficial outcomes and is not recommended. (Class III; Level of Evidence B-R). (New recommendation)

10. Use of stent retrievers is indicated in preference to the MERCI device. (Class I; Level of Evidence A). The use of mechanical thrombectomy devices other than stent retrievers may be reasonable in some circumstances (Class IIb, Level B-NR). (New recommendation)

11. The use of a proximal balloon guide catheter or a large-bore distal-access catheter rather than a cervical guide catheter alone in conjunction with stent retrievers may be beneficial (Class IIa; Level of Evidence C). Future studies should examine which systems provide the highest recanalization rates with the lowest risk for nontarget embolization. (New recommendation)

12. The technical goal of the thrombectomy procedure should be a TICI grade 2b/3 angiographic result to maximize the probability of a good functional clinical outcome (Class I; Level of Evidence A). Use of salvage technical adjuncts, including intra-arterial fibrinolysis, may be reasonable to achieve these angiographic results if completed within 6 hours of symptom onset (Class IIb; Level of Evidence B-R). (New recommendation)

13. Angioplasty and stenting of proximal cervical atherosclerotic stenosis or complete occlusion at the time of thrombectomy may be considered, but the usefulness is unknown (Class IIb; Level of Evidence C). Future randomized studies are needed. (New recommendation)

14. Initial treatment with intra-arterial fibrinolysis is beneficial for carefully selected patients with major ischemic strokes of <6 hours' duration caused by occlusions of the MCA (Class I; Level of Evidence B-R). However, these data are derived from clinical trials that no longer reflect current practice, including the use of fibrinolytic drugs that are not available. A clinically beneficial dose of intra-arterial r-tPA is not established, and r-tPA does not have US Food and Drug Administration approval for intra-arterial use. As a consequence, endovascular therapy with stent retrievers is recommended over intra-arterial fibrinolysis as first-line therapy (Class I; Level of Evidence E). (Revised from the 2013 guideline)

15. Intra-arterial fibrinolysis initiated within 6 hours of stroke onset in carefully selected patients who have contraindications to the use of intravenous r-tPA might be considered, but the consequences are unknown (Class III; Level of Evidence C). (Revised from the 2013 guideline)

16. It might be reasonable to favor conscious sedation over general anesthesia during endovascular therapy for acute ischemic stroke. However, the ultimate selection of anesthetic technique during endovascular therapy for acute ischemic stroke should be individualized on the basis of patient risk factors, tolerance of the procedure, and other clinical characteristics. Randomized trial data are needed (Class IIb; Level of Evidence C). (New recommendation)

Imaging

1. Emergency imaging of the brain is recommended before any specific treatment for acute stroke is initiated (Class I; Level of Evidence A). In most instances, nonenhanced CT will provide the necessary information to make decisions about emergency management. (Unchanged from the 2013 guideline)

2. If endovascular therapy is contemplated, a non-invasive intracranial vascular study is strongly recommended during the initial imaging evaluation of the acute stroke patient but should not delay intravenous r-tPA if indicated. For patients who qualify for intravenous r-tPA according to guidelines from professional medical societies, initiating intravenous r-tPA before noninvasive vascular imaging is recommended for patients who have not had noninvasive vascular imaging as part of their initial imaging assessment for stroke. Noninvasive intracranial vascular imaging should then be obtained as quickly as possible (Class I; Level of Evidence A). (New recommendation)

3. The benefits of additional imaging beyond CT and CTA or MRI and MRA such as CT perfusion or diffusion- and perfusion-weighted imaging for selecting patients for endovascular therapy are unknown (Class IIIb; Level of Evidence C). Further randomized, controlled trials may be helpful to determine whether advanced imaging paradigms using CT perfusion, CTA, and MRI perfusion and diffusion imaging, including measures of infarct core, collateral flow status, and penumbra, are beneficial for selecting patients for acute reperfusion therapy who are within 6 hours of symptom onset and have an ASPECTS <6. Further randomized, controlled trials should be done to determine whether advanced imaging paradigms with CT perfusion, MRI perfusion, CTA, and diffusion imaging, including measures of infarct core, collateral flow status, and penumbra, are beneficial for selecting patients for acute reperfusion therapy who are beyond 6 hours from symptom onset. (New recommendation)

Systems of Stroke Care

1. Patients should be transported rapidly to the closest available certified primary stroke center
or comprehensive stroke center or, if no such centers exist, the most appropriate institution that provides emergency stroke care as described in the 2013 guidelines (Class I; Level of Evidence A). In some instances, this may involve air medical transport and hospital bypass. (Unchanged from the 2013 guideline)

2. Regional systems of stroke care should be developed. These should consist of the following:
   a. Healthcare facilities that provide initial emergency care, including administration of intravenous r-tPA, such as primary stroke centers, comprehensive stroke centers, and other facilities, and
   b. Centers capable of performing endovascular stroke treatment with comprehensive periprocedural care, including comprehensive stroke centers and other healthcare facilities, to which rapid transport can be arranged when appropriate (Class I; Level of Evidence A). (Revised from the 2013 guideline)

3. It may be useful for primary stroke centers and other healthcare facilities that provide initial emergency care, including administration of intravenous r-tPA, to develop the capability of performing emergency noninvasive intracranial vascular imaging to most appropriately select patients for transfer for endovascular intervention and to reduce the time to endovascular treatment (Class IIb; Level of Evidence C). (Revised from the 2013 guideline)

4. Endovascular therapy requires the patient to be at an experienced stroke center with rapid access to cerebral angiography and qualified neurointerventionalists. Systems should be designed, executed, and monitored to emphasize expeditious assessment and treatment. Outcomes for all patients should be tracked. Facilities are encouraged to define criteria that can be used to credential individuals who can perform safe and timely intra-arterial revascularization procedures (Class I; Level of Evidence E). (Revised from the 2013 guideline)

Disclosures

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<th>Writing Group Member</th>
<th>Employment</th>
<th>Research Grant</th>
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*Modest.
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Reviewers

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*Mosted.
†Significant.

References


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Embolectomy for stroke with emergent large vessel occlusion (ELVO): report of the Standards and Guidelines Committee of the Society of NeuroInterventional Surgery


INTRODUCTION

Stroke is the leading cause of adult disability in North America and is the fifth most common cause of death. The natural history of patients with acute ischemic stroke and occlusion of a major intracranial vessel such as the internal carotid artery (ICA), middle cerebral artery (MCA), or basilar artery is dismal, with high rates of mortality and low rates of disability-free survival. We introduce the term ‘Emergent Large Vessel Occlusion (ELVO)’ to describe this clinical scenario.

Among acute ischemic stroke, ELVO accounts for the greatest proportion of patients with long-term disability. For the past two decades the use of endovascular therapy has been performed in many centers across the world. The therapies have spanned from infusion of thrombolytic agents to mechanical embolectomy with the introduction of first-generation devices, aspiration-based embolectomy techniques, and the use of stent-retriever based procedures. However, these embolectomy trials were single-arm trials demonstrating safety of the procedure and technique or superiority over another, without direct comparison with standard medical therapy alone.

In the past 3 years, several major trials have been published comparing endovascular therapy with standard medical therapy alone. The purpose of this document is to summarize the results of these trials and synthesize the level of evidence supporting the use of embolectomy in patients with ELVO.

MATERIALS AND METHODS

This document was prepared by the Standards and Guidelines Committee of the Society of NeuroInterventional Surgery, a multidisciplinary society representing the leaders in the field of endovascular therapy for neurovascular disease. The strength of the evidence supporting each recommendation was summarized using a scale previously described by the American Heart Association.

DISCUSSION AND RECOMMENDATIONS

Role of intravenous thrombolysis

In 1996 the FDA approved the use of recombinant tissue plasminogen activator (tPA) for the treatment of acute ischemic stroke within 3 h of symptom onset, based on the landmark NINDS trial. This medication is delivered intravenously (IV), with a total dose of 0.9 mg/kg delivered 10% as a bolus and the remainder as an infusion over 60 min. In 2009, based on a pooled analysis of multiple randomized trials including the European Cooperative Acute Stroke Study III, the time window for IV tPA was expanded to 4.5 h from symptom onset. Additional relative exclusion criteria for patients in the 3–4.5 h time window included age >80, use of any anticoagulant regardless of International Normalized Ratio (INR), the combination of both prior stroke and diabetes, and National Institute of Health Stroke Scale (NIHSS) score ≥25. While the FDA approval for tPA has not been changed to reflect this time window, national guidelines have endorsed this usage.

The primary limitation with IV tPA is the limited rates of recanalization for ELVO. In a study using continuous transcranial ultrasound insonation, rates of complete recanalization with ELVO were only 29% for M1 segment of the MCA, 20.3% for combined M1 segment and distal ICA, and 6% for total ICA occlusion.

Summary and recommendation: IV thrombolysis should be offered to all eligible patients presenting within 3.0 h of symptom onset (AHA Class I, level of evidence A). Patients who meet the additional criteria also benefit from IV thrombolysis between 3.0 and 4.5 h from symptom onset (AHA Class I, level of evidence B). Intra-arterial thrombolysis should not be withheld in eligible patients in whom subsequent endovascular therapy is planned.

Intra-arterial thrombolysis

Intra-arterial pharmacological thrombolysis using pro-urokinase infusion in the Prolyse in Acute Cerebral Thromboembolism Trial I (PROACT-I)


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and PROACT II trials was safe and more effective than placebo infusion for patients with acute MCA occlusion within 6 h of symptom onset.\cite{5,6} In PROACT II, the Thrombolysis In Cerebral Ischemia (TICI) grade 2–3 recanalization rate in the treatment arm was 66%, although TICI 3 rates were only 19%.\cite{7} A meta-analysis combined the results from PROACT and PROACT-II with results from the Japanese Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT) and found higher rates of good and excellent clinical outcomes in patients treated with thrombolysis compared with placebo.\cite{8}

While no randomized trials have compared intra-arterial thrombolysis (IAT) with embolectomy, it is difficult to recommend primary IAT over embolectomy. This is primarily because the rates of near complete and complete recanalization using the TICI score (TICI 2b and TICI 3, respectively) appear to be higher with mechanical embolectomy than with IAT alone, especially with current mechanical thrombectomy device technology.\cite{9} Regardless, there may still be a role for IAT in cases where anatomic reasons preclude direct embolectomy.

Summary and recommendation: Intra-arterial thrombolysis is reasonable in patients presenting within a major stroke with occlusion of the middle cerebral artery in whom direct catheter access for embolectomy is precluded for anatomic reasons, as long as thrombolysis can be completed within 6 h from symptom onset (AHA Class IIa, level of evidence B).

**Embolectomy for ELVO**

Feasibility and safety trials

The first device specifically designed for intracranial embolectomy was the Merci retriever (Stryker Neurovascular, Fremont, California, USA). The initial Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial showed TICI 2–3 recanalization rates of 60% and reasonable clinical outcomes with good clinical outcome (modified Rankin Scale (mRS) score 0–2) of 43.5%.\cite{10} The follow-up Multi Merci trial, which also allowed patients who had received IV thrombolysis to be included, continued to show reasonable recanalization rates of 68%, although a good outcome was only seen in 34%.\cite{11} However, neither of these trials was randomized. Similarly, device safety trials for suction embolectomy using the Penumbra system (Penumbra, Alameda, California, USA) demonstrated high rates of Thrombolysis in Myocardial Infarction (TIMI) 2/3 recanalization (81.6% using this technique), although a favorable clinical outcome was only seen in 25%.\cite{12} More recently, stent-retriever technology has been evaluated. The SWIFT trial established safety and efficacy of recanalization for the Solitaire FR device (Covidien, Mansfield, Massachusetts, USA), with 69% of patients achieving TIMI 2/3 recanalization and 58% having a favorable outcome (defined as 0 mRS 0–2 or return if pre-stroke mRS is pre-stroke mRS >2, or improvement in NIHSS ≥10 points).\cite{13} That trial also showed the superiority of the Solitaire device over the Merci retriever, with only 30% of patients randomized to the Merci device achieving 30% TIMI 2/3 recanalization. The latest device to be approved by the FDA in the USA is the Trevo (Stryker Neurovascular). The Trevo 2 trial demonstrated 86% TICI 2/3 recanalization (versus 60% in the MERCI group), and 40% had a favorable clinical outcome (mRS 0–2).\cite{14,15} While all of these trials showed increasing rates of recanalization as experience with stent-retrievers grew, no direct comparison with best medical therapy was performed.

Recent randomized trials comparing endovascular therapy with best medical management: lessons learned

In the SYNTHESIS expansion trial, patients were randomized to receive either IV tPA or endovascular therapy.\cite{16} No specific treatment protocol for endovascular therapy was required, nor was documentation of ELVO required for randomization. This trial showed similar rates of favorable clinical outcomes at 90 days for patients in both groups, despite an approximately 60 min delay in the start of endovascular therapy. In addition, the recanalization rates with endovascular therapy were not published.

In the MR RESUCE trial, 127 patients were randomized to either best medical therapy or best medical therapy combined with embolectomy.\cite{17} Pre-treatment imaging was either MRI (using both diffusion and perfusion weighted sequences) or CT perfusion. Patients were stratified into either ‘penumbral’ or ‘non-penumbral’ patterns based on the size of infarct core and presumed volume of territory at risk. Embolectomy showed no benefit in this trial compared with best medical therapy. Embolectomy in MR RESUCE included the Merci or Penumbra device, and although the TICI 2/3 rate was 67%, only 27% had a TICI 2b/3 recanalization. This may be a major reason why this trial was not successful. Time was also likely to have been a contributing factor as median time from onset to enrollment was 5.5 h. Prior data from single-arm trials had suggested that recanalization beyond the 6 h window may not be beneficial.\cite{18}

The IMS III trial was the largest randomized trial of endovascular stroke therapy.\cite{19,20} A total of 656 patients were randomized in a 2:1 fashion to a combination of IV tPA plus endovascular therapy (either additional tPA infusion or the use of an embolectomy device) or to IV tPA alone. Documentation of ELVO was not required for randomization. Patients were treated at a time of 208 min from symptom onset. Overall, the TICI 2/3 recanalization rate was 65% for ICA occlusions and 81% for occlusions involving the M1 segment of the MCA. TICI 2b/3 rates for these vessels were 38% and 44%, respectively. For the overall cohort, endovascular therapy showed no benefit over IV tPA alone. However, review of the subgroups as well as trial design does reveal some important subtleties.

The documentation of ELVO was not required for randomization in IMS III. In fact, among the patients allocated to receive endovascular therapy, 16% did not have any thrombus or treatable thrombus (as defined as ICA, M1 or proximal M2 segment MCA occlusion). Among the IMS III group of patients with documented ELVO by CT angiography (CTA), Rankin shift analysis showed a trend towards benefit to treatment.\cite{21} In addition, patients with an admission NIHSS of ≥20 also had a strong trend towards benefit from IAT for ELVO, both in the acute phase\cite{22} and also when follow-up was carried out at 6 months.\cite{23}

Another important relationship was the time from symptom onset to recanalization, a link which had already been shown for the precursor EMS and IMS II trials.\cite{24} In the IMS III trial, when recanalization could have been achieved before 347 min, patients benefited from the addition of endovascular therapy when evaluating quality-adjusted life years.\cite{25} However, when recanalization occurred later, there was no clinical benefit. A strong trend towards benefit was seen in patients who received IV tPA <2 h and who then had their groin puncture within 90 min of IV tPA administration.\cite{26} The likelihood of recanalization also played a role, with the trial spanning several generations of embolectomy devices and techniques. Of the patients who were actually administered IAT, the majority of patients were treated with IAT alone (138 patients, 41.3%). Most of the embolectomy procedures in IMS III used the Merci devices (95 patients, 28.1%), with a small portion treated with the Penumbra system (54 patients, 16.2%). Stent-retriever based techniques, which have been shown to have some of the highest recanalization rates, were only used in five patients (1.5%).
Summary: Lack of benefit for the overall cohort in MR RESCUE and IMS III overshadowed signals of benefit to selected subgroups. Patients with confirmed large vessel occlusion from the IMS III study as well as those treated early showed strong trends toward benefit from the addition of endovascular therapy. In addition, these trials did not make extensive use of modern embolectomy techniques, which have been shown to have higher recanalization rates than first and second generation techniques.

Current trials: MR CLEAN, ESCAPE, EXTEND-IA

Based upon the lessons learned from the aforementioned trials, several groups set out to design new trials to truly test the ability of the most recent techniques of endovascular therapy in patients with documented ELVO. A core component of these trials was the requirement of documented vessel occlusion with non-invasive imaging (ie, CTA or MR angiography (MRA)) prior to randomization. In addition, several of these trials placed strict time constraints in order to ensure rapid recanalization. Finally, the devices used in these trials were the third generation of embolectomy devices and have been shown to have some of the highest recanalization rates. Key inclusion criteria and differences between these trials are summarized in Table 1.

**MR CLEAN**

MR CLEAN is a multicenter randomized clinical trial of best medical therapy versus best medical therapy with IAT, including intra-arterial thrombolysis, mechanical embolectomy or both, in patients with anterior circulation ELVO. Conducted in 16 centers in the Netherlands, 500 patients were randomized, with 233 patients assigned to the interventional arm and 267 assigned to the control arm. The groups were well balanced, with a median NIHSS score of 17 in the intervention group and 18 in the control group; 25.7% of the patients in the intervention group had ICA occlusions compared with 29.3% in the control arm. Nearly all patients received IV tPA (intervention arm 87.1%; control arm 90.6%) with excellent time to IV tPA treatment (intervention arm 85 min; control arm 87 min). Time to groin puncture in the intervention arm was 260 min.

In assessment of the primary outcome, there was an OR of 1.67 (95% CI 1.21 to 2.30) of better outcome as assessed by mRS 0–2 at 90 days in the intervention arm. This benefit also extended to the secondary outcome measures. Statistically significant benefit or trends towards benefit were also seen in nearly all predefined subgroups, with the exception of those with pretreatment Alberta Stroke Program Early CT Score (ASPECTS) 0–4. TICI 2b/3 recanalization was seen in 58.7% of the patients treated in the intervention arm. Comparing CTA at 24 h, absence of residual occlusion was seen in 75.4% of patients in the intervention arm compared with only 32.9% in the control arm. Final infarct volume was also significantly less in the intervention arm (49 mL vs 79 mL).

No significant safety concerns were seen, with similar intracerebral hemorrhage rates (7.7% vs 6.4%) and mortality rates (18.9% vs 18.4% at 30 days). Procedural complications included embolization into new territory in 8.6%, vessel dissection in 1.7%, and vessel perforation in 0.9%.

This trial represented the first clinical trial showing benefit for IAT in patients with ELVO in the post-IV tPA era. Compared with prior trials, ELVO was confirmed with pretreatment vessel imaging and modern device technology in the form of stent-retrievers was used. There was also a higher proportion of ICA occlusion, which may have relative benefit than other occlusion locations. This benefit was also seen despite only a modest TICI 2b/3 recanalization rate.

**ESCAPE**

The Endovascular treatment for Small Core and Anterior circulation Proximal occlusion with Emphasis on minimizing CT to recanlization times (ESCAPE) trial is a randomized trial primary performed in Canada focusing on patients with ELVO within 12 h of symptom onset with minimum NIHSS score >5 and with baseline CT showing ASPECTS >5. The study investigators have emphasized rapid imaging to treatment times, with a goal of 60 min from initial image on non-contrast CT (NCCT) scan to groin puncture, and a goal of recanalization within 90 min from first CT image.

Conducted in 22 centers in Canada, the USA and Europe, 315 patients were randomized, with 165 patients assigned to the intervention arm and 150 patients assigned to the control arm. The groups were well balanced, with a median NIHSS score of 16 in the intervention group and 17 in the control. In the intervention arm, 27.6% of the patients had intracranial ICA occlusions compared with 26.5% in the control arm. Most patients received IV tPA as well (intervention arm 72.7%; control arm 78.6%). Median time from imaging to groin puncture was 51 min.

**Table 1** Brief summary of recently published trials comparing best medical therapy alone with best medical therapy plus embolectomy

<table>
<thead>
<tr>
<th></th>
<th>MR CLEAN</th>
<th>EXTEND-IA</th>
<th>ESCAPE</th>
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<tr>
<td>Number randomized</td>
<td>500</td>
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<td>315</td>
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<tr>
<td>Inclusion criteria</td>
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<td>19.1%</td>
<td>40%</td>
<td>29.3%</td>
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<td>mRS 0–2, medical+IAT</td>
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<tr>
<td>Recanalization (% TICI 2b/3)</td>
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<td>86%</td>
<td>72.4%</td>
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<td>Number needed to treat to have one additional patient independent at 90 days</td>
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</table>

ASPECTS, Alberta Stroke Program Early CT Score; CTA, CT angiography; CTP, CT perfusion; IAT, intra-arterial thrombolysis; MRA, MR angiography; MRP, MR perfusion; mRS, modified Rankin Scale; NCCT, non-contrast CT; TICI, Thrombolysis In Cerebral Ischemia.
When evaluating the primary endpoint, there was an OR of 1.7 for improved outcomes with the addition of embolectomy as opposed to best medical therapy alone, with 53% of the intervention arm achieving mRS 0–2 at 90 days versus 29% in the control arm. In addition, this benefit extended across all pre-specified subgroups, including patients below and above the age of 80 or those with and without cervical ICA occlusion. There were no safety concerns, with the rates of symptomatic intracranial hemorrhage of 2.7% in the intervention arm and 3.6% in the control arm. There was also a significant reduction in mortality, from 19.0% in the control arm to 10.4% in the intervention arm.

EXTEND IA

The Australian study EXTEND IA (Extending the time for Thrombolysis in Emergency Neurological Deficits with Intra-Arterial therapy) trial is a phase II randomized trial of ELVO patients with anterior circulation occlusion and a favorable imaging profile on CT or MRI advanced imaging including a mismatch ratio of >1:2, absolute mismatch >10 mL, and an ischemic core volume <70 mL. While only 70 patients were randomized, the study was halted by the Data and Safety Monitoring Board (DSMB) for reaching the pre-specified efficacy endpoint.

All patients were treated with IV tPA and 35 patients received IAT in addition. As with the other trials discussed here, baseline characteristics were similar, with a mean NIHSS score of 13 in the control group and 17 in the intervention group. Also similar to the other trials, 31% of patients in both groups were ICA occlusions.

For the primary endpoint of mRS 0–2 at 90 days there was a significant treatment benefit, with 71% of patients in the intervention arm reaching independence compared with 40% in the control arm (p=0.01). There were no safety concerns, with symptomatic hemorrhage rates of 6% in the control arm and 0% in the intervention arm.

Soon to be published embolectomy trials: SWIFT-PRIME and REVASCAT

SWIFT-PRIME

The Solitaire FR as Primary Treatment for Acute Ischemic Stroke (SWIFT-PRIME) trial is an international randomized controlled trial of IAT using the Solitaire stent-retriever in patients with anterior circulation ELVO. All patients were randomized to IV tPA alone or IV tPA with the addition of embolectomy. Patients were initially selected based on advanced imaging using target mismatch, but an amendment in February 2014 allowed enrollment if baseline imaging showed ASPECTS ≥6. The trial was also halted early, and preliminary analysis has shown a significant improvement in 90-day outcomes in the intervention arm compared with IV tPA alone.

REVASCAT

The RandomizEd Trial of reVascularizAtion With Solitaire FR Device Versus Best mediCal Therapy in the Treatment of Acute Stroke Due to anTerior Circulation Large Vessel Occlusion Presenting Within 8 Hours of Symptom Onset (REVASCAT) trial is a trial conducted in the Catalonia region of Spain, with the intra-arterial procedures being performed at four comprehensive stroke centers. Similar in design to other recent trials, patients were randomized to either best medical therapy (including IV tPA when eligible) or best medical therapy combined with embolectomy using the Solitaire device. Patients were eligible for randomization within 8 h of symptom onset. On December 2014, following the first pre-planned interim analysis, the DSMB concluded that equipoise no longer existed and the study was discontinued.

Choice of pretreatment imaging

A consistent theme across all of these studies was the use of pretreatment vessel imaging using CTA (or MRA) in order to confirm ELVO. Confirmation of vessel occlusion as quickly as possible is likely to be one of the reasons these studies were positive where others had failed. It will probably be important to have mechanisms in place to obtain rapid CTA (or MRA) on patients with a significant clinical deficit who may be candidates for embolectomy.

A large completed infarct core is a well-established exclusion criterion for endovascular treatment. The size of infarct, however, has varied across several studies, as has the choice of imaging in order to establish the size of the infarct core. Across these three studies, a variety of exclusions were used. MR CLEAN did not specifically exclude patients using any lower limit of NCCT ASPECTS value. ESCAPE excluded patients with NCCT ASPECTS value <6 and those with no collateral filling of the affected territory on CTA, as well as other exclusion criteria on CT perfusion, if performed. SWIFT-PRIME also used perfusion imaging to identify a ‘target mismatch’, including having a core volume of <50 mL. Later, the trial also allowed inclusion of patients with ASPECTS ≥6. EXTEND IA also used CT perfusion imaging to select patients as described above. REVASCAT excluded those with NCCT ASPECTS <7 (<8 in those aged ≥85 in a protocol amendment in mid-2014).

We will further summarize the details of pretreatment imaging in a separate review. At the present time there is inadequate randomized literature to recommend one imaging modality over another.

Time frame for treatment

The aforementioned studies varied in their times from onset to treatment as well as from imaging to treatment. While MR CLEAN and SWIFT-PRIME restricted treatment to those in whom groin puncture could be performed within 6 h of onset, REVASCAT allowed enrollment up to 8 h and ESCAPE permitted treatment up to 12 h. In both ESCAPE and SWIFT-PRIME there were time criteria from imaging to puncture as well: 60 min from NCCT to puncture in ESCAPE and 90 min from CTA confirmed occlusion to groin puncture in SWIFT-PRIME. These studies highlight the need for rapid mobilization of the neurointerventional team and the need for adequate support staff to meet these time goals.

Summary and recommendation: For patients with anterior circulation stroke and documented ELVO affecting the ICA or M1 segment of the MCA and a corresponding clinical deficit, the addition of endovascular embolectomy results in superior clinical outcomes compared with best medical therapy alone. Embolectomy needs to be performed as rapidly as possible for the greatest clinical benefit, and is best when performed within 6 h from onset of symptoms (AHA Class I, level of evidence A).

FUTURE DIRECTIONS

Now that the efficacy of IAT for patients with ELVO has been established, it is important that research continues, both for procedural and peri-procedural care. There are many additional factors in developing successful systems of care for patients with ELVO. The ability to perform rapidly embolectomy is a requirement for comprehensive stroke centers, but not all patients are initially seen at those centers. As such, changes in current pre-
hospital identification and transport mechanisms must be considered with an eye towards ensuring rapid access to embolectomy for all patients. Eligible patients evaluated at centers not capable of performing embolectomy need to be transported to comprehensive centers as quickly as possible.

In addition, we need to better elucidate the optimal imaging protocols for identifying patients most likely to benefit. Post-procedural care is also a vital component of good patient outcomes and should be emphasized. In addition, a quality improvement process within the institution which monitors outcomes and identifies opportunities to improve care on an ongoing basis will also likely improve the care we can deliver for these patients. Further optimization of embolectomy techniques needs to happen, as well as comparison of techniques (stent-retrievers vs direct aspiration; balloon guide catheters vs local aspiration). Refinement of techniques should also focus on minimizing emboli to additional territories, which occurred in 5.6% of the patients in the MR CLEAN trial.

Another major area for further research is the role of embolectomy in patients presenting beyond the 6 h window, such as those who awaken with symptoms of stroke. Research should also focus on whether physiologic imaging using MR perfusion or CT perfusion techniques can help select patients in these time windows.

CONCLUSION

Twenty years ago the landmark NINDS trial demonstrated a benefit to IV tPA compared with conventional therapy for patients within 3 h from stroke onset and began a transformation in acute stroke therapy. Now we have multiple randomized multicenter prospective trials providing Level 1, Class A evidence that, in patients with anterior circulation stroke and an ELVO, the addition of embolectomy to best medical therapy is superior to best medical therapy alone. We feel this represents a watershed moment in the care of these patients with the deadliest forms of stroke. Centers performing embolectomy should strive to duplicate the excellent recanalization rates and rapid treatment times achieved in these trials. Future directions should focus on optimizing systems of care to maximize patient access to rapid embolectomy, as well as further research refining the techniques of embolectomy and patient selection.

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Correction notice

This article has been corrected since it published online first. The fifth author’s name has been corrected.

Contributors

All authors contributed.

Competing interests

None.

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Embolectomy for stroke with emergent large vessel occlusion (ELVO): report of the Standards and Guidelines Committee of the Society of NeuroInterventional Surgery


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Initial hospital management of patients with emergent large vessel occlusion (ELVO): report of the standards and guidelines committee of the Society of NeuroInterventional Surgery


ABSTRACT

Objective To summarize the current literature regarding the initial hospital management of patients with acute ischemic stroke (AIS) secondary to emergent large vessel occlusion (ELVO), and to offer recommendations designed to decrease the time to endovascular treatment (EVT) for appropriately selected patients with stroke.

Methods Using guidelines for evidenced-based medicine proposed by the Stroke Council of the American Heart Association, a critical review of all available medical literature supporting best initial medical management of patients with AIS secondary to ELVO was performed. The purpose was to identify processes of care that most expeditiously determine the eligibility of a patient with an acute stroke for interventions including intravenous fibrinolysis with recombinant tissue plasminogen activator (IV tPA) and EVT using mechanical embolectomy.

Results This review identifies four elements that are required to achieve timely revascularization in ELVO. (1) In addition to non-contrast CT (NCCT) brain scan, CT angiography should be performed in all patients who meet an institutional threshold for clinical stroke severity. The use of any advanced imaging beyond NCCT should not delay the administration of IV tPA in eligible patients. (2) Activation of the neurointerventional team should occur as soon as possible, based on either confirmation of large vessel occlusion or a prespecified clinical severity threshold. (3) Additional imaging techniques, particularly those intended to physiologically select patients for EVT (CT perfusion and diffusion–perfusion mismatch imaging), may provide additional value, but should not delay EVT. (4) Routine use of general anesthesia during EVT procedures, should be avoided if possible. These workflow recommendations apply to both primary and comprehensive stroke centers and should be tailored to meet the needs of individual institutions.

Conclusions Patients with ELVO are at risk for severe neurologic morbidity and mortality. To achieve the best possible clinical outcomes stroke centers must optimize their triage strategies. Strategies that provide patients with ELVO with the fastest access to reperfusion depend upon detail-oriented process improvement.

INTRODUCTION

Within the past year, clinical trials have established American Heart Association (AHA) Class I Level A Evidence demonstrating the clinical benefit of modern endovascular therapy,1–5 in addition to best medical therapy for patients with acute ischemic stroke (AIS) presenting with emergent large vessel occlusion (ELVO). These studies reiterate that time to revascularization remains an important factor in any effort to achieve good clinical outcomes. Hence, it is now imperative to focus on innovations in the delivery of care and process improvements to create rapid access to both therapies, each critically time dependent.6–9 Secondary analysis of the MR CLEAN trial shows that the benefit of revascularization decreases non-linearly with time.8 It is important to remember that the effect of time reported in this trial is a summation of all patient outcomes, and the decline in the likelihood of a good outcome for any individual patient may be even more profound. Therefore, the goal of intervention is to achieve revascularization as quickly as possible for the benefit of the patient.

DEFINITIONS/ABBREVIATIONS

AIS – acute ischemic stroke
ASPECTS – Alberta Stroke Program Early Computed Tomographic Scoring
BRISK – Brisk Recanalization Ischemic Stroke Kit
CPSS – Cincinnati Pre-hospital Stroke Scale
Clinical Penumbra – term that implies a discordance between the clinical severity of a stroke and the volume of irreversibly injured brain (infarct core)
CSC – comprehensive stroke center
**Standards**

CTA – CT angiography

CTP – CT Perfusion

Delivery Innovation – efforts made improve the quality and efficiency of care delivery

Door to CT time – time interval between patient arrival at PSC or CSC and CT acquisition

Door to Needle Time – time interval between patient arrival at PSC or CSC and IV tPA bolus

Door to puncture time – time interval between patient arrival at PSC or CSC and groin access for embolectomy at CSC

DTR – Door to first recanalization – time interval between patient arrival at PSC or CSC and restoration of antegrade flow in the occluded blood vessel at CSC (usually time of stent-retriever deployment)

Door to final angiographic run – time interval between patient arrival at PSC or CSC and final angiographic run at CSC at which time final reperfusion score (mTICI) is assigned

DWI – diffusion-weighted imaging

ELVO – Emergent Large Vessel Occlusion

EMS – Emergency Medical Services

ER – Emergency Room

EVT – Endovascular Therapy (such as embolectomy)

Futile infarct – an amount of irreversibly injured brain thought to be incompatible with a favorable or good outcome (see MALCOM)

FAST – Face, arm, speech test

GA – general anesthesia (general endotracheal anesthesia (GETA) also used)

Ischemic Penumbra – oligemic tissue at risk for infarction if rapid revascularization is not achieved

LAMS – Los Angeles Motor Score

LSW – last seen well (does not imply time of onset)

LVO – large vessel occlusion (typically M1 segment and proximal); some authors may include M1 equivalent (2 M2 segment occlusions)

MAC – monitored anesthesia care

MALCOM – maximal admission lesion volume compatible with favorable outcome

NIHSS – National Institute of Health Stroke Scale

NCCCT – Non-contrast CT scan

NNT – number needed to treat (1/absolute difference *100)

Onset to treatment time – time interval from stroke onset to treatment (particular treatment requires specification)

Onset time – when patient last awake and symptom free or known to be “normal”

Picture to puncture – time interval from non-invasive imaging confirmation of ELVO (also known as the qualifying image) to groin puncture

PSC – primary stroke center (i.e. one where EVT is generally not available)

PSC picture to CSC puncture – see picture to puncture above; an important PSC:CSC pair stroke target for performance review

PWI – perfusion-weighted imaging (refers to MRI exclusively)

Qualifying Image – this is the image that demonstrates clot occluding blood flow and deemed to potentially require embolectomy

Recanalization – reperfusion is achieved by recanalization (reopening the blood vessel) but recanalization does not always guarantee reperfusion

Reperfusion – preferred term to describe antegrade flow restoration to a cerebral vascular territory. Reperfusion generally implies recanalization was achieved. The degree of reperfusion is most commonly categorized, at present, according to the mTICI score (see below)

RACE – Rapid Arterial oCclusion Evaluation

ROSIER – Recognition of Stroke in the Emergency Room

Stroke of unknown onset – category of strokes in which the time of onset is unknown thus complicating time threshold treatment decisions (includes wake-up strokes)

Time of onset – the time a stroke started (as distinct from wake-up and LSW)

mTICI – this denotes the modified Thrombolysis in Cerebral Infarction perfusion scale

mTICI 0 – no antegrade flow

mTICI 1 – contrast material passes beyond the area of occlusion but does not opacify the cerebral bed distal to the occlusion lesion

mTICI 2a – <50% opacification of the cerebral vascular bed beyond the lesion

mTICI 2b – >50% opacification of the cerebral vascular bed beyond the lesion

mTICI 3 – complete reperfusion

Wake-up stroke – one category of stroke with an unknown time of onset

**MATERIALS AND METHODS**

This document was prepared by the Standards and Guidelines Committee of the Society of NeuroInterventional Surgery (SNIS), a multidisciplinary society representing leaders in the field of endovascular therapy for neurovascular disease. The strength of the evidence supporting each recommendation was summarized using a scale previously described by the AHA. In cases where data were insufficient, either no recommendation was made or a recommendation was made based on the consensus of expert practice experience. Other aspects of this care continuum, such as prehospital management, the role of endovascular treatment (EVT), and post-procedural care, are dealt with separately.

**Discussion and recommendations**

For the patient with potential ELVO, we believe there are five initial assessment/management goals before endovascular reperfusion therapy:

1. Confirm an AIS (ie, exclude hemorrhage).
2. Determine candidacy for IV tissue plasminogen activator (tPA) and rapidly administer to all eligible patients.
3. Confirm or exclude the presence of a large vessel occlusion.
4. Determine candidacy for embolectomy, and then activate the neurointerventional team (if at a comprehensive stroke center (CSC)), or transfer to a CSC (if patient is at a primary stroke center (PSC)).
5. Provide optimal medical management to limit infarct expansion until reperfusion is established.

It is also important to note that in many cases, these goals can be accomplished in parallel. Various stroke process improvement strategies can be employed to efficiently accomplish the above initial management goals. Since hospital infrastructures vary between PSCs and CSCs with established endovascular teams, the goals in this document which are specific to PSCs are separately highlighted. The SNIS ideal stroke process timelines are presented in **table 1**. Although we recognize that most PSCs and CSCs may not be able to meet these idealized time targets, we believe the concepts and strategies presented herein will allow PSCs (door to needle time, PSC to puncture, etc) and CSCs (door to needle time, door to puncture time, door to first recanalization, etc) to achieve these goals within 18–24 months.
**Table 1  Society of Neurointerventional Surgery suggested stroke process time metrics**

<table>
<thead>
<tr>
<th>Action</th>
<th>Time (min)†</th>
<th>SNIS ‘ideal’ time‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Door to physician</td>
<td>&lt;10 On arrival</td>
<td></td>
</tr>
<tr>
<td>Door to NCCT/CTA</td>
<td>&lt;25 On arrival</td>
<td></td>
</tr>
<tr>
<td>Door to stroke team</td>
<td>&lt;15 &lt;10 min</td>
<td></td>
</tr>
<tr>
<td>Door to NCCT interpretation</td>
<td>&lt;45 &lt;15 min</td>
<td></td>
</tr>
<tr>
<td>Door to CTA interpretation</td>
<td>N/A &lt;20 min</td>
<td>(or 10 min after acquisition)</td>
</tr>
<tr>
<td>Door to IV tPA</td>
<td>&lt;50 &lt;30 min</td>
<td></td>
</tr>
<tr>
<td>Door to CTP/CTA (optional)</td>
<td>N/A &lt;30 min</td>
<td></td>
</tr>
<tr>
<td>CSC Door to puncture</td>
<td>N/A &lt;60 min</td>
<td></td>
</tr>
<tr>
<td>CSC Door to recanalization</td>
<td>N/A &lt;90 min</td>
<td></td>
</tr>
<tr>
<td>PSC picture to CSC puncture§</td>
<td>N/A &lt;90 min</td>
<td></td>
</tr>
</tbody>
</table>

*Assuming emergency medical services prenotification.
†AHA 2013 standard.
‡Assuming direct transfer to biplane neuroangiography suite when feasible.
§Assuming emergency medical services prenotification.

**Stroke team activation**

Stroke code team activation (‘brain attack’ team of stroke nursing coordinators, emergency room physician, stroke neurologist, radiologist, CT and/or MR technologists) should be standardized independently of the mechanism by which a patient with AIS presents (emergency medical services, EMS transport, emergency department walk-in, or an in-hospital stroke). However, specific processes will be truncated and tailored if a patient is first managed at a PSC rather than a CSC. A dedicated AIS or ‘brain attack’ (or any chosen name) response team should always be available to implement the parallel processing required to optimize care for these patients, rapidly accomplishing the five initial assessment/management goals. At a minimum, this activation should occur for all patients with suspected AIS presenting within 6 h of the time the patient was last seen to be well.

**Recommendation:** Early non-contrast CT (NCCT) imaging and final interpretation (ideally, <15 min from presentation to PSC or CSC) is essential as further stroke care delivery is dependent on the results of this examination (AHA Class I, Level of Evidence A).

Therefore, nothing apart from hemodynamic instability or airway concerns should delay transport to the CT scanner. **Ideally, patients should be transported directly from the EMS arrival entrance to the CT scanner whenever possible.** Thus, EMS prenotification to alert the team and ensure the CT scanner is ready is strongly recommended. Supplemental oxygen administration and blood pressure measurements are standard of care considerations but, again, should not delay CT transport.

The in-house CT technologist must be an integral member of the ‘brain attack’ response team so that the CT room can be vacated and prepared for the arrival of the patient with AIS. In parallel, obtaining large-bore IV access should be of utmost importance for blood samples, iodinated contrast for CT angiography (CTA) imaging, and most importantly, IV tPA bolus/infusion. However, delays in obtaining IV access should not delay obtaining the NCCT scan. Early response of the anesthesia service may help to expedite processes, especially in situations of patient non-compliance, airway management, hemodynamic lability, vascular access, and preparation for advanced imaging and endovascular intervention.

The next two major steps are the administration of IV tPA to eligible patients and the evaluation of potential large vessel occlusion (LVO) using non-invasive imaging, predominantly CTA. Centers will have to customize workflow, but in general, these two steps should occur in parallel, as quickly as possible, and with the understanding that CTA should not delay administration of IV tPA. Examples of potential workflows are as follows:

1. At some centers, routine CTA is part of their workflow for all patients with suspected AIS.

2. For centers where CTA is not part of routine imaging in all patients with AIS, the local institution should determine a clinical severity threshold. This may be the National Institute of Health Stroke Scale (NIHSS) or other severity scale (Cincinnati Pre-hospital Stroke Scale (CPSS)), Face, Arm, Speech Test (FAST), Los Angeles Motor Score (LAMS), Rapid Arterial Occlusion Evaluation (RACE), Recognition of Stroke in the Emergency Room (ROSIER), etc. Patients meeting a prespecified threshold should have both NCCT and CTA performed upon first trip to the CT scanner.

3. In other centers where IV tPA can be initiated in the CT scanner (recommended), it would be reasonable to use the CT scanner as the first step in the treatment suite. In this workflow, IV tPA can be initiated before CTA, in the CT scanner.

The common thread in all of these workflows is that the patient does not repeatedly go back to the scanner. These workflows can be applied to both PSCs and CSCs.

If there is concern that the prothrombin time/international normalized ratio, either point of care interventional neuroradiology testing can be performed in the CT suite (where allowed) or in the laboratory where <20 min turnaround times should be standard (note that these tests are ineffective for new oral anticoagulants (direct thrombin or factor Xa inhibitors)). Otherwise, no blood sample data other than the finger stick blood glucose are required to make a decision as to whether to administer IV tPA.

**NCCT imaging**

NCCT is an excellent means of establishing if a patient with AIS is a candidate for IV tPA, as it can accurately identify hemorrhage, large areas of infarction with edema, or other findings such as large mass lesions, which would preclude IV tPA administration. However, NCCT is suboptimal for the identification of LVOs—a prerequisite to EVT for ELVO. Although the hyperdense middle cerebral artery sign can indicate LVO, it may not be sufficiently sensitive to reliably identify patients with ELVO even with thinner slice acquisition and process optimization. In addition, NCCT is not as sensitive in the identification of extremely early ischemic change, and this also has implications before EVT, as will be discussed below. Despite efforts to improve NCCT sensitivity for the detection of early ischemic change with post-processing of the acquired data (windowing and leveling) and structured scoring systems such as the Alberta Stroke Program Early CT Score (ASPECTS), NCCT has overall weak sensitivity and interobserver agreement for detecting early ischemic change. Nevertheless, NCCT remains the first-line imaging in these patients, primarily because of its ability to quickly exclude hemorrhage and ASPECTS extremes (really good scores and really bad scores, particularly in combination with the CTA collateral score (see below)), and is probably adequate for most clinical decision-making.
IV tPA
Based on the results of the two-part National Institute of Neurological Disorders and Stroke rtPA Stroke Trials,16 IV tPA (0.9 mg/kg, maximum dose 90 mg) was approved by the Food and Drug Administration (FDA) for use in patients with AIS presenting within 3 h of symptom onset. Subsequent trials (European Cooperative Acute Stroke Study (ECASS I, ECASS II, Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS A, ATLANTIS B)) confirmed the benefit of thrombolytic therapy for patients with AIS and time-to-treatment interactions in individual and pooled analyses.6,26–29 While some studies report that IV tPA is beneficial up to 6 h from stroke onset, it is only FDA approved within 3 h, but may be administered up to 4.5 h after the onset of symptoms based on the results of the ECASS III trial.30

Recommendation: Endovascular therapy should complement and not replace IV administration of recombinant tPA in eligible patients (AHA Class I, Level of Evidence A).

Acute non-invasive vascular imaging (CTA)
ELVO is an acute vascular emergency (just like pulmonary embolism and aortic dissection) that is often clinically devastating11,32 and can predict failure of IV tPA according to its location.33 Identification of LVO in association with moderate to severe acute stroke should prompt consideration of emergency EVT.1,3–4 CTA, widely available at most hospitals, is a rapid and reliable method of identifying or excluding LVO in patients with AIS.

Clinical studies had erroneously suggested that NIHSS thresholds were an adequate surrogate marker to identify patients with ELVO. However, these early studies might have been subject to selection bias and the limited availability of emergent non-invasive brain vascular imaging. In recent clinical studies, where non-invasive vascular imaging (mostly CTA) was performed routinely in patients with AIS, we have learned the following:

▸ ELVO is more common than we thought (table 2);
▸ Arbitrary NIHSS cut-off points are too inaccurate to identify ELVO;
▸ NIHSS accuracy depends on time from onset and LVO location.

Using a NIHSS cut-off value of 10, more than half of ELVOs would have been missed in the study by Maas et al15 (48% sensitivity). Heldner et al17 found that a NIHSS cut-off value of 10 would have missed 30% of anterior circulation strokes and 60% of posterior circulation strokes and that accuracy is reduced at more delayed time points. Despite the inaccuracy of NIHSS in predicting ELVO, it has a role as a patient selection mechanism for endovascular stroke intervention as very low NIHSS with an ELVO may not require endovascular reperfusion therapy. The majority of endovascular trials specified a minimum NIHSS for enrollment (IMS-3,18 MR CLEAN,1 ESCAPE,2 REVASCAT3 SWIFT PRIME4), and randomized populations with significantly elevated mean NIHSS >10. Confirmation of LVO in patients with low NIHSS, has important clinical implications39 although optimal management of patients (either with EVT or medically) remains unknown.

On modern helical CT scanners, a CTA scan from the aortic arch to the cranial vertex can be performed rapidly, usually in 15–20 s. It has high diagnostic yield (>50%)30 and the highest accuracy of any non-invasive imaging study for AIS and LVO.41 Combined head and neck scanning allows assessment of the aortic arch, carotid bifurcations, superimposed cerebral pathology (proximal internal carotid artery (ICA) ruptured plaques/occlusion or cervical dissections), as well as excellent vascular resolution of the embolus location, length, circle of Willis, and distal collaterals. Some may use the detailed anatomic evaluation for EVT planning, including considerations such as balloon guide catheter placement, proximal aspiration catheter selection, and stent retriever deployment zones. The need for any treatment of a proximal cervical carotid stenosis or occlusion can also be assessed at this time. Although the patient’s renal function may remain unknown on presentation with AIS, NCCT with CTA may still be performed without prior determination of renal function in the case of a clinically devastating stroke.

Recommendation: The risk of iodinated contrast nephrotoxicity should never delay CTA to determine the presence or absence of a clinically devastating ELVO42–43 (AHA Class I, Level of Evidence B). Ideally, identification of ELVO should be completed within 10 min of CTA acquisition and the treating team informed.

MR angiography (MRA) has less sensitivity/specificity and requires more acquisition time than CTA, it may be a suitable alternative for those with severe iodinated contrast allergies. With MRA, one can adequately confirm an ICA or M1 ELVO, for which EVT is required. In the recently published endovascular stroke intervention trials,1–5 CTA or MRA imaging was performed without significant delay during IV tPA infusion. In patients with renal insufficiency, there is no advantage in MRA of the neck as adequate imaging would also require gadolinium contrast, contraindicated owing to risks of nephrogenic systemic fibrosis.

For those centers that have abbreviated MRI protocols to optimally assess core infarct volumes for tissue-based imaging selection (see below), and cannot quickly obtain an accurate MRI screening checklist, a low-dose body tomogram (to include chest and abdomen) can also be performed at the time of NCCT/CTA to screen for a pacemaker or other foreign body that might preclude MR imaging of the patient with ELVO.

Recommendation: CTA is the most accurate and efficient non-invasive means of confirming or excluding the presence of an ELVO and should be performed as quickly as possible in those patients in whom an LVO (severe stroke) is suspected (AHA Class I, Level of Evidence B). Any facility that manages or receives patients with stroke (primary stroke, comprehensive stroke, or other) must have the capability to rapidly perform CTA to identify patients with ELVO. At a minimum, CTA vessel imaging should be performed in all patients who meet a predefined clinical severity threshold. MRA can be substituted for CTA in those patients with severe iodinated contrast allergy. If circumstances dictate that non-invasive vascular imaging (CTA or MRA) will unnecessarily delay EVT, it is reasonable to forgo CTA and perform catheter-directed digital subtraction angiography in conjunction with EVT as rapidly as possible.

ELVO team activation
Stroke code activation of the ‘ELVO’ team (neurointerventional surgeon, interventional technologist, nurse, and in some cases the anesthesiologist) is usually separate from activation of the

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Studies evaluating the presence of large vessel occlusions in consecutive patients with acute ischemic stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Series</td>
<td>Year published</td>
</tr>
<tr>
<td>Maas et al15</td>
<td>2009</td>
</tr>
<tr>
<td>Hansen et al30</td>
<td>2014</td>
</tr>
<tr>
<td>Heldner et al17</td>
<td>2013</td>
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</table>
medical, or non-interventional, ‘brain attack’ response team and will require separate, tiered activation. The criteria for activation of the interventional team can be either a clinical threshold (such as NIHSS, or other severity scale) in the prehospital or hospital setting, or based on confirmation of ELVO by CTA. Any additional advanced imaging modalities employed for tissue and/or EVT selection (multiphase CTA, CT perfusion (CTP) or MR diffusion-weighted imaging–perfusion-weighted imaging (DWI–PWI)), are usually at the discretion of the ELVO team, and should not delay team activation. The role of these additional imaging modalities is discussed below.

For patients evaluated at PSCs or other hospitals not performing EVT, transfer to a CSC as soon as possible is recommended. This call can, as with ELVO team activation, be based on either a clinical severity threshold (such as the full NIHSS, or abbreviated clinical scores such as CPSS, FAST, LAMS, RACE, ROSIER), or confirmation of ELVO by CTA. Each PSC will need to develop a rapid mechanism of identifying these patients. It is generally appropriate to transfer to the closest CSC in order to achieve the greatest maximal benefit. Transfer protocols should be jointly developed by the PSC and CSCs involved, and preferably rehearsed in advance. Ideally, the patient should be ready to be transported as soon as IV tPA bolus has been administered, and as the infusion is starting. The exact method of transport as well as timing of CSC notification will have to be individualized to each PSC–CSC pair, but the goal should always remain the same—access to EVT as fast and safely as possible. In some cases, it may be necessary to mobilize transfer resources based on clinical severity threshold, before definitive confirmation of ELVO.

Informed consent for embolectomy can be obtained by any participating physician. We recommend that the family is provided with a brief summary of the published embolectomy trials, in order to facilitate the consent process. If the family is not available and the patient is not able to give consent, it may be reasonable to proceed with embolectomy in specific clinical situations where it has been established as the standard of care. Generally, this is in patients with a moderate to severe clinical deficit (such as those with an NIHSS score of ≥6), documented occlusion of the M1 segment of the middle cerebral artery, with or without concomitant occlusion of the intracranial ICA, lack of large completed infarction by imaging, and where treatment can occur within 6 h from symptom onset. These criteria may further evolve as additional studies are published, and each center should have their own criteria for cases where informed consent need not be performed.

Recommendation: Independently of a patient’s candidacy for IV tPA, once an ELVO is suspected either by prehospital triage or initial evaluation using a clinical scoring system and/or confirmed by CTA, the patient should be efficiently transported by the brain attack and ELVO response teams to the angiography suite, with groin puncture times ideally <60 min from arrival. For patients with ELVO evaluated at a PSC, transfer to a CSC should be initiated if groin puncture can be achieved within 6 h of symptom onset (AHA Class 1, Level of Evidence A). Beyond 6 h, the benefit of embolectomy is less certain (AHA Class 2b, Level of Evidence C).

Advanced imaging of the infarct core (CTA collateral score/CTP/MR DWI)

Once vascular imaging has confirmed an ELVO, additional advanced imaging may be useful to ensure the patient is a candidate for embolectomy. Only the MR CLEAN trial entirely deferred screening patients for EVT with advanced imaging, possibly contributing to the lower overall clinical outcomes in their population in comparison with ESCAPE, EXTEND-IA, and SWIFT PRIME (although time to recanalization, and the modified TICI 2b/3 rates achieved also contributed). The goal of imaging-based tissue selection is to identify patients who may benefit from endovascular reperfusion therapy and exclude patients who might be subjected to futile or potentially harmful recanalization. Accurately determining the infarct core has important implications for EVT, and also for the treatment of patients outside established time windows (ie, beyond 6 h from the time the patient was last seen to be well). Indeed, there is probably a maximal admission lesion volume compatible with favorable outcome (MALCOM) or infarct for which EVT would be futile (futile infarct). Final infarct volumes are a stronger predictor of outcome than recanalization, and this volume threshold may vary with age. As a standard NCCT interpretation alone is a poor predictor of infarct core (see above) and infarct growth rates are highly variable, time from onset thresholds for selecting patients with ELVO for EVT may not be an appropriate selection criterion and be shown to be insufficient and too simplistic.

The most sensitive and specific technique for detecting early infarction and the infarct core is MR DWI, even when employing structured reporting. Infarct core volumes that are >70–100 mL before embolectomy may prohibit a clinical benefit from reperfusion, and more recent data suggest that MALCOM may be lower and may vary by age. For example, Ribo et al55 presented data showing that only 12% of patients with admission infarcts >39 mL achieved a favorable outcome (modified Rankin Scale 0–2) and that octogenarians had a threshold of 15 mL. Whereas MRI may accurately disqualify patients for embolectomy and possibly improve outcomes, the use of DWI to select patients for embolectomy is not widely available or practical at many institutions, is controversial, and has not been validated in a clinical trial. In addition, any infarct volume threshold and outcome data associated with these imaging methods may be a function of the speed and quality of the recanalization. For these reasons, NCCT and CTA are most commonly used and provide most data. The CTA collateral score seems to be useful and may improve the usefulness of CT in comparison with DWI.

The CTA collateral score uses information obtained during the initial CTA acquisition, and in some cases supplemented by additional phases of acquisition (multiphase CTA (mCTA)), to estimate stroke volume. The CTA collateral score, has been compared with DWI-MRI, and was used as an imaging criterion in the ESCAPE trial. Lack of collateral filling beyond the occluded territory (collateral score of 0) is strongly predictive of a DWI lesion of ≥100 mL. Similarly, in another study, poor collateral patterns strongly correlated with a larger admission DWI lesion, and recanalization did not prevent or attenuate infarct growth. However, caution must be exercised in a single-phase CTA technique as the infarct core may be overestimated with incorrect (early arterial) acquisition techniques. To overcome these limitations and improve the physiologic selection of patients for embolectomy, the Calgary group developed a mCTA protocol to triage patients with AIS and ELVO. To eliminate any chance of overestimating the core by an early acquisition or poor contrast bolus, the Calgary CTA protocol generates time-resolved images from skull base to vertex in three phases (early, equilibrium, and late) separated by 8 s. To assess the accuracy of this technique, correlation of the mCTA collateral scoring method with DWI lesion volume would require additional comparative trials, ideally a trial comparing collateral score alone against DWI-MRI for patient selection.
The collateral score on mCTA correlates well with the ASPECTS score on NCCT and can be used to increase diagnostic accuracy and confidence of the NCCT interpretation. In addition, mCTA scans take <20 s to acquire, require no additional contrast despite a marginally increased radiation dose, are relatively insensitive to patient motion, and require no complex post-processing. Finally, mCTA can be performed on any modern CT scanner.

Bayesian decision-making
For any individual patient, the physician’s decision to perform EVT is dichotomous: either proceed to angiography or not. Any delay in making this decision, creates a fait accompli: time is brain—the greater the amount of time required to reach the decision, the lesser is the likelihood of a good outcome. According to Khatri et al., the chance of a good clinical outcome decreases 10% for every 30 min delay in revascularization.

The Bayesian approach to decision-making is helpful for the clinician. A 45-year-old with an NIHSS of 17, M1 occlusion, 50 min from onset is likely to benefit from successful endovascular thrombectomy irrespective of the details of the rest of the imaging. On the other hand an 86-year-old with an NIHSS of 17 with an M1 occlusion and pre-existing cognitive impairment, 300 min from stroke onset with severe arterial tortuosity in the arch and neck may have more limited benefit but greater risk from EVT irrespective of findings on brain imaging.

Data show that the key factors for decision-making in patients with ELVO are premorbid neurological status, age, efficiency of the interventional team (can TICI 2b/3 revascularization be achieved within 90 min), and an approximation of core infarct size (<70–100 mL). Thus, a combination of ASPECTS on NCCT together with collateral assessment on CTA (single or multi-phase) may be sufficient for making a decision about EVT (and the decision can be taken in a shorter period of time).

Recent trials show a significant treatment effect, and in some cases the effect size is large. Patients with AIS at the margins of the experimental inclusion/exclusion criteria would probably still benefit from revascularization. In the future, with further improvement in techniques, technology, and workflow, additional gains in safety, efficiency, and improvement in revascularization rates should be achieved. Extrapolation from trial data to clinical practice may cause physicians to proceed with EVT in patients who do not strictly meet trial inclusion criteria but might still benefit from treatment.

Advanced imaging for tissue at risk/penumbra (CTP/MR–PWI)
Ischemic penumbra defines oligemic tissue at risk for infarction if rapid revascularization is not achieved. In all of the above discussions, the concept of penumbra is evaluated using a combination of the severity of the clinical deficit and location of the LVO. This concept is the ‘clinical penumbra’, or ‘clinical–diffusion mismatch’. When this approach is used, no additional physiologic imaging is used to categorize the volume of tissue at risk. However, a variety of physiologic imaging tools aim to quantify a mismatch between volume of irreversibly damaged tissue (infarct core) and tissue at risk (penumbra). These techniques rely predominantly on perfusion imaging techniques using either dynamic CT- or MR-based imaging after injection of appropriate contrast medium.

The goal of CTP/MR DWI–PWI-based physiologic selection for endovascular stroke intervention is to detect infarct core, and also to physiologically select patients with a mismatch of potentially salvageable (‘at-risk’) ischemic tissue (penumbra, Tmax/mean transit time/time to peak) and non-salvageable infarcted tissue (core infarct, relative cerebral blood volume/relative cerebral blood flow or MR-DWI). Several clinical trials have used minimum absolute mismatch ratios as an inclusion criterion (MR RESCUE, EXTEND-IA, and SWIFT PRIME) for intervention. However, various post-processing software applications and vendors have different methodologies for calculating core and penumbral volumes from CTP or MR-PWI data.

Standardization of post-processing techniques and definitions for core infarction and penumbral volumes depend on post-processing calculations, as opposed to MR-DWI, which preserves a sensitive physiological marker of irreversible infarction (restricted diffusion of water in infarcted tissue). Owing to these drawbacks of perfusion imaging (CTP or MR-PWI), some have postulated that a surrogate for the penumbra may simply be reflected by the patient’s clinical examination or NIHSS. At this time, the clinical penumbra may be the best indicator to select patients for embolectomy as long as an accurate and small core infarct estimate is available.

A study comparing clinical penumbra (NIHSS/DWI core or even NIHSS/CTA collateral score mismatch) with CTP and/or PWI is needed to resolve the perfusion imaging utility debate and time delay concerns of advanced imaging. Until such perfusion processing algorithms are standardized, validated, volumetric, fully automated, and do not cause any delays in reperfusion, these techniques cannot be recommended. Furthermore, with the MR CLEAN trial demonstrating efficacy of EVT in a broad range of patients without tissue-based or advanced imaging selection, a comparative trial is warranted to study if patients who are excluded by CTP or MR-DWI–PWI selection criteria would inevitably be subjected to futile or even harmful reperfusion with EVT.

Future designs of these trials must also consider the time taken to select a patient as a suitable candidate for embolectomy—the imaging we use to assess a patient with ELVO presenting within 2 h vs 10 h after symptom onset may be different. Perhaps perfusion imaging is suitable for patients with ELVO and a low NIHSS score, stratifying interventional management based on matched versus mismatch patterns. Additionally, wake up or unknown time window strokes will be more dependent on advanced imaging techniques such as CTP or MR-DWI–PWI. The time frame for treatment and the optimal advanced imaging technique, if any, for embolectomy patients are intriguing factors requiring research.

Advanced imaging techniques such as multiphase CTA, CTP, or MR–DWI–PWI may offer benefits of patient and tissue selection for successful endovascular reperfusion therapy, but no consensus has been established.

Infarct core assessment can be accomplished with a variety of CT/CTA or MR-DWI-based techniques (CT-ASPECTS, CTA collateral score, DWI-ASPECTS, DWI volume). Conversely, penumbral imaging has not been validated and, as a minimum, requires standardized post-processing techniques for interpretation. Furthermore, a clinical penumbra (NIHSS) may serve as a gross, but adequate surrogate for penumbral tissue.
Upon arrival at the angiography suite

Parallel workflow upon arrival at the biplane neuroangiography suite is also imperative.68 The ELVO team should have specific role assignments when they arrive. In addition, a standardized stroke kit (BRISK: brisk recanalization ischemic stroke kit) (tubing, drapes, syringes, catheters, devices, etc) that contains all equipment necessary for the case may be useful. Alternatively, an accessory kit can be created which quickly customizes the known standard angiography kit for an embolectomy case. Team members will have specific role assignments, but all members should be familiar with all duties so that critical functions are duplicated. Other “safe short cuts” may include not shaving the groin and delaying Foley catheter placement until after blood flow restoration.69

Although the use of general anesthesia (GA) for embolectomy may delay the start of treatment, advocates feel that the safety, quality, and speed of the procedure are improved. Conversely, operators using conscious sedation or monitored anesthesia care (MAC) protocols believe this allows for earlier treatment, less hemodynamic fluctuation, and neurological assessment of the patient throughout the case, despite concerns that patient movement could result in an increased incidence of vessel dissection or wire perforation. Converging evidence appears to favor the latter approach for patients with ELVO undergoing embolectomy.69,74 GA was actively discouraged in the ESCAPE trial and was used in <10% of patients, suggesting that most patients can be treated with conscious sedation.

Data presented by the MR CLEAN investigators at the 2015 International Stroke Conference offer further insight into potential effects of using GA during endovascular stroke procedures.73 Of 216 patients who entered the neuroangiography suite, 79 patients had embolectomy performed under GA and 137 under MAC with 6 (4.4%) of the latter group converting to general endotracheal anesthesia (GETA) during the case. Although there was no significant difference in time to revascularization between the two groups, there was a difference in time to treatment initiation (the MAC group was 28 min faster). More importantly, in an analysis adjusted for age, NIHSS, time from onset, previous stroke, diabetes, atrial fibrillation, and ICA terminus occlusion, the beneficial treatment effect was lost in the GETA group (common adjusted OR=1.09 (0.69 to 1.71) and found only in the MAC group (common adjusted OR=2.13 (1.46 to 3.11).

Recommendation: Embolectomy procedures should be performed with conscious sedation or MAC whenever possible. GETA should be reserved for patients who are not considered able to protect their airways for the procedure while supine or who are too uncooperative for the procedure to be performed safely (AHA Class 1b, Level of Evidence C).

Prehospital ELVO management

This topic will be the subject of a separate article. Prehospital triage of the patient with ELVO to an appropriate stroke center is critical for timely therapy. For ELVO suspected by the EMS (particularly if this suspicion is based on a clinical scoring system such as the NIHSS, LAMS, CPS, RACE, ROSIER) during transport to hospital, SNIS advocates that EMS transports the patient directly to a CSC. Early identification of severe stroke can save hours if the patient with ELVO is taken to a CSC or other endovascular-capable stroke treatment center.

Although there appears to be a treatment effect in the ‘drip and ship’ paradigm,1–3 it is less robust, and IMS-3 data supported significant time savings (without IV tPA opportunity cost) when patients go directly to a CSC.76 If a patient is taken to a PSC, the EMS team should consider waiting for an ELVO to be excluded (by CTA) before completing the transport. If an ELVO is confirmed, immediate transport of the patient to a CSC is required. EMS teams should make every effort to prenotify all receiving hospitals with time last known well, family contact information, blood pressure, history of anticoagulant use, estimated time of arrival, and stroke severity using either (LAMS, RACE, or other agreed assessment tool).

Widespread deployment of mobile stroke treatment units (MSTUs) might potentially reduce times to embolectomy for ELVO via earlier activation of the ELVO team in the field and bypassing the emergency department altogether. The MSTU could potentially eliminate the need for in-house imaging, laboratories, and IV tPA administration; allow for earlier ELVO team activation and angioplasty procedure; and even identify/confirm large artery occlusion (by on-board CTA capability). Indeed, until such time as MSTUs proliferate throughout the country the wisdom of the Helsinki group should not go unnoticed, “The key to success in reducing delays is to do only the basics when the patient has arrived, and to do as much as possible before and during transport.”

Recommendation: A patient in the field with a suspected ELVO by EMS (based on an appropriate field severity score) should be triaged to the closest CSC, bypassing other facilities as patient stability, local policy, and additional transport time (geography) allow (AHA Class I, Level of Evidence A).

Summary

There is now the highest level of medical evidence (AHA Class I, Level of Evidence A) that embolectomy using the latest technology is the standard of care for patients with ELVO, with or without an IV tPA bridge. Any hospital that receives patients with stroke must have highly coordinated systems of care to deliver fast and efficient door to picture, needle, and puncture times all while providing the best medical management until reperfusion is achieved. To improve the provision of care, processes (delivery innovation) should be iterative and designed so that teams can cycle back, evaluate their performance, and drive process improvement for the benefit of all patients with ELVO. Finally, this committee believes that prospective data reporting (such as that provided by the SNIS neurovascular quality initiative) should be carried out for all EVT procedures for stroke.

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13Department of Neuroradiology, University of Kentucky, Lexington, Kentucky, USA
14Radiology Imaging Associates, Interventional Neuroradiology, Englewood, Colorado, USA

Costants


Initial hospital management of patients with emergent large vessel occlusion (ELVO): report of the standards and guidelines committee of the Society of NeuroInterventional Surgery


J NeuroIntervent Surg published online August 31, 2015

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Imaging Selection for Neuro-endovascular Cases

Michele H. Johnson, MD

Slides are not available for online viewing
Let’s Get technical: Devices in Neuro-endovascular Procedures

Charles C. Matouk, MD

Slides were not available for online viewing
Comprehensive Stroke Centers and Transfer of Acute Patients

David M. Greer
Yale University School of Medicine

DISCLOSURES

• Grant support
  – U01 NS062851-02 (CLEAR III)
  – U01 NS062091 (ATACH II)
  – 5P50 NS044227-10 (ICTUS 2/3)

• I serve as editor-in-chief for Seminars in Neurology
4 trials (ECASS I and II, ATLANTIS A and B), enrolled subsets of patients in the ≤3-hour time period and found effects largely similar to the NINDS trials.

Data from:
- ECASS I, II, III
- NINDS Parts 1 and 2
- ATLANTIS A and B
- EPITHET

Lees KR Lancet 2010;375:1695-703
Effect of the Use of Ambulance-Based Thrombolysis on Time to Thrombolysis in Acute Ischemic Stroke: A Randomized Clinical Trial

Martin Ebinger, MD; Benjamin Winter, MD; Matthias Wendt, MD; Carolin Waldschmidt, MD; Michal Rozanski, MD; Alexander Kunz, Daniel Gierthmacher, MD; Kersten Villinger, MD; Jochen E. Fiebach, MD; Bruno-Marcel Mackert, MD; Matthias Endres, MD; Heinrich J. Aue

STEMO availability shortened alarm-to-treatment time by 15 minutes.
STEMO deployment shortened alarm-to-treatment time by 25 minutes.

STEMO availability increased thrombolysis rate to 29% from 21%.
STEMO deployment increased thrombolysis rate to 33%.

STEMO was associated with no increased risk of ICH or 7-day mortality.
Stroke Systems of Care for Intra-arterial Treatment

- Same general principle applies: time = brain
- Treatment should be geared toward IV thrombolysis as quickly as possible...
- And then consideration of transfer to patients with possible large vessel occlusion
- Not all centers can provide IA services, and those that do cannot necessarily do so 24/7
- Good relationships are of utmost importance

Who to consider for transfer?

- Any patient with a large vessel clinical syndrome
- Patients who have evidence of large vessel stenosis/occlusion on CTA/MRA
- If you can’t get vascular imaging quickly, and the patient appears to have a significant deficit, err on the side of transferring to avoid missing a major treatment opportunity
- Getting set up to get stat creatinine and CTA head and neck are paramount
When you’re considering transferring a patient...

- Call early!
- Stroke check list for EMS
- Continuing vital signs and neuro checks during transfer
- All standard for PSCs and CSCs

Partnership is essential

- Share outcome measures
  - Disposition
  - Functional outcome
  - Mortality
  - Complications
  - Successful treatments: IV and IA
PSC vs. CSC?

• VTE prophylaxis
• DC on antithrombotic tx
• Anticoag for afib/flutter
• Thrombolytic therapy
• Antithrombotic by end of HD 2
• DC on statin
• Stroke education
• Assessed for rehab

• NIHSS for IS patients
• mRS at 90 days
• Severity Measurement for SAH and ICH patients
• Procoagulant reversal agent initiation for ICH
• Hemorrhagic transformation rate
• Nimodipine treatment administered (SAH)
• Median time to revascularization
• TICI reperfusion grade (IA thrombolysis)

PSC vs. CSC: Key Differences

• PSCs focus on acute care, and primarily ischemic stroke
• CSCs:
  – Care for multiple complex stroke patients, those with severe deficits, or multi-organ disease
  – Have advanced therapies such as:
    • NICU
    • endovascular care
    • comprehensive neurosurgical care
    • Rehab therapies (physiatrist)
  – Examples of types of patients:
    • Large ischemic or hemorrhagic strokes
    • Those with strokes from unusual etiologies or requiring specialized testing or therapies
    • Those requiring multispecialty management
  – CSCs serve as a resource center for other facilities in the region, such as PSCs
Keys for CSC

- Taking care of multiple complex stroke patients
- Big focus on neurointensive care practice
- Big focus on neuro-rehabilitation
- Big focus on 90 day mRS for interventional (IV and IA) patients

Complexity of Care at a Comprehensive Stroke Center

- All acute care is geared toward getting the patient treated as quickly as possible
- Streamlining the IV TPA process
- Streamlining the IA/cath lab process
- Emphasis on door-to-needle times, door-to-CT times, door-to-groin puncture times
- Ability to perform multiple procedures at once (multiple teams available at all hours)
Time is brain, remember?

- Door to needle <45 minutes
- IA activation to groin puncture <65 minutes
- Door to groin time <125 minutes

- Aiming for:
  – IA activation to groin puncture <45 minutes
  – Door to groin time <90 minutes
  – How do we shave off these minutes?

What is the optimal flow?

- Coordination with EMS to bring to CSC directly for suspected large vessel occlusion
- Patient stops at triage, gets weighed and stat labs, then straight to CT/CTA
- Pharmacy alerted for possible acute stroke and based on weight begins preparing IV TPA (or have nursing in ED do this)
- Based on imaging, rapid prep of cath lab for immediate IA treatment
Management of Large Anterior Circulation Hemispheric Infarction

Kevin N. Sheth, MD

Chief, Division of Neurocritical Care & Emergency Neurology

Yale University School of Medicine

Disclosures

- Remedy Pharmaceuticals, Inc
“Malignant” Infarction
Magnitude of the problem

- 70,000 US patients with malignant infarction every year
- Case fatality rates as high as 60-80%
- Revascularization therapies reach limited numbers of patients
- Only proven therapy is surgery which may not be available to elderly patients and can be quite morbid

“Malignant” Infarction – Clinical Features

- Declining level of consciousness
- Headache
- Nausea/vomiting
- Brainstem signs
- Paralysis ipsilateral to hemispheric infarction
Differential Diagnosis

Hydrocephalus
Herniation
Midline shift
Brainstem

Level of arousal is the common finding!

Frank J. Neurology 1995
Ropper AH. Lateral displacement of the brain and level of consciousness in patients with an acute hemispheric mass. *NEJM*. 1986

**Current State of Knowledge**

1. No prophylactic anti-edema therapy or elevation of sodium

2. Maintain eunatremia, eucarbia, and normothermia

3. Anti-edema therapy may be triggered with change in clinical exam *not* only by radiological exam!

4. Anti-edema therapy may be instituted as a bridge but should not take the place of or delay surgery
“Malignant” Infarction – Clinical Predictors

- Onset of nausea/vomiting within 24 hours of symptom onset
- SBP ≤ 180 mmHg after 12 hours from symptom onset
- History of hypertension
- History of heart failure
- Elevated white blood cell count
- Younger age
- No history of stroke
- Female sex
- Heart weight
- Abnormal ipsilateral circle of willis
- Carotid occlusion
Who is at risk for “Malignant” Infarction

- Find out if you have a large vessel occlusion
  - NIHSS > 10
- Get an urgent MRI
  - Within 6 hours, the number to remember is 80
  - Within 12-18 hours, the number to remember is 150
- This is one the case in stroke where imaging volumes have been proven to be greater predictors of outcome than the NIHSS

Prediction of Malignant Middle Cerebral Artery Infarction by Magnetic Resonance Imaging Within 6 Hours of Symptom Onset: A Prospective Multicenter Observational Study

Goetz Thornalla, MD, Frank Hartmann, PhD, Eric Juestel, MD, Oliver C. Singer, MD, Fritz-Georg Lehnhardt, MD, Martin Köhrmann, MD, Jan F. Kersten, MSc, Anna Krietermann, MD, Marek C. Humpich, MD, Jan Sobesky, MD, Christian Giedd, MD, Ano Villringer, MD, PhD, Jens Fiehler, MD, Tobias Neumann-Haeffele, MD, Peter D. Schellinger, MD, and Joachim Rother, MD
Decompressive Craniectomy – Important Questions

- Does DC improve outcomes after stroke? Which outcomes?
- What factors guide patient selection?
  - Age?
  - Side of stroke?
- What is the optimal timing of DC after symptom onset?

---

### Table: Sensitivity, Specificity, NPV, PPV, and Correct Classifications

<table>
<thead>
<tr>
<th>Prespecified Analysis</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>NPV (95% CI)</th>
<th>PPV (95% CI)</th>
<th>Correct Classifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>DWI lesion &gt; 82 ml</td>
<td>0.52 (0.32-0.71)</td>
<td>0.98 (0.94-1.00)</td>
<td>0.90 (0.83-0.94)</td>
<td>0.88 (0.62-0.98)</td>
<td>125/140 (89.3%)</td>
</tr>
<tr>
<td>NIHSS score &gt; 18</td>
<td>0.63 (0.42-0.80)</td>
<td>0.71 (0.61-0.79)</td>
<td>0.89 (0.80-0.95)</td>
<td>0.34 (0.21-0.49)</td>
<td>97/140 (69.3%)</td>
</tr>
<tr>
<td>ICA + MCA occlusion</td>
<td>0.70 (0.50-0.86)</td>
<td>0.63 (0.53-0.72)</td>
<td>0.90 (0.81-0.96)</td>
<td>0.31 (0.20-0.44)</td>
<td>90/140 (64.3%)</td>
</tr>
</tbody>
</table>

5% confidence interval given in parentheses.

NPV = negative predictive value; PPV = positive predictive value; DWI = diffusion weighted imaging; NIHSS = National Institutes of Health Stroke Scale; ICA = internal carotid artery; MCA = middle cerebral artery.
Decompressive Craniectomy – Prospective Randomized Trials

- Four prospective RCT
  - DECIMAL
  - DESTINY
  - HAMLET
  - DESTINY II

Decompressive Craniectomy – Pooled Analysis of 3 RCT

- Pre-planned (prospective) pooled analysis of the 3 European trials

- Individual data for patients aged 18 – 60 yo who had DC w/in 48 hours for large MCA infarction (either hemisphere)

- 1st outcome: 1-year dichotomized mRS (0-4) vs. 5 or death

- 2nd outcomes: a) 1-year case fatality; b) mRS 0-3 vs. 4-death

Decompressive Craniectomy – Pooled Analysis of 3 RCT

- Numbers needed to treat:
  - Need to treat 2 to prevent one death
  - Need to treat 2 to prevent mRS 5 or death
  - Need to treat 4 to prevent mRS 4 to death

Decompressive Craniectomy – DESTINY II: Older Adults

- RCT of early DHC vs. medical management in ICU for large MCA stroke in patients > 60 yo

- 1° endpoint: survival “w/o severe disability,” defined as mRS 0-4, at 6 months

- 2° endpoints: 12-month survival, NIHSS score, mRS score, Barthel index, quality of life (SF-36, EQ-5D), depression (HDRS), adverse events

NEJM 2014;370(12):1091-1100

Decompressive Craniectomy – DESTINY II: Older Adults

- 112 patients randomized (surgery = 49, medical = 63)

- Treatment initiated within 48 hours of symptom onset

- DSMB stopped recruitment after 82 patients (surgery = 40, medical = 42) had been assessed for 1° outcome

NEJM 2014;370(12):1091-1100
Neurosurgical Options

- In patients younger than 60 years of age who deteriorate neurologically within 48 hours despite medical therapy, decompressive craniectomy with dural expansion is effective. (Class I, Level of Evidence B)

- Suboccipital craniectomy with dural expansion should be performed in patients with cerebellar infarctions who deteriorate neurologically despite maximal medical therapy. (Class I, Level of Evidence B)
Neurosurgical Options

- While the optimal trigger for decompressive craniectomy is unknown, it is reasonable to use a decrease in level of consciousness and its attribution to brain swelling as selection criteria. (Class IIa, Level of Evidence A)

- The efficacy of decompressive craniectomy in patients older than 60 years of age and the optimal timing of surgery are uncertain. (Class IIb, Level of Evidence C)

Family Conversations

- Clinicians may discuss with family members that half of the surviving patients with massive hemispheric infarctions, even after decompressive craniectomy, are severely disabled and a third are fully dependent on care (Class IIb; Level of Evidence C).
Prior Examples of High Mortality Disease

- Polio and myasthenia gravis were the acute neurological diseases with greater than 30-50% mortality rate for hospitalized patients
- At the peak of their epidemics, the supply of iron lungs could not meet demand
- This need fueled innovation, originally in Denmark and Europe, that led to the use of positive pressure ventilation and intensive care “units”
- Mortality rates for hospitalized patients plummeted to single digits
• Age 49, IRB chairman, associate editor of *Anesthesiology*, chief of cardiac anesthesiology

• L MCA stroke, decompressive craniectomy, 31 day ICU stay, 8 months of intensive rehab at UT Galveston

---

**In Our Own Words**

“Instead of attending hospital meetings, I go to sessions at the local aphasia center. Following years of intensive physical therapy, I can now walk slowly with a cane. I recently completed my fifth full-length book, Charles Banov’s *Office Upstairs: A Doctor’s Journey*.” I also spend my premature retirement reading *The Washington Post* and *The Wall Street Journal*, watching movies, playing scrabble, and looking at family albums. I go on short walks and long wheelchair rides. I take personal pride in work ethic and refusal to capitulate. I also take pleasure in continually exceeding the expectations of my physicians and therapists. This is not the life I enjoyed prior to my stroke. Nor is it how I envisioned spending my fifties. However, it is still a life worth living. I only have it due to aggressive interventions I received after my stroke, and the therapy I continue to pursue.”
Case Study

Jennifer L. Dearborn-Tomazo MD, MPH

Slides were not available for online viewing
Traditionally High Mortality and Limited Recovery Post-ICH

- Mortality
  - 6 month 30-50%

- Only 20% of ICH patients are independent at 6 months vs 60% of ischemic stroke patients


Hematoma Expansion
Hematoma growth

- Davis: 218 acute ICH pts scanned within 3 h
  - 73% have some hematoma expansion over the first 24 hours
  - 32% have >33% expansion by 24 h
  - For each 10% ↑ in ICH:
    - 5% ↑ in death
    - 16% ↑ in 1 pt on mRS (worse functional outcome)
- CHANT: 268 acute ICH pts scanned within 6 h
  - 65% had some expansion over 72 h
  - 26% had > 33% expansion by 72 h
  - Expansion > 33% had OR ~4 of worse outcome/death


BP lowering to prevent ICH growth
INTERACT – Phase 1

- Randomized, multicenter, open-label trial of BP lowering
- Treatment within 6 h of onset
- Presenting SBP 150–220 mm Hg
- Randomized to intensive treatment = goal SBP 140 vs. guideline treatment = goal SBP 180
- CT at baseline, 24 h and 72 h
- Outcomes blinded to treatment

ICH expansion results

<table>
<thead>
<tr>
<th></th>
<th>Guideline (n=172)</th>
<th>Intensive (n=174)</th>
<th>Difference (95% CI)*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haematoma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline volume (mL)</td>
<td>12.7 (11.6)</td>
<td>14.2 (14.5)</td>
<td>•</td>
<td>•</td>
</tr>
<tr>
<td>Mean volume at 24 h (mL)</td>
<td>15.4 (14.7)</td>
<td>15.2 (17.5)</td>
<td>•</td>
<td>•</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Guideline (n=172)</th>
<th>Intensive (n=174)</th>
<th>Difference (95% CI)*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proportional increase (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td>36.3% (15.8 to 56.8%)</td>
<td>13.7% (5.9 to 21.5%)</td>
<td>22.6% (0.6 to 44.5%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Adjusted median (95% CI)†</td>
<td>16.2% (8.8 to 24.1%)</td>
<td>6.2% (-0.7 to 13.4%)</td>
<td>10.0% (0.0 to 20.5%)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Guideline (n=172)</th>
<th>Intensive (n=174)</th>
<th>Difference (95% CI)*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absolute increase (mL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td>2.7 (1.4 to 4.0)</td>
<td>0.9 (-0.9 to 2.7)</td>
<td>1.7 (-0.5 to 4.0)</td>
<td>0.12</td>
</tr>
<tr>
<td>Adjusted mean (95% CI)†</td>
<td>2.6 (1.1 to 4.2)</td>
<td>0.9 (-0.6 to 2.5)</td>
<td>1.7 (-0.5 to 3.9)</td>
<td>0.13</td>
</tr>
<tr>
<td>Substantial growth†‡</td>
<td>40 (23%)</td>
<td>26 (15%)</td>
<td>8% (-1.0 to 17.0%)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Anderson et al. Lancet Neurol 2008; 7: 39
Effects of early treatment to lower BP on absolute (A) and proportional increase (B) in hematoma volume

INTERACT results

- Early intensive BP control decreased ICH growth
  - Mean growth 36% vs. 14%
  - RRR for substantial growth: 36%

- No adverse events

- No difference in clinical outcomes
  - Study not designed for clinical outcomes
  - Baseline ICH volume not equal in each group
INTERACT2

- 2839 patients with ICH within 6 hours
- Initial SBP 150-220
- Randomized to goal < 140 or <180
- Any agent- open label- but outcomes blinded to treatment

Table 1. Baseline Characteristics of the Participants.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intensive Blood Pressure Lowering (N=1299)</th>
<th>Guideline-Recommended Blood Pressure Lowering (N=1473)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from onset of ICH to randomization (h)</td>
<td>9.7</td>
<td>9.7</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>6.8-14</td>
<td>7.9-14</td>
</tr>
<tr>
<td>Age (y)</td>
<td>63 (0.67.1)</td>
<td>64 (1.72.6)</td>
</tr>
<tr>
<td>Male (n, %)</td>
<td>899 (68.2)</td>
<td>892 (61.7)</td>
</tr>
<tr>
<td>Race (n, %)</td>
<td>967 (74.7)</td>
<td>973 (65.8)</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td>179±17</td>
<td>176±17</td>
</tr>
<tr>
<td>Systolic</td>
<td>101±15</td>
<td>101±15</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>10±1</td>
<td>11±1</td>
</tr>
<tr>
<td>GCS score</td>
<td>6.45±1</td>
<td>6.74±1</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>54±14</td>
<td>54±14</td>
</tr>
<tr>
<td>History of hypertension — no/total no. (%)</td>
<td>101(97.6)</td>
<td>100(96.9)</td>
</tr>
<tr>
<td>History of diabetes — no/total no. (%)</td>
<td>167/1398(12.6)</td>
<td>167/1398(12.1)</td>
</tr>
<tr>
<td>Prior intracranial hemorrhage — no/total no. (%)</td>
<td>115/1398(8.3)</td>
<td>114/1428(8.0)</td>
</tr>
<tr>
<td>Prior ischemic or antiplatelet stroke — no/total no. (%)</td>
<td>137/1399(10.3)</td>
<td>136/1429(10.6)</td>
</tr>
<tr>
<td>Prior stroke or TIA — no/total no. (%)</td>
<td>39/1399(2.8)</td>
<td>42/1428(2.9)</td>
</tr>
<tr>
<td>Diabetes mellitus — no/total no. (%)</td>
<td>113/1399(8.1)</td>
<td>115/1428(8.0)</td>
</tr>
<tr>
<td>Use of warfarin/anticoagulation — no/total no. (%)</td>
<td>53/1399(3.9)</td>
<td>53/1428(3.7)</td>
</tr>
<tr>
<td>Use of aspirin or other antiplatelet agent — no/total no. (%)</td>
<td>123/1399(9.8)</td>
<td>123/1429(9.0)</td>
</tr>
<tr>
<td>Baseline hematoma volume — ml</td>
<td>10±1</td>
<td>11±1</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>6±10</td>
<td>6±10</td>
</tr>
<tr>
<td>Deep location of hematoma — no/total no. (%)</td>
<td>1066/1399(77.8)</td>
<td>1066/1428(73.3)</td>
</tr>
<tr>
<td>Location of hematoma — left/total no. (%)</td>
<td>646/1399(47.8)</td>
<td>650/1428(45.7)</td>
</tr>
<tr>
<td>Intracranial extension of hematoma — no/total no. (%)</td>
<td>171/1394(12.2)</td>
<td>169/1434(12.0)</td>
</tr>
</tbody>
</table>

*There were no significant differences between the groups in any of the characteristics listed here. ICH denotes intracerebral hemorrhage. NIHSS denotes the National Institutes of Health Stroke Scale (NIHSS) range from 0 (normal neurologic status) to 42 (pupil depression). Scores on the Glasgow Coma Scale (GCS) range from 3 (fully comatose) to 15 (fully conscious). Deep location refers to location in the basal ganglia or thalamus.
### Table 3. Primary, Secondary, and Safety Outcomes at 90 Days.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intensive Blood-Pressure Lowering (N = 1399)</th>
<th>Guideline-Recommended Blood-Pressure Lowering (N = 1430)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome: death or major disability — no./total no. (%)</td>
<td>719/1382 (52.0)</td>
<td>785/1412 (55.6)</td>
<td>0.87 (0.75–1.01)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

#### Secondary outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intensive Blood-Pressure Lowering (N = 1399)</th>
<th>Guideline-Recommended Blood-Pressure Lowering (N = 1430)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score on the modified Rankin scale — no./total no. (%)</td>
<td></td>
<td></td>
<td>0.87 (0.77–1.00)</td>
<td>0.04</td>
</tr>
<tr>
<td>0. No symptoms at all</td>
<td>112/1382 (8.1)</td>
<td>107/1412 (7.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. No substantial disability despite symptoms</td>
<td>292/1382 (21.1)</td>
<td>254/1412 (18.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Slight disability</td>
<td>259/1382 (18.7)</td>
<td>266/1412 (18.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Moderate disability requiring some help</td>
<td>220/1382 (15.9)</td>
<td>234/1412 (16.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Moderate-severe disability requiring assistance with daily living</td>
<td>250/1382 (18.1)</td>
<td>268/1412 (19.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Severe disability, bed-bound and incompetent</td>
<td>83/1382 (6.0)</td>
<td>113/1412 (8.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Death by 90 days</td>
<td>146/1382 (12.0)</td>
<td>170/1412 (12.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Primary, Secondary, and Safety Outcomes at 90 Days.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intensive Blood-Pressure Lowering (N = 1399)</th>
<th>Guideline-Recommended Blood-Pressure Lowering (N = 1430)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health-related quality of life</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Problems with mobility — no/total no. (%)</td>
<td>767/1200 (63.9%)</td>
<td>821/1231 (66.7%)</td>
<td>0.88 (0.74-1.04)</td>
<td>0.13</td>
</tr>
<tr>
<td>Problems with self-care — no/total no. (%)</td>
<td>369/1200 (30.8%)</td>
<td>412/1231 (33.6%)</td>
<td>0.83 (0.70-0.97)</td>
<td>0.02</td>
</tr>
<tr>
<td>Problems with usual activities — no/total no. (%)</td>
<td>511/1200 (42.6%)</td>
<td>551/1231 (44.6%)</td>
<td>0.99 (0.84-1.17)</td>
<td>0.80</td>
</tr>
<tr>
<td>Problems with pain or discomfort — no/total no. (%)</td>
<td>411/1199 (34.5%)</td>
<td>552/1221 (45.5%)</td>
<td>0.81 (0.69-0.95)</td>
<td>0.01</td>
</tr>
<tr>
<td>Problems with anxiety or depression — no/total no. (%)</td>
<td>406/1192 (34.1%)</td>
<td>465/1220 (38.0%)</td>
<td>0.84 (0.72-0.98)</td>
<td>0.05</td>
</tr>
<tr>
<td>Overall health utility score</td>
<td>0.60±0.39</td>
<td>0.51±0.40</td>
<td></td>
<td>0.002</td>
</tr>
</tbody>
</table>

Supplementary Table S2. Effects of early blood pressure lowering treatment on hemostatic volume.

Blood Pressure Lowering

<table>
<thead>
<tr>
<th>Hemostatic volumes</th>
<th>Intensive Group (N = 691)</th>
<th>Guideline Group (N = 735)</th>
<th>Absolute (all) or proportional (%) decrease in intensive group (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline to 24 hours - ref</td>
<td>Baseline 18.7±18.7</td>
<td>Baseline 15.1±14.9</td>
<td>78.6±24.9</td>
<td>Guideline action intensive</td>
</tr>
<tr>
<td>Growth of the hemostatic volume - ref</td>
<td>24 hours minus baseline 3.9±2.4</td>
<td>24 hours minus baseline 4.8±2.9</td>
<td>6.1±5.9</td>
<td>Absolute: mean (95% CI)</td>
</tr>
<tr>
<td>- adjusted mean (95% CI)</td>
<td>3.1±1.2 to 5.1</td>
<td>4.8±2.9 to 6.6</td>
<td>1.8±0.5 to 3.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Relative - mean, % (95% CI)</td>
<td>16.7±10.2 in 70.0±9.0</td>
<td>20.2±13.5 in 70.0±9.0</td>
<td>7.5±24.0 to 77.0</td>
<td>0.706</td>
</tr>
<tr>
<td>- adjusted median, % (95% CI)</td>
<td>17.2±9.2 in 22.7</td>
<td>21.7±13.2 to 28.3</td>
<td>4.5±3.3 to 28.3</td>
<td>0.209</td>
</tr>
<tr>
<td>Proportion of patients with subclinical growth of the hemostatic volumes</td>
<td>Hemostatic - no/total (%)</td>
<td>Hemostatic - no/total (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>179 (26.3)</td>
<td>125 (26.4)</td>
<td>0.4±3 (4.4 to 6.3)</td>
<td>0.699</td>
</tr>
</tbody>
</table>
BP Variability in INTERACT

A and D: Adjusted for age, sex, and randomized group;

B and E: Adjusted for above plus region, ICH volume at baseline, and high NIHSS scores

First 24 h

Days 2-7

INTERACT Conclusions

- Rapid blood pressure lowering to SBP <140 safe
  - For pts presenting 150-220

- Seems to improve broad range of outcomes without significantly reducing ICH expansion
  - How?
  - Benefit seen in % of pts mRS 1

- Perhaps steady BP control in first 24 h more important
AHA Guidelines 2015

- For patients with initial SBP 150-220 and without contraindication to BP lowering, SBP treatment to goal 140 mmHg is **safe**
  - And **may** improve functional outcome

- For patients with SBP > 220, reasonable to aggressively lower with IV infusions and frequent monitoring
  - No goal given

Blood pressure- my conclusions

- At this point it is unclear whether aggressive BP reduction reduces ICH growth
  - Trials conflicting
- More aggressive BP control may improve outcomes- how?
- Target unknown!
- Awaiting results of ATACH

- Patients with acute ICH and SBP > 220 I lower 25% over 1 h (230 → 170) and then to 150 over the next few hours
  - Indications/contraindications on a case-by-case basis
Hematoma Expansion

Warfarin-associated ICH

- ICH volume 2x greater in patients with OAT ICH
- Hemorrhage expansion (defined as >33% increase in ICH volume) 2x more common
  - 56% of patients with OAT ICH vs. 26% of SICH, p=0.006
- Mortality was substantially higher in OAT ICH
  - 62% versus 17%, p<0.001

- ICH in an anticoagulated patient is likely the most critical neuro emergency you will see
  - Act quickly, watch the patient carefully, get them to NICU!

Reversal of Warfarin

- Agents used for reversal
  - Fresh frozen plasma (FFP)
  - Vitamin K
  - Recombinant factor VIIa
  - Prothrombin complex concentrates (PCC)

- Issues to consider
  - FFP carries viral risk, half-life is only 8-12 h
  - PCC factor concentrations vary by batch/manufacturer
  - PCC and rFVIIa have smaller volumes and more rapid administration than FFP
  - Vitamin K needed in addition to others

Vitamin K

- Factors II, VII, IX, X, proteins C and S!
- IV → reversal of INR beginning 4-6 hours
  - PREFERRED ROUTE- 10 mg IV over 10 min
    - Risk? Anaphylaxis (very rare- don’t let it stop you!)
- Subcutaneous → variable absorption- reversal beginning 8-12 h
- Oral- better than subQ (second choice)

- Reversal of warfarin is persistent!

Prothrombin Complex Concentrates

- Different formulations- newest approved (Kcentra) has inactivated forms of coagulation Factors II, VII, IX and X, and antithrombotic Proteins C and S
- Dosing

<table>
<thead>
<tr>
<th>Pre-treatment INR</th>
<th>2 – &lt; 4</th>
<th>4 – 6</th>
<th>&gt; 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose* of Kcentra (units of Factor IX) / kg body weight</td>
<td>25</td>
<td>35</td>
<td>50</td>
</tr>
<tr>
<td>Maximum dose† (units of Factor IX)</td>
<td>Not to exceed 2500</td>
<td>Not to exceed 3500</td>
<td>Not to exceed 5000</td>
</tr>
</tbody>
</table>
Prothrombin complex concentrates versus fresh frozen plasma

<table>
<thead>
<tr>
<th></th>
<th>PCC</th>
<th>FFP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood type</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Thawing time</td>
<td>None</td>
<td>30–45 min/unit</td>
</tr>
<tr>
<td>Infection risk</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Thrombosis risk</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Clotting factor concentration</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Infusion volume</td>
<td>Less than 200 ml</td>
<td>1,000–3,000 ml</td>
</tr>
<tr>
<td>Speed of INR correction</td>
<td>Quicker *(20-45min)</td>
<td>Slower (hours)</td>
</tr>
<tr>
<td>Availability</td>
<td>Now Available!</td>
<td>Available</td>
</tr>
<tr>
<td>Expensive</td>
<td>Yes</td>
<td>Moderate</td>
</tr>
<tr>
<td>Duration</td>
<td>unclear</td>
<td>6-8 hrs!!</td>
</tr>
</tbody>
</table>

Bershad and Suarez. Neurocritical Care, 2010: 12 (3), 403-413

With updates 7/2013 to reflect new availability of inactivated 4 factor KCentra.

What should you do?

- Warfarin → Vitamin K 10 mg IV STAT over 10 min
- Plus PCCs or FFP
- If no PCCs avail-> FFP 10-20 ml/kg (4-6 units for average pts) STAT
  - May need lasix between doses- volume 1-1.5 L
- Recheck INR q6 hrs- redose FFP as needed (not PCC’s)
- Goal INR <1.4
  - Need 2 consecutive nl INR’ s before you can stop checking q6!
- Close neuro checks!! All pts to Neuro-ICU!
- Repeat HCT in 6 h, sooner if any change in exam
Newer oral anticoagulants

- Dabigatran - direct thrombin inhibitor
- Rivaroxaban or apixaban - factor Xa inhibitors

- Overall, short half-lives (5-15 hours)
- Vitamin K not useful
- Consult with hematologist useful

- If taken within 2 hours, consider activated charcoal
- Dabigatran removed by hemodialysis

- Preliminary data suggests PCCs reverse rivaroxaban and apixaban
  - Provide thrombin downstream of factor Xa
- Perhaps activated PCC (FEIBA) useful for dabigatran
- Directed antidotes in development

Surgical Evacuation

- Cerebellar hemorrhage >3 cm w/ neurological deterioration or brain stem compression and ventricular obstruction

- Structural lesion if chance for good outcome and lesion surgically accessible
- What about everyone else?
Surgical Trial for ICH (STICH)

- 1033 patients enrolled from > 20 countries
  - Nearly double the total # pts enrolled (561) in all prior trials combined
- Early surgical evacuation vs. medical therapy
  - 25% of medical group declined and had late surgery
- Enrollment based on surgeon being "uncertain about the benefits of either treatment"
- Patients with GCS ≥ 5
- Outcome determined by prognosis based GOS (taking into account age, admission GCS, and ICH volume)
- Surgery mostly by craniotomy
- NO OVERALL DIFFERENCE


<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>Early surgery (n=468)</th>
<th>Initial conservative treatment (n=497)</th>
<th>Absolute benefit (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favourable</td>
<td>122 (26%)</td>
<td>118 (24%)</td>
<td>2.3 (-3.2 to 7.7)</td>
</tr>
<tr>
<td>Unfavourable</td>
<td>346 (74%)</td>
<td>378 (76%)</td>
<td>--</td>
</tr>
<tr>
<td>Not recorded</td>
<td>1</td>
<td>1</td>
<td>--</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
</tr>
<tr>
<td>Alive*</td>
</tr>
<tr>
<td>Dead</td>
</tr>
<tr>
<td>Prognosis-based modified Rankin index</td>
</tr>
<tr>
<td>Favourable</td>
</tr>
<tr>
<td>Unfavourable</td>
</tr>
<tr>
<td>Not recorded</td>
</tr>
<tr>
<td>Prognosis-based Barthel index</td>
</tr>
<tr>
<td>Favourable</td>
</tr>
<tr>
<td>Unfavourable</td>
</tr>
<tr>
<td>Not recorded</td>
</tr>
</tbody>
</table>

Data are number (%). * Includes 17 patients who were alive at 6 months but status was unknown.

Table 4: Outcomes at 6 months
STICH2

- 601 patients randomized to early surgery vs. early conservative management
- GCS > 8
- Supratentorial ICH, 10-100 mL
- within 48 h of onset
- ≤ 1 cm of cortex
- Craniotomy
## STICH 2 Results

<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>Early surgery group</th>
<th>Initial conservative treatment group</th>
<th>p-value</th>
<th>Absolute difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>303</td>
<td>299</td>
<td>0.32**</td>
<td>0.4% (2% to 0.4%)</td>
</tr>
<tr>
<td>Mortality at 3 months</td>
<td>258</td>
<td>251</td>
<td>0.09*</td>
<td>5.6% (0.6% to 12.1%)</td>
</tr>
</tbody>
</table>

### Tables

#### Table 1: Effects at 6 months

<table>
<thead>
<tr>
<th>Event</th>
<th>Early surgery</th>
<th>Initial conservative treatment</th>
<th>p-value</th>
<th>Absolute difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR)</td>
<td>97 (92-100)</td>
<td>100 (95-105)</td>
<td>0.19</td>
<td>0.0% (-2% to 3%)</td>
</tr>
</tbody>
</table>

### Notes

Data are numbers or median (IQR), unless otherwise indicated. Exact p-values were calculated with Chi-squared tests. Proportions are provided for the primary outcome. Events were not available for trials in the early surgery group and for those in the initial conservative group. NOS was not available for one patient in the early surgery group and five patients in the initial conservative group. 

GOS = Glasgow Outcome Scale. 

* p < 0.05; ** p < 0.01; *** p < 0.001

---

#### Table 2: Effects at 12 months

<table>
<thead>
<tr>
<th>Event</th>
<th>Early surgery</th>
<th>Initial conservative treatment</th>
<th>p-value</th>
<th>Absolute difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR)</td>
<td>97 (92-100)</td>
<td>100 (95-105)</td>
<td>0.19</td>
<td>0.0% (-2% to 3%)</td>
</tr>
</tbody>
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GOS = Glasgow Outcome Scale. 

* p < 0.05; ** p < 0.01; *** p < 0.001

---

#### Table 3: Effects at 2 years

<table>
<thead>
<tr>
<th>Event</th>
<th>Early surgery</th>
<th>Initial conservative treatment</th>
<th>p-value</th>
<th>Absolute difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR)</td>
<td>97 (92-100)</td>
<td>100 (95-105)</td>
<td>0.19</td>
<td>0.0% (-2% to 3%)</td>
</tr>
</tbody>
</table>

### Notes

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GOS = Glasgow Outcome Scale. 

* p < 0.05; ** p < 0.01; *** p < 0.001
AHA Guidelines on surgery

- Cerebellar ICH with neurological deterioration and/or hydrocephalus should have surgical evacuation as soon as possible
- For most other patients, no clear benefit of surgical evacuation
  - Watch and wait approach
- Supratentorial evacuation in deteriorating patients might be considered as a life-saving measure
- Decompressive craniectomy +/- ICH evacuation might reduce mortality for comatose patients with midline shift or refractory ICP elevations

Minimally invasive surgical evacuation

- NIH-funded randomized clinical trial of minimally invasive surgery versus best medical management
- 500 patients worldwide
- Supratentorial ICH
- Yale is the only participating hospital in CT - send us your ICH patients!
Neuroprotection trials

- iDEF- intermediate dose deferoxamine
  - Iron-chelating agent
  - Anti-inflammatory
  - Potential neuroprotectant
- NIH-funded randomized clinical trial
- Yale currently enrolling

Prevent Complications

STOP
Seizures and ICH

- Seizures are more frequent in ICH than in ischemic stroke
- Seizure risk 8% after ICH
- Most seizures at onset or ≤ 24 h of ICH
- More commonly associated with lobar than deep ICH
- Poorer outcomes
  - Neuronal injury and destabilization of critically ill patient
  - Nonconvulsive seizures may contribute to coma
  - Seizures associated with deterioration of NIHSS and increase in midline shift


Management of Seizures

- Use anticonvulsants for seizure at onset of ICH or witnessed seizures in hospital
- Monitor patients who aren’t waking up for subclinical seizures
  - Bedside routine EEG if pt unresponsive
  - Continuous if patient fluctuating
Prophylactic AEDs?

- No

- AHA 2015: Prophylactic AEDs should not be used.
  - Based on 2 studies showing higher mortality in patients treated prophylactically with AEDs (primarily phenytoin)
  - Also don’t seem to prevent lesion-related epilepsy

Supportive Measures

- Intubation
  - Airway protection
  - ICP management
- Aspiration prevention
  - Dysphagia screening for all patients before po intake
- Ventriculostomy placement
  - IVH, hydrocephalus, elevated ICP
- Normothermia – duration of fever an independent predictor of death
- Normoglycemia
DVT Prevention

• DVT prophylaxis
  – SCDs better than just stockings
    • DVT at day 10 (by U/S) in 4.7% vs 15.9%
  – SC heparin safe and effective beginning at 48 hrs
    • Trial of SQH starting on day 10, 4 or 2
    • Fewer PE’s and DVTs in earlier group
    • No difference in rebleeding

• START SCDs (pneumatic compression dressings) on admission
• START SC prophylactic heparin or LMWH once ICH size is stable in immobile patients after 1-4 days from onset

AHA guidelines 2015.

Thanks!

• Happy to answer questions!
Back To Basics: Secondary Stroke Prevention

Walter N. Kernan, MD
Professor of Medicine
Yale School of Medicine
October 1, 2015

Presenter Disclosure Information
Walter N. Kernan, MD

Topic
Secondary Prevention of Ischemic Stroke and TIA

Conflict of Interest
Yale University is receiving pioglitazone and placebo from Takeda Pharmaceuticals America, Inc. for use in an NINDS-funded clinical trial.

Unlabeled Use
None discussed
For Today

- Putting secondary prevention in a holistic context
- Selected interventions
  - Hypertension therapy
  - Statin therapy
- Emerging approaches
THREE QUESTIONS

• What did you enjoy doing before?
• What do you want to be able to do?
• What do you fear?

Lawrence M. Brass

Secondary Prevention

“Limiting the impact or the recurrence of an illness in patients already afflicted by it.”

Conventional Linear Concept

Ischemic Stroke \[:-\]
Neuronal Loss
\[\downarrow\text{Cognition}\]
\[\downarrow\text{Physical function}\]
\[\downarrow\text{Social function}\]

- BP control
- Antithrombotic Rx
- Anticoagulation Rx
- Statin Rx
- Vascular surgery
- Nutrition

+ OT
 PT
 Psychiatry
 Social Work

The Waitress
Edouard Manet
Stroke Prognosis

Risk Of Event

Years Following Ischemic Stroke

Recurrent Stroke - NoMASS

Fatal & NF Cardiac Event - NoMass

MS Dhamoon *Stroke* 2006;66:641.
Stroke Prognosis

Risk Of Event

Years

Recurrent Stroke - NoMASS
MI After Stroke - NoMass
First Stroke – US Population


MRA for LD

Right

Left
Cognition After Incident Stroke - REGARDS
(model of patient with stroke at 3 years)

SIS Score
(Global Cog Function)

Years

DA Levine JAMA 2015;314:41-51

Ms. LGP

HPI
- 67 year-old
- 6 months s/p right MCA-distribution cerebral infarction.

PMH
- Diabetes
- Hypertension
- Asthma

Meds
- Clopidogrel
- Aspirin
- HCTZ
- Lisinopril
- Nifedipine XL
- Lipitor
- Singular
- Advair
- Albuterol
- Aspart insulin
- Glargine insulin

PE
- Looks well, weak LUE
- BMI 27 kg/m², BP 160/75

Labs
- HbA1c 8.2%
- Creatinine 0.9 mg/dL
- LDL 78 mg/dL

ECG
- NSR
Key Questions
Beyond the Acute Phase after Stroke or TIA

1. What caused the stroke or TIA?
   - Proximal arterial stenosis?
   - High-risk cardiac source of embolus?
2. What is the blood pressure?
3. Is the patient receiving optimal preventive pharmacotherapy?
   - Anti-platelet medications, statin, etc
4. Are weight and behavioral risk factors being optimally managed?
HYPERTENSION

Ms. LGP

HPI
- 67 year-old
- 6 months s/p right MCA-distribution cerebral infarction.

PMH
- Diabetes
- Hypertension
- Asthma
- Clopidogrel
- Aspirin
- HCTZ
- Lisinopril
- Nifedipine XL
- Lipitor
- Aspart insulin
- Glargine insulin

PE
- Looks well, weak LUE
- BMI 27 kg/m², BP 160/75

Labs
- HbA1c 8.2%
- Creatinine 0.9 mg/dL
- LDL 78 mg/dL

ECG
- NSR
**PROGRESS Trial**

Results by Achieved BP

<table>
<thead>
<tr>
<th>Systolic Blood Pressure Achieved (mm Hg)</th>
<th>Annual Rate of Stroke (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>1</td>
</tr>
<tr>
<td>120</td>
<td>2</td>
</tr>
<tr>
<td>140</td>
<td>4</td>
</tr>
<tr>
<td>160</td>
<td>8</td>
</tr>
<tr>
<td>180</td>
<td></td>
</tr>
</tbody>
</table>

H Arima J Hypertension 2006;24:1201

---

**Secondary Prevention of Small Subcortical Strokes (SPS3)**

Eligibility:
- Recent subcortical ischemic stroke
- Age > 30 years
- No carotid stenosis or embolic source

N=3020

- SBP 130-149: 4 years
- SBP <130: 4 years

All Stroke

## SPS3 Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Higher Target N=1519 % per pt-year</th>
<th>Lower Target N=1501 % per pt-year</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Stroke</td>
<td>2.77%</td>
<td>2.25%</td>
<td>0.81</td>
<td>0.08</td>
</tr>
<tr>
<td>Ischemic</td>
<td>2.4%</td>
<td>2.0%</td>
<td>0.84</td>
<td>0.19</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>0.38%</td>
<td>0.23%</td>
<td>0.61</td>
<td>0.16</td>
</tr>
<tr>
<td>MI</td>
<td>0.70%</td>
<td>0.62%</td>
<td>0.88</td>
<td>0.59</td>
</tr>
</tbody>
</table>


## Lower BP Targets in DM

The ACCORD (non-blind) BP Trial

Participants:
- Age > 40 years
- Type 2 DM
- CVD or substantial atherosclerosis

RX:
- Current standard
- Adjustments made based on office BP values

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intensive Therapy (Target=&lt;120 SBP)</th>
<th>Standard Therapy (Target &lt;140 SBP)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%/yr</td>
<td>N</td>
</tr>
<tr>
<td>MACE*</td>
<td>208</td>
<td>1.87</td>
<td>237</td>
</tr>
<tr>
<td>Stroke</td>
<td>36</td>
<td>0.32</td>
<td>62</td>
</tr>
</tbody>
</table>

*MACE=Myocardial infarction, stroke, cardiovascular death

**Systolic Blood Pressure Intervention Trial (SPRINT)**

**Eligibility:**
- Hypertension (SBP > 130 mmHg)
- Age > 50 years
- At risk: clinical or subclinical CVD other than stroke

![Diagram showing SBP ranges and outcomes](image)

N = 9361

5 years

SBP < 140

SBP < 120

5 years

- MI
- ACS
- CHF
- Stroke
- CV Death


**Guidelines and More Guidelines – 2013**

**Initiating BP Rx after stroke**

- **ESH/ESC**
  - > 140/90

- **AHA/ACC/CDC**
  - > 140/90

- **JNC 8**
  - > 150/90 (≥ age 60 y)
  - > 140/90 (< age 60 y)

PA James JAMA 2013
The Minority Report on JNC 8

We, the panel minority, believed that evidence was insufficient to increase the SBP goal from its current level of less than 140 mm Hg . . .


AHA Recommendations

Class IIa Revised Wording
Goals for target BP level or reduction from pretreatment baseline are uncertain and should be individualized, but it is reasonable to achieve a systolic pressure <140 mm Hg and a diastolic pressure <90 mm Hg.

Class IIb New
For patients with a recent lacunar stroke, it might be reasonable to target a systolic BP of <130 mm Hg.
Many Patients Are Not at Goal

<70% of stroke patients have BP <140/90

**Things that may help**
- No co-pays
- Education
- Simple regimen
- Self-monitoring
- Case management (Pharmacist)


A Few Ideas

- All patients should monitor at home
  – Goal <135/85 or 130/85
- Check orthostatic BP in stroke patients
  – To avoid over-treatment
- Salt and alcohol restriction lower BP
- Spironolactone is good choice for resistant HTN
- Consider ambulatory monitoring more often

Age 67
BP 160/75
**Current Rx:**
HCTZ 12.5
Lisinopril 20
Nifedipine XL 20

STATIN THERAPY
Use High-Intensity Statin Therapy for Most Patients after Ischemic Stroke

**SPARCL**
Atorvastatin 80 mg if stroke d/t athero

**ACC/AHA 2013**
< Age 75 y: high-intensity statin*
> Age 75 y: mod-intensity statin†

*High-intensity: atorvastatin 40-80, rosuvastatin 20
†Mod-intensity: atorvastatin 10, pravastatin 40, others

NJ Stone Circulation 2013. SPARCL Investigators NEJM 2006;355:549

---

**Age 67**
LDL 78 mg/dL

**Current Rx:**
Atorvastatin 20 mg
Non-Cardiovascular Effects of Statins

**Unlikely**
- Cognitive impairment (poor quality data)
- Myalgia
- Liver disease
- Cataracts, Suicide

**Likely**
- Diabetes (mostly in patients at risk for DM)
- Myositis (maybe 0.5/1000 PY)
- ICH (SPARCL, HPS Trials v. many others)


Is Low LDL Still The Goal?

- **2013 AHA/ACC**
  - Initiate Rx based on risk
  - Statins first
  - No LDL goal

- **2014-2015 Science**
  - Ezetimibe trial
  - PCSK-9 trials

**Proprotein Convertase Subtilisin-Kexin Type 9 (PCSK9) Inhibitors**

Two are FDA Approved
- Alirocumab (*Praluent*)
- Evolocumab (*Repatha*)

**FDA Indication:** adjunct to diet and maximally tolerated statin therapy for adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease who require additional lowering of LDL-cholesterol.

**Caveats:**
1. Only limited post-hoc data show an effect on CV Events
2. $1000/month

*Medical Letter. 8/17/15*

---

**Is Low LDL Still The Goal?**

- **2013 AHA/ACC**
  - Initiate Rx based on risk
  - Statins first
  - No LDL goal

- **2014-2015 Science**
  - Ezetimibe trial
  - PCSK-9 trials

**What to Do**
- Initiate Rx based on risk
- Statins first
- Add/substitute non-statins proven to work
  - Using LDL goal
  - In higher risk patients

*NJ Stone NEJM 2015;372:1564; CP Cannon NEJM 2015;372:2387*
## Ms. LGP

| HPI   | 67 year-old
|       | 6 months s/p right MCA-distribution cerebral infarction. |
| PMH   | Diabetes, Hypertension, Asthma |
| Meds  | Clopidogrel, Aspirin, HCTZ, Lisinopril, Nifedipine XL, Lipitor |
|       | Singular, Advair, Albuterol, Aspart insulin, Glargine insulin |
| PE    | Looks well, weak LUE |
| Labs  | BMI 27 kg/m², BP 160/75 |
|       | HbA1c 8.2%, Creatinine 0.9 mg/dL |
|       | LDL 78 mg/dL |
| ECG   | NSR |
Go with Aspirin

2014 AHA Guidelines on 2° Prevention

The combination of aspirin and clopidogrel might be considered for initiation within 24 hours of a minor ischemic stroke or TIA and for continuation for 90 days (Class IIb; Level of Evidence B). (New recommendation)

WN Kernan Stroke 2014;45:2160
MRA for LD

OAC + Aspirin

A-Fib + CAD
Anticoagulation + Aspirin = Reasonable

A Special Case for Dual Therapy
AHA Secondary Stroke Prevention Guidelines 2014
Class IIb New
EMERGING APPROACHES
**Nutrition After Stroke: An Overlooked Option**

- Weight management
- Dietary Pattern
- Salt restriction

*Unproven

---

**The Mediterranean Diet Prevents MACE**

Incidence of Stroke, MI, or CV Death

- Control - low-fat
- Med Diet - nuts
- Med Diet - EVOO

P<0.05 Control vs Med Diets

R Estruch NEJM 2013;368:1278
### Specific Effect in Stroke?

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>N (endpoints)</th>
<th>Hazard Ratio for Med Diet</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary (MACE*)</td>
<td>288</td>
<td>0.70</td>
<td>0.003</td>
</tr>
<tr>
<td>Stroke</td>
<td>139</td>
<td>0.61</td>
<td>0.005</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>106</td>
<td>0.77</td>
<td>0.20</td>
</tr>
<tr>
<td>Death from CV Causes</td>
<td>87</td>
<td>0.83</td>
<td>0.41</td>
</tr>
<tr>
<td>Death from any Cause</td>
<td>346</td>
<td>0.89</td>
<td>0.32</td>
</tr>
</tbody>
</table>

*Stroke, MI, CV Death

R Estruch NEJM 2013;368:1278
AHA Guidelines and Nutrition

Obesity
- Screen (Class I)
- Treatment of uncertain benefit (Class IIb)

Nutrition
- Assess (Class IIa)
- Counsel for sodium intake < 2.4g (Class IIa)
- Counsel for Mediterranean diet (Class IIa)

Recommendations

1. Address both the impact of a stroke and the risk for recurrence
2. Collaborate with the primary care provider
   “Trust but verify.”
3. Hang on to your stroke patients
   “Brain once at risk, always at risk.”
Thank You
Notice how so many of these relate directly to principles of sociocultural theories of learning and apprenticeship (McCormick p 192).

wnk2, 12/31/2005
AFIB Monitoring: You Don’t Know What You Are Missing

Nimrod Lavi, MD

slides were not available for online viewing.
Disclosures

• **Grant Support:** VA Health Services Research and Development (CDA 11-262)
• **Medical Advisory Council:** Acorda Therapeutics

---

**Case Presentation: Managing Hypertension after an Ischemic Stroke**

Jason J. Sico, MD, FACP
Director, Stroke Care, VACHS
Yale University School of Medicine
Assistant Professor
Departments of Neurology and Internal Medicine
10.01.15
Objectives

• To review the importance of effective hypertension management for post-stroke persons

• To discuss a case of outpatient hypertension management in a patient with an ischemic stroke

• To understand ‘stroke specific’ considerations when managing hypertension
Hypertension

• 72 million Americans have hypertension
  – Most common condition seen by Primary Care Providers
  – 30% of adult US population
  – 75% of adult stroke population
  – Prevalence increases with age

• Elevations in systolic and diastolic blood pressure are associated with increased stroke risk
  – Blood pressure lowering associated with a 30% to 40% reduction stroke risk
  – Hypertension is responsible for 50% of ischemic strokes
  – Recurrent strokes occur more commonly among patients with hypertension

http://www.cdc.gov/nchs/data/databriefs/db133.htm#what

Case Presentation: History

• An 76-year-old right-handed gentleman with hypertension, dyslipidemia, and diabetes presents to your clinic for follow-up after a recent hospitalization.

• One month prior he was hospitalized for acute onset of left-sided face, arm, and leg weakness; he was found to have an ischemic lacunar infarction in the right posterior limb of the internal capsule.
Case Presentation: History

- Past Medical History:
  - Hypertension
  - Hyperlipidemia
  - Diabetes

- Social History:
  - Quit smoking 30 years ago

- Medications:
  - HCTZ 25 mg qam (previously on lisinopril 10 mg qam)
  - Atorvastatin 40 mg qhs
  - Aspirin 81 mg qam

Case Presentation: Examination

**Vitals:** T 98.6, BP 170/110, HR 76, RR 12, O2 saturation 97%

**General:** NAD; obese

**HEENT/Neck:** NC/AT; no carotid bruits

**CV:** RR; S1, S2; no M/R/G

**Neurologic Examination**

**Mental status:** without aphasia; SLUMS 22

**CNs:** left lower facial droop without hemianopia

**Motor:** 4/5 LUE/LLE weakness; mildly increased tone

**Sensory:** no double simultaneous extinction; decreased vibration, proprioception, and PP in LEs

**Cerebellar:** intact F → N → F, slower on the left

**DTR’s:** increased on the left with extensor plantar reflect

**Gait:** hemiplegic gait; uses a quad cane
Case Presentation: Examination

Vitals: T 98.6  BP 170/110, HR 76, RR 12, O2 saturation 97%
General: NAD; obese
HEENT/Neck: NC/AT; no carotid bruits
CV: RR; S1, S2; no M/R/G
Neurologic Examination
Mental status: without aphasia; SLUMS: 22
CNs: left lower facial droop without hemianopia
Motor: 4/5 LUE/LLE weakness; mildly increased tone
Sensory: no double simultaneous extinction; decreased vibration, proprioception, and PP in LEs
Cerebellar: intact F → N → F, slower on the left
DTR’s: increased on the left with extensor plantar reflect
Gait: hemiplegic gait; uses a quad cane

How best do we manage this patient’s hypertension?
AHA/ASA Guideline

Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack
A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons

Walter N. Kernan, MD, Chair; Bruce O'biagile, MD, MSc, MAS, Vice Chair; Henry R. Black, MD; Dawn M. Bravata, MD; Marc I. Chinowitz, MBCB, FAHA; Michael D. Ezekowitz, MBCB, PhD; Margaret C. Fang, MD, MPH; Marc Fisher, MD, FAHA; Karen L. Fortin, MD, MPH, FAHA; Donald V. Heck, MD, S. Claiborne (Clay) Johnston, MD, PhD; Scott E. Kasner, MD, FAHA; Steven J. Kittner, MD, MPH, FAHA; Pamela H. Mitchell, PhD, RN, FAHA; Michael W. Rich, MD; DeBeno Richardson, PhD; Lee H. Schwamm, MD, FAHA; John A. Wilson, MD; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease

Abstract—The aim of this updated guideline is to provide comprehensive and timely evidence-based recommendations on the prevention of future stroke among survivors of ischemic stroke or transient ischemic attack. The guideline is addressed to all clinicians who manage secondary prevention for these patients. Evidence-based recommendations are provided for control of risk factors, intervention for vascular obstruction, antithrombotic therapy, warfarin for cardioembolism, and antiplatelet therapy for noncardioembolic stroke. Recommendations are also provided for the prevention of recurrent stroke in a variety of specific circumstances, including aortic arch stenosis, arterial dissection, patent foramen ovale, hyperhomocysteinemia, hypotensive states, antiphospholipid antibody syndrome, sickle cell disease, cerebral

Hypertension

Table 1. New or Substantially Revised Recommendations for 2014*

<table>
<thead>
<tr>
<th>Section</th>
<th>2014 Recommendation</th>
<th>Description of Change From 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Initiation of BP therapy is indicated for previously untreated patients with ischemic stroke or TIA who, within the first several days, have an established BP &gt; 140 mm Hg systolic or &gt; 90 mm Hg diastolic (Table 2, Level of Evidence C). Initiation of therapy for patients with BP &gt; 150 mm Hg systolic and &lt;110 mm Hg diastolic is unclear (Table 2, Level of Evidence C).</td>
<td>Clarification of parameters for initiating BP therapy</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Resumption of BP therapy is indicated for previously treated patients with known hypertension for both prevention of recurrent stroke and prevention of other vascular events in those who have had an ischemic stroke or TIA and are beyond the first several days (Class IA, Level of Evidence A).</td>
<td>Clarification of parameters for resuming BP therapy</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Goals for target BP level or reduction from pretreatment baseline are uncertain and should be individualized but is reasonable to achieve a systolic pressure &lt; 140 mm Hg and a diastolic pressure &lt; 90 mm Hg (Class IIb, Level of Evidence B). For patients with a recent transient ischemic attack, it might be reasonable to target a systolic BP of &lt; 130 mm Hg (Class IIb; Level of Evidence B).</td>
<td>Revised guidance for target values</td>
</tr>
</tbody>
</table>
## Hypertension

### Table 1. New or Substantially Revised Recommendations for 2014*

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<tr>
<th>Section</th>
<th>2014 Recommendation</th>
<th>Description of Change From 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Initiation of BP therapy is indicated for previously untreated patients with ischemic stroke or TIA who, after the first several days, have an established BP of 140 mm Hg systolic or 90 mm Hg diastolic (Class 1, Level of Evidence B). Initiation of therapy for patients with BP = 140 mm Hg systolic and &lt;90 mm Hg diastolic is at current best clinical practice (Level of Evidence C).</td>
<td>Clarification of parameters for initiating BP therapy.</td>
</tr>
</tbody>
</table>

Resumption of BP therapy is indicated for previously treated patients with known hypertension for both prevention of recurrent stroke and prevention of other major events in those who have had an ischemic stroke or TIA and are beyond the first several days (Class 1, Level of Evidence A). Goals for target BP level or reduction from permanent baseline are uncertain and should be individualized, but it is reasonable to achieve a systolic pressure <140 mm Hg and a diastolic pressure <90 mm Hg (Class A, Level of Evidence B). For patients with a recent ischemic stroke, it might be reasonable to target a systolic BP of <130 mm Hg (Class A); Level of Evidence B). |

| Goals for target BP level or reduction from permanent baseline are uncertain and should be individualized, but it is reasonable to achieve a systolic pressure <140 mm Hg and a diastolic pressure <90 mm Hg (Class A, Level of Evidence B). For patients with a recent ischemic stroke, it might be reasonable to target a systolic BP of <130 mm Hg (Class A); Level of Evidence B). | Revised guidance for target values. |

*Class of Evidence: A: Consensus of opinion; B: Predominantly evidence from randomized trials; C: Other evidence sources.
‘Stroke Specific’ Considerations

• Obstructive Sleep Apnea
  – Independent risk factor for ischemic stroke
  – 60-80% of ischemic stroke patients have OSA
  – Associated with reduction in blood pressure
  – Half of patients with OSA are ‘non-dippers’

• ‘Non-dipping’ response
  – 25% of patients with hypertension; 50-80% with ischemic stroke
  – Symptomatic and asymptomatic cerebrovascular disease more common in ‘non-dippers’ versus ‘dippers’
  – Corrected with treating OSA and evening ACE-inhibitor use
‘Stroke Specific’ Considerations

• Post-Stroke Cognitive Impairment
  – spectrum of cognitive impairments caused by various types of cerebrovascular disease that occurs as a result of interaction between a variety of vascular risk factors. Affects 20 to 80% of patients after stroke.
  – Lacunar infarct is most common subtype that predisposes to vascular dementia.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4200648/

‘Stroke Specific’ Considerations

• Post-Stroke Depression
  • DSM IV: “a mood disorder due to stroke with major depressive-like episode”
  • Prevalence: 10 to 47% of patients at 6-months
  • May hinder rehabilitation, impairs quality of life
  • Associated with poorer medication adherence
  • Treatment: nortriptyline, citalopram, fluoxetine

The Patient Health Questionnaire-2 (PHQ-2)

<table>
<thead>
<tr>
<th>Over the past 2 weeks, how often have you been bothered by any of the following problems?</th>
<th>Not At All</th>
<th>Several Days</th>
<th>More Than Half the Days</th>
<th>Nearly Every Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Little interest or pleasure in doing things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Feeling down, depressed, or hopeless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
Case Presentation: Next Steps

- **Pharmacological Management:**
  - Lisinopril is restarted at dinner time
  - Home blood pressure cuff provided

- **Obstructive Sleep Apnea Assessment:**
  - Found to have an apnea hypopnea index of 61 events/hour (severe sleep apnea)
  - Started on CPAP

- **Neurocognitive and behavioral Assessment:**
  - Pill box prescribed and home nursing
  - Citalopram initiated

The End

Thank you for your time

Any Questions?

Jason.sico@yale.edu
Carotid Endarterectomy: Old But Gold

Timur P. Sarac, M.D.
Professor and Chief, Section of Vascular Surgery
Yale University School of Medicine
Co-Director Heart and Vascular Center
Yale New Haven Hospital

No conflicts to report for this topic

Why Carotid Endarterectomy?
Stroke Natural History
- Framingham Study Evans County and Toronto Data

• Symptomatic Patients:
  – Stroke rate in patients w/ previous stroke – 5-9%/yr and 42% over 5 yrs
  – Stroke rate in patients with tia: 12%/year and 50% over 5 years
• Asymptomatic Patients:
  – Stroke rate in patients with > 75% stenosis – 7%/yr
  – Stroke rate in patients with < 75% stenosis – 2%/year
History

- Carotid derivation: Greek “karroo” meaning “to stupefy”
- 1546 Ambroise Pare: “two branches which they call the carotides, or suporales, the sleep arteries, because they being obstructed or stopped, we presently fall asleep.
- 1905 Chiari theorized emboli from the carotid arteries caused stroke.
- 1914 J. Ramsey Hunt: focused on the carotid arteries as the source of transient ischemic attacks, and noted decreased carotid pulses in some patients who suffered from strokes:
  “… the thought naturally arises that some obstructive lesion of the vessel would be a predisposing factor in the problem of senile softening of the brain.”

History

- 1927 E.Moniz – did the first cerebral angiograms and noted the association between carotid occlusion and stroke.
- 1953 C. Miller Fisher – 24% of autopsies in patients in stroke were from hemorrhagic infarcts, implicating the carotid arteries as the precipitating event.
  “No case of vascular disease of the brain is completely investigated if the carotid arteries are not examined”. 
Carotid Endarterectomy
The Early Operations

Carotid Endarterectomy
Early Results
Carotid Endarterectomy
Early Reports

• Debakey 1965 Annals of Surgery
  – Retrospective review of 812 carotid endarterectomies
  – 40% tia, 50% > 24 hr lateralizing symptoms, 10% asymptomatic.
  – 81% improved symptoms, 45% completely asymptomatic; this was in an era when aspirin not routine, no antihypertensive, no statins.
  – Survival at 1 yr 85%, 3 yrs 75%, 5 yrs 67%.

Carotid Endarterectomy
Early Reports

• Deweese and Rob - J Cardio Vasc Surg 1971
  – Retrospective review of 313 CEAs
  – 16% asymptomatic, 54% tias, 30% completed strokes
  – First analysis of timing of CEA

<table>
<thead>
<tr>
<th>Timing</th>
<th>&lt;24 hours</th>
<th>1-13 days</th>
<th>&gt; 14 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better</td>
<td>37%</td>
<td>40%</td>
<td>26%</td>
</tr>
<tr>
<td>Worse</td>
<td>50%</td>
<td>24%</td>
<td>20%</td>
</tr>
<tr>
<td>Same</td>
<td>13%</td>
<td>36%</td>
<td>54%</td>
</tr>
<tr>
<td>Mortality</td>
<td>44%</td>
<td>10%</td>
<td>6%</td>
</tr>
</tbody>
</table>

– 47/50 asymptomatic patients symptom free long term
Carotid Endarterectomy  
Many Retrospective Reviews

- Bernstein – Am J Surg 1983
  - Reviewed 330 CEAs
  - 0.9% mortality, 3.3% stroke rate
- Goldstone JVS 1986
  - 275 CEAs for symptomatic stenosis
  - Combined stroke at death 4.5%
  - 3.2% 5 year risk of recurrent stroke
- Hertzer Ann Surg 1986
  - 5.3% combined stroke and death rate.

# CEA Rapidly Increased

![Graph showing the increase in CEA frequency from 1971 to 1986.](image)
Medical Skepticism Towards CEA

Carotid Endarterectomy – An Expression of Concern.  

The Case Against Surgery for Asymptomatic Carotid Stenosis.  
Br Chambers and JW Norris. Stroke 1984;16(6);964-7.

Early Medical Skepticism  
Rationale – Stroke Articles 1984

• Symptomatic Patients  
  – Only 10% of patients with tias suffered strokes  
  – NEJM 1985 ECIC Bypass - showed no benefit to surgery  
  – Mortality Rates from Strokes decreased from 95-73/100,000 between 1971 and 1985.

• Asymptomatic Patients  
  – Symptoms rarely develop in patients with < 80% stenosis  
  – Asymptomatic bruit study showed patients had a stroke rate of 1-2%/yr.

• Canadian and British Studies discovered stroke reduction with aspirin.
• No randomized prospective trials.
Surgeon’s Response

“Lies, damn lies, and statistics”

Marc Twain

What is the True Risk of CEA?

• McCrory and Goldstein, Stroke, 24:1285, 1993
  – Retrospective review of 12 academic centers looking at the results in 1160 patients
• Stroke + MI + Death - 6.9%
  however
• > 75 yrs - 11.8%
• SX - 9.5%
• Angina - 9.9%
• Pre-CABG - 40%
CEA vs AGE

  - Medicare - New England, 1984-85
- Age Mortality
  - 65-69: 1.1%
  - 70-74: 2.8%
  - 75-79: 3.2%
  - >80: 4.7%

What is the True Risk of CEA?

- Reviewed 25 studies
  - Mortality: 1.62%
  - Asymptomatic Stroke: 1.31%
  - Symptomatic Stroke: 1.81%
  - Asympt – Stroke + Death: 3.35%
  - Symptomatic Stroke + Death: 5.64%
  - Single Surgeon: 2.3%
The Trials

- **Symptomatic**
  - ECST – European Carotid Surgery Trial
  - NASCET – North American Asymptomatic Carotid Atherosclerosis Trial

- **Asymptomatic**
  - VA Asymptomatic Carotis Atherosclerosis trial
  - ACAS – Asymptomatic Carotid Atherosclerosis Study

---

ACAS

*JAMA 1995;273:1421-8.*

- Prospective randomized trials involving 39 centers in Canada and US, included neurologists, neurosurgeons, and vascular surgeons.
- 1667 patients with > 60% stenosis treated at randomized to CEA + bets medical therapy, or best medical therapy.
- All patients had angiograms or duplex, and strokes from angio counted as a surgical stroke

<table>
<thead>
<tr>
<th>EVENT</th>
<th>CEA</th>
<th>Medical</th>
<th>5 yr risk reduction</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral stroke/death</td>
<td>5%</td>
<td>11%</td>
<td>53%</td>
<td>&lt;.004</td>
</tr>
<tr>
<td>Ipsi stroke and any periop event</td>
<td>8%</td>
<td>19%</td>
<td>57%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Any stroke/death</td>
<td>25%</td>
<td>32%</td>
<td>19%</td>
<td>=0.08</td>
</tr>
</tbody>
</table>
ACAS TRIAL DESIGN Critique

- Two step selection process: hospital and surgeon <3% stroke & death
- Ongoing eval: > 1 periop event led to audit for continued participation
- Multiple exclusions
- 25 pts screened for every 1 randomized

WENNBERG, JAMA, 1998;279:1278

NASCET
NEJM 1991;325;445-53.

- Randomized prospective trial of symptomatic patients in 50 centers in Us and Canada.
- 444 patients with > 50% stenosis by arteriogram randomly assigned to CEA – BMT or BMT.

<table>
<thead>
<tr>
<th>EVENT</th>
<th>CEA</th>
<th>Medical</th>
<th>5 yr risk reduction</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral stroke</td>
<td>9%</td>
<td>26%</td>
<td>65%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Any Stroke</td>
<td>13%</td>
<td>28%</td>
<td>54%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Any stroke/death</td>
<td>16%</td>
<td>32%</td>
<td>51%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Major ipsilat stroke</td>
<td>3%</td>
<td>13%</td>
<td>81%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Any major stroke</td>
<td>4%</td>
<td>13%</td>
<td>72%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Any major stroke and death</td>
<td>8%</td>
<td>18%</td>
<td>36%</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>
NASCET TRIAL DESIGN Critique

- 25 cea’s/yr per surgeon
- <6% stroke and death per surgeon
- Multiple exclusions: >79yrs, co morbidity likely to cause death in 5 yrs, severe cardiac disease; uncontrolled htn, dm, usa, or mi within 6 m
- Only 1/3 of pts operated on at trial sites were enrolled.

Wennberg, JAMA, 1998, 279:1278

INTERVENTIONALISTS CONCLUSIONS

NASCET and ACAS represent only a healthy subset of patients with carotid disease and their results are not applicable to the typical patient.
Cleveland Clinic
Single Center

- 3422 patients
- Global Results ALL CEAs
  - Symptomatic and Asymptomatic
  - Redo and 2x Redos
  - Combined CEA & CABG
  - High and Low lesions
  - Radiation

Sarac et al. JVS 2002

Cleveland Clinic Data
1989-2000

Sarac et al. JVS 2002
CEA vs CAS

Carotid Wall Stent Trial
26th International Stroke Conference

<table>
<thead>
<tr>
<th>Stroke</th>
<th>Carotid Stent N = 108</th>
<th>Carotid Endart N = 113</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two Days</td>
<td>6.5%</td>
<td>0.9%</td>
</tr>
<tr>
<td>30 Days</td>
<td>10.2%</td>
<td>3.5%</td>
</tr>
<tr>
<td>One Year</td>
<td>12%</td>
<td>3.5%</td>
</tr>
</tbody>
</table>
Carotid Stent and Morbidity
Jordan et al., JVS 1998

- Retrospective review of carotid artery stents vs. CEA
- 414 procedures in 377 patients
  - 312 stents
  - 121 CEAs (regional anesthesia)
Recent Results of Carotid Artery Stents

<table>
<thead>
<tr>
<th>Author</th>
<th># Pts</th>
<th>Year</th>
<th>Major Stroke</th>
<th>Minor Stroke</th>
<th>Death</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mathias</td>
<td>633</td>
<td>1999</td>
<td>1.1%</td>
<td>1.6%</td>
<td>0.3%</td>
<td>3%</td>
</tr>
<tr>
<td>Bergeron</td>
<td>99</td>
<td>1999</td>
<td>0%</td>
<td>1%</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Dangas</td>
<td>133</td>
<td>2000</td>
<td>0.9%</td>
<td>5.3%</td>
<td>0.7%</td>
<td>6.1%</td>
</tr>
<tr>
<td>Wholey</td>
<td>475</td>
<td>2000</td>
<td>1.5%</td>
<td>2.7%</td>
<td>0.9%</td>
<td>5.1%</td>
</tr>
<tr>
<td>Roubin</td>
<td>528</td>
<td>2001</td>
<td>1%</td>
<td>4.8%</td>
<td>1.6%</td>
<td>7.4%</td>
</tr>
</tbody>
</table>

Subsequent Carotid Trials

- CAVATAS II
- SAPPHIRE
- CREST/Archer
- CARESS
- SHELTER
- Cabernet
- Space
- Maveric
Open Minded Position

Are there people who might benefit from carotid artery stenting?

“High Risk” Identification Based on Treatment Options

CEA
- Radiation
- Reoperative
- Distal lesions
- Proximal lesions
- Laryngeal nerve
- Cervical fixation
- CAD
- COPD

Both
- FMD
- Arteritis
- Infection
- Aneurysm
- Advanced Age
- Contra Occlusion
- Renal Failure
- Symptoms

CAS
- Kinks and coils
- Arch anatomy
- Severe AIOD
- Intraluminal thrombus
High Risk Carotids

Surgery
- Restenosis
- XRT
- Radical Neck
- CN Palsies
- Cardiac/Pulm
- High/Low Lesions
- Contralateral Occl

Intervention
- Elderly
- String Signs
- Thrombus
- Acute Stroke
- Dissection

- Tortuosity
- Poor Access
- Coag/Platelet
- Severe Ca++

Physiologic Risk - High vs Low
Cleveland Clinic

- 3061 patients
  - 20% high risk
  - 80% low risk
- High Risk
  - CAD w/ PTCA or CABG with in 6 m of procedure
  - CHF
  - COPD
  - Renal Insufficiency (Cr > 3.0)

Ouriel et al. JVS 2000
High Risk vs Low Risk

Cleveland Clinic

- Low risk patients undergoing carotid endarterectomy should not be placed into clinical trial for carotid stents until long term data available.
- Carotid stent trials should only compare patients with high physiologic & anatomic risks to carotid endarterectomy until further data is available on true risk and long term follow up of carotid stents patients.

Ouriel et al. JVS 2000
Physiologic High Risk
- EF < 20%
- Class 3 or 4 angina
- MI 4 weeks preop
- CABG 6 weeks preop
- Pulmonary failure
  - (FEV$_{1.0}$ < 1L)
  - Home O$_2$

24% high risk
451 patients
Compared mortality and stroke rate
Compared regional anesthesia to general anesthesia

Jordan et al. JVS 2002
High Risk vs Low Risk
UAB JVS 2002

SPACE TRIAL

- 1,214 patients were randomly carotid angioplasty with stenting and carotid endarterectomy.
- Kaplan-Meier estimates of ipsilateral ischemic strokes up to 2 years after the procedure and any periprocedural stroke or death do not differ between the carotid artery stenting and the carotid endarterectomy groups.
- **Recurrent stenosis of 70% or more is significantly more frequent in the carotid artery stenting group** compared with the carotid endarterectomy group, with a life-table estimate of 10.7% versus 4.6% (p=0.0009) and 11.1% versus 4.6% (p=0.0007), respectively.
Contemporary Results - CREST Trial
*NEJM July 2010; 3636:11-21.*

- Randomly assigned 2502 patients with symptomatic or asymptomatic carotid stenosis to undergo carotid-artery stenting or carotid endarterectomy. IT DID NOT START THIS WAY.
- The primary composite end point was stroke, myocardial infarction, or death from any cause during the periprocedural period or any ipsilateral stroke within 4 years after randomization.

**Results:**
- The 4-year rate of stroke or death was 6.4% with stenting and 4.7% with endarterectomy (hazard ratio, 1.50; P = 0.03).
- The 4 year rate for death was 0.7% with stenting and 0.3% with endarterectomy. P = 0.18)
- The 4 year rate for stroke was 4.1% for CAS vs. 2.3% for CEA, P = 0.01), and for myocardial infarction (1.1% vs. 2.3%, P = 0.03).
- After this period, the incidences of ipsilateral stroke with stenting and with endarterectomy were similarly low (2.0% and 2.4%, respectively; P = 0.85).
• for death (0.7% vs. 0.3%, P = 0.18), for
• stroke (4.1% vs. 2.3%, P = 0.01), and for
  myocardial infarction (1.1% vs. 2.3%, P = 0.03).
• After this period, the incidences of ipsilateral
  stroke with stenting and with
  endarterectomy
• were similarly low (2.0% and 2.4%,
  respectively; P = 0.85).

Removal of the Disease or
Plaque Compression
1. Patients who are at high risk for carotid endarterectomy (CEA) and who also have symptomatic carotid artery stenosis ≥ 70%. Coverage is limited to procedures performed using FDA approved carotid artery stenting systems and embolic protection devices;

2. Patients who are at high risk for CEA and have symptomatic carotid artery stenosis between 50% and 70%, in accordance with the Category B IDE clinical trials regulation (42 CFR 405.201), as a routine cost under the clinical trials policy (Medicare NCD Manual 310.1), or in accordance with the National Coverage Determination on CAS post approval studies (Medicare NCD Manual 20.7);

3. Patients who are at high risk for CEA and have asymptomatic carotid artery stenosis ≥ 80%, in accordance with the Category B IDE clinical trials regulation (42 CFR 405.201), as a routine cost under the clinical trials policy (Medicare NCD Manual 310.1), or in accordance with the National Coverage Determination on CAS post approval studies (Medicare NCD Manual 20.7).

“If a person begins with certainties, they will end in doubts. But if a person begins with doubts, they will end with certainties.”

Francis Bacon

CREST 2
Conclusions: Vascular Surgeons Offer Comprehensive Care
Carotid Artery Stenting: Will the CREST Trials Change the Current Management Paradigm? Insights into the Management of Extracranial Carotid Stenosis

Carlos Mena, MD. F.A.C.C., F.S.C.A.I
Assistant Professor Department of Internal Medicine
Medical Director Vascular Medicine Program
Section of Cardiovascular Medicine
Yale University School of Medicine

Disclosure

• Abbott
• BARD CR
• Gore
• Pathway Medical
Case Presentation

Carotid Artery stenting: Case Presentation

65 yo male with hx of:

- **Symptomatic LICA stenosis with contra lateral CTO:**
  - **US: 430**
  - **CT-A 90%**
- **CAD: Abnormal MIBI with inferior ischemia**
- **Depressed LVEF 35%**
- **CKD with Cr: 1.8**
Carotid Artery stenting: Case Presentation

Is there a role for Carotid Stenting?
Timeline of Clinical Trials

- ARCHeR: N = 581
- CAPTURE: N = 4,225
- EXACT: N = 2,145
- PROTECT: N = 332
- CAPTURE 2: N = 6,361
- SAPPHIRE: N = 747
- CREST: N = 2,502
- CHOICE: N = 6,872 (enrolling)
- ACT I: N = 1,372 (enrolling)
- SPACE (EU): N = 1,183
- EVA-3s (EU): N = 527
- ICSS (EU): N = 1,710
- NASCET
- ACAS
- AHA Guidelines (pub. 1995)
- FDA Approval for High Risk Patients

Carotid Artery Stent Trials
(Registries & Randomized)

One Month Outcomes
Death/MI/Stroke
CREST: Study Design

- RCT & blinded endpoint adjudication
- Rigorous training and credentialing
- Symptomatic and Asymptomatic
- Intention to treat

CREST: Primary Endpoints

- Periprocedural (<=30 days):
  - Stroke
  - Death
  - Myocardial Infarction
- Post – procedural
  - Ipsilateral Stroke
**CREST: Major Eligibility Criteria**

- **Symptomatic**
  - > 50% by angio
  - >70 by US
  - >70 by CTA/MRA if US <70%

- **Asymptomatic**
  - >60% by angio
  - 70% by Angio
  - 80% by CTA/MRA if US <70%

---

**Primary Endpoint ≤ 4 years**

(any stroke, MI, or death within peri-procedural period plus ipsilateral stroke thereafter)

<table>
<thead>
<tr>
<th>CAS vs. CEA</th>
<th>Hazard Ratio, 95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.2 vs. 6.8%</td>
<td>HR= 1.11; 95% CI: 0.8-1.5</td>
<td>0.51</td>
</tr>
</tbody>
</table>
### Peri-procedural Stroke and MI

<table>
<thead>
<tr>
<th>Condition</th>
<th>CAS vs. CEA</th>
<th>Hazard Ratio 95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>4.1 vs. 2.3%</td>
<td>HR = 1.79; 95% CI: 1.14-2.82</td>
<td>0.01</td>
</tr>
<tr>
<td>MI</td>
<td>1.1 vs. 2.3%</td>
<td>HR = 0.50; 95% CI: 0.26-0.94</td>
<td>0.03</td>
</tr>
</tbody>
</table>

---

### Ipsilateral Stroke after Peri-procedural Period

<table>
<thead>
<tr>
<th>CAS vs. CEA</th>
<th>Hazard Ratio, 95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0 vs. 2.4%</td>
<td>HR = 0.94; 95% CI: 0.50-1.76</td>
<td>0.85</td>
</tr>
</tbody>
</table>
What is CREST telling us:

EU vs. US CAS Outcomes: Why the Difference?
# Multicenter Randomized Trials of CAS vs. CEA

## 30-Day Outcome (Death/Stroke)

<table>
<thead>
<tr>
<th>Trial</th>
<th>CEA</th>
<th>CAS</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVA-3S (30 days)</td>
<td>3.9%</td>
<td>9.6%</td>
<td>0.01</td>
</tr>
<tr>
<td>SPACE (30 days)</td>
<td>6.3%</td>
<td>6.8%</td>
<td>0.09</td>
</tr>
<tr>
<td>ICSS (120 days)</td>
<td>4.7%</td>
<td>8.5%</td>
<td>0.001</td>
</tr>
<tr>
<td>CREST</td>
<td>5.4%</td>
<td>6.7%</td>
<td>0.30</td>
</tr>
</tbody>
</table>

## Operator Experience and Outcomes

<table>
<thead>
<tr>
<th>Trial</th>
<th>Operator Experience</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVA-3S</td>
<td>Poor (12 lifetime CAS or 35 supra-aortics with 5 CAS)</td>
</tr>
<tr>
<td>SPACE</td>
<td>Adequate for era</td>
</tr>
<tr>
<td>ICSS</td>
<td>Poor (50 stents anywhere, 10 lifetime CAS)</td>
</tr>
<tr>
<td>CREST</td>
<td>Adequate for era</td>
</tr>
</tbody>
</table>
### Rates of Use of EPD

<table>
<thead>
<tr>
<th>Trial</th>
<th>EPD Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVA-3S</td>
<td>Not mandated until after the first 80 patients treated; ~20% of all CAS strokes</td>
</tr>
<tr>
<td>SPACE</td>
<td>27%</td>
</tr>
<tr>
<td>ICSS</td>
<td>72% (“known to receive EPD”)</td>
</tr>
<tr>
<td>CREST</td>
<td>&gt;95%</td>
</tr>
</tbody>
</table>

### Management of MI as an Endpoint

<table>
<thead>
<tr>
<th>Trial</th>
<th>MI Ascertainment and Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVA-3S</td>
<td>Not a primary endpoint. &lt;br&gt;Ascertainment not described. &lt;br&gt;CAS: 0.4% CEA: 0.8%</td>
</tr>
<tr>
<td>SPACE</td>
<td>Not a primary or secondary endpoint. &lt;br&gt;No routine ascertainment. &lt;br&gt;No MI’s reported.</td>
</tr>
<tr>
<td>ICSS</td>
<td>Not a primary endpoint. &lt;br&gt;No routine ascertainment. &lt;br&gt;CAS: 0.4% CEA: 0.5%</td>
</tr>
<tr>
<td>CREST</td>
<td>Part of the primary endpoint. &lt;br&gt;Routine surveillance. &lt;br&gt;CAS: 1.1% CEA: 2.3%</td>
</tr>
</tbody>
</table>
The Role of Age

CREST 4-Year Primary Outcome By Age: Does the “Best Fit” Line Tell the Real Story?
Changes in Hazard Ratio by Age Group Per Protocol*

*From FDA executive summary; Exponential trend line added by sponsor.
Primary Composite Endpoint by Symptomatic or Octogenarian Status

- Symptomatic: 8.70% CAS, 7.50% CEA
- Asymptomatic: 5.30% CAS, 5.60% CEA
- Non-octogenarians: 6.70% CAS, 11.60% CEA
- Octogenarians: 7.50% CAS, 6.20% CEA

Cranial Nerve Injury and Access Site Complications Requiring Treatment
<table>
<thead>
<tr>
<th>Procedure related cranial nerve injury</th>
<th>CAS N = 1,131</th>
<th>CEA N = 1,176</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0%</td>
<td>5.3% (62/1176)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Unresolved at one month</td>
<td>0.0%</td>
<td>3.6% (42/1176)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Unresolved at six months</td>
<td>0.0%</td>
<td>2.1% (25/1176)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

### Access Site Complications Requiring Treatment

<table>
<thead>
<tr>
<th>Count</th>
<th>Hematoma</th>
<th>Bleeding</th>
<th>Infection</th>
<th>Occlusion</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS</td>
<td>2</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>CEA</td>
<td>5</td>
<td>5</td>
<td>7</td>
<td>0</td>
<td>11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Per Protocol</th>
<th>CAS N = 1,131</th>
<th>CEA N = 1,176</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access Site Complication Requiring Treatment</td>
<td>1.1%</td>
<td>3.7%</td>
<td>0.0001</td>
</tr>
</tbody>
</table>
## Minor Stroke Resolution

![Image](http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM247780.pdf)

* Fisher's exact p-values were not adjusted for multiple comparisons; p-values for descriptive purposes only

### Death, Stroke and MI within 30 Days

<table>
<thead>
<tr>
<th></th>
<th>CAS N = 1,131</th>
<th>CEA N = 1,176</th>
<th>Difference</th>
<th>Unadjusted p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All death, stroke, or MI</strong></td>
<td>5.8% (65)</td>
<td>5.1% (60)</td>
<td>0.7%</td>
<td>0.5200</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>0.53% (6)</td>
<td>0.26% (3)</td>
<td>0.27%</td>
<td>0.3335</td>
</tr>
<tr>
<td><strong>Any stroke</strong></td>
<td>4.1% (46)</td>
<td>1.9% (22)</td>
<td>2.2%</td>
<td><strong>0.0019</strong></td>
</tr>
<tr>
<td><strong>Major stroke</strong></td>
<td>0.9% (10)</td>
<td>0.4% (5)</td>
<td>0.5%</td>
<td>0.2005</td>
</tr>
<tr>
<td><strong>Minor stroke</strong></td>
<td>3.2% (36)</td>
<td>1.5% (18)</td>
<td>1.7%</td>
<td><strong>0.0088</strong></td>
</tr>
<tr>
<td><strong>MI</strong></td>
<td>2.0% (22)</td>
<td>3.4% (40)</td>
<td>-1.5%</td>
<td><strong>0.0387</strong></td>
</tr>
</tbody>
</table>
**Overall CREST Results: Neurological Residual Deficits Associated with Minor Strokes, Equal at 6 Months**

![Graph](https://example.com/graph.png)

**NIH Stroke Scale (NIHSS)**
- Comparison: CAS vs. CEA
- **1 Month:**
  - CAS: 1.10% (n = 12)
  - CEA: 0.62% (n = 7)
  - Difference: Δ = 0.50%
- **6 Months:**
  - CAS: 0.60% (n = 7)
  - CEA: 0.60% (n = 7)
  - Difference: Δ = 0.02%

**Modified Rankin Score (mRS)**
- Comparison: CAS vs. CEA
- **1 Month:**
  - CAS: 1.20% (n = 14)
  - CEA: 0.50% (n = 6)
  - Difference: Δ = 0.70%
- **6 Months:**
  - CAS: 0.80% (n = 9)
  - CEA: 0.50% (n = 6)
  - Difference: Δ = 0.30%

**Lack of Association of Minor Stroke with Long Term Mortality**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>HR</th>
<th>95% CI</th>
<th>Log Rank P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI vs. Control</td>
<td>2.81</td>
<td>[1.53 - 5.17]</td>
<td>0.0005</td>
</tr>
<tr>
<td>Minor Stroke vs. Control</td>
<td>0.52</td>
<td>[0.13 – 2.09]</td>
<td>0.34</td>
</tr>
<tr>
<td>MI vs. Minor Stroke</td>
<td>5.18</td>
<td>[1.15 – 23.4]</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Source: [FDA Advisory Committee Meeting Materials](http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM247780.pdf)
The Role of MI

Biomarker-Only MI Carries Significant Long-Term Mortality

HR: 3.40 (95%CI: 1.67-6.92)
HR: 3.57 (95%CI: 1.46-8.68)
**Similar Association of Any Stroke or MI on Long Term Mortality**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>HR</th>
<th>Confidence Interval</th>
<th>Log Rank P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI vs. Control</td>
<td>2.81</td>
<td>[1.53 - 5.17]</td>
<td>0.0005</td>
</tr>
<tr>
<td>Any Stroke vs. Control</td>
<td>2.77</td>
<td>[1.54 - 4.97]</td>
<td>0.0004</td>
</tr>
<tr>
<td>MI vs. Any Stroke</td>
<td>0.99</td>
<td>[0.43 - 2.23]</td>
<td>0.97</td>
</tr>
</tbody>
</table>


---

**Embolic Protection Device**
Interventional Emboli
(Clinical Need)

Control vs. PercuSurge
SAFER ~50% reduction
(SVG)

* Al-Mubarak et al., 2001

Therapeutic Options:
Current Embolic Protection Categories

Distal Occlusive Devices

Distal Filters

Proximal Occlusion
and Flow Reversal
Death and Stroke With and Without CPD
“A Systematic Review of the Literature”


Distal Protection devices
A Lower Primary Endpoint Rate was Observed in CAS Patients Treated with the Accunet® EPS

<table>
<thead>
<tr>
<th>CAS</th>
<th>CEA</th>
<th>95% CL</th>
<th>PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.1%</td>
<td>6.6%</td>
<td>2.26%</td>
<td>0.0245</td>
</tr>
</tbody>
</table>

Accunet®

| Used   | 6.6% | 6.6% | 1.80% | 0.0080 |

2.6% Margin of Non-inferiority

Note: Only includes each subject’s first occurrence of the event.

YCRG
Yale Cardiovascular Research Group

Death, Stroke and MI within 30 Days by EPS Usage (PP)

<table>
<thead>
<tr>
<th>Per Protocol</th>
<th>Accunet EPS Used N = 1,073</th>
<th>EPS Not Used N = 24</th>
<th>Difference [95% CI]¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Death, Stroke, and MI²</td>
<td>5.3%</td>
<td>20.8%</td>
<td>-15.5% [-31.8%, 0.8%]</td>
</tr>
<tr>
<td>Death²</td>
<td>0.4%</td>
<td>8.3%</td>
<td>-7.9% ANM</td>
</tr>
<tr>
<td>All Stroke²</td>
<td>3.8%</td>
<td>8.3%</td>
<td>-4.5% ANM</td>
</tr>
<tr>
<td>Major Stroke</td>
<td>0.7%</td>
<td>4.2%</td>
<td>-3.4% ANM</td>
</tr>
<tr>
<td>Minor Stroke</td>
<td>3.1%</td>
<td>4.2%</td>
<td>-1.1% ANM</td>
</tr>
<tr>
<td>MI²</td>
<td>1.9%</td>
<td>8.3%</td>
<td>-6.5% ANM</td>
</tr>
</tbody>
</table>

¹ By normal approximation.
² Hierarchical event in first row, all other are non-hierarchical events.
⁴ ANM: Assumptions Not Met
Proximal Protection devices: EMPIRE trial

- 96.3% GORE Flow Reversal System Technical Success (n = 236)
- 3.7% GORE Flow Reversal System Technical Failure (n = 9)
  - Intolerance (n = 3)
  - Balloon sheath balloon rupture (n = 2)
  - Tortuous anatomy (n = 2)
  - Unable to position device (n = 2)
- 99.2% Carotid Stent Technical Success (n = 243)
Is One EPD Better Than The Other One?

Proximal vs Distal: What are the issues

- Unprotected lesion crossing
- Inadequate device apposition to vessel wall
- Pore size
- Loss of debris during capture
### Table 2: Lesion Characteristics and Procedural Data

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FilterWire EZ (n = 27)</th>
<th>MO.MA (n = 26)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stenosis assessment by Doppler ultrasound</td>
<td>3.1 ± 0.9</td>
<td>3.3 ± 0.8</td>
<td>0.143</td>
</tr>
<tr>
<td>PIIV (m/s)</td>
<td>1.1 ± 0.3</td>
<td>1.2 ± 0.4</td>
<td>0.493</td>
</tr>
<tr>
<td>Diameter stenosis (%)</td>
<td>82 ± 6</td>
<td>88 ± 6</td>
<td>0.199</td>
</tr>
<tr>
<td>Stenosis assessment by CTA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLA (mm²)</td>
<td>3.99 ± 1.28</td>
<td>5.57 ± 1.82</td>
<td>0.340</td>
</tr>
<tr>
<td>MLD (mm)</td>
<td>2.01 ± 0.41</td>
<td>1.89 ± 0.3</td>
<td>0.431</td>
</tr>
<tr>
<td>Diameter stenosis (ECST, %)</td>
<td>86 ± 5</td>
<td>89 ± 6</td>
<td>0.027</td>
</tr>
<tr>
<td>Diameter stenosis (VASCET, %)</td>
<td>70 ± 8.8</td>
<td>74 ± 12</td>
<td>0.170</td>
</tr>
<tr>
<td>Hounsfield units</td>
<td>31.7 ± 8.8 (19–50)</td>
<td>31.7 ± 11.7 (14–50)</td>
<td>1.000</td>
</tr>
<tr>
<td>Long lesion (&gt;15 mm)</td>
<td>13 (48)</td>
<td>14 (64)</td>
<td>0.678</td>
</tr>
<tr>
<td>Lesion eccentricity (&gt;1.2)</td>
<td>18 (67)</td>
<td>17 (65)</td>
<td>0.922</td>
</tr>
<tr>
<td>Uceration/thrombus</td>
<td>2 (7.4%)</td>
<td>9 (35%)</td>
<td>0.019</td>
</tr>
<tr>
<td>Type I aortic arch</td>
<td>20 (74)</td>
<td>22 (87)</td>
<td>0.344</td>
</tr>
<tr>
<td>Variants of Willis circulation</td>
<td>7 (26)</td>
<td>10 (38)</td>
<td>0.328</td>
</tr>
<tr>
<td>Stenosis predilation</td>
<td>7 (26)</td>
<td>10 (38)</td>
<td>0.328</td>
</tr>
<tr>
<td>Procedural time (s)¹</td>
<td>928 ± 236</td>
<td>602 ± 223</td>
<td></td>
</tr>
<tr>
<td>Occlusion time (s)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Macroscopic evidence of debris</td>
<td>7 (26)</td>
<td>7 (27)</td>
<td>0.934</td>
</tr>
</tbody>
</table>

---

![Graph showing microembolic signals (MES)]
Asymptomatic Patients:

\[ \text{CAS} = \text{CEA} \]
Are All Asymptomatic Patients Similar?

TABLE 2. Relationship Between Risk Factors and Ipsilateral Cerebrovascular Event During Follow-Up, Determined by Cox Regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>1.1</td>
<td>1.0-1.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Gender</td>
<td>1.0</td>
<td>0.2-4.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Body mass index</td>
<td>1.0</td>
<td>0.9-1.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>1.0</td>
<td>1.0-1.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>1.0</td>
<td>1.0-1.0</td>
<td>0.8</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>1.6</td>
<td>0.4-7.4</td>
<td>0.5</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>1.0</td>
<td>0.3-3.8</td>
<td>1.0</td>
</tr>
<tr>
<td>History of hypercholesterolemia</td>
<td>1.1</td>
<td>0.3-5.2</td>
<td>0.9</td>
</tr>
<tr>
<td>History of coronary artery disease</td>
<td>1.2</td>
<td>0.4-3.8</td>
<td>0.7</td>
</tr>
<tr>
<td>RMI-2a reductase inhibitor use</td>
<td>1.0</td>
<td>0.3-3.4</td>
<td>1.0</td>
</tr>
<tr>
<td>Presence of LVNC</td>
<td>4.4</td>
<td>0.6-33.7</td>
<td>0.09</td>
</tr>
<tr>
<td>Presence of AF</td>
<td>5.2</td>
<td>1.6-17.3</td>
<td>0.005</td>
</tr>
<tr>
<td>Presence of H.O.</td>
<td>3.8</td>
<td>1.1-17.3</td>
<td>0.005</td>
</tr>
<tr>
<td>Presence of the thinnest FC</td>
<td>17.0</td>
<td>2.2-132.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean lumen area</td>
<td>1.2</td>
<td>0.9-1.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Mean wall area</td>
<td>1.1</td>
<td>0.5-1.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Mean LVNC area</td>
<td>1.6</td>
<td>1.1-2.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean calcium area</td>
<td>2.4</td>
<td>0.9-6.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Mean IPH area</td>
<td>2.6</td>
<td>1.4-4.5</td>
<td>0.005</td>
</tr>
<tr>
<td>Maximum %LVNC of walls</td>
<td>1.6</td>
<td>1.2-2.0</td>
<td>0.004</td>
</tr>
<tr>
<td>Maximum wall thickness</td>
<td>1.6</td>
<td>1.1-2.3</td>
<td>0.005</td>
</tr>
<tr>
<td>Minimum lumen area</td>
<td>1.3</td>
<td>0.7-2.5</td>
<td>0.4</td>
</tr>
</tbody>
</table>

P<0.005

P<0.001
**CREST-2**

- Two parallel multi-center randomized, observer blinded endpoint trials
- NINDS funded clinical trial (U01 NS080168)
- Notice of award received March 11\textsuperscript{th}, 2014
- Clinical Coordinating Center – Mayo Clinic Florida
- Statistical and Data Coordinating Center – University of Alabama at Birmingham

**CREST-2 Parallel Study Design**

(n = 1,240 in each trial)

```
S → R
CAS + Medical
n = 620

Medical
n = 620

R → S
CEA + Medical
n = 620

Medical
n = 620

YCRG
Yale Cardiovascular Research Group
```
Primary Aims

- In patients with ≥70% asymptomatic stenosis, to assess:
  - The treatment differences between medical management and CEA
  - The treatment differences between medical management and CAS

Secondary Aims

To assess:

- Differences in cognitive function in patients randomized to intensive medical management compared to those randomized to CEA or CAS at 4 years of follow-up.

- Differences in major stroke events at 4-years.

- Differences in primary outcomes affected by age, sex, severity of carotid stenosis, risk factor level, and duration of asymptomatic period.
Sources of patients

- Primary Care MDs
- Carotid Bruit patients
- Residents and Fellows
- Symptomatic Contralateral Carotid Stenosis patients

Which Trial?
Which Procedure?

Treatment Groups in CREST-2
(n = 1,240 in each trial)

S → R
CAS n = 620
Med n = 620

S → R
CEA n = 620
Med n = 620

S = Screened
R = Randomized
Endpoint
**Which Trial? Which Procedure?**

Based on CREST:

- For ages 50-74 years, no favored procedure
- For ages <50 years, CAS is the favored procedure
- For ages >74 years, CEA is the favored procedure
- **BUT,** in CREST asymptomatic patients had few events, so there were wide confidence intervals

*So, the choice of CEA or CAS cannot be mandated in CREST-2…*

…*and* individual patient characteristics and preferences may supersede guidelines

---

**What Will Happen when a Carotid Patient comes to Clinic**

≥ 70% Stenosis

- Surgeon OR Interventionist
- **Look for contraindications for surgery**
- **Look for contraindications for stenting**
- Decide type of revascularization best for patient
- Refer for appropriate RCT in CREST-2 (CEA vs Medical-only or CAS vs Medical-only)
Selected CEA Exclusions: needs good history & physical

- Radical neck dissection
- Surgically inaccessible lesions
- Adverse neck anatomy that limits surgical exposure
- Presence of tracheostomy stoma
- Laryngeal nerve palsy contralateral to target vessel

Selected CAS Exclusions: generally needs a good CTA or MRA

- Severe atherosclerosis of the aortic arch or origin of the innominate or common carotid arteries
- Type III, calcified aortic arch anatomy
- Angulation or tortuosity (≥90°) of the innominate, common or internal carotid artery
Selected CAS Exclusions

- Excessive or circumferential calcification of the stenotic lesion
- Lesions >20 mm in length, sequential lesions, and narrow-mouth ulcers
- Inability to deploy or utilize an FDA-approved Embolic Protection Device (EPD)

UNLIKE CREST
this is not a ONE-CAS trial

<table>
<thead>
<tr>
<th>Company Name</th>
<th>Stent</th>
<th>Embolic Protection Device</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott</td>
<td>Acculink</td>
<td>RX Accunet OR Emboshield Nav6</td>
</tr>
<tr>
<td>Xact Stent</td>
<td>Emboshield Nav6</td>
<td></td>
</tr>
<tr>
<td>Boston</td>
<td>Carotid Wallstent</td>
<td>FilterWire EZ</td>
</tr>
<tr>
<td>Scientific</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medtronic</td>
<td></td>
<td>MOMA Proximal Cerebral Protection Device</td>
</tr>
</tbody>
</table>
Patients in both trials will take aspirin 325 mg per day for the entire follow-up period (CAS patients will also take clopidogrel per protocol).

Primary risk factors: systolic blood pressure and LDL cholesterol
- Managed by the study neurologist/internist
- Target systolic blood pressure <140 mmHg
- Target LDL <70 mg/dl

Secondary risk factor targets:
- Non-HDL cholesterol <100 mg/dl.
- Hemoglobin A1c <7.0%.
- Smoking cessation.
- Targeted weight management.
- > 30 minutes of moderate exercise 3 times a week.
New oral anticoagulants: Clinical pearls & cases

Alfred Ian Lee, M.D., Ph.D.
Assistant Professor of Medicine
Section of Hematology
Yale Cancer Center

Disclosures

None
Milestones in anticoagulation

- **Heparin**
  - 1916: Heparin isolated from dog liver as natural anticoagulant
  - 1930s: Heparin used in humans
  - 1980s: Low molecular weight heparins
  - 1991: Fondaparinux

- **Vitamin K antagonists (VKA)**
  - 1920s: Hemorrhagic cattle deaths after eating spoiled clover
  - 1940: Dicoumarol identified as natural anticoagulant
  - 1948: Warfarin (Coumadin) used as rat poison
  - 1952: Warfarin used in humans

- **Direct thrombin inhibitors (DTI)**
  - 1884: Leech anticoagulant described
  - 1950s: Hirudin used in humans
  - 1980s: Lepirudin, desirudin, & argatroban

- **New oral anticoagulants (NOAC)** a.k.a. target-specific oral anticoagulants (TSOACs)
  - 2010: Dabigatran approved for use in AF

---

**NOACs and the coagulation cascade**

- **Xa inhibitors**
  - Rivaroxaban
  - Apixaban
  - Edoxaban

- **DTIs**
  - Dabigatran
  - AZD0837
NOACs and the coagulation cascade

Overview of NOACs

<table>
<thead>
<tr>
<th>NOACs</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA approval</td>
<td>• Nonvalvular AF&lt;br&gt;• VTE treatment</td>
<td>• Nonvalvular AF&lt;br&gt;• VTE treatment&lt;br&gt;• VTE PPx after orthopedic surgery</td>
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</tr>
</tbody>
</table>
### Overview of NOACs

<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
</table>
| **FDA approval** | - Nonvalvular AF  
- VTE treatment | - Nonvalvular AF  
- VTE treatment  
- VTE PPx after orthopedic surgery | - Nonvalvular AF  
- VTE treatment  
- VTE PPx after orthopedic surgery |
| **$t_{1/2}$** | 12-17 hrs | 5-9 hrs | ~12 hrs |
| **Excretion** | Renal (80%) | Renal (67%)  
Hepatic | Hepatic  
Renal (25%) |
### Overview of NOACs

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FDA approval</strong></td>
<td>• Nonvalvular AF</td>
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<tr>
<td></td>
<td>• VTE treatment</td>
<td>• VTE treatment</td>
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</tr>
<tr>
<td></td>
<td>• VTE Ppx after orthopedic surgery</td>
<td>• VTE Ppx after orthopedic surgery</td>
<td>• VTE Ppx after orthopedic surgery</td>
</tr>
<tr>
<td><strong>t1/2</strong></td>
<td>12-17 hrs</td>
<td>5-9 hrs</td>
<td>~12 hrs</td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
<td>Renal (80%)</td>
<td>Renal (67%) Hepatic</td>
<td>Hepatic Renal (25%)</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>• Thrombin time (TT)</td>
<td>• Anti-Xa</td>
<td>• Anti-Xa</td>
</tr>
<tr>
<td></td>
<td>• Ecarin clotting time</td>
<td>• PT/INR</td>
<td>• PT/INR</td>
</tr>
<tr>
<td></td>
<td>• PTT</td>
<td>• PTT</td>
<td>• PTT</td>
</tr>
<tr>
<td></td>
<td>• Dabigatran level (Quest)</td>
<td>• Dabigatran level (Quest)</td>
<td>• Dabigatran level (Quest)</td>
</tr>
<tr>
<td><strong>Reversibility</strong></td>
<td>Hemodialysis ? PCC +/- rFVIIa</td>
<td>? PCC</td>
<td>? PCC</td>
</tr>
</tbody>
</table>

# Overview of NOACs

<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
</table>
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• VTE treatment  
• VTE PPx after orthopedic surgery | • Nonvalvular AF  
• VTE treatment  
• VTE PPx after orthopedic surgery |
| **t<sub>1/2</sub>** | 12-17 hrs | 5-9 hrs | ~12 hrs |
| **Excretion** | Renal (80%)  
Hepatic | Renal (67%)  
Hepatic | Hepatic  
Renal (25%) |
| **Monitoring** | • Thrombin time (TT)  
• Ecarin clotting time  
• PTT  
• Dabigatran level (Quest) | • Anti-Xa  
• PT/INR  
• PTT  
• Rivaroxaban level (Quest) | • Anti-Xa  
• PT/INR  
• PTT |
| **Reversibility** | Hemo dialysis  
? PCC +/- rFVIIa | ? PCC | ? PCC |
| **DDI** | P-glycoprotein transporter | P-glycoprotein transporter  
CYP3A4 | P-glycoprotein transporter  
CYP3A4 |
| **Complications** | Bleeding (esp. elderly)  
Dyspepsia | Bleeding | Bleeding |
Efficacy of NOACs compared to conventional therapy

Recurrent VTE + VTE-related death

<table>
<thead>
<tr>
<th></th>
<th>RR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>1.09 (0.76 - 1.57)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>0.91 (0.68 - 1.21)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Apixaban</td>
<td>0.94 (0.65 - 1.39)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>0.89 (0.71 - 1.12)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Bleeding risk of NOACs compared to conventional therapy

<table>
<thead>
<tr>
<th>Major Bleeding</th>
<th>RR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>0.73 (0.48 - 1.10)</td>
<td>NS</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>0.55 (0.38 - 0.84)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Apixaban</td>
<td>0.31 (0.17 - 0.55)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>0.85 (0.60 - 1.21)</td>
<td>NS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Major and CRNB</th>
<th>RR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>0.63 (0.31 - 0.77)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>0.94 (0.81 - 1.07)</td>
<td>0.27</td>
</tr>
<tr>
<td>Apixaban</td>
<td>0.44 (0.36 - 0.55)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>0.83 (0.72 - 0.94)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

(Yeh CH et al, Blood 2014;124:1020)
### Bleeding risk of NOACs: summary

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
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<tbody>
<tr>
<td><strong>Compared to VKA:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>Same</td>
<td>Same</td>
<td>↓</td>
</tr>
<tr>
<td>Major or clinically relevant bleeding</td>
<td>Same or ↓</td>
<td>Same or ↓</td>
<td>↓</td>
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<td>ICH</td>
<td>Same or ↓</td>
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<td>Same or ↓</td>
</tr>
<tr>
<td>GI bleeding</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Elderly</td>
<td>? Same or ↑</td>
<td>Same</td>
<td>Same</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>?</td>
<td>?</td>
<td>?</td>
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<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

**Risk factors for bleeding on NOACs:**
- advanced age
- renal insufficiency
- low body mass
- concomitant anti-Plt therapy


### Cases
**Case 1: A.B.**

A.B. is a 25 year-old man with a 3-year history of recurrent DVT and PE due to antiphospholipid antibody syndrome (APS). Previously, he failed warfarin and enoxaparin due to noncompliance. Now he requests to change to NOAC.

| Is he a candidate for NOAC? | No |

---

**NOACs: when/when not to use**

- VTE plus poor medication compliance? **No, due to short t_{1/2}**
- VTE plus renal dysfunction? **Not if ClCr < 20-30 mL/min**
- VTE plus severe liver dysfunction? **No**
- VTE plus increased bleeding risk? **No, especially if GI bleeding (dabigatran/rivaroxaban)**
- VTE in patient with cancer? **Case-by-case; LMWH favored**
- VTE in patient with HIT? **No; DTI or fondaparinux favored**
- VTE in patient with APS? **Case-by-case; VKA favored**
- VTE and stable on warfarin or LMWH? **Case-by-case**
- VTE in young patient with low bleeding risk? **Yes**
**NOACs and renal impairment**

**Moderate renal insufficiency: CrCl ~30-50 mL/min**

### VTE or VTE-related death

- **Odds Ratio**
  - Rivaroxaban
  - Dabigatran
  - Total

- **Risk Ratio**
  - Rivaroxaban
  - Dabigatran
  - Total


### Major or clinically relevant bleeding

- **Odds Ratio**
  - Rivaroxaban
  - Apixaban
  - Dabigatran
  - Total

- **Risk Ratio**
  - Rivaroxaban
  - Apixaban
  - Dabigatran
  - Total

Case 1: A.B.

A.B. is a 25 year-old man with a 3-year history of recurrent DVT and PE due to antiphospholipid antibody syndrome (APS). Previously, he failed warfarin and enoxaparin due to noncompliance. Now he requests to change to NOAC.

*Is he a candidate for rivaroxaban? No*

*He is transitioned back to warfarin with tight INR monitoring.*

Case 2: D.C.

D.C. is a 71 year-old male who 2 months ago was diagnosed with a proximal left leg DVT. He has been on rivaroxaban 20 mg q.d. He now presents to clinic with worsening left leg swelling and pain. Doppler ultrasound shows progression of his earlier DVT.

*Did this patient “fail” rivaroxaban? How do we “monitor” NOACs?*
NOACs: monitoring

**Examples from real patients**

- **Dabigatran**
  
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>11.3</td>
<td>12.2</td>
</tr>
<tr>
<td>INR</td>
<td>1.04</td>
<td>1.25</td>
</tr>
<tr>
<td>APTT</td>
<td>19.6</td>
<td>38.1</td>
</tr>
</tbody>
</table>

- **Rivaroxaban**
  
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>10.7</td>
<td>12.7</td>
</tr>
<tr>
<td>INR</td>
<td>0.92</td>
<td>1.13</td>
</tr>
<tr>
<td>APTT</td>
<td>23.6</td>
<td>38.9</td>
</tr>
</tbody>
</table>

References:

NOACs: monitoring
Dabigatran and rivaroxaban drug levels

Antithrombotic Therapy: Laboratory Support of Dose Selection and Therapeutic Monitoring

Dabigatran (Pradaxa)
91115 Dabigatran with Reflex to Thrombin Time

Monitor drug levels in elderly patients and those with excessive bleeding or thrombosis, suspected overdose, planned invasive procedures, or renal insufficiency.

Rivaroxaban (Xarelto)
90361 Rivaroxaban

Monitor therapeutic drug levels in patients with increased or decreased drug clearance, poor treatment response, or suspected overdose.

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D.C. is a 71 year-old male who 2 months ago was diagnosed with a proximal left leg DVT. He has been on rivaroxaban 20 mg q.d. He now presents to clinic with worsening left leg swelling and pain. Doppler ultrasound shows progression of his earlier DVT.

Did this patient “fail” rivaroxaban? How do we “monitor” NOACs?

<table>
<thead>
<tr>
<th>Test Name</th>
<th>ARIXAROBAN</th>
<th>In Range</th>
<th>Out Of Range</th>
<th>Reference Range mcg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombin Time</td>
<td></td>
<td>11.7’</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>1.09’</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTT</td>
<td>27.3’</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RESULT HAS BEEN VERIFIED.

Dosage Peak mcg/L (at steady state) | Trough * mcg/L
---|---
20 mg qD | 300 - 408 | 2 - 161
15 mg qD | 182 - 408 | 3 - 133
10 mg qD | 91 - 196 | 1 - 38
Case 2: D.C.

D.C. is a 71 year-old male who 2 months ago was diagnosed with a proximal left leg DVT. He has been on rivaroxaban 20 mg q.d. He now presents to clinic with worsening left leg swelling and pain. Doppler ultrasound shows progression of his earlier DVT.

*Did this patient “fail” rivaroxaban? How do we “monitor” NOACs?*

*Based on progression of DVT despite a therapeutic rivaroxaban level, he is deemed to have failed rivaroxaban and is transitioned to enoxaparin.*

Case 3: N.J.

N.J. is a 69 year-old female with metastatic breast cancer, currently on hormonal therapy with exemestane. Two months after her initial diagnosis, she develops dyspnea and is found to have bilateral PE and DVT. She is treated with LMWH, but after 3 months, she requests to change to NOAC as she is becoming intolerant of subcutaneous injections.

*Are NOACs reasonable to use in patients with cancer-associated VTE?*

*If so, is she a suitable candidate for NOAC?*
NOACs and cancer-associated VTE

Rivaroxaban  Enoxaparin/VKA

Active cancer
Yes 2/114 (1.8)
No 48/236 (2.1)

Edoxaban  Enoxaparin/UFH/VKA

Medical History: Cancer
History of Cancer
378 14 (3.7)
363 28 (7.1)

No History of Cancer
3740 116 (3.1)
3729 116 (3.2)

Efficacy

No. patients 354 301
Recurrent VTE 5% 7%
Clinically relevant bleeding 14% 16%
Major bleeding 2% 5%

Efficacy & safety

(Prins MH et al, Lancet Haematology 2014;1:e37)
**NOACs in cancer VTE at Yale**

<table>
<thead>
<tr>
<th>Median age, yrs (range)</th>
<th>68 (21-88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, no. (%)</td>
<td>40 (53.3%)</td>
</tr>
<tr>
<td><strong>Diagnosis, no. (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>10 (13.3%)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>10 (13.3%)</td>
</tr>
<tr>
<td>Colon Cancer</td>
<td>7 (9.3%)</td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td>7 (9.3%)</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>6 (8.0%)</td>
</tr>
<tr>
<td>Pancreatic Cancer</td>
<td>5 (6.7%)</td>
</tr>
<tr>
<td>Bladder Cancer</td>
<td>4 (5.3%)</td>
</tr>
<tr>
<td>Acute Myeloid Leukemia</td>
<td>3 (4.0%)</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>3 (4.0%)</td>
</tr>
<tr>
<td>Leukemia (other than AML)</td>
<td>3 (4.0%)</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>3 (4.0%)</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>3 (4.0%)</td>
</tr>
<tr>
<td>Myelodysplastic Syndrome</td>
<td>2 (2.6%)</td>
</tr>
<tr>
<td>Other (1 patient each): Anal, Esophageal, Gastric, Germ Cell Seminoma, Glioblastoma, Pituitary, SCC Tonsil, Thymic, Uterine</td>
<td>9 (12.0%)</td>
</tr>
</tbody>
</table>

Stage III-IV solid tumors were associated with bleeding (p=0.0151)

<table>
<thead>
<tr>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
</tr>
<tr>
<td>Clinically relevant bleeding</td>
</tr>
<tr>
<td>Epistaxis</td>
</tr>
<tr>
<td>GI bleed</td>
</tr>
<tr>
<td>Hematuria</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
<tr>
<td>Other, 1 each: hemoptysis, intramuscular, intracranial pericardial, urogenital</td>
</tr>
<tr>
<td>Fatal bleeding</td>
</tr>
</tbody>
</table>
### NOACs and cancer-associated VTE

A practical checklist when considering NOACs in cancer patients

<table>
<thead>
<tr>
<th>Patient assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk factors for bleeding</strong></td>
</tr>
<tr>
<td>No major bleeding events in the past 2 months</td>
</tr>
<tr>
<td>Absence of intracranial or visceral tumor at high risk for major bleeding</td>
</tr>
<tr>
<td><strong>Platelets</strong></td>
</tr>
<tr>
<td>Platelet count ≥50,000 per μL</td>
</tr>
<tr>
<td>No anticipated decrease due to disease or chemotherapy</td>
</tr>
<tr>
<td><strong>Coagulation studies</strong></td>
</tr>
<tr>
<td>Normal PT, PTT, and fibrinogen</td>
</tr>
<tr>
<td><strong>Liver function tests</strong></td>
</tr>
<tr>
<td>No significant hepatic impairment (e.g., Child-Pugh B or C, cirrhosis)</td>
</tr>
<tr>
<td><strong>Renal function</strong></td>
</tr>
<tr>
<td>CrCl &gt; 30 ml/min (rivaroxaban)</td>
</tr>
<tr>
<td>CrCl &gt; 15 ml/min (dabigatran and apixaban)</td>
</tr>
<tr>
<td>No anticipated fluctuations due to nephrotropic chemotherapy or other drugs</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
</tr>
<tr>
<td>No concomitant use of drugs with strong effect on CYP3A4 and/or P-glycoprotein</td>
</tr>
<tr>
<td>Fig. 1 lists strong CYP3A4 and/or P-glycoprotein inhibitors and inducers</td>
</tr>
<tr>
<td>Table 4 lists chemotherapy drugs that modulate CYP3A4 and/or P-glycoprotein</td>
</tr>
<tr>
<td>Good medication compliance</td>
</tr>
</tbody>
</table>

**DDI**

![DDI Diagram](image)

(Nov 2014; 19:82)

---

### Case 3: N.J.

N.J. is a 69 year-old female with metastatic breast cancer, currently on hormonal therapy with exemestane. Two months after her initial diagnosis, she develops dyspnea and is found to have bilateral PE and DVT. She is treated with LMWH, but after 3 months, she requests to change to NOAC as she is becoming intolerant of subcutaneous injections.

**Are NOACs reasonable to use in patients with cancer-associated VTE?**

Maybe

**If so, is she a suitable candidate for NOAC?**

Maybe

**Following an extensive risk/benefit discussion and thorough assessment of bleeding risk, DDIs, and cancer prognosis, she elects to stay on LMWH.**
Case 4: N.F.

N.F. is a 78 year-old man with AF, CAD/CABG, and diabetes. He has been on dabigatran for a year. One month ago, he fell, and over the next few weeks he developed progressive headache. He comes to the emergency department now with severe headache and right-sided weakness. Head CT shows a large acute-on-chronic subdural hematoma with 14 mm midline shift.

How do we manage his bleeding?

NOACs and bleeding

What’s the most important piece of information to obtain when evaluating a patient with NOAC-associated bleeding?

When the last dose of NOAC was taken
(Repair the short $t_{1/2}$ of these agents!)
NOACs and bleeding

- **Initial measures:**
  - Determine last NOAC dose
  - Consider charcoal if < 2 hrs from last NOAC dose
  - Check labs: CBC, renal/liver function, PT/INR, PTT, TT
  - Check medications: look for anti-Plt agents and other potentially interfering drugs
  - Hold NOAC; supportive care; transfusions

- **For moderate or severe bleeding,** consider:
  - PCC
  - Hemodialysis (for dabigatran, if less than 12 hrs)
  - DDAVP; Amicar; cryoprecipitate; Plt transfusions

- **Avoid surgery for 48 hrs if possible**

Management of bleeding in Case 4 (N.F.)

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  - Hemodialysis (for dabigatran, if less than 12 hrs)
  - DDAVP; Amicar; cryoprecipitate; Plt transfusions

- **Avoid surgery for 48 hrs if possible**

**How do we manage his bleeding?**

- **8 hrs earlier**
  - CBC, creatinine, LFTs normal
  - PT/INR, PTT normal
  - TT: sent, pending for next wk

- **On aspirin**
  - Give PCC
  - Proceed with hemodialysis
  - Give DDAVP + Plt because of aspirin

With above measures, SDH stabilizes radiographically, and he undergoes craniotomy on hospital day 3 without problems.
**TT in dabigatran-associated bleeding**

<table>
<thead>
<tr>
<th>Day after last dabigatran dose</th>
<th>TT (sec; normal: 15-22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt; 120</td>
</tr>
<tr>
<td>2</td>
<td>97.6 – 119.8</td>
</tr>
<tr>
<td>3</td>
<td>69.3</td>
</tr>
<tr>
<td>4</td>
<td>30.7</td>
</tr>
<tr>
<td>5</td>
<td>22.7</td>
</tr>
</tbody>
</table>

**TT is ultrasensitive to the presence of dabigatran**

What is the outcome of NOAC patients with major bleeding vs those on VKA?

*NOAC patients who bleed might fare better than those on VKA*

(Hylek EM et al, J Am Coll Cardiol 2014;63:2141)
The future of NOACs and bleeding: reversal agents

- **Idarucizumab**
  - Humanized mAb against dabigatran

- **Andexanet**
  - FXa inactivator

- **Perosphere**
  - FXa inactivator

---

**Coagulation & Benign Hematology Conference**

~Every other Friday, 10:30-11:30 am

*NP-11 Conference Room*
Case Study

Hardik P. Amin, MD

slides were not available for online viewing