


**The Acute Stroke Menu:  
Something off the Back Page**


*Innovative ways to use IV t-pa and other  
assorted therapies available outside the  
standard treatment window*

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**Summary:  
Limitations in IV TPA**

- Still only utilized in 2-4% of patients
  - Time delays and fixed treatment window
  - Physician resistance
- Special populations: Uncertainty about??
  - Elderly
  - Dissections
  - Minor strokes



**Insight into novel use of  
IV TPA for ischemic stroke**

OK to treat mild patients


- Poor natural history and outcomes without treatment

OK to treat elderly patients

- Clear benefit; slightly higher bleed rates


OK to treat dissection

- Often unknown at time of presentation
- Risk is higher in vertebral vessels




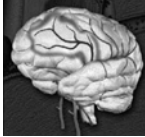
**Classification of future therapies  
by mechanism of action:**

1. Restoring blood supply to ischemic brain
2. Minimizing metabolic demand
3. Blocking neuronal ischemic cascade
4. Preventing/minimizing complications
  - Neurological
  - Medical



**Restore Blood Supply to the  
Brain**

- Improved IV thrombolysis
  - Expanded time window
  - Safer/Better thrombolytics
- Intra-arterial pharmacological thrombolysis
- Intra-arterial mechanical thrombolytic reperfusion




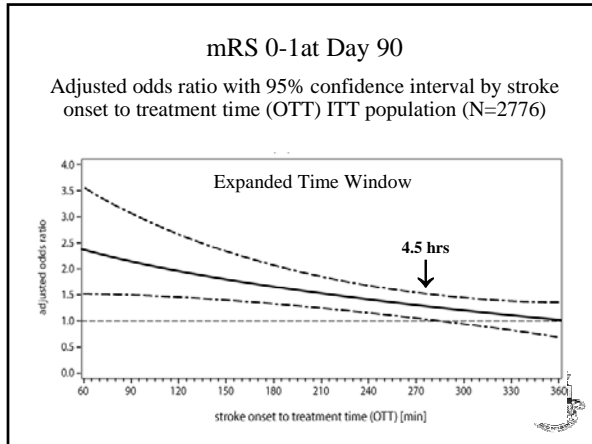
**Expanded Time Window**

Odds Ratios for Favorable Outcome

<u>Time</u>	<u>Odds Ratio</u>	<u>95% Conf. Interval</u>
0-90	2.8	1.8, 4.5
91-180	1.6	1.1, 2.2
181-270	1.4	1.1, 1.9
271-360	1.2	0.9, 1.5

The ATLANTIS, ECASS, and NINDS Study Group Investigators  
*Lancet. 2004 Mar 6;363(9411):768-74*





Safer and Better Thrombolytic Medications

Beyond t-pa...

Recanalization Strategies

- Thrombolytics  
rt-PA, TNK, rPA, prourokinase, desmoteplase
- Fibrinolytic agents  
Ancrod, defibrase
- GP IIb/IIIa agents  
Abciximab, eptifibatide
- Anti-thrombotic agents  
Heparin, LMWH

Recanalization Strategies  
Combination Approaches

- GUSTO V Cardiac Trial  
– Half dose reteplase + abciximab
- CLEAR Stroke Trial  
– Low dose tPA + eptifibatide
- AbESTT  
– Abciximab in Emergent Stroke Treatment Trial

INTRARTERIAL THROMBOLYSIS

- With IV t-PA, occlusion is absent in 20%
- Re-canalization averages 70% IA, 35% IV
- Outcome improves with re-canalization
- VBI often Rx up to 24 hours, bleed rate 7%  
Anterior circulation often Rx past 6 hours
- Chosen strokes have poor outcomes
- Neurology, ER, VIR are involved

INTRARTERIAL THROMBOLYSIS


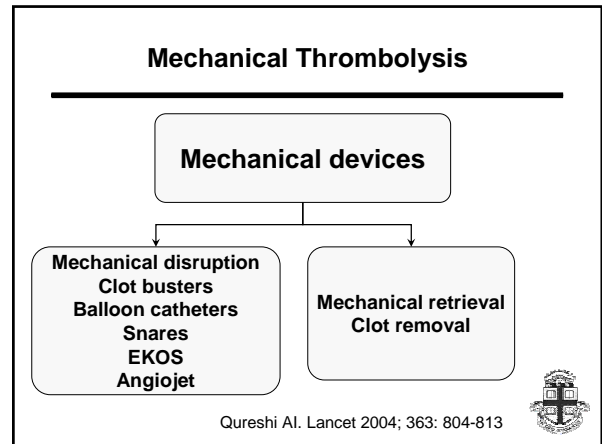
Cochrane Database of Systematic Reviews meta-analysis:

*“Risks of thrombolysis are offset by reduced dependence in survivors, so that significantly more patients are alive and independent after treatment”*

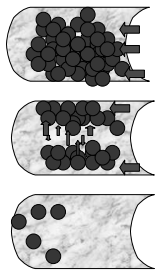
## INTRARTERIAL THROMBOLYSIS

Second AHA International Evidence Evaluation Conference:  
*“IA thrombolysis given 3 to 6 hours after stroke onset is now a Class IIb recommendation”*


Class IIb = acceptable, clinically useful, alternative or treatment supported by good evidence

### Mechanical Thrombolysis

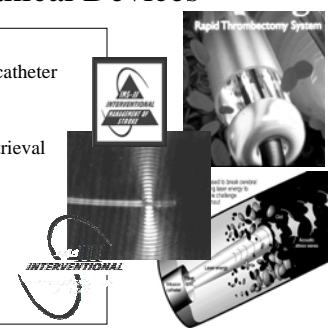
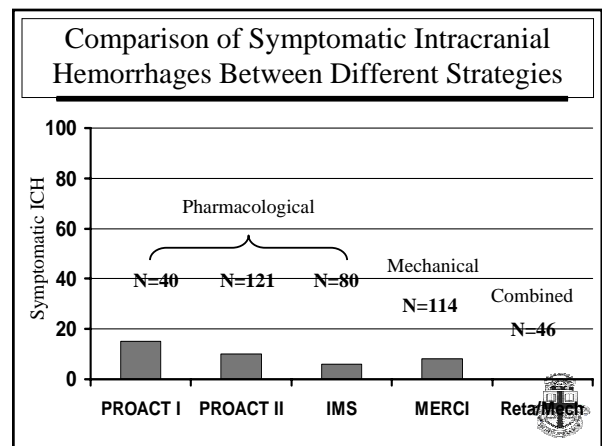
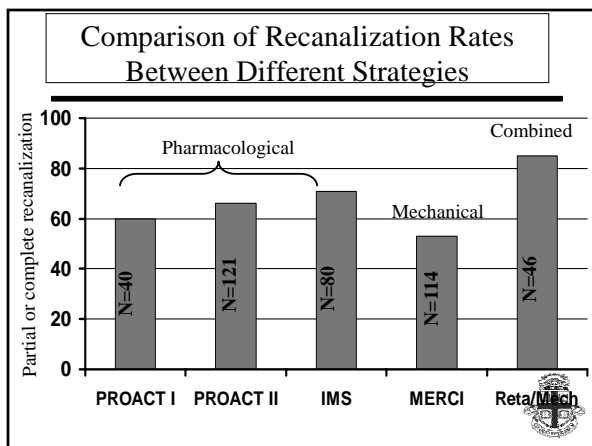


Qureshi AI. Lancet 2004; 363: 804-813.



### Intra-arterial Approaches Mechanical Devices

- IMS-2 Trial
  - tPA with ultrasound catheter
- MERCI Trial
  - “Cork-screw” clot retrieval
- TIME 1 Trial
  - Angiojet device
- IMS III (2006)
  - IV rt-pa vs. IV/IA

## Blocking Neuronal Ischemic Pathway:

### Neuroprotection



## HYPOTHERMIA

- Known to be neuroprotective for years
- Positive results in 2 studies with global ischemia
- Multiple mechanisms for neuroprotection
- COOL AID Trial



## MAGNESIUM

- Safety proven in stroke
- Late administration decreases efficacy
- FAST - Mag



## NXY-059

- Free-radical-trapping agent
- Recently reported randomized trial of NXY-059 in 1699 patients at 158 hospitals in 24 countries
- Drug infused (IV) x 72 hours
- Inclusion criteria:
  - NIHSS >6
  - Onset < 6 hours
  - Motor weakness
  - (could receive tPA)

Lees KR, Zivin JA, Ashwood T, et al. NXY-059 for acute ischemic stroke. *New Engl JMed.* 2006;354:588-600.



## SAINT I Trial

- 200 centers – Europe, Asia, Australia
- 1<sup>st</sup> positive clinical neuroprotective trial!!
- Decreased hemorrhage with t-PA use
- No significant AE's
- SAINT 2 – ongoing in US, international



## Preventing and Managing Medical and Neurological Complications



### Future Strategies for Preventing or Minimizing Stroke Complications

- **Organized stroke care**
- Electronic or biochemical monitoring of neurological status
- Early prophylaxis/treatment aspiration pneumonia
- Nutrition and hydration
- DVT prevention
- Medical & Surgical management cerebral edema
- Biochemical assessment of brain tissue viability
- Early mobilization while preserving patient safety
- Pharmacological enhancement of early neurological recovery



### Stroke Centers Primary and Comprehensive Systems

**Special Report**

**Recommendations for Comprehensive Stroke Centers  
A Consensus Statement From the Brain Attack Coalition**

Mark J. Alberts, MD, Richard E. Latchaw, MD, Warren R. Selman, MD, Timothy Shephard, RN, Mark N. Hadley, MD, Lawrence M. Brass, MD, Walter Koroshetz, MD, John R. Marler, MD, John Basso, MD, Richard D. Zorowitz, MD, Jason B. Cowie, PhD, Ellen Magnus, MBA, Diane Mulligan, Andrew Jagals, MD, Robert O'Connor, MD, C. Michael Cawley, MD, JJ. Conner, MD, Jose A. Boscá-Delbosque, CN, RN, Marian Ester, Margo Warren, Michael D. Walker, MD, for the Brain Attack Coalition

JAMA July, 2005

**ASA Policy Recommendations**

**Recommendations for the Establishment of Stroke Systems of Care  
Recommendations From the American Stroke Association's Task Force on the Development of Stroke Systems**

Task Force Members:  
Lee B. Schwamm, MD, Jeffrey Panatik, MD, Jon R. Anderson, DPM, PhD, MPH, MS, Larry B. Goldstein, MD, Richard D. Zorowitz, MD, Timothy J. Shephard, PhD, CNRN, CNRN, CNA, Paul Morgan, MD, MPH, Mark Goren, MD, I. Chhabria, MD, MPH, MS, PhD, Patrick W. Duncan, PhD, Phil Grunick, MD, Jeffrey Frank, MD, Steven E. Strass, MD, DS, Bruce Smith, MD, William Anderson, MD, Kate B. Horton, RN, MS, Ellen Magnus, MBA, Robert J. Adams, MD



JCAHO September 2006  
331 PSC Programs



Stroke March, 2005

### Organized Stroke Care Saves Lives

- 21% reduction in early mortality
- 18% reduction in 12 month mortality
- Decreased length of hospital stay
- Decreased need for institutional care

(Duncan, *Stroke* 2002)  
(Jorgensen, *Stroke* 1994)



### Summary

- New ways exist to use standard IV t-pa
- Future strategies will focus on stroke mechanism and systems
- New medications and devices are on the horizon
- The horizon is now!

