Understanding the new IV tPA labeling

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Disclosures

• No disclosures relevant to this talk
Outline

• Why
• What
• Implications

Why where changes made?
Alteplase label

- NINDS 1996
  - FDA approved IV tPA <3 hours
- ECASS III 2011
  - FDA did not approve IV tPA 3-4.5 hours
  - Mandated label update

Alteplase label

- Updated February 2015
- “Physician labeling rule”
  - Standardized format
  - Clear section definitions
AHA/ASA 2013

- Guidelines have not been updated

What are the changes?

- Contraindications
- Warnings
Language

- “Significant disability or death”
- “Situations in which risk … is greater than the potential benefit”

Contraindications

- FDA mandated documentation
  - “Known hazards, not theoretical possibilities”
Contraindications

- Seizure at onset in patients with AIS was removed
- Previous stroke in patients with AIS was removed
- History of ICH in patients with AIS was moved to Warnings and Precautions and stated as recent ICH
- Examples of lab tests under bleeding diathesis were removed
- Examples of hypertension cutoff levels were removed

Seizure

- “Seizure at onset of AIS”
- Alteplase label
  - Removed
- AHA/ASA 2013 Guidelines
  - Not exclusion criterion
Previous stroke

- Recent (within 3 months) previous stroke
- Alteplase label
  - Removed
- AHA/ASA 2013 Guidelines
  - Exclusion criterion

ICH

- History of ICH
- Alteplase label
  - Moved from contraindications to warnings section
  - Stated as “recent ICH”
- AHA/ASA 2013 Guidelines
  - Exclusion criterion
Bleeding diatheses lab tests

- INR < 1.7 or PT > 15 sec
- Platelets < 100,000 mm³
- Heparin in prior 48 hours and elevated aPTT
- Alteplase label
  - Changed to “bleeding diathesis”
- AHA/ASA 2013 Guidelines
  - Consider PT, aPTT, INR in all
  - Do not delay tPA
  - Novel anticoagulants poorly understood

Bleeding diatheses lab tests

- Alteplase label
  - Changed to “bleeding diathesis”
- AHA/ASA 2013 Guidelines
  - Consider PT, aPTT, INR in all
  - Do not delay tPA
  - Novel anticoagulants poorly understood
Hypertension

• Uncontrolled hypertension at time of treatment (eg, >185 mm Hg systolic or >110 mm Hg diastolic)

• Alteplase label
  • Changed to “current severe uncontrolled hypertension”

• AHA/ASA 2013 Guidelines
  • IV tPA reasonable if BP can be lowered (<185/110)
  • Optimum BP range likely individual

Warning and Precautions

• FDA mandated documentation:

• “Most clinically significant safety concerns”
Warnings and precautions

- Minor neurological deficit or rapidly improving symptoms was removed
- Blood glucose level warnings were removed
- Severe neurological deficit was removed from Warnings & Precautions but added to Adverse Reactions (Section 6.1)
- Major early infarct signs was removed

Minor or rapidly improving signs

- “Treatment of patients with minor neurologic deficit or rapidly improving symptoms is not recommended”
- Alteplase label
  - Removed
- AHA/ASA 2013 Guidelines
  - Relative exclusion criterion
Blood glucose level

• Blood glucose <50 mg/dL
• Alteplase label
  • Removed
• AHA/ASA 2013 Guidelines
  • Relative exclusion criterion

Severe stroke

• Severe deficit (NIHSS >22)
• Alteplase label
  • Removed
• AHA/ASA 2013 Guidelines
  • Relative exclusion criterion
Early infarct signs

- Alteplase label
  - Removed
- AHA/ASA 2013 Guidelines
  - Higher risk of sICH
  - Good outcome more likely
  - Not associated with adverse outcome

Historic

- Age
  - Age >77 associated with bleed risk
  - Efficacy reduced but still favorable

Current
Age in old labeling
Wilder, 9/20/2015
<table>
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<th>Old label</th>
<th>New label</th>
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<td>Previous stroke</td>
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<td>Seizure at onset</td>
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<td>Specific hypertension</td>
<td>“Current, severe uncontrolled”</td>
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<tr>
<td>cutoff</td>
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<td>Specific labs</td>
<td>“Bleeding diathesis”</td>
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<td>History of ICH</td>
<td>Moved from contraindication to warnings</td>
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<tr>
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<tr>
<td>Major early infarct</td>
<td>Removed</td>
</tr>
<tr>
<td>signs</td>
<td></td>
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<tr>
<td>Minor/rapidly improving</td>
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**Implications**
Implications

- Mild/rapidly improving stroke
- Stroke mimics
- Advanced age

Mild or rapidly improving stroke
Mild stroke

• Mild often defined as NIHSS ≤4
  • Hemianopia
  • Monoplegia
  • Aphasia

Mild stroke

• Mortality 1.3%
• 29.4% unable to return home
• 30.3% unable to ambulate independently
• 1.8% SICH

Romano et al. JAMA Neurol. 2015
Minor Stroke or RISS: mRS Distribution at 3 Months

Austrian Stroke Unit Registry

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<td>3</td>
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</table>

n=890; OR 1.49, 95% CI 1.17–1.89; \( P<0.001 \)

11 sICH (2.5%) occurred in patients treated with rt-PA, whereas no sICH occurred in patients without rt-PA treatment.

Occurrence of sICH increased with higher NIHSS scores.

*Mild deficit was defined as 0 to 5 points on the NIHSS at baseline. OR=odds ratio; CI=confidence interval.

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Mild stroke

- PRISMS
- Double-blind, randomized, multi-center
- NIHSS ≤5 and not clearly disabling
- IV tPA + ASA 325 mg vs. placebo
Rapidly improving stroke

- Risk for deterioration

Mimics
Mimics

• Retrospective
• n=512 IV tPA
• n = 69 mimics
• 0% sICH

Chernyshev et al. Neurology 2010

Mimics

• Low risk - treat everyone?

• Goal
  • Treat all eligible patients
  • Do not treat inappropriately
Mimics

- Advanced imaging
- Takes time
- Limited availability

Telestroke
Mimics

- Retrospective U of L analysis
- 400 patients treated IV tPA
- Stroke mimics
  - Drip & ship - 27.4%
- U of L ED - 13.5%
- No ICH or serious adverse events
  
  Personal communication Wei Liu, MD

Telestroke mimic score

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>Adjusted OR (95% CI)</th>
<th>Points</th>
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<tbody>
<tr>
<td>Age (per y)</td>
<td>-0.025</td>
<td>0.98 (0.96 to 0.99)</td>
<td>-0.2y</td>
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<tr>
<td>Atrial fibrillation</td>
<td>-0.781</td>
<td>0.48 (0.36 to 0.66)</td>
<td>-1.0</td>
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<tr>
<td>Hypertension</td>
<td>-0.909</td>
<td>0.46 (0.45 to 0.56)</td>
<td>-1.8</td>
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<tr>
<td>Seizure</td>
<td>0.891</td>
<td>2.71 (1.10 to 6.17)</td>
<td>+6</td>
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<tr>
<td>Facial weakness</td>
<td>-1.246</td>
<td>0.32 (0.22 to 0.45)</td>
<td>-9.0</td>
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<tr>
<td>NIHSS &gt;14</td>
<td>-0.591</td>
<td>0.56 (0.31 to 0.98)</td>
<td>-5</td>
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</table>

- ≤5 or lack of facial weakness suggestive of mimic
- ≥20 suggestive of stroke

Advanced age

- Age >77
- Remains in Warnings section
Advanced Age

- Age >80 compared to younger
  - Higher mortality
  - Lower probability of good outcome
- Similar rates of sICH
- Similar rates of favorable response

Berrouschott et al. Stroke 2005

Advanced age

- Retrospective U of L analysis
- n=35
- age ≥90
- median NIHSS 16
- 5.7% sICH
- Discharge mRS ≤2
  - 28.6%
- Discharge mRS ≤3
  - 45.7%

Personal communication Wei Liu, MD
Education

- Internal ED
  - Seizure
  - Mild
  - Improving
  - Age

Education

- External ED
  - Any neurologic change
  - Don’t need labs to start tPA if not anticoagulated
Conclusion

• Labeling updates
• Drug not changed
• AHA/ASA guidelines not yet changed
• New opportunity for discussion of treatment

Thank you
The odds ratio for a good outcome was 1.57 (95% CI 1.12 to 2.18).