Brain Attack!
Thrombolysis for acute stroke

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Case Study – Mr J B

71 year old smoker
DM II on OHA
Sinus rhythm
BP 168/92

2 hour right hemiparesis
still weak

Worried?
Acute Stroke Therapy

[Diagram showing infarction, collateral flow, penumbra, and thrombus]
The Ischaemic Penumbra In Action

A = diffusion (admission)
B = perfusion (admission)
C = diffusion at 24 hrs
D = diffusion at 72 hrs
“The typical patient loses 1.9 million neurons each minute in which stroke is untreated”
## Proven acute stroke treatments

<table>
<thead>
<tr>
<th>Intervention</th>
<th>% patients</th>
<th>Prevention of death/dependency per 100 treated</th>
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Thrombolysis the result we want...
What we’re afraid of...
Evolution of thrombolysis

1970’s  Single case reports and basic animal work
1980’s  Thrombolysis in acute coronary syndrome
1988   Review of thrombolysis (in posterior stroke)
1993   Haley E, US (27 patients)
1993   Mori E, Japan (31 patients)
1995   NINDS, US (333 patients)
1995   ECASS, Europe (620 patients)
1997   ECASS II, Europe (800 patients)
Outcomes in Randomized Trials of rt-PA within 3 hours of AIS

(3 trials, n=869)

NNT 10

Difference/1000:
- 141 extra alive and independent (P<0.01)
- 130 fewer dependent survivors (P<0.01)
- 12 fewer deaths (NS)

PLA 08/1415
Time is Brain

Symptom - to - needle time in minutes

Outcome (correct; 95% CI) from 1st - 3rd hour

Upper 95% CI Mean Lower 95% CI

*NNT at absolute point of time  ** NNT for each 90 min interval

NNT: 3.5*
NNT: 7*
NNT: 9* (13)**
NNT: 11* (>30)**

60 90 120 150 180 210 240 270 300 330 360

4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
### tPA in real life

<table>
<thead>
<tr>
<th>Studies</th>
<th>Mortality (at 3/12)</th>
<th>mRs 0-1 (at 3/12)</th>
<th>S-ICH †</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trials* (n=1391)</td>
<td>17.3%</td>
<td>12%</td>
<td>8.6%</td>
</tr>
<tr>
<td>SITS-MOST (n=6483)</td>
<td>11.3%</td>
<td>38.9%</td>
<td>7.3%</td>
</tr>
<tr>
<td>CASES (n=1135)</td>
<td>22.3%</td>
<td>36.8%</td>
<td>4.6%</td>
</tr>
<tr>
<td>STARS (n=389)</td>
<td>13%</td>
<td>35%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Placebo (n=1384)</td>
<td>18.4%</td>
<td>9.0%</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

Quinn TJ Critical Care 2007; 11:124-8
What we’re afraid of...
Time is Brain

<table>
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<tr>
<th>Symptom-to-needle time in minutes</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>150</th>
<th>180</th>
<th>210</th>
<th>240</th>
<th>270</th>
<th>300</th>
<th>330</th>
<th>360</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper 95% CI</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>4.0</td>
<td></td>
<td>3.5</td>
<td>3.0</td>
<td>2.5</td>
<td>2.0</td>
<td>1.5</td>
<td>1.0</td>
<td>0.5</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Lower 95% CI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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NNT: 3.5* (11)**
NNT: 7* (13)**
NNT: 9* (13)**
NNT: 11* (>30)**
Thrombolysis with Alteplase
3 to 4.5 Hours after Acute Ischemic Stroke

Werner Hacke, Markku Kaste, Erich Bluhmki, Miroslav Brozman, Antoni Dávalos, Donata Guidetti, Vincent Larrue, Kennedy R. Lees, Zakaria Medeghri, Thomas Machnig, Dietmar Schneider, Rüdiger von Kummer, Nils Wahlgren, Danilo Toni,

for the ECASS Investigators
ECASS III

N=821
Mean age – 65 years
Median time to t’lysis – 3 hours 59 minutes

3 – 3.5 hours = 10%
3.5 – 4 hours = 50%
4 – 4.5 hours = 40%

1° endpoint = disability at 90 / 7

Hacke et al. NEJM 2008;359:1317-29
ECASS III

Hacke et al. NEJM 2008;359:1317-29
### ECASS III

<table>
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<tr>
<th>Endpoint</th>
<th>tPA</th>
<th>Placebo</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No / minor disability at 90/7</td>
<td>52.4%</td>
<td>45.2%</td>
<td>1.34</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(1.02 – 1.76)</td>
<td></td>
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<th>Endpoint</th>
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<th>Placebo</th>
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</tr>
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<tr>
<td>Any ICH</td>
<td>27.0%</td>
<td>17.6%</td>
<td>0.001</td>
</tr>
<tr>
<td>Symptomatic ICH</td>
<td>2.4%</td>
<td>0.2%</td>
<td>0.008</td>
</tr>
<tr>
<td>Mortality</td>
<td>7.7%</td>
<td>8.4%</td>
<td>0.68</td>
</tr>
</tbody>
</table>
Future 'lytics
It’s Eurovision All Over Again

SITS register (2003-5) March 2005

Unpublished Data
People to look out for

- Less than 80 years old
- Clear focal deficit of presumed vascular cause
- Previously in reasonable shape
- *Clear* time of onset (send witnesses)
- Can get to ASU within ? 3 hours of symptom onset
Further screening

- BP < 180 / 110
- 2.2 mmol/L < BM < 22 mmol/L
- Favourable CT head (no blood or huge infarct)
- Diabetic patients with previous stroke less likely to benefit
- Warfarin (INR < 1.4)