Thrombolytic therapy should be the first line treatment in acute ischemic stroke

Dr. Md Abul Kalam Azad
Does Rx do more good than harm?

• Benefits of the treatment (eg reduced disability)?

• Risks (eg fatal bleeding)?
“First, do no harm.”
Magic Bullet?

- Some patients will fare better with t-PA,
- some will have no benefit, and
- unfortunately some will fare worse.

Schneck MJ. NEJM1998;338(11):762
• Use is limited <5% of the AIS patient
• 25% stroke during sleep

Molina & Saver 2005
“Conditions that can masquerade as stroke.”

- a hemiplegic migraine
- transient ischemic attack
- metabolic and functional causes of weakness,
- postictal states such as Todd’s paralysis
- exposure to toxins
- hypertensive disorders, and
- many other conditions that mimic stroke
NINDS Trial 1&2

• Treated within 3 hours
• Primary outcome: Minimal or no disability after 3 months
• Treatment group: 50%, Placebo 38%, absolute improvement 12%
• To improve 1 more patient to have a normal or near normal outcome was 8.5=9
• ICH: 24-36 hrs after Rx was 6.4% vs 0.6%
ECASS 3 trial

- 821 patients
- At 3 months tPA vs placebo - 52%-45%
- 7% absolute improvement
- 1:14 to treat
- ICS 2.4%-0.2%
- Exclusion included: age >80 yrs, severe stroke, with anticoagulants, h/o DM or stroke

Hacke W et al. NEJM 2008;359:1317-29
<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug</th>
<th>Dose</th>
<th>Interval (hours)</th>
<th>Symptomatic ICH</th>
<th>Primary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAST-I, 1995 (5)</td>
<td>Streptokinase</td>
<td>1.5 µU</td>
<td>0-6</td>
<td>16%</td>
<td>No difference between groups</td>
</tr>
<tr>
<td>MAST-E, 1996 (6)</td>
<td>Streptokinase</td>
<td>1.5 µU</td>
<td>0-6</td>
<td>21.2%</td>
<td>No difference between groups</td>
</tr>
<tr>
<td>ASK, 1996 (7)</td>
<td>Streptokinase</td>
<td>1.5 µU</td>
<td>0-4</td>
<td>12.6%</td>
<td>No difference between groups</td>
</tr>
<tr>
<td>ECASS, 1995 (8)</td>
<td>t-PA</td>
<td>1.1 mg/kg</td>
<td>0-6</td>
<td>19.8%</td>
<td>No difference between groups in BI and mRS scores at 90 days</td>
</tr>
<tr>
<td>NINDS, 1995 (9)</td>
<td>t-PA</td>
<td>0.9 mg/kg</td>
<td>0-3</td>
<td>6.4%</td>
<td>No difference between groups at 24 hours; significant improvement in functional status at 90 days in treated group (global odds ratio for favorable outcome, 1.7 [95% CI, 1.2-2.6])</td>
</tr>
<tr>
<td>ECASS II, 1998 (10)</td>
<td>t-PA</td>
<td>0.9 mg/kg</td>
<td>0-6</td>
<td>8.8%</td>
<td>No difference between groups</td>
</tr>
<tr>
<td>ATLANTIS, 1999 (11)</td>
<td>t-PA</td>
<td>0.9 mg/kg</td>
<td>3-5</td>
<td>7.0%</td>
<td>No difference between groups</td>
</tr>
</tbody>
</table>
What is the balance of RISK and BENEFIT?
But at a price
Thrombolysis increases risk of symptomatic and fatal intracranial haemorrhage

- In the Cochrane review,
- a definite risk of fatal intracranial haemorrhage
- OR 3.60, 95% CI 2.28 to 5.68
- with no significant heterogeneity

Sandercock P, Trial 2008;9:37
Effects on death at the end of follow-up.

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>tPA n/N</th>
<th>Control n/N</th>
<th>Peto OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mori 1992</td>
<td>2/19</td>
<td>2/12</td>
<td></td>
</tr>
<tr>
<td>Haley 1993</td>
<td>1/14</td>
<td>3/13</td>
<td></td>
</tr>
<tr>
<td>JTSG 1993</td>
<td>3/51</td>
<td>4/47</td>
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<tr>
<td>ECASS 1995</td>
<td>69/313</td>
<td>48/307</td>
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<tr>
<td>NINDS 1995</td>
<td>54/312</td>
<td>54/312</td>
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<tr>
<td>ECASS II 1998</td>
<td>43/409</td>
<td>42/391</td>
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<tr>
<td>ATLANTIS B 1999</td>
<td>33/307</td>
<td>21/306</td>
<td></td>
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<tr>
<td>ATLANTIS A 2000</td>
<td>16/71</td>
<td>5/71</td>
<td></td>
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</tbody>
</table>

Total (95% CI)

<table>
<thead>
<tr>
<th>tPA</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1496</td>
<td>1459</td>
</tr>
</tbody>
</table>

Total events: 221 (tPA), 189 (Control)

Test for heterogeneity: Ch² = 14.42, df = 7 (P = 0.04), I² = 51.4%

Test for overall effect: Z = 1.48 (P = 0.14)
• 17 were treated for every 1 avoiding an unfavorable outcome.
• 1% increase in mortality (1 in 100 patients die because of thrombolytics) and
• 5% increase in nonfatal intracranial hemorrhage (1 in 20),
• for a total of 6% harmed (1 in 17 suffers death or brain hemorrhage).

Newman D. 2010. The NNT Group
IST-3, Lancet 2012; 379(9834): 2352-63

• N=3035
• Time: 0-6hrs
• Short term mortality: 4% at 1 week
• Primary outcome:(alive and independent at 6 months): no difference
• Over all benefit: No benefit
Intra arterial Thrombolysis

• PROACT II
  – Intra arterial Prourokinase
  – 6 Hour time window
  – Relative risk reduction of 15% in functional outcome
  – No difference in mortality
  – Procedural complication 9%
  – Early Intra cerebral haemorrhage 10%
Barriers to widespread use of thrombolysis

• Delays in "door-to-needle" time
  – at the population level
  – at the level of the emergency services and emergency physicians
  – at the hospital level

Barriers to widespread use of thrombolysis

- Uncertainty of treatment in some categories of patient
- The major investment in stroke service provision
• How big is the overall benefit?
• What is the latest time window?
• Which grades of stroke severity and which types of stroke more likely to respond?
• Should patients >80 years receive thrombolysis?
• Which types of patients are most likely to be harmed by, and
• Which to benefit from treatment (e.g. with or without other major medical conditions)?

Wardlaw JM, et.al. 2009
Thank you