2015 AHA/ASA Focused Update of the 2013 Guidelines for the Early Management of Patients with Acute Ischemic Stroke Regarding Endovascular Treatment

A Guideline for Healthcare Professionals from the American Heart Association, American Stroke Association
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This slide presentation was developed by a member of the Stroke Council Professional Education Sub-Committee
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The writers used the following sources to develop these guidelines

• Randomized controlled trials with early intravenous and intra-arterial interventions
• Randomized controlled trials of stent retrievers
• Meta-analysis pertaining to stroke endovascular care, especially anesthesia
• Data from registries
Definition of Class of Recommendation and Levels of Evidence used in AHA/ASA Recommendations

<table>
<thead>
<tr>
<th>CLASS (STRENGTH) OF RECOMMENDATION</th>
<th>LEVEL (QUALITY) OF EVIDENCE‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLASS I (STRONG)</strong></td>
<td><strong>LEVEL A</strong></td>
</tr>
<tr>
<td>Benefit &gt;&gt;&gt; Risk</td>
<td>High-quality evidence‡ from more than 1 RCTs</td>
</tr>
<tr>
<td></td>
<td>Meta-analyses of high-quality RCTs</td>
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<tr>
<td></td>
<td>One or more RCTs corroborated by high-quality registry studies</td>
</tr>
<tr>
<td><strong>CLASS IIa (MODERATE)</strong></td>
<td><strong>LEVEL B-R</strong></td>
</tr>
<tr>
<td>Benefit &gt;&gt; Risk</td>
<td>Moderate-quality evidence‡ from 1 or more RCTs</td>
</tr>
<tr>
<td></td>
<td>Meta-analyses of moderate-quality RCTs</td>
</tr>
<tr>
<td><strong>CLASS IIb (WEAK)</strong></td>
<td><strong>LEVEL B-NR</strong></td>
</tr>
<tr>
<td>Benefit &gt; Risk</td>
<td>Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies</td>
</tr>
<tr>
<td></td>
<td>Meta-analyses of such studies</td>
</tr>
<tr>
<td><strong>CLASS III: No Benefit (MODERATE)</strong></td>
<td><strong>LEVEL C</strong></td>
</tr>
<tr>
<td>(Generally, LOE A or B use only)</td>
<td>Randomized or nonrandomized observational or registry studies with limitations of design or execution</td>
</tr>
<tr>
<td></td>
<td>Meta-analyses of such studies</td>
</tr>
<tr>
<td></td>
<td>Physiological or mechanistic studies in human subjects</td>
</tr>
<tr>
<td><strong>CLASS III: Harm (STRONG)</strong></td>
<td><strong>LEVEL E</strong></td>
</tr>
<tr>
<td>Risk &gt; Benefit</td>
<td>Consensus of expert opinion based on clinical experience when evidence is insufficient, vague, or conflicting</td>
</tr>
</tbody>
</table>

COR and LOE are determined independently (any COR may be paired with any LOE). A recommendation with LOE C or E does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).
† For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.
‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic review the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.
• Provide an update to the early management of patients with acute ischemic stroke regarding endovascular treatment
• Understand the basis of this update: Recent endovascular trials that compared intravenous thrombolysis with combination of intravenous thrombolysis and rescue therapy (Intra-arterial thrombolysis, devices or both)
• Explore the reason why some of the Intra-arterial trials did not show significant improvement in outcome compared to intravenous therapy alone in large vessel occlusion related ischemic stroke
• Provide updated evidence based recommendations on endovascular interventions in management of hyperacute ischemic stroke
• Develop an awareness of the ancillary processes such as anesthesia that may effect outcome
• Understand the need for different levels of care (concept of stroke ready, primary stroke and comprehensive stroke hospitals)
SOME COMMONLY USED TERMS and IMAGES

- Thrombolysis in Cerebral Infarction (TICI)
- Alberta Stroke Program Early CT Score (ASPECTS)
Thrombolysis in Cerebral Infarction (TICI)

• 4 Grades
  – 0 = no perfusion and no distal flow
  – 1 = incomplete or partial reperfusion without distal flow
  – 2a = incomplete or partial reperfusion with < 50% distal flow
  – 2b = incomplete or partial reperfusion with >50% distal flow
  – 3 = complete reperfusion with complete distal flow
Alberta Stroke Program Early CT Score (ASPECT)

• 10 point quantitative topographic CT scan score to assess early ischemic changes of the MCA region
• Assessed at 2 standardized regions
  • Ganglionic Level where the thalamus, basal ganglia and caudate are visible
  • Supraganglionic level which includes the corona radiata and centrum semiovale
Mapping of ASPECTS sites
Normal ASPECT score is 10
   Deduct 1 point for each area involved.

A score of 7 or less - Correlates with poor functional outcome and hemorrhage.

*Limitation – Only scores the MCA
INTRAVENOUS THROMBOLYSIS WITH Recombinant Tissue Plasminogen Activator

- Rapid intravenous therapy with recombinant tissue plasminogen activator (rtPA) in appropriate patients remains the Gold Standard of early treatment of acute ischemic stroke.
- Restoration of blood flow in IS patients is effective in reducing long term morbidity.
- IV rtPA administration improves functional outcomes at 3-6 months with given with in 4.5 hours of IS onset and should be administered.
- Since treatment effects are time dependent, every effort should be made to shorten to the time from stroke onset to IV rtPA
- Administration of IV rtPA should not delayed for vascular imaging (CT Angiogram, MR Angiogram).
New Randomized Clinical Trials Of Endovascular Stroke Treatment – Reviewed for this Update

Trials with Primarily Intra-arterial Fibrinolysis and/or First Generation Mechanical Embolectomy Devices

- SYNTHESIS expansion
- IMS III
- MR RESCUE

Trials with Primarily Stent Retrievers

- MR CLEAN
- SWIFT-PRIME
- ESCAPE
- EXTEND-IA
- REVASCAT
# Table of Abbreviations

- **ASPECTS** – Alberta Stroke Program Early CT Score  
- **CT** – Computed Tomography, **CTA** – computed tomography angiography; **d** – days, **EC** – extra-cranial, **hrs** – hours, **IA** – intra-arterial, **IAT** – intra-arterial therapy  
- **ESCAPE** – Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times.  
- **EXTEND IA** – Extending the Time for Thrombolysis in Emergency Neurological Deficits – Intra-arterial  
- **ICA** – Internal carotid artery  
- **IMS III** – Interventional Management of Stroke Trial III  
- **IQR** – interquartile range, **IV** - intravenous, **MCA** – middle cerebral artery, **min** – minutes, **MR** – magnetic resonance  
- **MR CLEAN** – The multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke  
- **MR RESCUE** – MR Recanalization of Stroke Clots Using Embolectomy  
- **ICH** – intracerebral hemorrhage, **mRS** – modified Rankin scale, **N** – number, **NIHSS**-National Institutes of Health Stroke Scale, **OR** – odds ratio, **rtPA** – recombinant tissue plasminogen activator, **SD** – standard deviation  
- **SWIFT PRIME** – The Solitaire FR (Flow restoration) with Intent for Primary Endovascular Treatment of Acute Ischemic Stroke  
- **T** – terminus (of the internal carotid artery), **TICI** – thrombolysis in cerebral infarction, **yrs** - years
SYNTHESIS Expansion: A randomized, open label, blinder-endpoint (PROBE) superiority trial

- 362 patients, randomized after IV rtPA within 4.5 hours of symptom onset for whom endovascular treatment was possible within 6 hours. Vascular Imaging was not required
- Randomized 1:1 IV rtPA (0.9mg/kg or endovascular treatment (EVT)
- EVT group was not given IV rtPA while waiting for intervention. Received IA t-PA via microcatheter and/or mechanical clot disruption with guide wire and/or Mechanical thrombectomy
- Median baseline NIHSS : 13 for each group
- Median onset to treatment time IV rtPA group was 2.75 hours and 3.75 hours in EVT group.
- Ninety two percent anterior circulation stroke
- EVT group: 66% IA rtPA and thrombus fragmentation with a guide wire only, in 34% a device was used,
- Stent retrievers were used in 14% in the EVT group. Rates and efficacy of recanalization not reported
- Results: No difference in primary outcome: mRS 0-1 or death at 3 months; symptomatic ICH at 7 days, or subgroups NIHSS <11 v ≥11; age ≤67 v >67 yrs.
Interventional Management of Stroke Trial (IMS III)

- PROBE design.
- Randomized acute ischemic stroke patients (NIHSS>10) who received IV rtPA (0.9mg/kg) to IV rtPA alone or (0.6mg/kg) followed by EVT, if occlusion persisted, with a device and/or IA rtPA in a 1:2 ratio.
- EVT: Stroke onset to Groin puncture time (mean± SD) 208 ± 47 mins.
- EVT was deployed in 77% of the EVT group; IA alone in 41%, device ± IA 59%
- Stent Retrievers were used in only 1.5%
- TICI 2b/3 achieved in 41%
- No difference in outcome mRS (0-2) between groups and trial stopped early after 656 patients (target 900) for futility
- Trend towards better outcome in patients with recanalization
118 patients 18-85y with large artery occlusion and anterior circulation ischemic stroke within 8 hours who were ineligible for IV rtPA or had persistent vessel occlusion after IV rtPA.

Randomized to either to Mechanical Thrombectomy (MT) (via Penumbra/Merci) or standard therapy (ST)

Stratified by penumbral imaging on DWI/PI or CTP, subdivided into favorable and unfavorable groups

Time to enrollment: 5.5 ± 1.4 hrs

Median baseline NIHSS: 17

Onset to groin puncture in EVT group: 6.35 ± 1.2 (SD)

TICI 2b/3 recanalization in: 25%

Primary outcome mRS shift: Did not differ between groups.

No difference in outcome between MT and ST in patient groups with pre-specified favorable and unfavorable penumbral patterns
Analysis of Earlier Trials

- These studies used primarily IA rtPA and first generation endovascular devices alone or in combination.
- Recanalization rates were between 25% - 41% reflecting the methods available at the time.
  - More recent studies have shown that newer stent retrievers are more effective than the first generation devices.
  - The low use of these devices could have been the reason for lower recanalization rates in the endovascular group leading to a non-significant difference between the endovascular and the IV rtPA group.
STENT RETRIEVERS
Newest Technology

C. Roth et al. Stroke. 2010; 41: 2559-2567
PREDOMINANTLY STENT BASED TRIALS
Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke (MR CLEAN)

- A PROBE, two-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, middle cerebral artery (M1 or M2), or anterior cerebral artery (A1 or A2)] established by computed tomographic angiography (CTA), magnetic resonance angiography (MRA), or digital-subtraction angiography (DSA), and a score of 2 or higher on the NIHSS.
- Initiation of endovascular treatment within 6 hours of stroke onset had to be possible.
- Patients who were eligible in agreement with national guidelines received IV rtPA. Those with a non-favorable response were eligible for inclusion.
Results:
- Randomized 1:1 (usual care, IA treatment plus usual care)
- Occlusion site: M1 (64%), ICA + M1 (27%)
- Onset to groin puncture: 260 (210-313 IQR) minutes
- Stent retriever used in: 81.5%
- TICI 2b/3 revascularization in 59%; Stroke to reperfusion time: 322 (279-394 IQR) minutes
- The treatment effect was estimated as an odds ratio, adjusted for pre-specified prognostic factors, that IA treatment would lead to lower mRS at 90 days, as compared with usual care alone (shift analysis)
- **Outcome:** Absolute difference of 13.5% (95% CI, 1.21 to 2.30) in achieving mRS 0-2 in favor of the intervention group
- This difference became non-significant if reperfusion was delayed > 6.2 hours
PROBE two-arm superiority trial of 316 patients with acute ischemic disabling stroke, NIHSS > 5, capable of being randomized up to 12 hours after onset.

CT/CTA, NECT and CTA (multiphase): door to imaging <25 minutes

Small infarct core (ASPECTS = 6-10 or CTP)

Occluded proximal artery in anterior circulation, MCA - M1 or 2 or more M2, moderate to good collaterals (filling of 50% of the pial MCA on CTA)

1:1 randomization of 58 patients who received IV rtPA within 4.5 hours

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

The primary outcome was the odds ratio that the intervention would lead to lower scores on the mRS at 90 days (shift analysis)
Results:

• Interim analysis after the O’Brien Fleming stopping boundary was crossed.

• **Primary Outcome:** The adjusted odds ratio (indicating the odds of improvement of 1 point on the mRS) was 3.1 (95% CI, 2.0 to 4.7) favoring endovascular intervention.

• The difference in proportion of patients with a mRS of 0-2 at 90 days was 53% in favor of the intervention group vs- 23.7% in the control group (p<0.001).

• Retrievable stents were used in 86.1% who underwent an endovascular procedure.

• TICI 2b/3 recanalization was observed in 72.4% in the endovascular group.

• The number randomized after 6 hours was too small to reach any conclusions regarding intervention beyond 6 hours.
• **Purpose:**
  – To determine if patients experiencing an Acute Ischemic Stroke due to large vessel occlusion, treated with combined IV t-PA and Solitaire FR within 6 hours of symptom onset have less stroke-related disability than those patients treated with IV t-PA alone.

• **Methods:**
  – Global, multi-center, prospective, randomized, open, blinded endpoint (PROBE) IDE Study
  ◆ *Intervention*: IV rtPA with Solitaire FR Device
  ◆ *Control*: IV rtPA alone
  – 39 enrolling centers
Inclusion Criteria

• Acute ischemic stroke
• Age 18-80
• Pre-stroke mRS ≤ 1
• ASPECTS ≤ 6
• Baseline NIHSS 8-29 at time of randomization
• Initiation of IV rtPA within 4.5 hours of onset of stroke
• CTA or MRA confirmation of large vessel occlusion in ICA, M1 segment of MCA or carotid terminus
• Endovascular treatment can be initiated within 6 hours of onset of stroke symptoms and within 90 minutes from CTA/MRA to groin puncture
SWIFT-PRIME: Radiological Criteria

- If CTA or MRA was part of local standard of care, it was performed at initial evaluation prior to commencing IV rtPA; if not, it was performed after review of the initial imaging and signing of informed consent.

- Initially, CT perfusion or multimodal MRI was required and enrollment was restricted to patients with the target mismatch profile (as assessed by specialized software) and defined as: the ischemic core lesion measured 50 mL or less, the volume of tissue with a time to maximum delay of more than 10 seconds was 100 mL or less, and the mismatch volume was at least 15 mL and the mismatch ratio was more than 1.8.

- Midway through the trial, the inclusion criteria there 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 scores (ASPECTS > 6 was required).
Results:

- 196 patients were randomized after IV rtPA up to 6 hours from onset to groin puncture to Solitaire IA therapy or control.
- Two primary outcomes (shift analysis): mRS at 90 days ($p < 0.001$) and increased proportion with mRS 0-2 at 90 days - 60% in the endovascular group and 35% in the rtPA alone group., risk ration 1.70, 95% CI, 1.23-2.33)
- No differences in death or symptomatic ICH (sICH)
- TICI 2b/3 recanalization: = 88% in the endovascular group.
The Extending the Time for Thrombolysis in Emergency Neurological Deficits- Intra-Arterial (EXTEND-IA) Inclusion/Exclusion and Randomization

- Seventy participants who were eligible using “standard criteria” to receive IV rtPA within 4.5 hours of stroke onset were randomized in a PROBE design either to receive either IV rtPA only or IV rtPA 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 commencing IV rtPA. Occlusion of the ICA or of M1 or M2 on CT angiography was required. In addition, CT or MRI perfusion imaging had to show (a) mismatch ratio of greater than 1.2, and (b) absolute mismatch volume of greater than 10 mL, and (c) infarct core lesion volume of less than 70mL based on specialized software.

- Exclusion criteria for coagulopathies as in SWIFT-PRIME.

- The co-primary outcomes were reperfusion at 24 hours and early neurologic improvement (≥8-point reduction on the NIHSS or a score of 0 or 1 at day 3). The mRS at 90 days was a secondary outcome.
Results Interim Analysis:

• Trial halted showed that stopping criteria had been met
• Occlusion sites: ICA 31%, MCA 54%
• Percentage of ischemic territory that had undergone reperfusion at 24 hours was greater in the endovascular group than in the IV rtPA group.
• Outcomes: Endovascular therapy, initiated at a median of 210 (IQR 166-251, IQR) minutes after the onset of stroke, increased early neurologic improvement at 3 days (80% vs. 37%, p=0.002)
• More patients achieved functional independence in the endovascular group (mRS 0-2, 71% vs. 40%; p=0.01).
• There were no significant differences in rates of death or sICH
• Recanalization to TICI2b/3 was achieved in 86% of patients in the endovascular group at a median of 248 (IQR 204-277) minutes after stroke onset.
• 206 patients with acute ischemic stroke
• PROBE design
• NIHSS ≥ 6
• Intracranial ICA or M1 occlusion by CTA, MRA or DSA.
• Patients who had received IV rtPA were eligible, if there was if there was no significant neurological improvement (criteria specified in the protocol) at 30 minutes post 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 <7 on NECT or <6 on DWI-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 >8.
• Only 95% confidence intervals were reported
Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy (REVASCAT)

- Site of occlusion: ICA 26%, M165%.
- Participants were randomized 1:1 to receive either medical therapy alone or thrombectomy with a stent retriever.
- IV rtPA was administered to 73%.
Results:

- The primary outcome analysis showed a common odds ratio of improvement in the distribution of the modified Rankin scale score (shift analysis) favoring endovascular treatment (adjusted odds ratio 1.7, 95% CI 1.05 to 2.8).
- The proportion of patients with a mRS of 0-2 at 90 days was 43.7% in the intervention group and 28.2% in the control group (adjusted odds ratio 2.1, 95% CI 1.1 to 4.0).
- There were no significant differences in death or sICH.
- Ninety-five per cent of those in the endovascular group underwent thrombectomy.
- TICI 2b/3 recanalization was observed in 66% of the endovascular group.
- Across the pre-specified subgroups, there were no significant interactions according to NIHSS score, vessel-occlusion site, baseline ASPECTS score, administration of IV rtPA, age or time of randomization, although for the latter dichotomized at 4.5 hours the p-value for interaction was 0.9 with the later group doing worse. No data are given for those who underwent groin puncture after 6 hours.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SYNTHESSES EXPANSION</th>
<th>IMS111</th>
<th>MR RESCUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment groups</td>
<td>IA/ANYDEVICE/ BOTH VS IV rtPA</td>
<td>0.6mg/kg IV+IA rtPA/any device or both</td>
<td>Standard IV rtPA +MERCI or PENUMBRA</td>
</tr>
<tr>
<td>Territory</td>
<td>Any</td>
<td>Any</td>
<td>Anterior Circulation</td>
</tr>
<tr>
<td>Age</td>
<td>18-80</td>
<td>18-82</td>
<td>18-85</td>
</tr>
<tr>
<td>IV rtPA</td>
<td>Required</td>
<td>Required &lt; 3 hours</td>
<td>Not Required</td>
</tr>
<tr>
<td>Time to IAT (hrs)</td>
<td>6</td>
<td>5</td>
<td>8 stop by 9</td>
</tr>
<tr>
<td>Severity (NIHSS)</td>
<td>≤ 25</td>
<td>≥ 10 OR 8-9 with occlusion</td>
<td>6-29</td>
</tr>
<tr>
<td>ASPECTS</td>
<td>No</td>
<td>&lt; 4</td>
<td>No</td>
</tr>
<tr>
<td>Vascular Imaging</td>
<td>No</td>
<td>No</td>
<td>CTA/MRA occlusion</td>
</tr>
<tr>
<td>Other Imaging</td>
<td>No</td>
<td>&gt; 1/3 MCA infarction excluded</td>
<td>Multimodal/CT/MRI for stratification</td>
</tr>
<tr>
<td>Stent Retrievers Used</td>
<td>14 %</td>
<td>IA41%,IA+DEVICE59%,STENT RETRIEVERS1.5%</td>
<td>MERCI/PENUMBRA Type equation here.±IA rtPA</td>
</tr>
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## TIME TO IV rtPA, GROIN PUNCTURE, RECANALIZATION AND OUTCOMES

<table>
<thead>
<tr>
<th>DEVICES</th>
<th>SYNTHESES EXPANSION</th>
<th>IMS 111</th>
<th>MR RESCUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to IV rtPA hrs</td>
<td>2.75(2.33,3.33)</td>
<td>122±34/121/±34</td>
<td>6.35 ±1.2</td>
</tr>
<tr>
<td>Time to groin puncture E(min)</td>
<td>3.75 (3.23,4.33)</td>
<td>208±47</td>
<td></td>
</tr>
<tr>
<td>Recanalization 2b/3 TICI</td>
<td>NOT REPORTED</td>
<td>41%</td>
<td>25%</td>
</tr>
</tbody>
</table>

## TERRITORY CONTROL/TREATMENT

| Device in Active Group       | 91% IA alone 66% device 34% | 41% IA rtPA 38% ±device 21% device only 1.5% stent retriever | 58% MERCI 22% PENUMBRA 16% Both |

| Outcomes                    | No significance difference between groups | No significance difference between groups | No significance difference between groups |
RECENT STENT REVIEWER BASED INTRAARTERIAL INTERVENTIONS WITH REPORTED RESULTS

- MR CLEAN
- SWIFT-PRIME
- EXTEND-IA
- ESCAPE
- REVASCAT
# COMPARISON OF THESE STENT RETRIEVER BASED TRIALS

<table>
<thead>
<tr>
<th>TRAILS</th>
<th>MR CLEAN</th>
<th>SWIFT PRIME</th>
<th>EXTEND IA</th>
<th>ESCAPE</th>
<th>REVASCAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients (C/A*)</td>
<td>233/267</td>
<td>98/98</td>
<td>35/35</td>
<td>165/150</td>
<td>103/103</td>
</tr>
<tr>
<td>ASPECTS (median)</td>
<td>9/9</td>
<td>9/9</td>
<td>9/9</td>
<td>&gt;7</td>
<td></td>
</tr>
<tr>
<td>NIHSS (mean)</td>
<td>17/18</td>
<td>&gt;10</td>
<td>16/17</td>
<td>&gt;6</td>
<td></td>
</tr>
<tr>
<td>Enrollment by CTA/MRA/DSA</td>
<td>ICA 18.3/16, M1 168/77, M2 14/6</td>
<td>ICA 31%, M1 157/51, M2 11/1</td>
<td>ICA+M1 27%, M1/M2 68/71%</td>
<td>EC ICA 12.7%</td>
<td></td>
</tr>
<tr>
<td>rtPA IV (onset to treatment)</td>
<td>85/87 mins</td>
<td>110.5/117 mins</td>
<td>127/145 mins</td>
<td>110/125 mins</td>
<td></td>
</tr>
<tr>
<td>Intra-arterial Therapy</td>
<td>IA rt-PA 21%, SR 81.5%</td>
<td>88.8% SR</td>
<td>77% SR</td>
<td>72.5% SR</td>
<td></td>
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<tr>
<td>Time to Groin Puncture (median) mins</td>
<td>260</td>
<td>224</td>
<td>210</td>
<td>Not given</td>
<td></td>
</tr>
<tr>
<td>Recanalization To TICI 2B/3</td>
<td>58.7%</td>
<td>88%</td>
<td>86%</td>
<td>72.4%</td>
<td>66%</td>
</tr>
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</table>
## Comparative Outcomes

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>90 Day mRS 0-2</th>
<th>Odds</th>
<th>NNT</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active</td>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Active</strong></td>
<td><strong>Control</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SYNTHESIS expansion</td>
<td>30.4%</td>
<td>34.8%</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Alive without disability (n= 55)</td>
<td>Alive without disability (n= 63)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMS III</td>
<td>40.8%</td>
<td>38.7%</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>(n= 434) mRS &lt; 2</td>
<td>(n= 222) mRS &lt; 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MR RESCUE</td>
<td>3.9 Mean mRS score (n =64)</td>
<td>3.9 Mean mRS score (n = 54)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>REVASCAT</td>
<td>43.7% mRS &lt; 2 (n =103)</td>
<td>28.2% mRS &lt; 2 (n =103)</td>
<td>2.1 (1.1-4)</td>
<td></td>
</tr>
<tr>
<td>MR CLEAN</td>
<td>32.6% mRS &lt; 2 (n=233)</td>
<td>19.1% mRS &lt; 2 (n=267)</td>
<td>2.16 (1.39-3.38)</td>
<td>7 in favor of EVT</td>
</tr>
<tr>
<td>SWIFT -PRIME</td>
<td>60% mRS &lt; 2 (n=98)</td>
<td>35% mRS &lt; 2 (n=93)</td>
<td>2.75 (1.53-4.95)</td>
<td>4 in favor of EVT</td>
</tr>
<tr>
<td>ESCAPE</td>
<td>53.0% mRS &lt; 2 (n=164)</td>
<td>29.3% mRS &lt; 2 (n=147)</td>
<td>1.8 (1.4-2.4)</td>
<td>4 in favor of EVT</td>
</tr>
<tr>
<td>EXTEND-IA</td>
<td>71% mRS &lt; 2 (n=35)</td>
<td>40% mRS &lt; 2 (n=35)</td>
<td>4.2 (1.3-13)</td>
<td>3 in favor of EVT</td>
</tr>
</tbody>
</table>
Why are the Non-Stent Retriever Trial Outcomes different from Stent Retriever Trials?

• Stent retriever trials were very tightly linked to time from stroke onset to intervention
• Rates of recanalization were significantly higher in these trials compared to the earlier (MR RESCUE, IMS III and SYNTHESIS expansion)
• Recanalization correlated directly with outcomes. Higher recanalization rates groups had better outcomes
• The stent retriever trials while positive, demonstrated the importance of careful patient selection Stent retriever devices are the better option based on the current evidence
Conscious Sedation vs General Anesthesia

- General anesthesia with intubation and conscious sedation are the two most frequently used anesthetic approaches for patients with an acute ischemic stroke receiving endovascular therapy.
- 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 267 non-endovascular control patients (adjusted odds ratio 1.09, 95% CI, 1.69 to 1.71.), whereas for the 137 endovascular patients who did not receive general anesthesia the outcomes were better than for the 267 control patients (adjusted odds ratio 2.13, 95% CI, 1.46 to 3.11).
- Similar data showing worse outcomes in those undergoing general anesthesia as compared to conscious sedation for endovascular were reported in a recent meta-analysis of 9 non-randomized studies comprising 1956 patients (814 received general anesthesia and 1142 received conscious sedation) with the largest study having 1079 patients and the smallest study having 66 patients. In this meta-analysis, compared to conscious sedation, general anesthesia was linked to lower odds of a favorable functional outcome (OR 0.43; 95% CI, 0.35 to 0.80; P<0.01), higher odds of mortality (OR 2.59; 95% CI, 1.87 to 3.58; p<0.01), and fewer adverse respiratory events (OR 2.09; 95% CI, 1.36 to 3.23; p<0.01).
Conscious Sedation vs General Anesthesia

- No significant differences in the rates of asymptomatic ICH, symptomatic ICH, 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 two techniques. There was substantial heterogeneity ($I^2>50\%$) across the included studies for the outcomes of functional status ($I^2=55\%$), time to revascularization ($I^2=60\%$), time to groin puncture ($I^2=83\%$), and procedure time ($I^2=91\%$). 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 using meta-regression for the odds of having good functional outcomes yielded an odds ratio of 0.38; which was similar to the unadjusted estimate of 0.43; however, the 95% CI became statistically insignificant (0.12 to 1.22). As such, even after adjusting 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 due to an actual or expected inability to maintain airway patency. Moreover, it is also possible that lower recanalization rates observed with general anesthesia in some studies were due to greater numbers of more technically difficult vascular occlusions in those who received general anesthesia. On balance, data from 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.

- While conclusive proof is lacking, the present data is suggestive of better outcomes with conscious sedation as compared to general anesthesia.
THE RECENT TRIALS: EXPLANATION?

- Very sophisticated studies such as MR RESCUE, IMSIII and SYNTHESIS Expansion failed to show any benefit from endovascular therapy based MRI/CTA selection although SYNTHESIS did demonstrate a trend with recanalization and favorable outcome setting the grounds for further studies.

- Vascular Imaging is important for proper patient selection

- The studies used IA thrombolysis used first generation devices and a long variable enrollment with changing criteria that may have influenced the outcome.

- The low recanalization rates from earlier devices compared to the later stent based endovascular therapies may have influenced the rate and speed of recanalization
Patients eligible for IV rtPA should receive IV rtPA even if endovascular treatments are being considered.  

<table>
<thead>
<tr>
<th>Patients should receive endovascular therapy with a stent retriever if they meet all the following criteria:</th>
<th>Class I; LOE A (New Recommendation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) pre-stroke modified Rankin Score (mRS 0-1)</td>
<td></td>
</tr>
<tr>
<td>(2) acute ischemic stroke receiving IV rtPA within 4.5 hours of onset according to guidelines from professional medical societies,</td>
<td></td>
</tr>
<tr>
<td>(3) causative occlusion of the internal carotid artery or proximal middle cerebral artery (M1),</td>
<td></td>
</tr>
<tr>
<td>(4) age 18 years and over,</td>
<td></td>
</tr>
<tr>
<td>(5) National Institutes of Health Stroke Scale (NIHSS) score of 6 or greater,</td>
<td></td>
</tr>
<tr>
<td>(6) Alberta Stroke Program Early Computed Tomography Score (ASPECTS) of 6 or greater, and</td>
<td></td>
</tr>
<tr>
<td>(7) treatment can be initiated (groin puncture) within 6 hours of symptom onset</td>
<td></td>
</tr>
</tbody>
</table>
As with IV rtPA, 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.

<table>
<thead>
<tr>
<th>ENDOVASCULAR RECOMMENDATIONS</th>
</tr>
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<tbody>
<tr>
<td>As with IV rtPA, 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.</td>
</tr>
<tr>
<td>When treatment is initiated beyond 6 hours from symptom onset, the benefits of endovascular therapy are uncertain for patients with acute ischemic stroke who have causative occlusion of the internal carotid artery or proximal middle cerebral artery (M1). Additional randomized trial data are needed.</td>
</tr>
<tr>
<td>In carefully selected patients with anterior circulation occlusion who have contraindications to IV rtPA, endovascular therapy with stent retrievers completed within 6 hours of stroke onset is reasonable. There are inadequate data available at this time to determine the clinical efficacy of endovascular therapy with stent retrievers for those patients whose contraindications are time-based or non-time based (such as prior stroke, serious head trauma, hemorrhagic coagulopathy or receiving anticoagulant medications).</td>
</tr>
</tbody>
</table>
Although the benefits are uncertain, 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 middle cerebral arteries, anterior cerebral arteries, vertebral arteries, basilar artery or posterior cerebral arteries.

<table>
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<td>Although the benefits are uncertain, 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 middle cerebral arteries, anterior cerebral arteries, vertebral arteries, basilar artery or posterior cerebral arteries.</td>
</tr>
<tr>
<td>Class IIb; Level of Evidence C (New Recommendation)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ENDOVASCULAR RECOMMENDATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endovascular therapy with stent retrievers may be reasonable for some patients under age 18 years with acute ischemic stroke who have demonstrated 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.</td>
</tr>
<tr>
<td>Class IIb; Level of Evidence C (New Recommendation)</td>
</tr>
</tbody>
</table>

<table>
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<tbody>
<tr>
<td>Although the benefits are uncertain, 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 pre-stroke mRS &gt;1, ASPECTS score &lt;6 or NIHSS &lt;6 and causative occlusion of the internal carotid artery or proximal middle cerebral artery (M1). Additional randomized trial data are needed.</td>
</tr>
<tr>
<td>Class IIb; Level of Evidence B-R (New Recommendation)</td>
</tr>
</tbody>
</table>
### Observing patients following IV rtPA to assess for clinical response before pursuing endovascular therapy

Observing patients following IV rtPA 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)*

### The usefulness of mechanical thrombectomy devices other than stent retrievers

The usefulness of mechanical thrombectomy devices other than stent retrievers is not well established, either for technical efficacy or clinical benefit. Use of stent retrievers is indicated in preference to other mechanical thrombectomy devices. *(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)*

### The use of proximal balloon guide catheter or a large bore distal access catheter rather than a cervical guide catheter alone in conjunction with stent retrievers

The use of 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. Future studies should examine which systems provide the highest recanalization rates with the lowest risk for non-target embolization.

**Class IIa; Level of Evidence C**
*(New Recommendation)*
The technical goal of the thrombectomy procedure should be a TICI 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 IA 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)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Class</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angioplasty and stenting of proximal cervical atherosclerotic stenosis or complete occlusion at the time of thrombectomy may be considered but the usefulness is unknown. Future randomized studies are needed.</td>
<td>Class IIb; Level of Evidence C</td>
<td></td>
</tr>
<tr>
<td>Initial treatment with IA fibrinolysis is beneficial for carefully selected patients with major ischemic strokes of &lt;6 hours’ duration caused by occlusions of the MCA. However, these data derive from clinical trials that no longer reflect current practice, including use of fibrinolytic drugs that are not available. A clinically beneficial dose of IA rtPA is not established, and rtPA does not have FDA approval for IA use. As a consequence, endovascular therapy with stent retrievers is recommended over IA fibrinolysis as first-line therapy</td>
<td>Class I; Level of Evidence B-R</td>
<td></td>
</tr>
<tr>
<td>IA fibrinolysis initiated within 6 hours of stroke onset in carefully selected patients who have contraindications to the use of IV rtPA might be considered, but the consequences are unknown.</td>
<td>Class IIb; Level of Evidence C (Revised from 2013 guideline)</td>
<td></td>
</tr>
<tr>
<td>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 based on patient risk factors, tolerance of the procedure, and other clinical characteristics. Randomized trial data are needed.</td>
<td>Class IIb; Level of Evidence C (New recommendation)</td>
<td></td>
</tr>
</tbody>
</table>
### Emergency Imaging of the Brain

Emergency imaging of the brain is recommended before initiating any specific treatment for acute stroke. In most instances, non-enhanced CT will provide the necessary information to make decisions about emergency management.

<table>
<thead>
<tr>
<th>Class I; Level of Evidence A (Unchanged from the 2013 guideline)</th>
</tr>
</thead>
</table>

#### If Endovascular Therapy is Contemplated

If endovascular therapy is contemplated, a noninvasive intracranial vascular study is strongly recommended during the initial imaging evaluation of the acute stroke patient but should not delay IV rtPA if indicated. For patients who qualify for IV rtPA according to guidelines from professional medical societies, initiating IV rtPA before non-invasive vascular imaging is recommended for patients who have not had non-invasive vascular imaging as part of their initial imaging assessment for stroke. Non-invasive intracranial vascular imaging should then be obtained as quickly as possible.

<table>
<thead>
<tr>
<th>Class I; Level of Evidence A (New Recommendation)</th>
</tr>
</thead>
</table>

#### The Benefits of Additional Imaging Beyond CT and CTA or MR and MRA

The benefits of additional imaging beyond CT and CTA or MR and MRA, such as CT perfusion or diffusion- and perfusion-weighted imaging, for selecting patients for endovascular therapy are unknown. Further randomized, controlled trials may be helpful to determine whether advanced imaging paradigms employing 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 score < 6. Further randomized, controlled trials should be done to determine whether advanced imaging paradigms employing CT perfusion and 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.

| Class IIb; Level of Evidence C (New Recommendation) |
| Patients should be transported rapidly to the closest available certified primary stroke center (PSC) or comprehensive stroke center (CSC) or, if no such centers exist, the most appropriate institution that provides emergency stroke care as described in the 2013 Guidelines. In some instances, this may involve air medical transport and hospital bypass. | Class I; Level of Evidence A (Unchanged from the 2013 Guidelines) |
| Regional systems of stroke care should be developed. These should consist of: Health care facilities that provide initial emergency care including administration of IV rtPA, including PSCs, CSCs and other facilities Centers capable of performing endovascular stroke treatment with comprehensive peri-procedural care, including CSC and other health care facilities, to which rapid transport can be arranged when appropriate | Class I; Level of Evidence A Revised from the 2013 guideline) |
| It may be useful for PSCs and other health care facilities that provide initial emergency care including administration of IV rtPA to develop the capability of performing emergency noninvasive intracranial vascular imaging to most appropriately select patients for transfer for endovascular intervention and reduce time to endovascular treatment | Class IIb; Level of Evidence C (Revised from the 2013 guideline) |
| Endovascular therapy requires the patient to be at an experienced stroke center with rapid access to cerebral angiography and qualified neuro-interventionalists. Systems should be designed, executed and monitored to emphasize expeditious assessment and treatment. Outcomes on all patients should be tracked. Facilities are encouraged to define criteria that can be used to credential individuals who can perform safe and timely IA revascularization procedures | Class I; Level of Evidence E (Revised from the 2013 guideline) |
CASE

- 29 year female, seen in the ED within 1/12 hour of stroke onset
- Presentation: Aphasia, right hemiparesis and neglect
- Untreated Rheumatic Heart Disease
- Received full dose IV rtPA while waiting for intra-arterial intervention, no resolution of the MI occlusion
RESULTS AFTER FULL DOSE IV THROMBOLYSIS

Arrow points to left M1 occlusion

Courtesy Majaz Moonis MD – University of Massachusetts Medical School
Angiogram is showing TICI 2b reperfusion

Courtesy Majaz Moonis MD – University of Massachusetts Medical School
Post thrombectomy CT showing restoration of flow and absence of infarction
(white dot represents post angiogram contrast)

Courtesy Majaz Moonis MD – University of Massachusetts Medical School
Case

- Started IV rtPA within 30 minutes
- Alerted the Interventional Team
- Patient finished the IV rtPA and had a catheter in place by 4.2 hours
- No resolution of thrombolysis
- Stent retrieval used with quick reperfusion
- Complete resolution of symptoms
Conclusions

• Intravenous rtPA within 4.5 hours of stroke onset still remains the standard of care for most ischemic stroke patients
• In carefully selected patients with large vessel occlusion, after IV rtPA initiation, early mechanical thrombectomy within 6 hours of stroke onset, using stent retrievers leads to faster and more complete reperfusion
• This translates to:
  – Improved early neurological recovery
  – Improved functional outcome at 3 months
  – No significant safety concerns
• Early mechanical stent thrombectomy with or in some cases without IV rtPA should be the new standard of care
• Although less desirable, other mechanical devices may be permissible under circumstances where stent retrievers may not be the optimal choice
• Interventions without general anesthesia are associated with a better outcome.
CONCLUSIONS
Systems of Care Effect Outcome

• In order to successfully translate the results of these stent retriever based intra-arterial studies, it is important to develop a system of care where patients are able to receive intravenous rtPA in stroke ready hospitals or primary stroke centers and then be rapidly transferred to a center capable of delivering the advanced level of care using intra-arterial therapy.

• Having stroke ready hospitals, primary stroke centers and comprehensive stroke centers will help facilitate this model of care which is clearly superior to intravenous treatment alone in large vessel stroke in the anterior circulation.
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