EXTEND - IA TNK

Extending the time for Thrombolysis in Emergency Neurological Deficits – Intra-Arterial using Tenecteplase

A randomized controlled trial of 0.25mg/kg tenecteplase versus 0.9mg/kg alteplase prior to endovascular thrombectomy

Bruce Campbell
Co-PI and Medical Coordinator

Peter Mitchell
Co-PI and Head of Neurointervention

Stephen Davis and Geoffrey Donnan
Co-chairs

Acknowledging support from:

ClinicalTrials.gov NCT02388061
Background

- “Bridging” thrombolysis + thrombectomy remains standard of care for eligible patients with large vessel occlusion
- There are still delays to thrombectomy during inter-hospital transfers (especially from rural sites) and some IA procedures will fail due to poor arterial access
- Enhanced IV lytic strategies therefore have potential to improve outcome
- Tenecteplase is a genetically modified tPA with greater fibrin specificity and longer half-life permitting convenient single-bolus administration
  - tenecteplase has replaced alteplase as the standard lytic in STEMI
- Some previous studies have suggested improved reperfusion and clinical outcome with tenecteplase versus alteplase
* No ICA occlusion in TNK study and no data on 1st 1-2hr reperfusion rates

Reperfusion at 24hr

- alteplase
- endovascular
- alteplase
- tenecteplase

EXTEND-IA
Parsons et al NEJM 2012
### Individual patient data meta-analysis

<table>
<thead>
<tr>
<th></th>
<th>Tenecteplase 0.25mg/kg n=108</th>
<th>Alteplase 0.9mg/kg n=108</th>
<th>Odds Ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRS 0-1</td>
<td>43%</td>
<td>31%</td>
<td>1.9 (0.8-4.4)</td>
</tr>
<tr>
<td>mRS 0-2</td>
<td>52%</td>
<td>41%</td>
<td>1.9 (0.5-7.2)</td>
</tr>
<tr>
<td>ordinal mRS</td>
<td></td>
<td></td>
<td>1.4 (0.5-4.3)</td>
</tr>
<tr>
<td>early neuro improvement</td>
<td></td>
<td></td>
<td>3.3 (1.5-7.2)</td>
</tr>
<tr>
<td>SICH</td>
<td>3.7%</td>
<td>6.5%</td>
<td>0.7 (0.2-2.5)</td>
</tr>
</tbody>
</table>

Adjusted for age, NIHSS, onset to treatment time and trial

Huang et al IJS 2016
Individual patient data meta-analysis

(ordinal analysis trend but not statistically significant for superiority)
OR 1.4 (0.5-4.3)

Huang et al IJS 2016
0.40mg/kg TNK appeared similar to alteplase (not a formal non-inferiority study)
no significant difference in symptomatic ICH BUT
very mild stroke population (median NIHSS 4, 75% had NIHSS 0-7)
17% mimics, 15% large vessel occlusion

Logallo Lancet Neurol 2017
EXTEND-IA TNK HYPOTHESIS:
That tenecteplase is non-inferior to alteplase in achieving reperfusion at initial angiogram, when administered within 4.5 hours of ischaemic stroke onset, in patients planned to undergo endovascular therapy

TRIAL DESIGN
– investigator initiated, PROBE non-inferiority design,
  - non-inferiority margin 2.3% (50% of the lower 95%CI for proportion of substantial reperfusion in ESCAPE, EXTEND-IA & SWIFT PRIME 7.5% (95%CI 4.6-11.5%)
– test superiority if non-inferiority demonstrated
– interim sample size recalculation* at n=100 (range 120-276) – final sample n=202

*Mehta and Pocock Stat Med 2011
“LVO” patients eligible for thrombolysis

Randomise 50:50 (web-based)

- tenecteplase 0.25mg/kg
- alteplase 0.90mg/kg

Angiogram – baseline mTICI
- start asap (<6hr)

24hr MRI reperfusion
(recan/growth/ICH)
- 24hr NIHSS

3 day NIHSS

90 day centralized phone mRS

Blinded outcomes

13 centers in Australia and New Zealand (including 3 “spoke” sites)

Abbreviated 1 page consent form or deferral of consent for emergency treatment
**Inclusion criteria:**

- Age $\geq 18$ years (no upper limit), No NIHSS restrictions
- Ischemic stroke eligible for intravenous thrombolysis within 4.5 hours of stroke onset
- Imaging
  - Major vessel occlusion – **ICA, M1, M2 or basilar** amenable to clot retrieval
  - no maximum core volume (removed after $\sim 80$ patients enrolled but CTP performed)
- Able to commence intra-arterial therapy within 6 hours of onset
- Informed consent obtained from patient or legal representative or deferral for emergency treatment in some jurisdictions

**Exclusion criteria:**

- Severe premorbid disability ($mRS \geq 4$)
- Contra-indication to imaging with contrast agents
- Rapid neurological recovery (investigator’s discretion) prior to randomization.
EXTEND-IA TNK Recruitment

No. Participants Randomised - Expected
No. Participants Randomised - Actual

RMH Comprehensive Stroke Centre
CONSORT trial profile

Randomized (n=204)

- Removed (n=2) due to withdrawn informed consent or investigator randomization error*

Randomized to tenecteplase (n=101)

- Received tenecteplase (n=101)

  - Evaluable primary outcome (n=101)

    - Evaluable early neurological improvement at 3 days (n=101)

      - Lost to 90 day follow-up (n=0)

    - Evaluable modified Rankin scale at 90 days (n=101)

Randomized to alteplase (n=101)

- Received alteplase (n=101)

  - Evaluable primary outcome (n=101)

    - Evaluable early neurological improvement at 3 days (n=101)

      - Lost to 90 day follow-up (n=0)

    - Evaluable modified Rankin scale at 90 days (n=101)

intention to treat population same as per protocol population
## Demographics

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Tenecteplase</th>
<th>Alteplase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>101</td>
<td>101</td>
</tr>
<tr>
<td>Age – yr: Mean (SD)</td>
<td>70.4 (15.1)</td>
<td>71.9 (13.7)</td>
</tr>
<tr>
<td>Male sex – no. (%)</td>
<td>58 (58%)</td>
<td>52 (52%)</td>
</tr>
<tr>
<td>NIHSS score: Median (IQR)</td>
<td>17 (12-22)</td>
<td>17 (12-22)</td>
</tr>
<tr>
<td>Onset to Lysis – min Median (IQR)</td>
<td>125 (102-156)</td>
<td>134 (104-176)</td>
</tr>
<tr>
<td>Lysis to puncture – min Median (IQR)</td>
<td>43 (25-57)</td>
<td>42 (30-63)</td>
</tr>
<tr>
<td>Site of vessel occlusion (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal carotid artery (ICA)</td>
<td>24%</td>
<td>24%</td>
</tr>
<tr>
<td>Basilar artery</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>First segment of middle cerebral artery (M1)</td>
<td>59%</td>
<td>60%</td>
</tr>
<tr>
<td>Second segment of middle cerebral artery (M2)</td>
<td>15%</td>
<td>14%</td>
</tr>
</tbody>
</table>
Primary outcome
Substantial reperfusion at initial angiogram (TICI 2b/3 or no retrievable thrombus)

![Bar chart showing percent of substantial reperfusion at initial angiogram for Tenecteplase and Alteplase.]

- Risk difference: 0.12 (95% CI 0.02-0.21)
- Adjusted odds ratio: 2.6 (95% CI 1.1-5.9)
- Non-inferiority: p=0.002
- Superiority: p=0.02

very similar to EXTEND-IA – 4/35 (11%) had no retrievable thrombus by time of angiogram (longer lysis to puncture median 83min)
Secondary outcomes
Day 90 mRS

Modified Rankin scale
- 0
- 1
- 2
- 3
- 4
- 5
- 6

Tenecteplase (n=101)
- 28%
- 21%
- 14%
- 14%
- 8%
- 6%
- 10%

Alteplase (n=101)
- 18%
- 23%
- 9%
- 12%
- 14%
- 7%
- 18%

Ordinal cOR 1.7 (95%CI 1.0-2.8), p=0.037  (adjusted age, NIHSS)
mRS 0-2 or no change from BL 65% vs 52%, p=0.06
mRS 0-1 or no change from BL 52% vs 43%, p=0.23
Early neurological recovery

Reduction of ≥8 NIHSS points or reaching 0-1 by day 3

72% tenecteplase vs 69% alteplase p=0.66
## Safety outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Tenecteplase</th>
<th>Alteplase</th>
<th>OR (95%CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>10/101 (10%)</td>
<td>18/101 (18%)</td>
<td>0.44 (0.18-1.1)</td>
<td>0.08</td>
</tr>
<tr>
<td>SICH *</td>
<td>1/101 (1%)</td>
<td>1/101 (1%)</td>
<td>1.0 (0.062-16.2)</td>
<td>0.99</td>
</tr>
<tr>
<td>PH §</td>
<td>6/101 (6%)</td>
<td>5/101 (5%)</td>
<td>1.2 (0.36-4.1)</td>
<td>0.76</td>
</tr>
</tbody>
</table>

* pre-specified SITS definition = PH2 + ≥4 point increase NIHSS

§ PH = parenchymal hematoma
Limitations

- Results apply to ischemic stroke patients with large vessel occlusion who are eligible for thrombolysis.
  - ~13% of all ischemic stroke patients but contribute disproportionately to the disability burden

- We studied 0.25mg/kg tenecteplase based on previous data that demonstrated improved outcomes compared with 0.10mg/kg dosing.
  - The NOR-TEST results reported during the recruitment phase of EXTEND-IA TNK suggest that 0.40mg/kg TNK deserves further study
Conclusions

• Compared to alteplase 0.9mg/kg, **tenecteplase 0.25mg/kg** led to:
  – More frequent reperfusion at initial angiogram
    • NNT 9.1 to avoid thrombectomy procedure
  – Improved functional outcomes
  – No safety concerns
• Convenience of single bolus
  – fast, avoids transporting patients with infusion
• Reduced cost
  – drug cheaper, fewer endovascular devices required
    • US wholesale $5861.87 per 50 mg TNK
      vs $8800.36 per 100 mg alteplase
Implications

• Tenecteplase is an attractive alternative to alteplase prior to endovascular thrombectomy

• TASTE (Parsons/Levi) and ATTEST-2 (Muir) trials are ongoing testing 0.25mg/kg TNK vs alteplase in non-endovascular patients

• EXTEND-IA TNK part 2 underway comparing 0.40mg/kg vs 0.25mg/kg tenecteplase prior to endovascular thrombectomy NCT03340493
Acknowledgements

• Recruiting Sites

**Australia:** Royal Melbourne Hospital (56) B.C.V. Campbell, P.J. Mitchell, S.M. Davis, B. Yan, R.J. Dowling, S. Bush, N. Yassi, A. McDonald; Royal Adelaide Hospital (33) T.J. Kleinig, R. Scroop, J. Taylor, R. Drew, J. Cranefield; Box Hill Hospital (24) H.M. Dewey, C.F. Bladin, P.S. Loh, P.M. Choi, Z. Ross, G. Thomas; Austin Hospital (21) V. Thijs, M. Simpson, M. Brooks, B. Coulton, D. Young; Western Hospital (20) T. Wijeratne, H. Tu, S. Celestino, E. Low; Gold Coast University Hospital (16) P. Bailey, H. Rice, L. de Villiers, B. Urbi; John Hunter Hospital (10) F. Miteff, M.W. Parsons, C.R. Levi, L. Kaauwai; Princess Alexandra Hospital (5) D. Shah, H. Brown, K. Redmond, D. Leggett; Royal Brisbane and Women’s Hospital (4) A.A. Wong, A. Coulthard; Monash Medical Centre (4) H. Ma, T. Phan, W. Chong, R.V. Chandra, L-A. Slater, K. Wong; Lyell McEwin Hospital (4) D. Field, V. Maxwell; Royal North Shore Hospital (2) M. Krause, T.J. Harrington, B. Steinfort, K. Faulder, S. Day.

**New Zealand:** Christchurch Hospital (3) T.Y. Wu, J.N. Fink, W. Collecutt, J. Eagle.

• Study Statistician – Prof Leonid Churilov
• CRO: Neuroscience Trials Australia – E Cowley, R McCoy, M Sallabarger
• DSMB: B. Snow (Chair), J. Kolbe, R. Stark, J. King, R. Macdonnell, J. Attia, C. D’Este (Independent Statistician)
• CSIRO (eCRF) – S McBride, K Harrap, C Stanbridge
• iSchemaView (RAPID) – G Albers, R Bammer
• Patients and families