Further Pragmatic Trials of Thrombectomy are Needed

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Disclosures

• Co-Chief Investigator for PISTE
  – Funded principally from Stroke Association (start-up phase) and HTA (main phase)
  – Unrestricted (and quite small) grants from Codman and Covidien to support start-up phase of PISTE

• Consulted on design of SWIFT-Prime (although not listened to)
### IA Treatment Trials: Key Features

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Target Vessels</th>
<th>Median NIHSS</th>
<th>Advanced Imaging Selection</th>
<th>IV rtPA Use</th>
<th>Onset to Randomisation Time (mins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR CLEAN</td>
<td>500</td>
<td>ICA, M1, M2, A1, A2</td>
<td>18</td>
<td>No</td>
<td>85%</td>
<td>204</td>
</tr>
<tr>
<td>ESCAPE</td>
<td>315</td>
<td>ICA, M1</td>
<td>16</td>
<td>Yes (multiphasic CTA collaterals)</td>
<td>76%</td>
<td>169</td>
</tr>
<tr>
<td>EXTEND-IA</td>
<td>70</td>
<td>ICA, M1, M2</td>
<td>15</td>
<td>Yes (CTP)</td>
<td>100%</td>
<td>-</td>
</tr>
<tr>
<td>SWIFT-Prime</td>
<td>196</td>
<td>ICA, M1</td>
<td>17</td>
<td>Yes (CTP)</td>
<td>100%</td>
<td>188</td>
</tr>
<tr>
<td>REVASCAT</td>
<td>206</td>
<td>ICA, M1</td>
<td>17</td>
<td>No (but perfusion imaging if &gt;4.5h)</td>
<td>73%</td>
<td>225</td>
</tr>
<tr>
<td>THRACE*</td>
<td>414</td>
<td>ICA, M1, BA</td>
<td>18</td>
<td>No (but 70% MRI selected)</td>
<td>100%</td>
<td>135</td>
</tr>
<tr>
<td>THERAPY*</td>
<td>108</td>
<td>ICA, M1, M2</td>
<td></td>
<td>No</td>
<td>100%</td>
<td>-</td>
</tr>
</tbody>
</table>

### Statistical Problems with Premature Stopping

"truncated RCTs will disproportionally contribute to meta-analytic estimates when RCTs occur early in the sequence of trials, with few subsequent studies, ... or RCTs result in a ‘freezing’ effect in which ‘correcting’ trials are never undertaken. To avoid applying overestimates of effect ... clinicians should view the results of individual RCTs with small sample sizes and small number of events with skepticism."

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**Special concern if:**

1. RCTs have a relatively small number of events (e.g. <200)
2. There is a substantial difference (e.g. a ratio of RR<0.7) in the RR between the RCTs and the non-truncated RCTs;
3. The RCTs have a substantial (>20%) weight in the meta-analysis.
Systematic Review: Substantial Heterogeneity of Effects

Reduced disability at 90 d

<table>
<thead>
<tr>
<th>Source</th>
<th>Odds Ratio (95% CI)</th>
<th>Favors Standard Therapy</th>
<th>Favors Endovascular Therapy</th>
<th>P Value</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>SYNTHESIS, 2013</td>
<td>0.86 (0.60-1.23)</td>
<td></td>
<td></td>
<td>.40</td>
<td>14.2</td>
</tr>
<tr>
<td>MR RESCUE, 27 2013</td>
<td>0.86 (0.45-1.63)</td>
<td></td>
<td></td>
<td>.65</td>
<td>10.1</td>
</tr>
<tr>
<td>IMS III, 28 2013</td>
<td>1.17 (0.88-1.57)</td>
<td></td>
<td></td>
<td>.28</td>
<td>15.3</td>
</tr>
<tr>
<td>MR CLEAN, 29 2015</td>
<td>1.66 (1.22-2.28)</td>
<td></td>
<td></td>
<td>.001</td>
<td>14.9</td>
</tr>
<tr>
<td>ESCAPE, 30 2015</td>
<td>2.53 (1.70-3.79)</td>
<td></td>
<td></td>
<td>&lt;.001</td>
<td>13.6</td>
</tr>
<tr>
<td>EXTEND-IA, 31 2015</td>
<td>3.22 (1.36-7.61)</td>
<td></td>
<td></td>
<td>.008</td>
<td>7.5</td>
</tr>
<tr>
<td>SWIFT-PRIME, 32 2015</td>
<td>2.55 (1.53-4.26)</td>
<td></td>
<td></td>
<td>&lt;.001</td>
<td>11.9</td>
</tr>
<tr>
<td>REVASCAT, 33 2015</td>
<td>1.57 (0.97-2.55)</td>
<td></td>
<td></td>
<td>.07</td>
<td>12.4</td>
</tr>
<tr>
<td>Overall</td>
<td>1.56 (1.14-2.13)</td>
<td></td>
<td></td>
<td>.005</td>
<td>100.0</td>
</tr>
</tbody>
</table>

$\chi^2 = 75.9\%, P < .01$

Bhadiwala et al. JAMA 2015;314:1832-1843.

How Generalisable are IAT Trials?

<table>
<thead>
<tr>
<th>MR CLEAN</th>
<th>REVASCAT</th>
<th>EXTEND-IA</th>
<th>ESCAPE</th>
<th>SWIFT-Prime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>500</td>
<td>206</td>
<td>70</td>
<td>315</td>
</tr>
<tr>
<td>Centres</td>
<td>16</td>
<td>4</td>
<td>10</td>
<td>20</td>
</tr>
</tbody>
</table>
Local Custom may not Translate Correctly

THRAVE
Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke

Inclusion Criteria:
• NIHSS Score 10-25
• Symptom onset <4 hours
• Occlusion of the ICA, MCA M1 or upper third of the basilar

Exclusion Criteria:
• Contraindications for IV thrombolysis
• Occlusion or stenosis of the pre-occlusive cervical ICA ipsilateral to the lesion
• Any cause prohibiting femoral catheterization

UK Assumption: CT+CTA = Standard non-advanced imaging selection (therefore trial design equivalent to PISTE and positive result informs UK practice)

French Practice: MRI is first-line imaging of choice for stroke, therefore 75% of patients selected by DWI+MRA, undisclosed % also perfusion imaging ("encouraged" but not mandatory)

How Representative of Real Life? EXTEND-IA Screening

Acute Ischaemic Stroke, not IVT treated 87%
IVT Eligible, not randomised 12%
How Many Would be Eligible by Protocol?

N=263 with multimodal CT <6h after onset

Did These Studies Include Consistent Populations?
Day 90 mRS Distribution in All Recent Published IAT Trials
Subgroups: Many Small, Limited

Bhadiwala et al. JAMA 2015;314:1832-1843.
Subgroups: Many Small, Limited

**Subgroups:**
- Age <70
- Sex
- NIHSS score
- ASPECTS score
- Time to randomization
- Location of occlusion
- Cerebral A1
- BA segments
- Prior revascularization
- IVt given
- Method of thrombolysis

**Favorable Standard Therapy**
- Favorable Endovascular Therapy
- P-value

**P-value for Interaction**
- <0.05
- <0.01
- <0.001

**Time to randomization**
- g2,3,10,12,15
- s3

**Randomized or IAT initiated >6h**
- ESCAPE – n=49
- REVASCAT – n=20

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**Subgroups:**
- Age <70
- Sex
- Time to randomization
- Location of occlusion
- Cerebral A1
- BA segments
- IVt given
- Method of thrombolysis

**Favorable Standard Therapy**
- Favorable Endovascular Therapy
- P-value

**P-value for Interaction**
- <0.05
- <0.01
- <0.001

**No IVT given MR CLEAN – n=55**
- REVASCAT – n=56
- ESCAPE – n=77

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**Gaps and Criticisms of Recent Trials**

- Potential serious over-estimation of effect size through early discontinuation of trials
- Limited numbers (as a consequence of large treatment effects): 
  - n= 1809 (n=1874 after PISTE)
- Many “invisible” selection criteria applied
- Not all primary data are yet published
  - Few secondary or subsidiary analyses
- Competing meta-analyses underway
  - But will have very limited power to address many subgroups
- Effectiveness outside highly specialised and optimised environments is not known

**Potential Sources of New Data**

- Ongoing or planned RCTs
  - **POSITIVE** (late presentation, favourable MRI)
  - **DAWN** (Wake-up & late presentation)
  - **BASICS** (Basilar artery occlusion)
  - **DEFUSE-3** (Late presentation, favourable MRI)
  - **PISTE-AI** (Acute presentation, comparing imaging selection)
  - Children of **MR CLEAN** (IVT v IAT, ...)
- Registry data?
  - Key factor is interaction of treatment effect with any given variable: lack of concurrent controls presents a serious limitation
- Feasibility of “pragmatic” RCTs to address gaps may have to wait for equipoise to be re-established
- **Further pragmatic RCTs will be needed**