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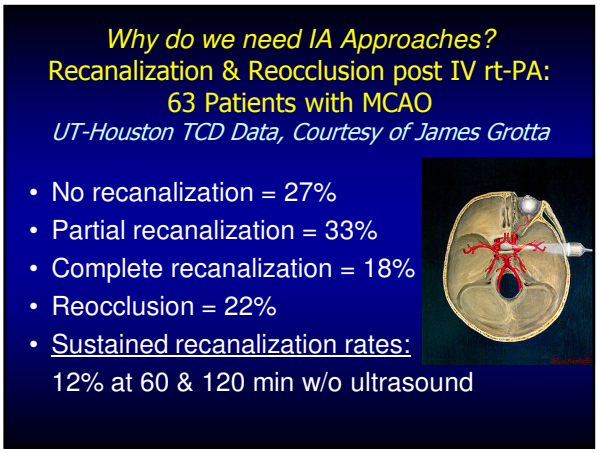

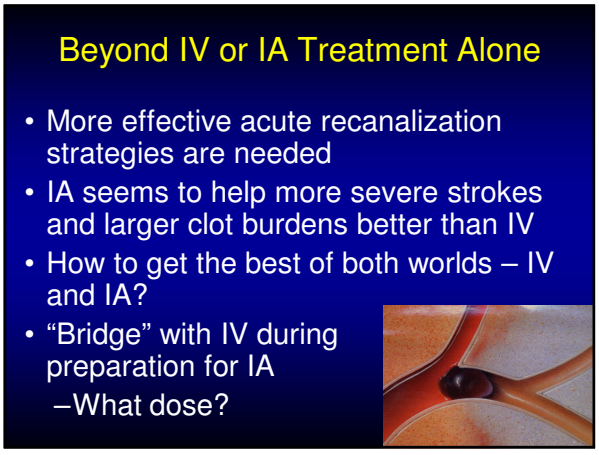

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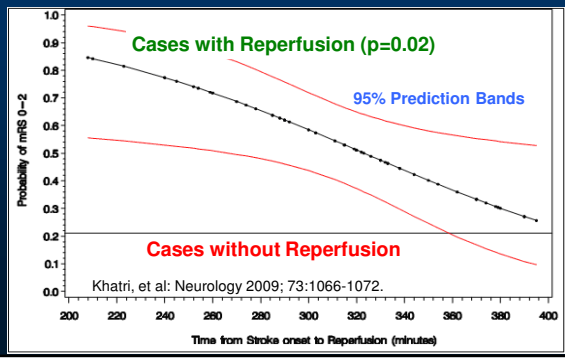
Probability of Good Clinical Outcome Over Time

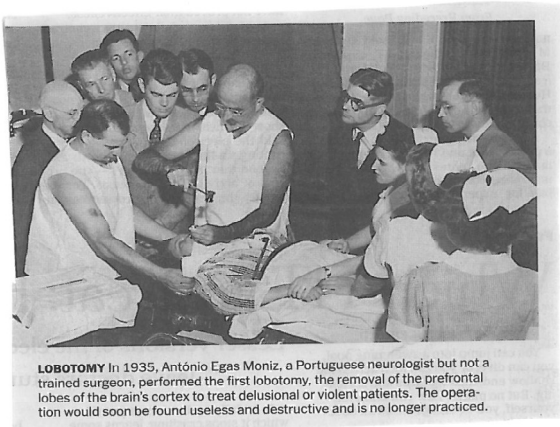
As predicted by unadjusted logistic regression



Khatri, et al: Neurology 2009; 73:1066-1072.

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



LOBOTOMY In 1935, António Egas Moniz, a Portuguese neurologist but not a trained surgeon, performed the first lobotomy, the removal of the prefrontal lobes of the brain's cortex 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

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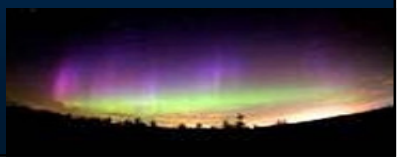
- Drug: IA t-PA (Investigational)

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

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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)

Device type	Trial	Baseline NIHSS	Successful recanalization%	SICH%	Independent outcome at 3 mos.	Mortality at 3 mos.
Coil retrievers	Multi-MERCI	19	54	9	36	31
	SWIFT	17.5	48	11	33	38
Aspiration	Penumbra	17	NR	11	25	33
Stent retrievers	SWIFT	17.5	83	2	58	17

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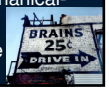
- To date, mechanical embolectomy devices have been cleared by the FDA & are recognized in national treatment guidelines as tools rather than treatments.
- Devices can remove clots, but we need to prove that they improve patient outcomes compared with standard therapy
- Optimal imaging protocol?
  - 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

- Khatri et al (AAN 2012): use of mechanical embolectomy almost doubled in the US from 2008 – 2010
- 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

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Lessons learned (continued)

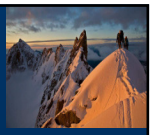
- Most IV/IA subjects treated with IA t-PA rather than mechanical thrombectomy
- Very small group treated with the most technically efficacious device class – the stent retrievers
- Trial included subjects with no occlusions or small distal occlusions less likely to benefit from mechanical retrieval
- 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

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 - PISTE (n=400) – just started
  - Australia - EXTEND IA (n=100) – just started
- **UPCOMING**
  - Covidien and others – ESCAPE/Canada (n=250)
  - Covidien - SWIFT PRIME/US & Europe (n=800)
  - Covidien - REVASCAT/Spain (n=400)
  - J&J – RIVER/Europe (and future US) (n=?)
  - DFG – TOMERAS/Germany (Leipzig) (n=614) (proposed)

Courtesy of P. Khatri