To Exclude or Not to Exclude: Revisiting tPA Exclusion Criteria

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Disclosures

• No financial disclosures

• I will be discussing off label use of alteplase (rt-PA)
Objectives

• Review epidemiology of stroke

• Review exclusion criteria for tPA

• Review literature regarding exclusions in case based format.
Background
795,000 people suffer a stroke each year.
  - 600,000 of these are first attacks
  - 185,000 are recurrent attack

Stroke is the fourth leading cause of death in the United States.

Over 143,579 people/year die from stroke.

Stroke is the leading cause of serious, long-term disability in the United States.
NIHSS

7pts  Level of Consciousness (AO, commands)
2pts  Gaze
3pts  Visual Fields
3pts  Facial Palsy
16pts Motor (4 each limb)
2pts  Ataxia
3 pts Language

You know how.

Down to earth.

I got home from work.

Near the table in the dining room

They heard him speak on the radio last night.
NIHSS

2 pts Dysarthria

MAMA
TIP-TOP
FIFTY-FIFTY
THANKS
HUCKLEBERRY
BASEBALL PLAYER
2 pts Neglect
<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms at all</td>
</tr>
<tr>
<td>1</td>
<td>No significant disability despite symptoms; able to carry out all usual duties and activities</td>
</tr>
<tr>
<td>2</td>
<td>Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance</td>
</tr>
<tr>
<td>3</td>
<td>Moderate disability; requiring some help, but able to walk without assistance</td>
</tr>
<tr>
<td>4</td>
<td>Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance</td>
</tr>
<tr>
<td>5</td>
<td>Severe disability; bedridden, incontinent and requiring constant nursing care and attention</td>
</tr>
<tr>
<td>6</td>
<td>Dead</td>
</tr>
</tbody>
</table>
Randomized, double-blind trial of intravenous recombinant tissue plasminogen activator (t-PA) for ischemic stroke.

Eligible: ischemic stroke with defined time of onset, NIHSS, baseline CT with out hemorrhage.

Exclusion by history and exam:

- Recent stroke or head trauma in 3 months
- Major surgery within 14 days
- History of ICH, SBP > 185 mm Hg or DBP > 110 mm Hg
- Rapidly improving or minor symptoms
- SSx of SAH
- GI or Urinary Bleed in 21 days
- Arterial puncture at a non-compressible site in 7 days
- Seizure at the onset of stroke.
Part 1: assessed changes at 24h
  - No significant difference between two groups at 24h.

Part 2: assessed outcome at 90 days/ 3 months
  - Patients treated with t-PA were at least 30% more likely to have minimal or no disability at three months.
  - ICH 6.4% in tPA group .6% in placebo
  - Mortality 17% in tPA group and 21% in placebo
Favorable Outcome: alteplase group 52.4% vs placebo 45.2%

ICH: alteplase 27.0% vs placebo 17.6%

Symptomatic ICH: alteplase 2.4% vs 0.2%

Mortality alteplase 7.7% and placebo 8.4%
Contraindicated in the following:

- Evidence of intracranial hemorrhage on pretreatment evaluation
- Suspicion of subarachnoid hemorrhage on pretreatment evaluation
- Recent (within 3 months) intracranial or intraspinal surgery, serious head trauma, or previous stroke
- History of intracranial hemorrhage
- Uncontrolled hypertension at time of treatment (e.g. > 185 mm Hg systolic or > 110 mm Hg diastolic)
- Seizure at the onset of stroke
Active internal bleeding
Intracranial neoplasm, arteriovenous malformation, or aneurysm
Known bleeding diathesis including but not limited to:
  - Current use of oral anticoagulants or an (INR) > 1.7 or a PT > 15 seconds
  - Administration of heparin within 48 hours preceding the onset of stroke and have an elevated aPTT at presentation
  - Platelet count < 100,000/mm³
Risks of Alteplase therapy should be weighed against the anticipated benefits:

- Patients with severe neurological deficit (e.g. NIHSS > 22) at presentation.
- Patients with major early infarct signs on CT scan.
- In patients with recent use of oral anticoagulants or heparin
Risks of Alteplase therapy should be weighed against the anticipated benefits:

- **Alteplase treatment can be initiated prior to the availability of coagulation study results.**

- However, infusion should be discontinued if either a pretreatment INR > 1.7 or PT > 15 seconds or an elevated aPTT.
Package *also* says...

- Treatment should be limited to facilities that can provide appropriate evaluation and management of ICH.

- *Therefore, treatment of patients with acute ischemic stroke more than 3 hours after symptom onset is not recommended.*

- Special diligence is required in making this diagnosis in patients whose blood glucose values are
  - \(< 50 \text{ mg/dL}\)
  - \(> 400 \text{ mg/dL}\).
The safety and efficacy of treatment with Alteplase in patients with minor neurological deficit or with rapidly improving symptoms prior to the start of Alteplase administration has not been evaluated.

Therefore, treatment of patients with minor neurological deficit or with rapidly improving symptoms is not recommended.
Recent major surgery

Cerebrovascular disease

Recent GI or GU bleeding

Trauma

HTN: SBP >175mmHg and/or DBP >110

High likelihood of left heart thrombus
Package says think carefully in...

- Acute pericarditis
- SBE
- Hemostatic defects (Hepatic or renal failure)
- Pregnancy
- Hemorrhagic ophthalmic conditions
- Septic thrombophlebitis
- Advanced age (>75)
So why use it?
When all you have is a Hammer

Every problem looks like a Thumb.
Because it works.
## Outcomes

<table>
<thead>
<tr>
<th>For Every 100 pts treated with IV Alteplase</th>
<th>0-1.5</th>
<th>1.5-3</th>
<th>3-4.5</th>
</tr>
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<td>Additional patients with Excellent Outcome</td>
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<td>17</td>
</tr>
<tr>
<td>Number Harmed</td>
<td>1.5</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Likelihood of Help vs. Harm</td>
<td>18</td>
<td>9</td>
<td>6</td>
</tr>
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Data combined from 7 trials: NINDS 1&2, ECAS I, II, & III, ATLANTIS A&B
rt-PA is the only FDA approved drug for acute ischemic stroke

rt-PA is only FDA approved for up to 3 hours

3-4.5 hours is recommended by an AHA/ASA Science Advisory when following additional exclusion criteria.
All stroke patients over a 39 month period (1996-99)

1168 were diagnosed with ischemic stroke

- 73.1% excluded because arrival > 3 hours
- 18.2% excluded because of “clinical improvement”
- 13.1% excluded because of “mild stroke”
- 7.2% received t-PA
Case 1

72M presents to VUMC ED via EMS:

1820 Had sudden onset of Right sided weakness and difficulty speaking. Wife called EMS. En route weakness improved.

1857 Noted by ED resident to have aphasia and R grip weakness.

1900 NIHSS 2 for aphasia
Case 1

Pertinent Facts:

- Onset 1820 now 1910
- Head CT normal
- On aspirin and clopidogrel
- Labs normal
t-PA: Yes? No?
Randomized, double-blind trial of intravenous recombinant tissue plasminogen activator (t-PA) for ischemic stroke.

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Eligible: ischemic stroke with defined time of onset, NIHSS, baseline CT with out hemorrhage.

Exclusion by history and exam:

- Rapidly improving or minor symptoms

13% of screened patients
All stroke patients over a 39 month period (1996-99)
- 1168 were diagnosed with ischemic stroke
  - 73.1% excluded because arrival > 3 hours
  - 18.2% excluded because of “clinical improvement”
  - 13.1% excluded because of “mild stroke”
  - 7.2% received t-PA
- 32% of those excluded because “too good to treat” were dependent or dead at discharge.
• 876 patients over 6 year period with acute ischemic stroke
• 162 patients did not receive tPA because “mild or rapidly improving.”
• 75% had “good” outcome at 3 months.

TABLE 2. Clinical Outcome 3 Months After Stroke

<table>
<thead>
<tr>
<th>mRS Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>72 (44)</td>
<td>50 (31)</td>
<td>26 (16)</td>
<td>10 (6)</td>
<td>2 (1)</td>
<td>0 (0)</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>
Case 1

t-PA: Yes? No?
72M received tPA.
Case 1
Case 1
Case 1
Case 1
72M received tPA and discharged to home with NIHSS of 1. Has done well with no residual deficits. Now on therapeutic anticoagulation.
36M with PMHx significant for migraines presents to VCH ED (VCH Employee) with Right side vision loss.

Time of onset was 0930.

Head CT normal at 1030

NIHSS: 2
t-PA: Yes? No?
Further information:

- Known history of migraines with visual aura.
- Known history of stroke 10 years prior, with PFO found. Declined closure at the time, maintained on aspirin.
- Was compliant with aspirin therapy until 4 months prior.
t-PA: Yes? No?
Background
Recombinant tissue-type plasminogen activator (tPA) is currently the only FDA approved treatment for acute ischemic stroke. Rapidly improving or minor symptoms is the most common reason for not treating with tPA, based on the presumption that these patients will have good outcomes without thrombolysis.

It is well documented that patients excluded from IV thrombolysis for mild or rapidly improving symptoms do not universally have a benign course. As many as 20-32% have a poor outcome (mRS ≥ 2) at discharge.

Methods
We used the AHA/ASA “Get with the Guidelines” database to identify consecutive patients between April 2006 and June 2010 from our tertiary care academic medical center who did not receive tPA with “rapidly improving or mild symptoms” indicated as the reason for exclusion. Poor outcome was defined as hospital discharge to location other than home or inability to ambulate independently at discharge. The medical record was reviewed to determine details of hospital course, infarct location, and reasons for poor outcome.

Results
There were 66 patients excluded from tPA treatment because of rapidly improving or mild symptoms. Eleven patients (16.7%) had poor outcomes. In 6 patients (9%), poor outcome was due to neurologic deficit and in 5 poor outcome was secondary to general medical conditions or deconditioning. Of the 6 patients with continued neurologic deficit, 4 were not treated due to “improvement”. All 6 patients with continued neurologic deficits had right hemisphere strokes, and one also had cerebellar infarcts.

Conclusions
Patients presenting with rapidly improving or mild symptoms do not universally have good outcomes. This may be particularly true in the case of right hemispheric ischemia where deficits are not fully reflected by NIHSS score. In conclusion, if a patient with a low NIHSS score is otherwise a candidate for tPA, a more detailed exam is warranted to better identify potentially disabling deficits that would be an indication for thrombolysis.

References
Results
<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Good</th>
<th>Poor</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n (%)</strong></td>
<td>66</td>
<td>55 (83.3)</td>
<td>11 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>63</td>
<td>61</td>
<td>72.4</td>
<td></td>
</tr>
<tr>
<td>Male Gender</td>
<td>29 (43.9%)</td>
<td>2</td>
<td>3 (27.3%)</td>
<td>0.323</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>34 (51.5%)</td>
<td>30 (54.5%)</td>
<td>4 (36.4%)</td>
<td>0.333</td>
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<tr>
<td>Non-White</td>
<td>27 (40.9%)</td>
<td>25 (45.5%)</td>
<td>7 (63.6%)</td>
<td></td>
</tr>
<tr>
<td>Time to Presentation (min)</td>
<td>93.4</td>
<td>96.4</td>
<td>78.4</td>
<td></td>
</tr>
<tr>
<td>NIHSS median</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Rapid Improvement</td>
<td>24 (36.4%)</td>
<td>20 (36.4%)</td>
<td>4 (36.4%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Hypertension</td>
<td>49 (74.2%)</td>
<td>40 (72.7%)</td>
<td>9 (81.8%)</td>
<td>0.713</td>
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<tr>
<td>Hyperlipidemia</td>
<td>28 (42.4%)</td>
<td>25 (45.5%)</td>
<td>3 (27.3%)</td>
<td>0.331</td>
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<tr>
<td>Diabetes Mellitus Type 2</td>
<td>15 (22.7%)</td>
<td>11 (20.0%)</td>
<td>4 (36.4%)</td>
<td>0.254</td>
</tr>
<tr>
<td>Smoker</td>
<td>24 (36.4%)</td>
<td>18 (32.7%)</td>
<td>6 (54.5%)</td>
<td>0.189</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>17 (25.8%)</td>
<td>14 (25.5%)</td>
<td>3 (27.3%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>9 (13.6%)</td>
<td>7 (12.7%)</td>
<td>2 (18.2%)</td>
<td>0.638</td>
</tr>
<tr>
<td>CHF</td>
<td>1 (1.5%)</td>
<td>1 (1.8%)</td>
<td>0</td>
<td>1.000</td>
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<tr>
<td>Prior stroke</td>
<td>18 (27.3%)</td>
<td>13 (23.6%)</td>
<td>5 (45.5%)</td>
<td>0.155</td>
</tr>
<tr>
<td>Length of Stay (days)</td>
<td>2.52</td>
<td>2.2</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Sex</td>
<td>Year</td>
<td>NIHSS</td>
<td>Rapidly Improving?</td>
</tr>
<tr>
<td>-----</td>
<td>-----</td>
<td>------</td>
<td>----------------------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>70</td>
<td>M</td>
<td>2006</td>
<td>5: 2 gaze 1 LUE 2 LLE</td>
<td>Yes</td>
</tr>
<tr>
<td>74</td>
<td>F</td>
<td>2006</td>
<td>7: 2 LOC 2 VF 2 face 1 dysarthria</td>
<td>Yes</td>
</tr>
<tr>
<td>80</td>
<td>F</td>
<td>2007</td>
<td>2: 1 face 1 neglect</td>
<td>Yes</td>
</tr>
<tr>
<td>79</td>
<td>F</td>
<td>2007</td>
<td>1: 1 face</td>
<td>No</td>
</tr>
<tr>
<td>67</td>
<td>F</td>
<td>2007</td>
<td>5: 1 RUE, 1 RLE 1 LUE 1 LLE 1 neglect</td>
<td>No</td>
</tr>
<tr>
<td>73</td>
<td>F</td>
<td>2007</td>
<td>2: 1 face 1 dysarthria</td>
<td>No</td>
</tr>
<tr>
<td>79</td>
<td>M</td>
<td>2009</td>
<td>2: 2 gaze</td>
<td>No</td>
</tr>
<tr>
<td>68</td>
<td>F</td>
<td>2010</td>
<td>5: 1 face 1 LUE 2 RUE 1 sensory</td>
<td>Yes</td>
</tr>
<tr>
<td>87</td>
<td>F</td>
<td>2010</td>
<td>3: 1 face 1 RUE 1 RLE</td>
<td>No</td>
</tr>
<tr>
<td>79</td>
<td>F</td>
<td>2010</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>54</td>
<td>M</td>
<td>2010</td>
<td>2: 1 sensory 1 dysarthria</td>
<td>No</td>
</tr>
</tbody>
</table>
Study Limitations

- This is a retrospective chart review with a small sample size.
- Patients were not randomized.
- Treatment bias.
- Outcomes are based on hospital discharge not 3 month outcomes.
- Few conclusions can be drawn.
Patients who did not receive t-PA because “too good to treat” had poor outcomes due to a neurologic cause presented with “right brain” symptoms or cerebellar symptoms.

The NIHSS does not capture the right hemisphere or cerebellum well.

Many of the patients with poor outcome and were “too good to treat” had rapidly improving symptoms. This could represent a separate disease process.
Future Questions

- Should “Get With the Guidelines” separate out low NIHSS and rapidly improving as separate t-PA exclusion criteria to allow for national performance tracking of the groups separately.

- Consider a randomized trial of low NIHSS to tPA and no tPA.

- Consider prospective database with 3 month outcomes of patients with low NIHSS and rapidly improving patients.
Does the National Institutes of Health Stroke Scale Favor Left Hemisphere Strokes?

Daniel Woo, MD; Joseph P. Broderick, MD; Rashmi U. Kothari, MD; Mei Lu, PhD; Thomas Brott, MD; Patrick D. Lyden, MD; John R. Marler, MD; James C. Grotta, MD; for the NINDS t-PA Stroke Study Group

- NINDS placebo arm
- Volume for right hemisphere stroke was statistically greater than for left hemisphere strokes
- NIHSS 16-20 median volume of infarct for L hemisphere strokes was 48mL compared with 133mL
NIHSS 0-5 mean volume of infarct for L hemisphere strokes was 3.2 cm³ compared with 8.8 cm³ for R hemisphere infarcts.
72 pts with isolated HH given thrombolysis
56% improved at 7 days
71% with mRS at 90 days
It is “safe” to give tPA
Case 2

36M was given tPA 1050 (1h and 20min after onset).

Discharged 48h later on aspirin with NIHSS 1

Follow up at about 50 days with NIHSS 0.
Case 2
Case 2
Case 3

34F presenting to ED with gradual weakness and numbness of right side.

0545 woke up normal
0600 noticed gradual progression of tingling in R arm and leg
0700 noticed R arm weakness
0800 presented to local clinic after dropping kids off a school
0924 arrived via Life Flight at VUMC
Case 3

CT scan was normal 0927

VITALS: P:80 BP: 119/69 Wt: 161
NIHSS 9: (1 LOC question; 1 facial droop; 3 RUE; 3 RLE; 1 sensory)

PMHx: migraines and hepatitis

It is now 1000 (4 hours). Delay was for INR and plts.
t-PA: Yes? No?
Case 3

1000 Examined by attending. Hoover negative. Concern for conversion disorder but exam was consistent also with stroke.

1012 tPA given for possible lacunar infarct.
Case 3

MRI was normal at 24h with continued symptoms that appeared functional.

+ Hoover (negative in ED)

Patient tearful and admitting multiple stressors

Psych consulted and agreed with conversion disorder 1012
Case 3

- tPA is a time sensitive decision.
- It is assumed 3-7% of IV tPA patients are stroke mimics.

<table>
<thead>
<tr>
<th>For Every 100 pts treated with IV Alteplase</th>
<th>0-1.5</th>
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<td>6</td>
</tr>
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</table>
• 512 patients of which 106 (21%) did not have DWI changes post treatment
• 69 (14%) stroke mimics
• 37% presumed neuroimaging negative cerebral ischemia
• No systemic hemorrhage, intracerebral hemorrhage or angioedema.
Etiologies of Stroke Mimics

- Seizure: 38%
- Migraine: 37%
- Conversion disorder: 21%
- Aseptic meningitis: 1%
- Epidural spinal mass: 1%
- Heat stroke: 1%
- Syncope/VT: 1%
39F at 37w gestation presented to ED with decreased responsiveness and inability to move left side.

PMHx: includes hypertension

LKN: 0930

NIHSS: 20 @ 1010

Stroke. 2005;36:e53-e55
Head CT normal.

SBP 200/100

Only taking prenatal vitamin.
t-PA: Yes? No?
Stroke in pregnancy is “rare.”

Three fold increase in incidence to the “non pregnant”

Pregnancy is a hypercoagulable state.

Patients who have thrombogenic states can not remain on coumadin.

Higher risk of venous and arterial thrombus.

Higher risk with patent foramen ovale or pulmonary AVM.
• Review of literature found 172 pregnant women treated with thrombolytic agents for “various” conditions and found maternal hemorrhagic complications in 8%.

• 8 stroke patients have been treated with iv rtPA in literature:
  • 3 in first trimester
  • 5 in second trimester
  • 2 patients with minor hemorrhage
  • 1 patient died from dissection of angioplasty

American Journal of Emergency Medicine 2012 (epub)
rtPA is a category C drug
Pregnancy and exclusion for all studies
Teratogenic effects were not observed in animal studies.
rt-PA does not cross the placenta.
30 patients in the literature received rt-PA for MI, PE, prosthetic valve thrombosis, DVT and CVT with complication rates similar to non pregnant patients. (Stroke. 2007;38:2612-2618)
Pt. was taken for IA rt-PA at 1430.
Case 4
Pt. was taken for IA rt-PA at 1430.
15mg of IA rt-PA was administered.
Posterior communicating artery opened.
Pt. was taken for IA rt-PA at 1430.
15mg of IA rt-PA was administered.
Posterior communicating artery opened.
Multiple attempt to cross M1 occlusion were made and unsuccessful.
Procedure was terminated.
Case 4

- NIHSS post procedure was 7 (9 hours after onset of symptoms).
- Pt. delivered by forceps-assisted vaginal delivery on day 3 post rt-PA.
- Child was a healthy male infant w/o neurologic deficits.
- At 2 month neurology follow-up patient had **NIHSS 0** and child was normal.

*Stroke*. 2005;36:e53-e55
References

- Heart Disease and Stroke Statistics — 2009 Update, American Heart Association
- Khatri P et. Al. “Strokes With Minor Symptoms” *Stroke.* 2010; 41:00-00.
References