Dr Bruce Campbell  MBBS BMedSc PhD FRACP

**EXTEND-IA** - Endovascular Therapy After Intravenous t-PA Versus t-PA Alone For Ischemic Stroke Using CT Perfusion Imaging Selection

**FINANCIAL DISCLOSURE:**
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**UNLABELED/UNAPPROVED USES DISCLOSURE:**
none
EXTEND-IA
Extending the time for Thrombolysis in Emergency Neurological Deficits – Intra-Arterial

A randomized controlled trial of endovascular thrombectomy after standard dose intravenous t-PA within 4.5 hours of stroke onset utilizing dual target imaging selection

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:
Australian Government
National Health and Medical Research Council

Solitaire FR™ device supplied free of charge by

ClinicalTrials.gov NCT01492725
Rationale

• In 2011 (before IMS-3, SYNTHESIS, MR-RESCUE neutral)
  – Futile recanalization noted in single arm studies (need better selection)
  – Major improvement in procedural success observed in patients ineligible for IMS-3 treated with stentriever versus our patients eligible for IMS-3

• Aimed to select patients with best chance of response to reperfusion - “dual target”
  – proven major vessel occlusion and
  – salvageable tissue downstream with ischemic core <70mL (CT perfusion)

• Treat as fast as possible
  (no waiting to assess “tPA failure”)

• Use the most effective device (stentriever)
RAPID for CT and MRI

Fast, standardized, fully automated, quantitative, thresholded mismatch

CT relCBF / Diffusion MRI

RAPID ischemic core segmentation
CT relCBF <30%

Tmax

RAPID Tmax > 6 sec segmentation

Ischemic core: 6mL Perfusion lesion: 58mL
Mismatch ratio = 9.7 Absolute mismatch = 52mL
→ Randomize patient

Ischemic core: 7mL Perfusion lesion: 55mL
Mismatch ratio = 7.6 Absolute mismatch = 48mL
→ Randomize patient

Straka et al JMRI 2010
TRIAL DESIGN - PROBE design, planned 100 patients

Patients eligible for tPA <4.5hr
No upper age limit, No NIHSS limits,
Premorbid mRS 0-1

Is there ICA/M1/M2 occlusion
+ mismatch (ratio>1.2, absolute>10mL) with ischemic core <70mL?

Randomise 50:50
(web-based)

IV tPA only
0.9mg/kg IV tPA + Solitaire FR clot retrieval
- start asap (<6hr)

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

3 day NIHSS*

90 day NIHSS & mRS

Blinded outcomes

*co-primary outcome
70mL ischemic core

Ischemic core volume: 73mL  Perfusion (Tmax>6s) lesion: 88mL
EXTEND-IA Recruitment

14 centres in Australia and New Zealand

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

MR-CLEAN results
DSMB halted EXTEND-IA recruitment (Haybittle-Peto boundary for efficacy)

Planned n=100
Generalizability

- In largest center 21 randomized + 7 with occlusion and clinical eligibility excluded for large core i.e. ~25% (95%CI 11-45%) excluded by CTP
CONSORT trial profile

Randomized (n=70)

**Alteplase + Endovascular (n=35)**
- Did not receive Angiogram (n=2)
  - 1 – major improvement (temporary)
  - 1 – major deterioration (unrecognized 2\textsuperscript{nd} embolism)
- Received angiogram (n=33)
  - 4 – already recanalized by tPA
  - 1 – ICA stent sufficient to restore flow
  - 1 – wire perforation pre-deployment

**Alteplase only (n=35)**
- Received tPA only (n=35)

*All analyses = intention to treat*
## Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IV tPA only</th>
<th>IV tPA + endovascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Age – yr: Mean (SD)</td>
<td>70.2 (11.8)</td>
<td>68.6 (12.3)</td>
</tr>
<tr>
<td>Male sex – no. (%)</td>
<td>17 (48.6%)</td>
<td>17 (48.6%)</td>
</tr>
<tr>
<td>NIHSS score: Median (IQR)</td>
<td>13 (9-19)</td>
<td>17 (13-20)</td>
</tr>
<tr>
<td>Onset to tPA – min Median (IQR)</td>
<td>145 (105-180)</td>
<td>127 (93-162)</td>
</tr>
<tr>
<td>Door-to-needle – min Median (IQR)</td>
<td>46 (35-70)</td>
<td>43 (19-61)</td>
</tr>
<tr>
<td>tPA to randomization – min Median (IQR)</td>
<td>36 (18-55)</td>
<td>29 (23-46)</td>
</tr>
</tbody>
</table>
## Initial imaging

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IV tPA only</th>
<th>IV tPA + endovascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of vessel occlusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA</td>
<td>11 (31%)</td>
<td>11 (31%)</td>
</tr>
<tr>
<td>MCA-M1</td>
<td>18 (51%)</td>
<td>20 (57%)</td>
</tr>
<tr>
<td>MCA-M2</td>
<td>6 (17%)</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Baseline Ischemic core – mL</td>
<td>19.6, 18 (4-29)</td>
<td>18.9, 12.3 (4-32)</td>
</tr>
<tr>
<td>Mean, Median (IQR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Perfusion lesion – mL</td>
<td>116, 115 (72-158)</td>
<td>105, 106 (76-137)</td>
</tr>
<tr>
<td>Mean, Median (IQR)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Procedural Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>median, (IQR)</th>
<th>IV tPA + endovascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>ONSET to groin puncture – min</td>
<td>210 (166-251)</td>
<td></td>
</tr>
<tr>
<td>CT to groin puncture – min</td>
<td>93 (71-138)</td>
<td></td>
</tr>
<tr>
<td>Groin puncture to TICI 2b/3 or completion</td>
<td>43 (24-53)</td>
<td></td>
</tr>
<tr>
<td>ONSET to mTICI 2b/3 or completion</td>
<td>248 (204-277)</td>
<td></td>
</tr>
</tbody>
</table>
# Procedural Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IV tPA + endovascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final mTICI (core lab adjudicated)</td>
<td>mTICI 2b/3 25/29 (86%)</td>
</tr>
<tr>
<td></td>
<td>mTICI 3 14/29 (48%)</td>
</tr>
</tbody>
</table>
Co-primary outcome
Reperfusion at 24hr

(Intention to treat)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>% Reperfusion at 24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>tPA only</td>
<td>median 37%</td>
</tr>
<tr>
<td>tPA + endovascular</td>
<td>100%</td>
</tr>
</tbody>
</table>

p<0.0001

median 37% vs 100%
Early neurological recovery
Reduction of ≥8 NIHSS points or reaching 0-1 by day 3

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>tPA only</th>
<th>tPA + endovascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>p=0.002</td>
<td>37%</td>
<td>80%</td>
</tr>
</tbody>
</table>

RMH Comprehensive Stroke Centre
Day 90 mRS

Combined Intravenous t-PA and Endovascular Therapy

Ordinal p=0.006 (unadj), p=0.02 (adj)
NNT 3 for ≥1 point better on mRS

Intravenous t-PA alone

mRS 0-2 p=0.01
71% vs 40% - NNT 3.2 for independence

mRS 0-1 p=0.09

RMH Comprehensive Stroke Centre
## Infarct volume & growth

<table>
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<th>IV tPA + endovascular</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Ischemic core</strong></td>
<td>18 (4-29)</td>
<td>12.3 (4-32)</td>
</tr>
<tr>
<td><strong>24hr Ischemic core</strong></td>
<td>49 (17-82)</td>
<td>18 (12-52)</td>
</tr>
<tr>
<td><strong>Infarct Growth</strong></td>
<td>35 (6-73)</td>
<td>11 (0-24)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>p=0.007 (adj)</em></td>
</tr>
</tbody>
</table>
## Adverse events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>IV tPA only</th>
<th>IV tPA + endovascular</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>7/35 (20%)</td>
<td>3/35 (9%)</td>
<td>0.18</td>
</tr>
<tr>
<td>SICH*</td>
<td>2/35 (6%)</td>
<td>0/35 (0%)</td>
<td>0.49</td>
</tr>
<tr>
<td>PH §</td>
<td>3/35 (9%)</td>
<td>4/35 (11%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Wire perforation</td>
<td>-</td>
<td>1/35 (2.9%)</td>
<td>-</td>
</tr>
<tr>
<td>Emboli</td>
<td>-</td>
<td>2/35 (5.7%)</td>
<td>-</td>
</tr>
</tbody>
</table>

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

§ PH = parenchymal hematoma
Limitations

• Sample size 70 - unable to interrogate subgroups (planned individual patient meta-analysis)

• Cannot exclude some benefit of endovascular therapy in patients excluded from this trial on the basis of large ischemic core/no mismatch.

• Purely volume-based criteria do not account for the location of the core, which is also relevant to clinical outcome.

• Early termination of the trial does create potential for overestimation of the effect size.
Conclusions

• **early** mechanical stent-thrombectomy after tPA using Solitaire FR led to:
  – Faster and more complete reperfusion

• In this population selected for vessel occlusion and salvageable tissue this translated to:
  – Improved early neurological recovery
  – Improved functional outcome at 3 months
  – No safety concerns
Implications

• tPA + mechanical stent-thrombectomy should be the new standard of care
• Systems re-organization and transfer protocols
• Details of selection paradigm remain a key discussion
  – EXTEND-IA indicates a population with high probability of major clinical response but others may derive some benefit – requires further study
Acknowledgements

• Recruiting Sites

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• Stanford Stroke Centre (RAPID) – G Albers, R Bammer
• Patients and families
Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection
