Hot Topics in Stroke

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Disclosures:

• Brooke Kearins: No disclosures
• Wendy Smith: No disclosures

Objectives:

• Discuss any recent studies, changes in practice or requirements and their impact on stroke programs
  • Dawn
  • DIFUSE 3
  • Extend IA-TNK
  • 2018 Guidelines for AIS
DAWN and DEFUSE 3

- 2 Trials assessing extending the time window past 6 hours have recently been stopped due to overwhelming efficacy.

- DAWN:
  - 6-24 hours post onset.
  - Imaging selection (RAPID)
  - Significant benefit in primary outcome (mRS 0-2 at 90 days)
  - NNT 2.8!!!

- DEFUSE 3:
  - Interim analysis suggested high likelihood of benefit.
DAWN

DWI or CTP Assessment with Clinical Mismatch
In the Triage of Wake-Up and Late Presenting Strokes
Undergoing Neurointervention with Trevo

To demonstrate superior functional outcomes at 90
days with Trevo plus medical management compared
to medical management alone
in appropriately selected patients treated
6-24 hours after last seen well
### Table 3: Efficacy Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Thrombectomy Group (N = 107)</th>
<th>Control Group (N = 99)</th>
<th>Absolute Difference (95% CI)</th>
<th>Adjusted Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary end points</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional independence at 90 days — no. (%)</td>
<td>52 (69)</td>
<td>33 (33)</td>
<td>39 (26–47)</td>
<td>33 (21–46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Secondary end points</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early response — no. (%)</td>
<td>51 (48)</td>
<td>18 (19)</td>
<td>29 (16–41)</td>
<td>3 (2–4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recanalization at 24 h — no. (%)</td>
<td>82 (77)</td>
<td>39 (39)</td>
<td>43 (27–51)</td>
<td>2 (2–4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change from baseline to infarct volume at 24 h — mTFCI</td>
<td>1 (13)</td>
<td>13 (13)</td>
<td>0 (0–13)</td>
<td>0 (0–13)</td>
<td></td>
</tr>
<tr>
<td><strong>Adequate recanalization</strong></td>
<td>1 (13)</td>
<td>13 (13)</td>
<td>0 (0–13)</td>
<td>0 (0–13)</td>
<td></td>
</tr>
<tr>
<td><strong>Incomplete response</strong></td>
<td>1 (13)</td>
<td>13 (13)</td>
<td>0 (0–13)</td>
<td>0 (0–13)</td>
<td></td>
</tr>
<tr>
<td><strong>Inadequate therapy</strong></td>
<td>1 (13)</td>
<td>13 (13)</td>
<td>0 (0–13)</td>
<td>0 (0–13)</td>
<td></td>
</tr>
</tbody>
</table>

- Absolute differences are reported in percentage points, except for the absolute difference in the score on the utility-weighted modified Rankin scale, which is reported in points.
- Adjusted differences were estimated with use of a Bayesian general linear model with adjustment for infarct volume at baseline.
- The utility-weighted modified Rankin scale ranges from 0 (death) to 10 (no symptoms or disability).
- Functional independence was defined as a score of 0, 1, or 2 on the modified Rankin scale, which ranges from 0 to 6, with higher scores indicating greater disability.
- Early response was defined as a decrease in the NIHSS score of 10 points or more from baseline or an NIHSS score of 0 or 1 on day 5, 6, or 7 of hospitalization or at discharge if it occurred before day 5.
- The 95% CI was calculated with use of Fisher’s exact test.

NNT = 2.8

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**Percent of Patients**

A. Intention-to-Treat Population

<table>
<thead>
<tr>
<th>Score on the Modified Rankin Scale</th>
<th>Thrombectomy (N=107)</th>
<th>Control (N=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>1</td>
<td>22</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>23</td>
<td>36</td>
</tr>
</tbody>
</table>

B. Subgroups According to Time of Stroke Onset

Last Known To Be Well 6 to 12 Hr before Randomization

<table>
<thead>
<tr>
<th>Score on the Modified Rankin Scale</th>
<th>Thrombectomy (N=95)</th>
<th>Control (N=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>1</td>
<td>22</td>
<td>17</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>30</td>
</tr>
</tbody>
</table>

Last Known To Be Well >12 to 24 Hr before Randomization

<table>
<thead>
<tr>
<th>Score on the Modified Rankin Scale</th>
<th>Thrombectomy (N=57)</th>
<th>Control (N=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>1</td>
<td>23</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>21</td>
</tr>
</tbody>
</table>

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**Percent of Patients**
Principle Investigators
Dr. Gregory W. Albers, Stanford University
Dr. Michael P. Marks, Stanford University

Funding
NIH StrokeNet

DEFUSE 3

- NIH-funded, prospective, randomized, multi-center, phase III, adaptive, blinded endpoint, controlled trial

- Paradigm shift
  - From clock-based selection to imaging-based selection

- Target population
  - Patients with anterior circulation ischemic strokes
  - Presenting within 6-16 hours of last known well
  - Imaging evidence of limited ischemic core and large penumbra
DEFUSE 3: 20-year history

- 1990s - DWI estimates ischemic core; perfusion imaging estimates critically hypoperfused tissue
- 2006 - DEFUSE: MR Target mismatch profile identifies patients who respond favorably to late window thrombolysis
- 2008 - RAPID software: Automated processing of advanced imaging data to estimate the volume of salvageable tissue
- 2012, 2016 - DEFUSE 2 / CRISP: MR/CT Perfusion target mismatch respond favorably to late window thrombectomy

Hypothesis and Design

- Hypothesis: Stroke patients with MCA and/or ICA occlusion and salvageable tissue identified by CT/MR perfusion benefit from endovascular thrombectomy between 6-16 h.
- Design: Eligible patients randomized to thrombectomy (FDA cleared device) vs. medical management alone
- Endpoint: Modified Rankin Scale, blinded assessor, day 90
  Primary: ordinal shift analysis; Secondary: mRS 0-2
**Key Clinical Inclusion Criteria**

- Age: 18 - 90 years
- NIHSS: ≥ 6
- Pre-stroke mRS: 0 - 2
- Femoral puncture: 6 - 16 hours

**Key Neuroimaging Inclusion Criteria**

1. Occlusion of the ICA and/or MCA M1
2. RAPID Target Mismatch Profile with core up to 70 ml
Early Termination

- A similar late-window study, DAWN, reported positive results in May 2017
- DEFUSE 3 was placed on hold for an early interim analysis
- Following this analysis, N = 182, the study was ended

Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Endovascular (N = 92)</th>
<th>Medical (N = 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr - median (IQR)</td>
<td>70 (59 - 78.5)</td>
<td>71 (59 - 80)</td>
</tr>
<tr>
<td>NIHSS score - median (IQR)</td>
<td>16 (10 - 20)</td>
<td>16 (12 - 21)</td>
</tr>
<tr>
<td>Stroke onset wake-up (%)</td>
<td>63%</td>
<td>47%</td>
</tr>
<tr>
<td>Treatment with intravenous tPA (%)</td>
<td>11%</td>
<td>9%</td>
</tr>
<tr>
<td>Qualifying imaging: CT Perfusion</td>
<td>75%</td>
<td>71%</td>
</tr>
<tr>
<td>Ischemic core volume, ml - median (IQR)</td>
<td>9 (2 - 26)</td>
<td>10 (2 - 24)</td>
</tr>
<tr>
<td>Perfusion lesion (Tmax&gt;6s) volume, ml - median (IQR)</td>
<td>115 (79-146)</td>
<td>116 (73 - 158)</td>
</tr>
<tr>
<td>Middle cerebral artery occlusion on baseline CTA / MRA</td>
<td>65%</td>
<td>60%</td>
</tr>
</tbody>
</table>
### Results: Primary Outcome

<table>
<thead>
<tr>
<th>Score on Modified Rankin Scale</th>
<th>Endovascular (n=92)</th>
<th>Medical (n=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>1</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>27</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>14</td>
<td>26</td>
</tr>
</tbody>
</table>

Odds ratio: 2.8 (1.6 - 4.7)  \( P<0.0001 \)

Adjusted odds ratio: 3.4 (2.0 - 5.8)  \( P=0.0004 \)

Number needed to treat: 2

### Secondary Outcome (mRS 0-2)

<table>
<thead>
<tr>
<th>Score on Modified Rankin Scale</th>
<th>Endovascular (n=92)</th>
<th>Medical (n=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>18</td>
<td>4</td>
</tr>
</tbody>
</table>

mRS 0-2 45% vs. 17%  \( P<0.0001 \)
Primary Safety Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Endovascular</th>
<th>Medical</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic ICH*</td>
<td>6.5%</td>
<td>4.4%</td>
<td>0.75</td>
</tr>
<tr>
<td>Death</td>
<td>14%</td>
<td>26%</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Late Window Paradox

<table>
<thead>
<tr>
<th></th>
<th>Favorable Outcome (%) Reached at 90 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endovascular</td>
<td>HERMES Early Window: 46%</td>
</tr>
<tr>
<td>Control</td>
<td>27%</td>
</tr>
</tbody>
</table>

P = 0.006 for difference in treatment effect

Late Window Paradox, Stroke, January 24, 2018
EXTEND - IA TNK
Extending the time for Thrombolysis in Emergency Neurological Deficits – Intra-Arterial using Tenecteplase

A randomized controlled trial of 0.25mg/kg tenecteplase versus 0.9mg/kg alteplase prior to endovascular thrombectomy

Bruce Campbell  Peter Mitchell
Co-PI and Medical Coordinator  Co-PI and Head of Neurointervention
Stephen Davis and Geoffrey Donnan  Co-chairs

Acknowledging support from:
Australian Government National Health and Medical Research Council

ClinicalTrials.gov NCT02388061

Background

- “Bridging” thrombolysis + thrombectomy remains standard of care for eligible patients with large vessel occlusion
- There are still delays in thrombectomy during inter-hospital transfers (especially from rural sites) and some IA procedures will fail due to poor arterial access
- Enhanced IV lytic strategies therefore have potential to improve outcome
- Tenecteplase is a genetically modified tPA with greater fibrin specificity and longer half-life permitting convenient single-bolus administration
  - tenecteplase has replaced alteplase as the standard lytic in STEMI
- Some previous studies have suggested improved reperfusion and clinical outcome with tenecteplase versus alteplase
EXTEND-IA TNK HYPOTHESIS:
That tenecteplase is non-inferior to alteplase in achieving reperfusion at initial angiogram, when administered within 4.5 hours of ischaemic stroke onset, in patients planned to undergo endovascular therapy

TRIAL DESIGN
– investigator initiated, PROBE non-inferiority design,
  - non-inferiority margin 2.3% (50% of the lower 95%CI for proportion of substantial reperfusion in ESCAPE, EXTEND-IA & SWIFT PRIME 7.5% (95%CI 4.6-11.5%)
  - test superiority if non-inferiority demonstrated
  - interim sample size recalculation* at n=100 (range 120-276) – final sample n=202

*Mehta and Pocock Stat Med 2011
Inclusion criteria:
- Age ≥18 years (no upper limit), No NIHSS restrictions
- Ischemic stroke eligible for intravenous thrombolysis within 4.5 hours of stroke onset
- Imaging
  - Major vessel occlusion – ICA, M1, M2 or basilar amenable to clot retrieval
  - no maximum core volume (removed after ~80 patients enrolled but CTP performed)
- Able to commence intra-arterial therapy within 6 hours of onset
- Informed consent obtained from patient or legal representative or deferral for emergency treatment in some jurisdictions

Exclusion criteria:
- Severe premorbid disability (mRS≥4)
- Contra-indication to imaging with contrast agents
- Rapid neurological recovery (investigator’s discretion) prior to randomization.

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Tenecteplase</th>
<th>Alteplase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>101</td>
<td>101</td>
</tr>
<tr>
<td>Age – yr: Mean (SD)</td>
<td>70.4 (15.1)</td>
<td>71.9 (13.7)</td>
</tr>
<tr>
<td>Male sex – no. (%)</td>
<td>58 (58%)</td>
<td>52 (52%)</td>
</tr>
<tr>
<td>NIHSS score: Median (IQR)</td>
<td>17 (12-22)</td>
<td>17 (12-22)</td>
</tr>
<tr>
<td>Onset to Lysis – min Median (IQR)</td>
<td>125 (102-156)</td>
<td>134 (104-176)</td>
</tr>
<tr>
<td>Lysis to puncture – min Median (IQR)</td>
<td>43 (25-57)</td>
<td>42 (30-63)</td>
</tr>
<tr>
<td>Site of vessel occlusion (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal carotid artery (ICA)</td>
<td>24%</td>
<td>24%</td>
</tr>
<tr>
<td>Basilar artery</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>First segment of middle cerebral artery (M1)</td>
<td>59%</td>
<td>60%</td>
</tr>
<tr>
<td>Second segment of middle cerebral artery (M2)</td>
<td>15%</td>
<td>14%</td>
</tr>
</tbody>
</table>
**Substantial reperfusion at initial angiogram (TICI 2b/3 or no retrievable thrombus)**

- **Tenecteplase**: 22%
- **Alteplase**: 10%

Risk difference: 0.12 (95%CI 0.02-0.21)
Adjusted odds ratio: 2.6 (95%CI 1.1-5.9)
Non-inferiority: p=0.002
Superiority: p=0.02

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**Day 90 mRS**

- **Tenecteplase (n=101)**: 28% 21% 14% 14% 8% 6% 10%
- **Alteplase (n=101)**: 18% 23% 9% 12% 14% 7% 18%

Ordinal cOR 1.7 (95%CI 1.0-2.8), p=0.037 (adjusted age, NIHSS)
mRS 0-2 or no change from BL 65% vs 52%, p=0.06
mRS 0-1 or no change from BL 52% vs 43%, p=0.23

RMH Comprehensive Stroke Centre
Safety outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Tenecteplase</th>
<th>Alteplase</th>
<th>OR (95%CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>10/101 (10%)</td>
<td>18/101 (18%)</td>
<td>0.44 (0.18-1.1)</td>
<td>0.08</td>
</tr>
<tr>
<td>SICH</td>
<td>1/101 (1%)</td>
<td>1/101 (1%)</td>
<td>1.0 (0.062-16.2)</td>
<td>0.99</td>
</tr>
<tr>
<td>PH</td>
<td>6/101 (6%)</td>
<td>5/101 (5%)</td>
<td>1.2 (0.36-4.1)</td>
<td>0.76</td>
</tr>
</tbody>
</table>

* pre-specified SITS definition = PH2 + ≥4 point increase NIHSS

PH = parenchymal hematoma

Conclusions

- Compared to alteplase 0.9mg/kg, tenecteplase 0.25mg/kg led to:
  - More frequent reperfusion at initial angiogram
    - NNT 9.1 to avoid thrombectomy procedure
  - Improved functional outcomes
  - No safety concerns
- Convenience of single bolus
  - fast, avoids transporting patients with infusion
- Reduced cost
  - drug cheaper, fewer endovascular devices required
    - US wholesale $5861.87 per 50 mg TNK vs $8800.36 per 100 mg alteplase
Implications

- Tenecteplase is an attractive alternative to alteplase prior to endovascular thrombectomy
- TASTE (Parsons/Levi) and ATTEST-2 (Muir) trials are ongoing testing 0.25mg/kg TNK vs alteplase in non-endovascular patients
- EXTEND-IA TNK part 2 underway comparing 0.40mg/kg vs 0.25mg/kg tenecteplase prior to endovascular thrombectomy NCT03340493

2018 Guidelines for the Early Management of Patients with Acute Ischemic Stroke

A guideline for healthcare professionals from the American Heart Association/American Stroke Association
EMS should develop triage paradigms and protocols:

- Use validated screens for stroke
- Identify regional hospitals that can give IV alteplase and those that can perform thrombectomy
- AHA Mission: Lifeline has proposed a severity based triage algorithm
  - Uncertainty exists over optimal algorithm and optimal prehospital LVO screen
  - Customization of proposed algorithm to account for local factors is needed
Stroke centers should have:

- Organized protocol for emergent evaluation of suspected stroke
- Designated acute stroke team
- Among patients receiving IV alteplase:
  - **Primary goal:** door to needle time of 60 minutes or less in ≥50% of cases - REVISED
  - Secondary goal door-to-needle time of 45 minutes or less in ≥50% of cases may be reasonable - NEW

Telemedical solutions can help to improve care when on-site expertise is not available

- Teleradiology shown to be useful for rapid image interpretation
- Telestroke can be effective for IV alteplase decision making - NEW
  - Meta-analysis comparing telestroke to stroke centers showed no difference in mortality or functional outcomes at 3 months
- Telestroke may be reasonable for triaging patients for mechanical thrombectomy
  - A single observational study showed similar rates of reperfusion and functional outcomes between telestroke patients and those admitted directly to a tertiary care center
Stroke systems must integrate IV alteplase capable and mechanical thrombectomy capable centers

- Thrombectomy requires patients to be at an experienced center
- Noninvasive vascular imaging can select patients for transfer to a thrombectomy capable center
  - Decisions around developing this capability require realistic expectations that account for local resource availability
- Guidelines and protocols must ensure rapid transfer 24/7

Urgent brain imaging is required in suspected stroke

- All should be imaged ≤ 20min of ED arrival - NEW
  - The benefit of IV alteplase and thrombectomy are time dependent
  - Reducing time from arrival to imaging can improve door to needle time
- Non-contrast CT is adequate in most cases
  - Primary goal is to exclude ICH
  - Routine MRI is not cost-effective
    - MRI will only change management in minority of cases
    - Inadequate data to establish who requires MRI
Studies show: Insufficient evidence to withhold treatment with alteplase based on NCCT hypodensity
- No interaction between NCCT hypodensity (ASPECTS score) and functional outcome in RCT pooled-analysis
  NINDS tPA trial and IST-3 did not exclude patients based on degree of CT hypodensity

• Should not withhold alteplase based on presence of a hyperdense MCA sign- NEW

• Routine use of MRI to exclude cerebral microbleeds (CMB) is not recommended-NEW
  - CMBs are associated with increased risk of sICH
  - BUT, rate of sICH in those with CMB is ~6%, which is similar to the risk of sICH overall in the NINDS tPA trial.

Advanced Imaging:
• Vascular and perfusion imaging should not delay alteplase treatment- NEW

• Use of imaging to select AIS cases for alteplase treatment with uncertain symptom duration is not recommended

• For patients who meet criteria for endovascular treatment, it is reasonable to proceed with CTA-NEW
  - Clinical prediction of LVO is imprecise.
  - NIHSS is best instrument, but even cut-point of ≥6 will miss cases of LVO
  - No need to wait for creatinine

NEW
Advanced imaging can select patients for thrombectomy 6-24 hours from last normal. NEW

- Two recent RCTs
  - CT Perfusion, or MRI/MR perfusion to select patients with salvageable brain tissue, despite prolonged time from last normal
  - Randomized to thrombectomy vs no-thrombectomy
  - Both trials showed large benefit for thrombectomy
    DAWN Trial: Good outcome (mRS 0-2) in 49% vs. 13%
    DEFUSE 3 Trial: Good outcome (mRS 0-2) in 45% vs. 17%

- Ideal blood pressure in AIS remains unknown
  - Observational studies variable
- No clear data on fluid choice, volume, or duration
- BP with IV alteplase:
  - BP <185/110 prior to administration
  - BP <180/105 for 24 hours after administration
  - Target based on BPs in RCT of IV alteplase
    Some data to suggest hemorrhage risk higher with higher BPs and BP variability, but exact BP that increases risk unknown
- BP with Intra-arterial Therapy
  - Optimal BP unknown
  - RCTs largely excluded BP >185/110
  - Reasonable to use <185/110 as guideline
Recommendations COR LOE

| IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) is recommended for selected patients who may be treated within 3 hours of ischemic stroke symptom onset or patient last known well or at baseline state. Physicians should review the criteria outlined to determine patient eligibility. | I | A |

| IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) is also recommended for selected patients who can be treated within 3 and 4.5 hours of ischemic stroke symptom onset or patient last known well. Physicians should review the criteria outlined to determine patient eligibility. | I | B-R |

| IV alteplase may be reasonable for mild stroke patients in 3-4.5 hr window. Treatment risks should be weighed against possible benefits. | IIb | B-NR |

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**Recommendations**

- IV tPA: Cortical Microbleeds - NEW
- Clinically silent CMBs in 25% of IV alteplase patients
- No randomized trials have directly addressed tPA in those with CMBs
- Data from two meta-analyses showed sICH more common with CMBs, but not higher than NINDS tPA trial
  - Rates higher if >10 CMBs (40%), but small numbers
  - Functional outcomes worse in patients with CMBs
  - Unclear if these negative effects fully negate benefit of thrombolysis

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In otherwise eligible patients who had a previously demonstrated small number (1-10) of cortical microbleeds on MRI, administration of IV alteplase is reasonable.</td>
<td>IIa</td>
<td>B-NR</td>
</tr>
<tr>
<td>In otherwise eligible patients who had a previously demonstrated high burden of CMBs (&gt;10) on MRI, treatment with IV alteplase may be associated with an increased risk of sICH and the benefits of treatment are uncertain. Treatment may be reasonable if there is potential for substantial benefit.</td>
<td>IIb</td>
<td>B-NR</td>
</tr>
</tbody>
</table>
• IV alteplase can be beneficial for patients with sickle cell disease and AIS - NEW
  – Case-control analysis of GWTG-Stroke found no significant impact on safety or outcomes in treatment with IV alteplase among 832 cases with sickle cell disease.

<table>
<thead>
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<th>LOE</th>
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</thead>
<tbody>
<tr>
<td>IV alteplase for adults presenting with an AIS with known sickle cell disease can be beneficial.</td>
<td>Ila</td>
<td>B-NR</td>
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Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
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<tbody>
<tr>
<td>In patients undergoing fibrinolytic therapy, physicians should be prepared to treat potential emergent adverse effects, including bleeding complications and angioedema that may cause partial airway obstruction.</td>
<td>I</td>
<td>B-NR</td>
</tr>
<tr>
<td>BP should be maintained &lt;180/105 mm Hg for at least the first 24 hours after IV alteplase treatment.</td>
<td>I</td>
<td>B-NR</td>
</tr>
<tr>
<td>The risk of antithrombotic therapy within the first 24 hours following IV alteplase (with or without EVT) is uncertain. Use might be considered in the presence of concomitant conditions for which such treatment given in the absence of IV alteplase is known to provide substantial benefit or withholding such treatment is known to cause substantial risk.</td>
<td>IIb</td>
<td>B-NR</td>
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IV Tenecteplase- NEW

- Administered as a 0.4mg/kg single IV bolus
- 3 phase II and 1 phase III trials comparing to alteplase
  - Appears to be similarly safe
  - Unclear if it is as or more effective
  - Largest trial of tenecteplase vs. alteplase:
    1100 subjects
    Minor deficits, with median NIHSS 4 and no LVO
    Failed to show superiority
    Similar safety and efficacy between treatments

Multiple randomized trials have shown thrombectomy benefit, up to 24 hours after symptom onset. NEW

- MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, EXTEND-IA, THRACE, DAWN, DEFUSE 3 Trials
- Benefit was consistent across age groups
- Patient selection criteria varies based on time
  6-24 hours since last normal, advanced imaging with CT perfusion or MRI/MR Perfusion is necessary to select patients
- Reperfusion to TICI 2b/3 should be achieved as early as possible
  - Better outcomes with faster times to reperfusion
- Stent retrievers are preferred devices
**Recommendations**

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<tr>
<td>Urgent anticoagulation with the goal of preventing early recurrent stroke, halting neurological worsening, or improving outcomes after AIS is not recommended for treatment of patients with AIS.</td>
<td>III (NB)</td>
<td>A</td>
</tr>
<tr>
<td>The usefulness of urgent anticoagulation in patients with severe stenosis of an internal carotid artery ipsilateral to an ischemic stroke is not well established.</td>
<td>IIb</td>
<td>B-NR</td>
</tr>
<tr>
<td>The safety and usefulness of short-term anticoagulation for nonocclusive, extracranial intraluminal thrombus in the setting of AIS are not well established.</td>
<td>IIb</td>
<td>C-LD</td>
</tr>
<tr>
<td>At present, the usefulness of argatroban, dabigatran, or other thrombin inhibitors for the treatment of patients with AIS is not well established. Further clinical trials are needed.</td>
<td>IIb</td>
<td>B-R</td>
</tr>
<tr>
<td>The safety and usefulness of factor Xa inhibitors in the treatment of AIS are not well established. Further clinical trials are needed.</td>
<td>IIb</td>
<td>C-LD</td>
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**Blood Pressure**

- Optimal BP strategy for stroke pts remains unclear and depends on the clinical situation
  - Some may have concomitant comorbidities that require acute BP lowering (aortic dissection, acute heart failure, etc)
  - Excessive BP lowering can worsen cerebral ischemia, though Lowering BP acutely by 15% is probably safe
  - Initial BP <220/120: reinitiating anti-HTN is safe but is not associated with improved outcomes
  - Initial BP >220/120: possibly reasonable to lower by 15% in the first 24 hrs
  - Neurologically stable pts: probably safe to restart anti-HTN if >140/90
  - Hypotension and hypovolemia should be corrected
• Dysphagia Screening:
  • Post-stroke dysphagia
    • Very common (37-78%)
    • Risk factor for pneumonia
    • Associated with worse pt outcomes

  - Screening
    - Insufficient data whether screening protocol decreases death or dependency, but that does not mean screening is ineffective
    - Overall, early screening is reasonable
    - Those who fail screening
      - usually older
      - more comorbidities
      - coming from a facility
      - presenting with weakness and speech difficulties
      - lower level of consciousness
      - higher stroke severity

Recommendations COR LOE

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<tr>
<td>Dysphagia screening before the patient begins eating, drinking, or receiving oral medications is reasonable to identify patients at increased risk for aspiration.</td>
<td>Ila</td>
<td>C-LD</td>
</tr>
<tr>
<td>It is reasonable for dysphagia screening to be performed by a speech-language pathologist or other trained healthcare provider.</td>
<td>Ila</td>
<td>C-LD</td>
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<tr>
<td>An instrumental evaluation is reasonable for those patients suspected of aspiration to verify the presence/absence of aspiration and to determine the physiological reasons for the dysphagia to guide the treatment plan.</td>
<td>Ila</td>
<td>B-NR</td>
</tr>
<tr>
<td>It is not well established which instrument to choose for evaluation of swallowing with sensory testing, but the choice may be based on instrument availability or other considerations (i.e. fiberoptic endoscopic evaluation of swallowing, videofluoroscopy, fiberoptic endoscopic evaluation).</td>
<td>Iib</td>
<td>C-LD</td>
</tr>
</tbody>
</table>
• Nutrition
  – Stroke pts should be started on a diet within 7 days
    FOOD RCTs
      -Supplemented diet: absolute reduction in risk of death: 0.7%
    Cochrane review (33 RCTs)
      -Available data suggest that PEG and NG are similar with regard to case-fatality, death, and dependency but PEG is associated with fewer treatment failures, less GI bleeding, and higher food delivery
  – Oral hygiene may reduce pneumonia risk
    Standardized screening and diet along with standardized oral hygiene with antibacterial rinse with chlorhexidine may reduce pneumonia

• DVT Prophylaxis
  – Pneumatic compression is more effective than routine care
    Primary outcome of DVT: 9.6% vs 14%
  – Benefit of prophylactic heparin (UFH or LMWH) is not well established
    Reductions in PE and DVT but increases in ICH and extracranial bleeds
  – LMWH vs UFH
    LMWH is once daily but is more expensive and associated with increased bleeding in elderly pts with kidney disease
  – Elastic stockings should not be used
• Brain Imaging
  – Noncontrast HCT is cost-effective as it differentiates AIS from ICH
  – DW-MRI is more sensitive than HCT for AIS, but studies have not found it cost-effective
  – In some pts DW-MRI will help with the diagnosis or with stroke localization
  – Routine DW-MRI use is not recommended and more research is needed to determine criteria for its cost-effective use

• Vascular Imaging
  – Extracranial
    Imaging should be performed within 24 hours of admission in pts with non-disabling AIS (mRS 0-2)
    Revascularization via CEA or CAS feasible in a 2-7 day time window
  – Intracranial
    Routine imaging is not recommended
    - WASID: no benefit of warfarin over ASA 325
    - SAMMPRIS: no benefit to adding stent to aggressive medical management
    - Added utility and cost-effectiveness is unproven

    In some pts reasonable to perform intracranial imaging to help plan secondary prevention strategies
• **Cardiac Evaluation**
  - **Cardiac monitoring**
    - Atrial fibrillation is a common cause of AIS and anticoagulation is associated with reduced stroke incidence compared with ASA
    - Monitoring should be performed at least 24 hrs
    - Prolonged monitoring identifies more atrial fibrillation but thus far the clinical benefit is uncertain
  - **Echocardiography**
    - Routine use is not recommended as evidence of cost-effectiveness is insufficient
    - In some pts ECHO data may help plan secondary preventive strategies
      - Intracardiac thrombus
      - PFO in selected pts

• **Cholesterol**
  - The 2013 ACC/AHA Cholesterol Guidelines recommend statins for pts with atherosclerotic cardiovascular disease (ASCVD), including stroke of atherosclerotic origin
  - No data for treatment or titration to a specific LDL level
  - **Measurement in stroke pts**
    - No benefit to measuring cholesterol routinely in atherosclerotic stroke pts not already taking a high-intensity statin
    - Maybe some benefit in measuring cholesterol levels in pts already on optimized statin as they might benefit from PCSK9 inhibitor treatment
    - Maybe some benefit in measuring cholesterol levels in pts with non-atherosclerotic origin stroke as primary prevention guidelines are based on LDL-C levels
• So, now what do we do????
  • Extend our acute stroke treatment windows- consider endovascular
  • TNK versus tPA- ?
  • Guidelines- treat each stroke patient as a true individual and base care off of their co-existing conditions and needs.

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  • Brooke Kearins- Bkearins@dh.org