The Exceptions:
When to treat with systemic thrombolysis despite contraindications

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Disclosures

• No personal conflicts of interest to disclose

• I will be discussing unlabeled, non-FDA approved uses of intravenous thrombolysis
Fantasy…

- 75 year-old woman seen in ED for right facial weakness and slurred speech
- Symptom onset witnessed by her husband 30 minutes ago
- No blood thinning medications
- BP 145/80, FSBG 94, NIHSS 7
- Husband: “She always said she would want that clot-busting medication if she had a stroke”
Reality…

• 38 year-old man seen in ED for right-sided weakness and aphasia
• Last seen 3 ½ hours ago, appeared normal then, though was intoxicated
• Stumbled and may have hit his head when symptoms began
• BP 167/80, FSBG 120, NIHSS 9
• Blood alcohol level 133
Last year’s talk

Moving beyond thrombolysis 101: tPA in special situations

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• Anticoagulant use
• Treating the oldest old
• Unusual situations (aneurysms, dissections, stroke mimics)
• Treating mild stroke symptoms
This year’s outline

• Severe hypertension

• Recent surgery or invasive procedures

• Seizure at symptom onset

• Unclear time of onset and wake-up strokes

• Treating mild or rapidly improving strokes
Purpose
—To critically review and evaluate the science behind individual eligibility criteria (indication/inclusion and contraindications/exclusion criteria) for intravenous recombinant tissue-type plasminogen activator (alteplase) treatment in acute ischemic stroke. This will allow us to better inform stroke providers of quantitative and qualitative risks associated with alteplase administration under selected commonly and uncommonly encountered clinical circumstances and to identify future research priorities concerning these eligibility criteria, which could potentially expand the safe and judicious use of alteplase and improve outcomes after stroke.

Methods
—Writing group members were nominated by the committee chair on the basis of their previous work in relevant topic areas and were approved by the American Heart Association Stroke Council's Scientific Statement Oversight Committee and the American Heart Association's Manuscript Oversight Committee. The writers used systematic literature reviews, references to published clinical and epidemiology studies, morbidity and mortality reports, clinical and public health guidelines, authoritative statements, personal files, and expert opinion to summarize existing evidence and to indicate gaps in current knowledge and, when appropriate, formulated recommendations using standard American Heart Association criteria. All members of the writing group had the opportunity to comment on and approved the final version of this document. The document underwent extensive American Heart Association internal peer review, Stroke Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke

A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.

Endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons

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The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on September 24, 2015, and the American Heart Association Executive Committee on October 5, 2015. A copy of the document is available at http://my.americanheart.org/statements by selecting either the “By Topic” link or the “By Publication Date” link. To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.

The online-only Data Supplement, which contains literature search strategies and Figures A, B, and C, is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/STR.0000000000000086/-/DC1.


Case #1

- 66 y/o man seen in the ED 90 minutes after the onset of left-sided weakness
- NIHSS 8 (left face/arm/leg weakness, dysarthria)
- CT negative for bleeding
- BP 220/109 on presentation, decreases to 201/95 when rechecked, then 204/100 after 10 mg of IV labetalol

- Next steps? Forgo tPA?
Hypertension and tPA

- Hypertension is very common in acute stroke
  - Major risk factor for stroke, stress reaction to acute brain injury and circumstances

- Almost all studies have used a BP threshold of 185/110 as a tPA exclusion

- Updated FDA label:
  - “Current severe uncontrolled hypertension” as exclusion, without specific thresholds – how to interpret this?
Hypertension and tPA

• BP on presentation is associated with risk of symptomatic hemorrhage
  • HAT score, GWTG retrospective analysis

• Excessive BP reduction can cause stroke worsening due to penumbral hypoperfusion

• Exact degree of BP reduction, optimal reduction strategy not well established
Hypertension and tPA

• AHA/ASA statement:
  • tPA “recommended in patients whose BP can be safely lowered to < 185/110 mm Hg with antihypertensive agents”
  • Needs to be maintained at this level for ≥ 24 hours

• No simple approach, but be aggressive to get to 185/110 level
  • Double the dose if initial IV agent does not work
  • Low threshold to switch to drip
  • Try to maintain BP in the 150-180 range
Case #2

- 81 year-old man seen in the hospital for the acute onset of right sided weakness and mild aphasia
- NIHSS 11
- BP 134/79, CT negative for ICH but does show likely acute thrombus in left M2 vessel
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- 81 year-old man seen in the hospital for the acute onset of right sided weakness and mild aphasia
- NIHSS 11
- BP 134/79, CT negative for ICH but does show likely acute thrombus in left M2 vessel
- 3 days post-op from knee replacement – change decision?
Recent surgery and tPA

- Inconsistent definitions of recent surgery across studies and guidelines
  - NINDS: 14 days
  - ECASS-3: 3 months
  - Recent intracranial or spinal surgery addressed separately, no other definition of “major surgery”

- Likely subject to publication bias, but case reports of safe tPA use in setting of recent surgery (several types) are in the literature
Recent surgery and tPA

- As in all tPA cases, need to weigh potential benefits of treatment against potential risks
  - How severe or disabling are the symptoms?
  - What is the patient’s risk of intracranial bleeding?
  - What is the risk of bleeding at the surgical site? Could this be managed by a surgeon?
  - Are there alternatives (direct to endovascular therapy)?
  - What are the patient’s and family’s risk tolerance?
Recent surgery and tPA

• For most recent surgeries:
  • Proceed with usual acute stroke work-up
  • Contact surgical team ASAP to discuss bleeding risks
  • If risks acceptable/manageable and stroke deficits are disabling, discuss with patient and treat if agreeable

• For surgeries at high risk for complications:
  • Intracranial, spinal, cardiac, vascular – hold on tPA
  • Obtain acute vascular imaging (CTA) and mobilize endovascular team if large vessel occlusion
Seizures at onset

• Seizure at onset of focal neurologic symptoms has been considered a tPA contraindication
  • NINDS and other tPA trials
  • 2013 AHA/ASA acute stroke guidelines

• Rationale: weakness or other focal symptoms likely to be a post-ictal (Todd’s) phenomenon
Seizures at onset

- Problems with using seizure at onset as a tPA exclusion:
  - Acute focal cerebral ischemia can trigger seizures (seizure and stroke NOT mutually exclusive)
  - Profound weakness, aphasia, etc., usually result from prolonged seizure activity
  - Focal deficits in patients with seizures will have symptoms inappropriately attributed to a post-ictal process
Seizures at onset

- Bleeding and other tPA complications are very uncommon in stroke mimics (including seizure)

Table 16. Summary of Studies Including ≥5 Patients Treated With Intravenous rtPA Who Had Seizures at Symptom Onset

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Seizure/Total SMs, n</th>
<th>Average Initial NIHSS Score</th>
<th>Any ICH, n</th>
<th>sICH, n</th>
<th>mRS Score of 0–1, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Winkler et al3319</td>
<td>Retrospective of prospective registry</td>
<td>6/7</td>
<td>10*</td>
<td>0</td>
<td>0</td>
<td>86</td>
</tr>
<tr>
<td>Chernyshev et al334</td>
<td>Retrospective of prospective registry</td>
<td>26/69</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>87</td>
</tr>
<tr>
<td>Zinkstok et al394</td>
<td>Multicenter, observational cohort</td>
<td>81/100</td>
<td>6</td>
<td>NA</td>
<td>2</td>
<td>75</td>
</tr>
<tr>
<td>Tsivgoulis et al336</td>
<td>Retrospective of prospective registry</td>
<td>11/56</td>
<td>6</td>
<td>NA</td>
<td>0</td>
<td>96</td>
</tr>
<tr>
<td>Förster et al337</td>
<td>Retrospective of prospective registry</td>
<td>20/42</td>
<td>6.5</td>
<td>NA</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Chang et al338</td>
<td>Retrospective</td>
<td>6/14</td>
<td>6*</td>
<td>0</td>
<td>0</td>
<td>NA†</td>
</tr>
</tbody>
</table>

†In that trial, 97% had an mRS score of 0 to 2.

ICH indicates intracerebral hemorrhage; mRS, modified Rankin Scale; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; rtPA, recombinant tissue-type plasminogen activator; sICH, symptomatic intracerebral hemorrhage; and SM, stroke mimic.
Seizures at onset

• Most patients with seizure at onset and ongoing disabling stroke symptoms should be treated with IV tPA
  • Including patients with diagnosis of epilepsy

• Caveat: look for red flag symptoms
  • Headache – think SAH or venous sinus thrombosis!
  • Fever – think HSV encephalitis!
  • Fluctuating symptoms – think non-convulsive status!
Case #3

- 59 year-old woman is brought to the ED after awakening with left-sided weakness
- LKN at 12 AM, current time 7 AM
- NIHSS 7 (left facial and arm weakness, right gaze preference, slurred speech)
- Head CT is normal

• Treat with tPA?
Wake up strokes

- Uncertain time of symptom onset is the major reason for tPA ineligibility in 25-30% of patients
  - Many of these are “wake up strokes”

- Case presentation is common:
  - Measurable, disabling stroke symptoms
  - No other tPA exclusions other than time
  - Normal CT scan, suggesting that stroke onset was recent
Wake up strokes

• Several small series of treating wake up strokes with IV tPA have been reported
  • Safety comparable to overall tPA experience (2.9%, 4.3%)

• Acute MRI may have better ability to identify acute brain injuries amenable to tPA treatment
  • DWI positive/FLAIR negative lesions: 62% sensitive, 75% specific for identifying strokes ≤ 4.5 hours
  • Basis for selection in ongoing NIH-funded MR-WITNESS clinical trial
The sponsor of the study had no role in study design, writing of the report. The corresponding author had full access to the study data and had final responsibility for the decision to submit for publication.
Wake up strokes

• **Summary:**
  
  • Although tempting, wake up strokes should not be treated with IV tPA at this time
  
  • Ongoing clinical trials can hopefully identify imaging findings (or other biomarkers) that can move us from a time-based decision to a tissue-based decision
  
  • Large vessel occlusion strokes may still be candidates for endovascular therapy (longer treatment time window)
Mild strokes and tPA

• Outcomes after mild stroke may not be as favorable as initially suspected
  • Analysis of GWTG patients (2011): in patients who did not receive tPA due to mild symptoms, nearly 30% were not discharged home

• Risks of ICH following tPA are lower in strokes of mild severity
  • Less area at risk for infarction
  • Literature estimates ~2% symptomatic ICH risk
Mild strokes and tPA

• What constitutes a mild but still potentially disabling stroke?
  • Language
  • Motor
  • Hemianopsia
  • Patient-specific factors

Table 12. Task Force Consensus: Definition and Clinical Context of Rapidly Improving Stroke Symptoms as an Exclusion Criterion for Intravenous Alteplase

<table>
<thead>
<tr>
<th>Improvement to a mild stroke such that any remaining deficits seem nondisabling</th>
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<tbody>
<tr>
<td>The following typically should be considered disabling deficits:</td>
</tr>
<tr>
<td>Complete hemianopsia (≥2 on NIHSS question 3) or severe aphasia (≥2 on NIHSS question 9), or</td>
</tr>
<tr>
<td>Visual or sensory extinction (≥1 on NIHSS question 11) or</td>
</tr>
<tr>
<td>Any weakness limiting sustained effort against gravity (≥2 on NIHSS question 6 or 7) or</td>
</tr>
<tr>
<td>Any deficits that lead to a total NIHSS score &gt;5 or</td>
</tr>
<tr>
<td>Any remaining deficit considered potentially disabling in the view of the patient and the treating practitioner. Clinical judgment is required.</td>
</tr>
</tbody>
</table>
Mild strokes and tPA

- Patients with mild but potentially disabling strokes should be considered for IV tPA
  - Outcome may not be as favorable as expected, risk of hemorrhage likely lower

- Additional data should clarify role of tPA in mild or rapidly improving stroke
  - PRISMS (clinical trial of IV tPA in mild stroke)
  - MaRISS (observational study of tPA and non-tPA treated patients with mild or rapidly improving stroke)
Conclusions

- Number of patients treated with IV tPA can be increased by:
  - Aggressive treatment of severe hypertension prior to tPA
  - Treating patients with recent surgery who have favorable benefit-risk ratio
  - Not using seizure at onset as exclusion criteria
  - Treating patients with mild or rapidly improving symptoms that are still disabling
  - Wake up strokes should still be considered ineligible for tPA though this may change in the future