What Did We Learn From IMS 3?

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Why do we need IA Approaches?
Recanalization & Reocclusion post IV rt-PA:
63 Patients with MCAO
UT-Houston TCD Data, Courtesy of James Grotta

• No recanalization = 27%
• Partial recanalization = 33%
• Complete recanalization = 18%
• Reocclusion = 22%
• Sustained recanalization rates:
  12% at 60 & 120 min w/o ultrasound

Beyond IV or IA Treatment Alone

• More effective acute recanalization strategies are needed
• IA seems to help more severe strokes and larger clot burdens better than IV
• How to get the best of both worlds – IV and IA?
• “Bridge” with IV during preparation for IA – What dose?
What did we learn from IMS 3

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Probability of Good Clinical Outcome Over Time

As predicted by unadjusted logistic regression

Cases with Reperfusion (p=0.02)

95% Prediction Bands

Cases without Reperfusion


April 18, 2012

• The Interventional Management of Stroke 3 (IMS 3) trial, comparing IV t-PA alone vs combination t-PA & IA therapy using either IA t-PA or mechanical thrombectomy in stroke patients suspended enrollment after crossing a pre-specified interim analysis threshold = even if the study continued, it would not produce the hypothesized result: that combination therapy is superior to IV t-PA alone
• Futility, not major safety concerns

LEGEND: In 1933, Antonio Egas Moniz, a Portuguese neurologist but not a trained surgeon, performed the first lobotomy: the removal of the prefrontal lobe of the brain to treat delusional or violent patients. The operation would soon be found useless and destructive and is no longer practiced.
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IMS 3 Primary Aim

• Whether a combined IV & IA approach to recanalization is superior to standard IV t-PA alone when initiated within 3 hrs of acute ischemic stroke onset
• Powered to detect a 10% absolute difference between the 2 groups with N = 900
• 2:1 randomization IV/IA : IV alone, 50+ sites
• Final sample size ~ 587 (~ 65% of planned)
• Dichotomized baseline NIHSSS (< 20 / ≥ 20)
• Estimated 40% rate of mRS 0-2 with IV t-PA

Design

• Consent/randomization prior to/anytime up to 40 min after IV bolus. If, at 40 min time point, no consent obtained/randomization not completed, the patient was no longer eligible for enrollment.
• After consent, the IV/IA group ➔ immediate angiography. If no clot: no more treatment.
• If clot: interventionalist chose from currently available, trial-defined, IA tx approaches: the tx they felt would be most effective in attempting to reopen the blocked artery. Choice of approach based on lesion, experience/training, & specified use of devices
• IA tx to be started < 5 hrs & completed <7 hrs of symptom onset.

Design

• Clinical Inclusion Criteria: Age 18 - 82 years
• Initiation of IV t-PA < 3 hours of onset of stroke symptoms
• An NIHSSS ≥ 10 at time IV rt-PA is begun or NIHSSS >7 & <10 with an occlusion seen in M1, ICA, or BA on CTA at institutions where baseline CTA imaging is standard of care for acute stroke
• Exclusion: Baseline CTA w/o evidence of an arterial occlusion (~ ½ without baseline CTA)
• The trial did not require baseline CTA imaging, if CTA is routinely performed prior to IV t-PA lesion information obtained was used to satisfy this exclusion
What did we learn from IMS 3

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Drug: IA t-PA (Investigational)

Devices:
- Standard Microcatheter Infusion (all commercially available models)
- EKOS Micro-Infusion (NeuroWave Infusion) System
- Concentric Merci® Retriever (all FDA approved commercially available models)
- The Penumbra System™ (all FDA approved commercially available models)
- Solitaire™ FR Revascularization Device (investigational in the US, Canada & Australia)

Primary Outcome Measures
- Efficacy: modified Rankin Scale score: dichotomized to 0-2 vs >2 at 3 months from randomization
- Safety: Death due to any cause within 3 months
- Presence of symptomatic ICH within the first 24 (+ 6) hrs

Secondary Outcome Measures
- Barthel Index, NIHSSS & Trail Making Test at 3 months
- Early response to treatment as determined by NIHSSS of 0-2 at 24 hrs from randomization
- Dichotomized mRS score (0-2) vs > 2 at 6, 9, & 12 months from randomization
- Incidence of parenchymal Type II (PH2) ICH and any asymptomatic ICH as determined by head CT scan obtained within the first 24 (+ 6 hrs) of randomization
What did we learn from IMS 3

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Perspective

• The earlier single-arm IMS 1 & IMS 2 trials (along with the Penumbra trial and the French RECANALISE study) demonstrated a strong relationship between time to revascularization & good functional outcome at 3 months. In IMS 1 & 2, revascularization > 6 hours resulted in outcomes similar to no revascularization.

• IMS 3 randomized after initiation of IV t-PA not always with knowledge of vessel status – dilution effect of reperfusion therapy.

• 3 Embolectomy devices are approved by the FDA as reperfusion options: MERCI (cleared in 2004), Penumbra (cleared in 2007), & Solitaire (cleared in March 2012).

• IV t-PA has been established in trials looking at clinical outcomes vs placebo, whereas embolectomy has evidence from only single-arm studies, due to different regulatory approval criteria for drugs vs devices.

Successful recanalization (TIMI 2 or 3) in all treatable vessels: VA, BA, ICA, MCA (M1/M2) (Raychev & Saver 2012)

<table>
<thead>
<tr>
<th>Device type</th>
<th>Trial</th>
<th>Baseline NIHSS</th>
<th>Successful recanalization%</th>
<th>SICH%</th>
<th>Independent outcome at 3 mos.</th>
<th>Mortality at 3 mos.</th>
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<tr>
<td>Coil retrievers</td>
<td>Multi-MERCI</td>
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<td>54</td>
<td>9</td>
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<td></td>
<td>SWIFT</td>
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<tr>
<td>Stent retrievers</td>
<td>SWIFT</td>
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<td>83</td>
<td>2</td>
<td>58</td>
<td>17</td>
</tr>
</tbody>
</table>
What did we learn from IMS 3

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• To date, mechanical embolectomy devices have been cleared by the FDA & are recognized in national treatment guidelines as tools rather than treatments.
• Devices can remove clots, but we need to prove that they improve patient outcomes compared with standard therapy.
• Optimal imaging protocol?
  – CT (with ASPECTS?), MR (DWI/PWI)
• MR RESCUE & START
• ? Subgroups to study in a more focused way

Reimbursement & ready availability of the devices have likely influenced enrollment in randomized trials

• Practice changes in the US, with more specialists being trained to use the devices & becoming much more comfortable with them.
• Hospitals, not just physicians, get reimbursed for the procedure, which could be an additional factor driving their use.
• The rising use of mechanical embolectomy may partially explain the difficulties that researchers have encountered in recruiting for randomized trials that investigate mechanical-embolectomy therapy.
• Procedures/therapies getting ahead of the evidence.

What did we learn?

• IV t-PA dose (2/3 vs. full)
• Technology advances faster than trials
  – IMS 3 amendments to add Penumbra, Solitaire, so these subgroups will be relatively small
• Possible dilution effect of recanalization rates when not consistently knowing vessel patency at time of randomization: ½ w/o CTA
• Definitive data regarding the efficacy of mechanical thrombectomy devices in improving final outcome over medical therapy alone awaits the conclusion of ongoing trials.
Lessons learned (continued)

• Most IV/IA subjects treated with IA t-PA rather than mechanical thrombectomy
• Very small group treated with the most technically efficacious device class – the stent retrievers
• Trial included subjects with no occlusions or small distal occlusions less likely to benefit from mechanical retrieval
• Safety was not the basis for trial stoppage and newer devices appear to have even lower (2-4%) Sx ICH rates

• IMS 3, with enrollment beginning in 2006, was the first phase 3 randomized trial testing interventional IA tx against IV t-PA within 3 hrs of stroke onset.
• For IA tx, we are somewhere analogous to the IV trials prior to the completion & results of The NINDS rt-PA Stroke Trial – multiple negative studies that led to refined protocols/approaches, time windows, different thrombolytics, & patient selection criteria until we hopefully will have a positive trial soon.

ISC 2013

• Feb 7: Full session on IMS 3 – Results & Perspectives (Lyden & Lees, moderators)
• IMS 3 Overall results & major subgroups (baseline NIHSS, time to IV t-PA, time to groin, baseline CT ASPECTS, and age) - Broderick
• Comparison of outcomes between IV & IV/IA approaches in subjects with baseline CTA showing ICA, M1, M2, & BA occlusions - Demchuk
• Comparison of outcomes by IA approach (Concentric Retriever, Penumbra, IA t-PA, Solitaire Retriever) & Interpretation in light of comparative trials – Tomsick
• The role of endovascular treatment in international healthcare systems: Global variations in the standard of care – Davis
• The future for randomized trials of endovascular approaches to AIS - Muir
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**IA Trial Landscape**

- **COMPLETED AND RESULTS PENDING**
  - Italy - Synthesis (n=350)
  - US - MR Rescue (n=120)
- **ONGOING**
  - Netherlands - MR CLEAN (n=500) - started 4/2010
  - France - THRACE (n=480) - started 6/2010
  - Penumbra - THERAPY/US & Europe (n=692) - started 8/2012
  - UK - HOST (n=400) - just started
  - Australia - EXTEND IA (n=100) - just started
- **UPCOMING**
  - Covidien and others - ESCAPE/Canada (n=250)
  - Covidien - REVASCAT/US & Europe (n=400)
  - Covidien - REVASCAT/Spain (n=400)
  - J&J - RIVER/Europe (and future US) (n=?)
  - DFG – TOMERAS/Germany (Leipzig) (n=614) (proposed)

Courtesy of P. Khatri