

The Exceptions:

When to treat with systemic thrombolysis despite contraindications

Adam Kelly, MD

Associate Professor of Neurology

Director, Highland Hospital Stroke Center



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

Adam G. Kelly, MD
Associate Professor of Neurology
Director, Highland Hospital Stroke Center



- 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



AHA/ASA Scientific Statement

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*

Stroke. 2016; 47:581-641



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

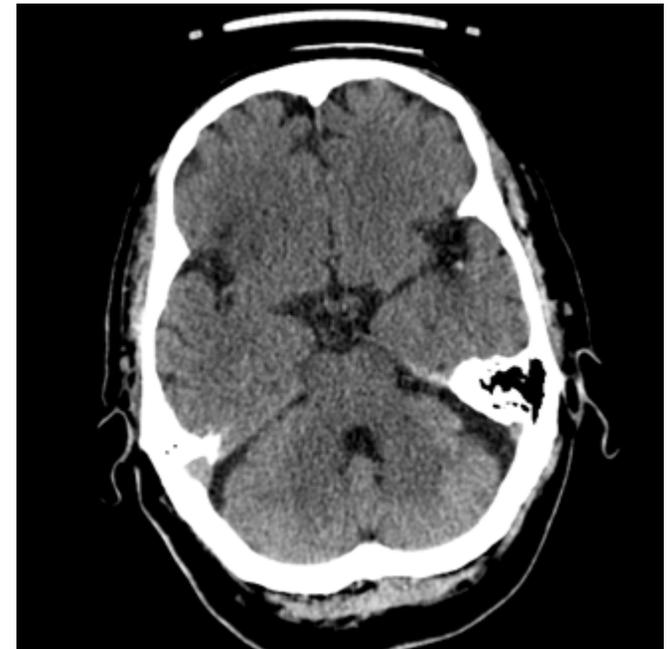
Hypertension and tPA

- 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



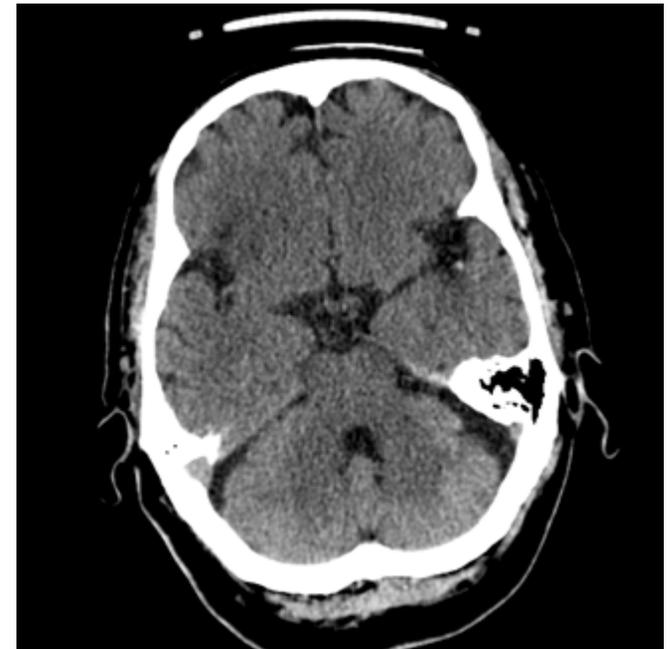
Case #2

- 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



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
- 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

| Study | Study Design | Seizure/Total SMs, n | Average Initial | | | mRS Score of 0–1, % |
|---------------------------------|---------------------------------------|----------------------|-----------------|------------|---------|---------------------|
| | | | NIHSS Score | Any ICH, n | slCH, n | |
| Winkler et al ³¹⁹ | Retrospective of prospective registry | 6/7 | 10* | 0 | 0 | 86 |
| Chernyshev et al ³³⁴ | Retrospective of prospective registry | 26/69 | 7 | 0 | 0 | 87 |
| Zinkstok et al ²⁹⁴ | Multicenter, observational cohort | 81/100 | 6 | NA | 2 | 75 |
| Tsivgoulis et al ³³⁶ | Retrospective of prospective registry | 11/56 | 6 | NA | 0 | 96 |
| Förster et al ³³⁷ | Retrospective of prospective registry | 20/42 | 6.5 | NA | 0 | NA |
| Chang et al ³³⁸ | Retrospective | 6/14 | 6* | 0 | 0 | NA† |

Stroke. 2016; 47:581-641



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

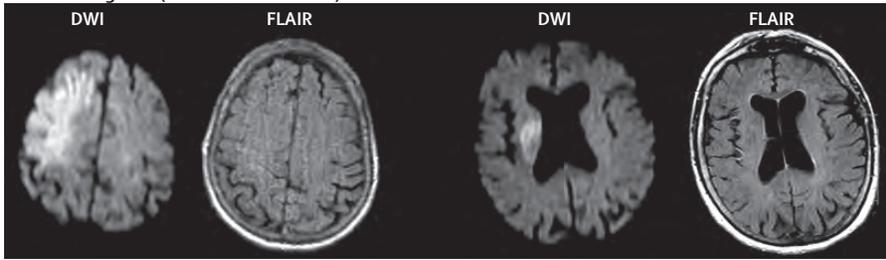


Wake up strokes

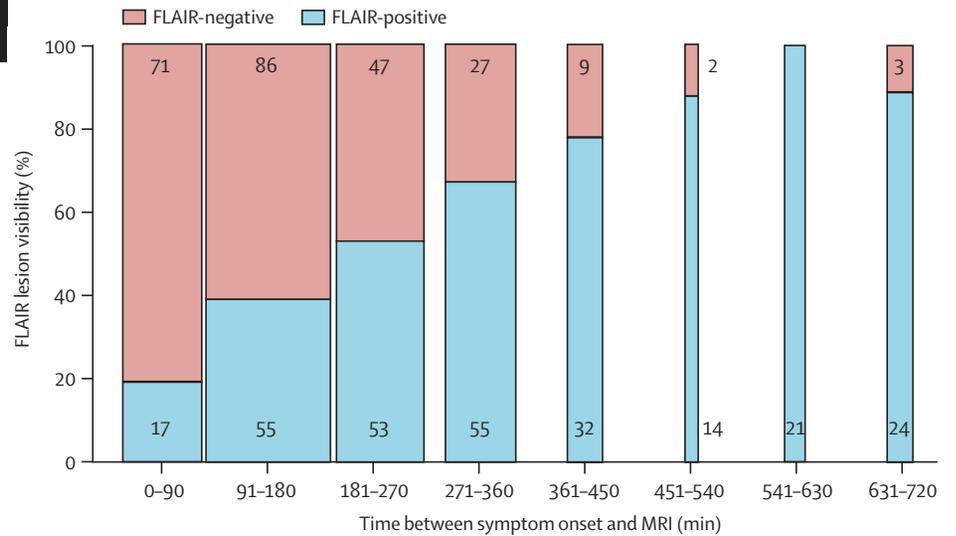
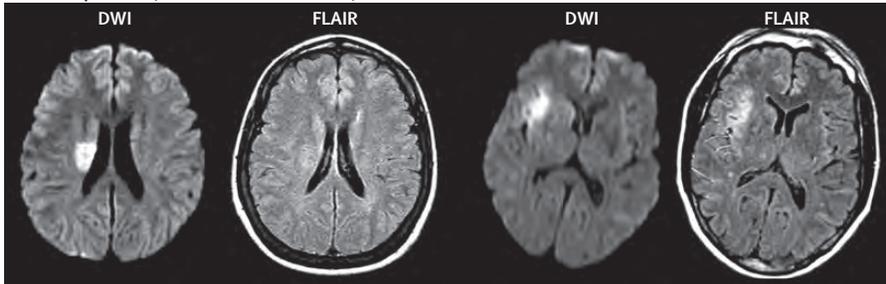
- Several small series of treating wake up strokes with IV tPA have been reported
 - Safety comparable to overall tPA experience (2.9%, 4.3%)
- Acute MRI may have better ability to identify acute brain injuries amenable to tPA treatment
 - DWI positive/FLAIR negative lesions: 62% sensitive, 75% specific for identifying strokes \leq 4.5 hours
 - Basis for selection in ongoing NIH-funded MR-WITNESS clinical trial



B FLAIR-negative (DWI-FLAIR mismatch)



C FLAIR-positive (no DWI-FLAIR mismatch)



Lancet Neurol. 2011; 10:978-986

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 Alteplase¹³⁷

Improvement to a mild stroke such that any remaining deficits seem nondisabling

The following typically should be considered disabling deficits:

Complete hemianopsia (≥ 2 on NIHSS question 3) or severe aphasia (≥ 2 on NIHSS question 9), or

Visual or sensory extinction (≥ 1 on NIHSS question 11) or

Any weakness limiting sustained effort against gravity (≥ 2 on NIHSS question 6 or 7) or

Any deficits that lead to a total NIHSS score > 5 or

Any remaining deficit considered potentially disabling in the view of the patient and the treating practitioner. Clinical judgment is required.

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

