Acute Stroke Treatment

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Four Interventions Proven to Improve Outcomes in Acute Stroke

1) Management of patients within a stroke unit (1993)

2) Administration of aspirin within 48 hours of stroke onset (1997)

3) Hemicraniectomy (2007)

4) Intravenous thrombolytic treatment within 4.5 hours of symptom onset (1995, 2008)

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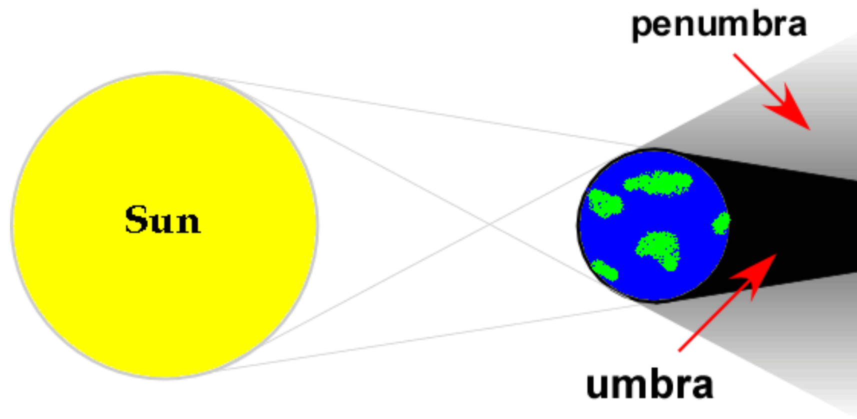
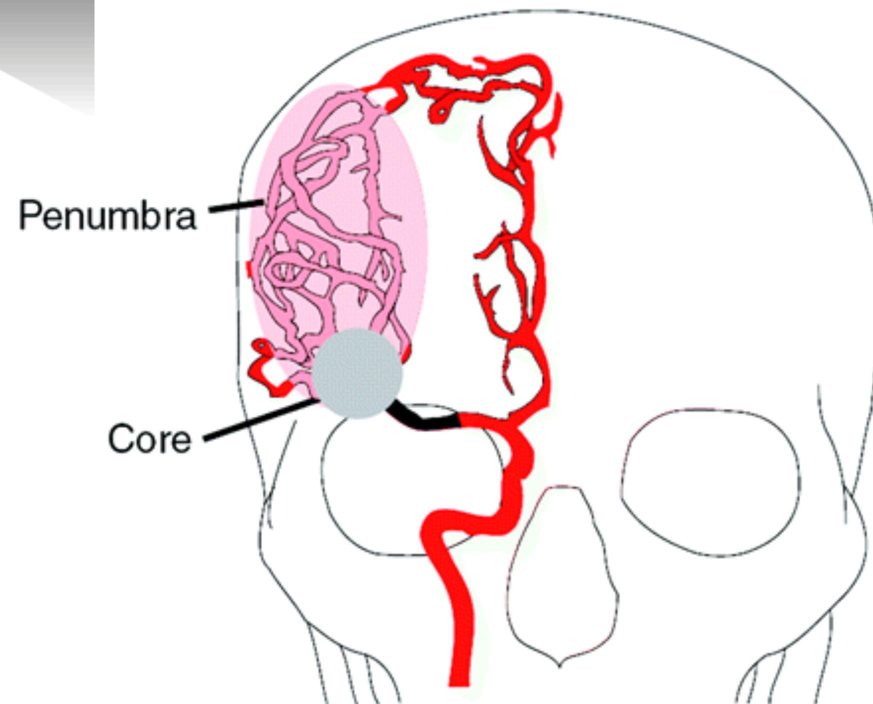
TISSUE PLASMINOGEN ACTIVATOR FOR ACUTE ISCHEMIC STROKE

The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group*

Ischemic Penumbra

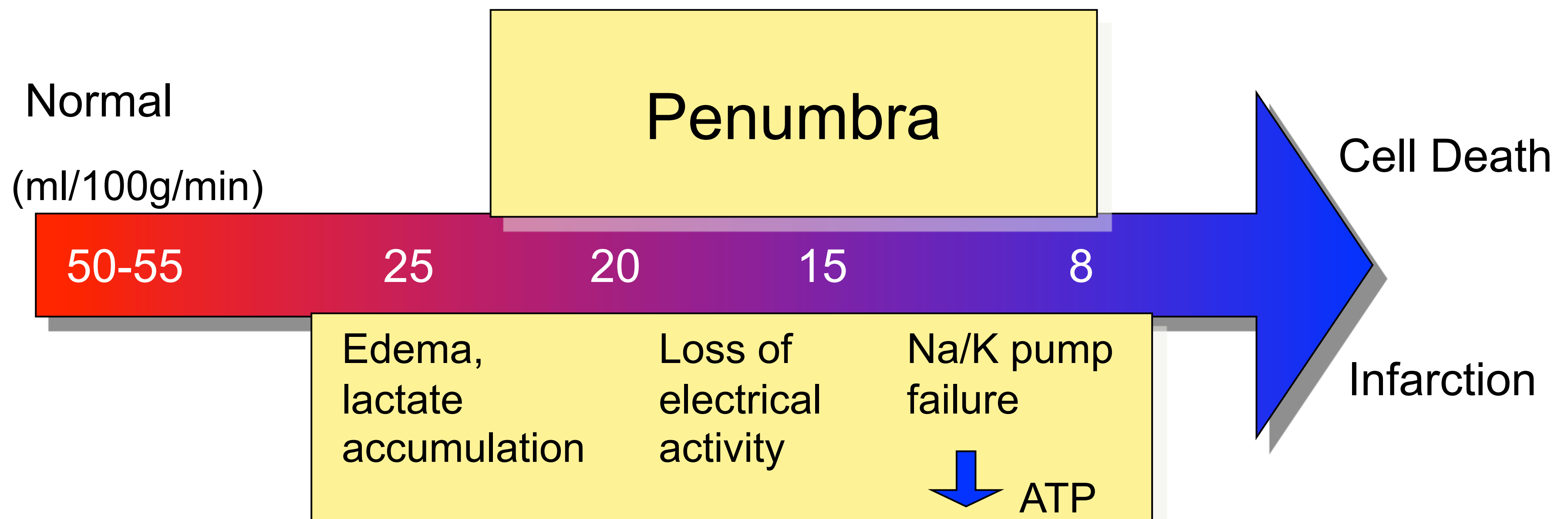


- Region of tissue with presumed reversible circulatory and metabolic/functional compromise

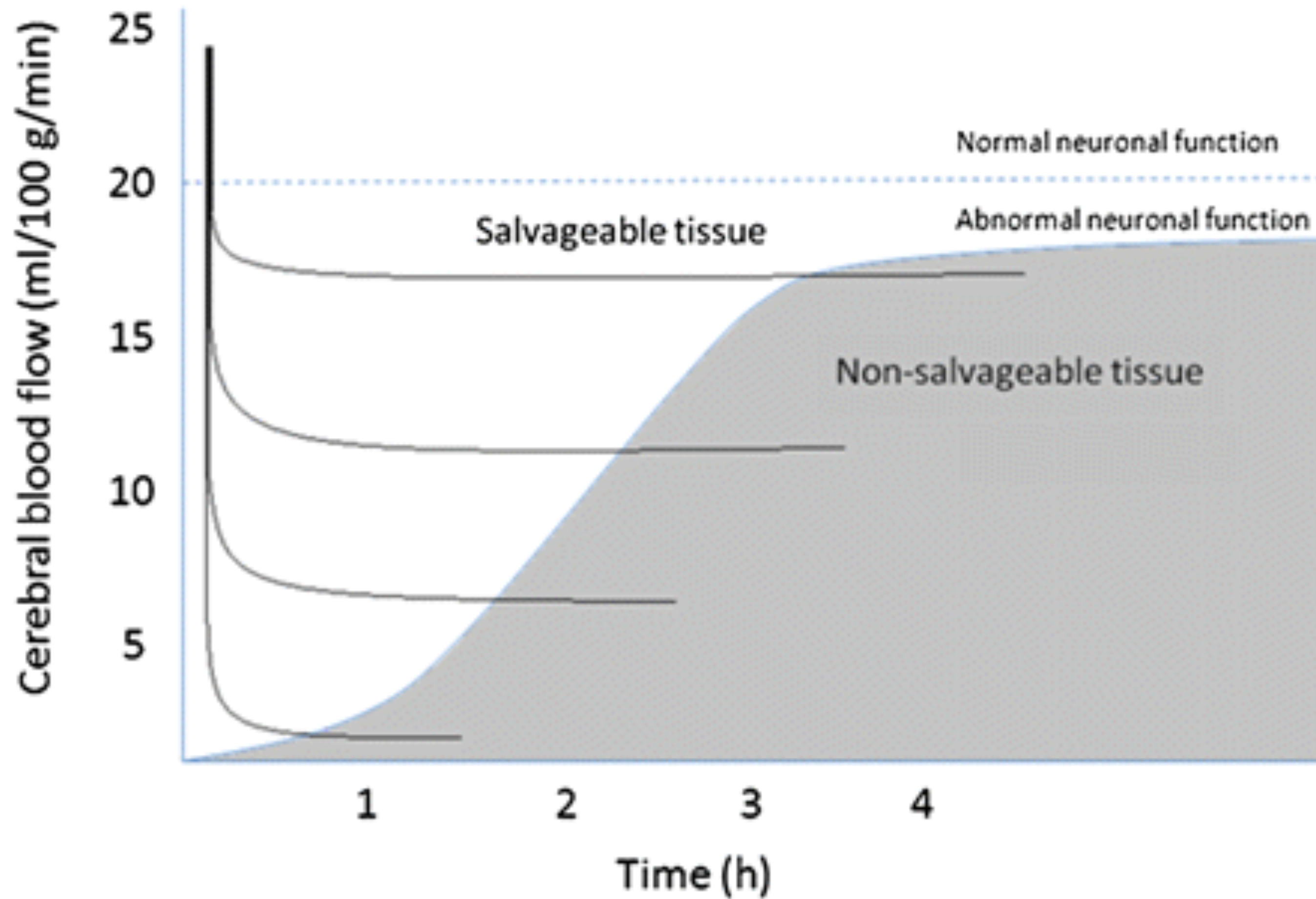


Gonzalez AJNR 27 Apr 2006

Effects of Cerebral Ischemia



Ischemic Thresholds



- Acute Treatment Options
  - Cytoprotection
    - Numerous targets in ischemic brain
    - Favorable pre-clinical data
    - No Phase III trial has shown efficacy in humans
  - Reperfusion
    - Narrow time window
    - Risks of treatment
    - Established efficacy

NINDS t-PA Stroke Trials

- Randomized, double-blind placebo-controlled trials
- Recombinant tissue plasminogen activator (alteplase) within 3 hours of symptom onset
- 624 patients enrolled between January 1991 and October 1994 across 8 sites

NEJM, 333:1581,1995

NINDS t-PA Stroke Trials

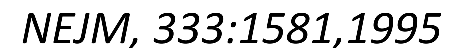
- Part One (n = 291)
  - Primary outcome measure:
    - > 4 point improvement on NIHSS

- Part Two (n = 333)
  - Primary outcome measure:
    - Composite endpoint based on functional recovery (Barthel Index, modified Rankin Scale, Glasgow Outcome Scale, NIHSS)

NEJM, 333:1581,1995

NINDS t-PA Stroke Trials

- Inclusion Criteria
  - > 18 years of age
  - Ischemic stroke with symptom onset < 3 hours
  - Measurable deficit on NIHSS
  - Head CT negative for hemorrhage



NEJM, 333:1581,1995

- Randomized to receive either t-PA or placebo, stratified according to time from symptom onset to treatment (0-90 minutes, 91- 180 minutes)

- Treatment arm
  - IV t-PA (0.9 mg/kg, max dose 90 mg)
  - 10% over one minute, remainder over one hour

- No antithrombotics during first 24 hours
- BP maintained < 185/110 mmHg

NEJM, 333:1581,1995

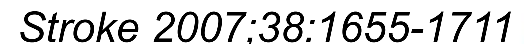
NINDS t-PA Stroke Trials

Exclusionary Criteria

- Rapid improvement
- Seizure at stroke onset*
- Suspected SAH despite normal CT
- Major surgery within 14 days
- Stroke or serious head trauma within 3 months
- History of intracranial hemorrhage
- GI or urinary tract hemorrhage within 21 days
- SBP > 185 mmHg or DBP > 110 mmHg at time of treatment
- Aggressive treatment to lower BP
- Glucose < 50 mg/dl
- Arterial puncture within one week at non-compressible site
- Heparin within 48 hours and an elevated PTT
- INR > 1.7 or plt count < 100k
- CT with infarct > 1/3 hemisphere

**Relative contra-indication*

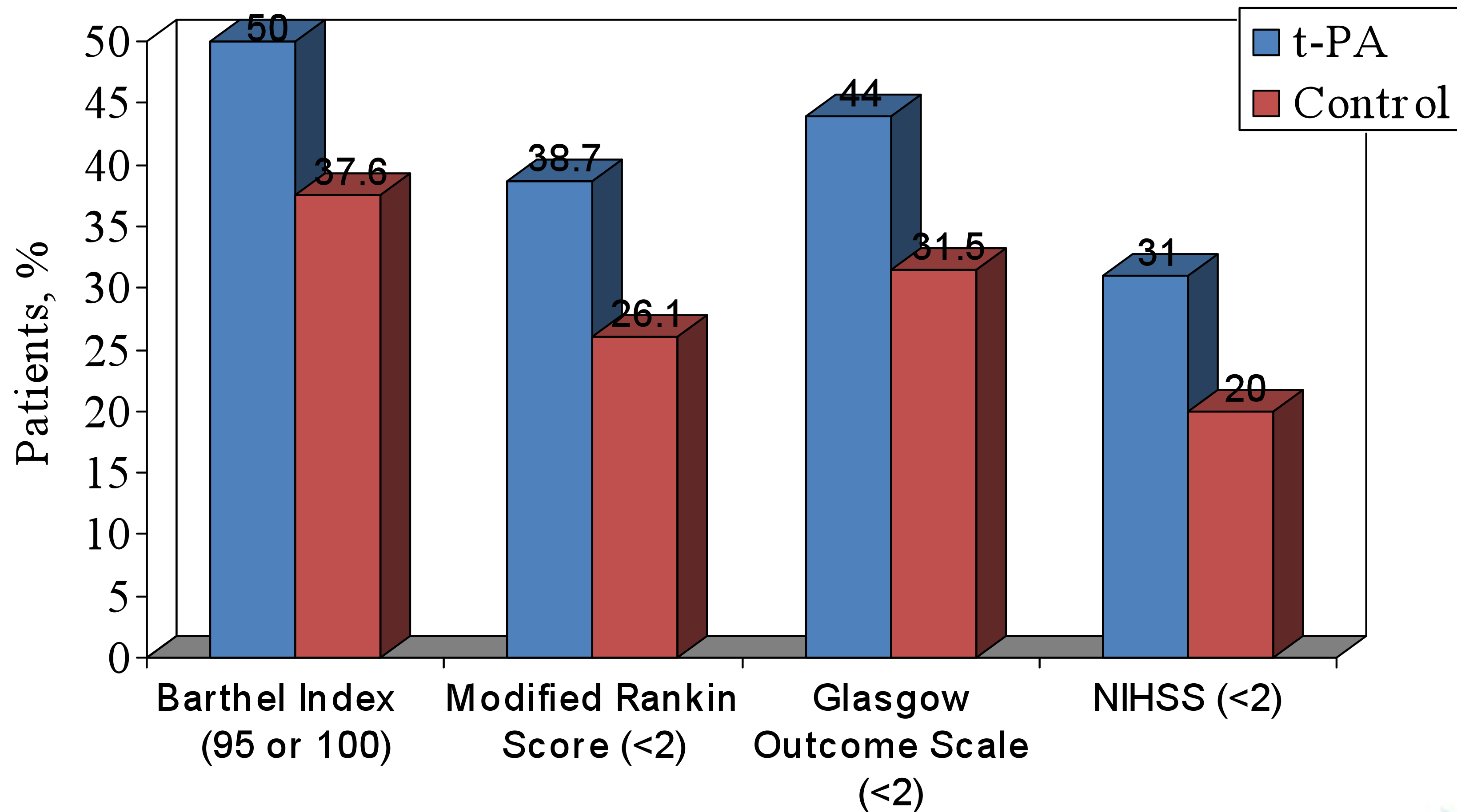
**Modified from original recommendations*



Stroke 2007;38:1655-1711

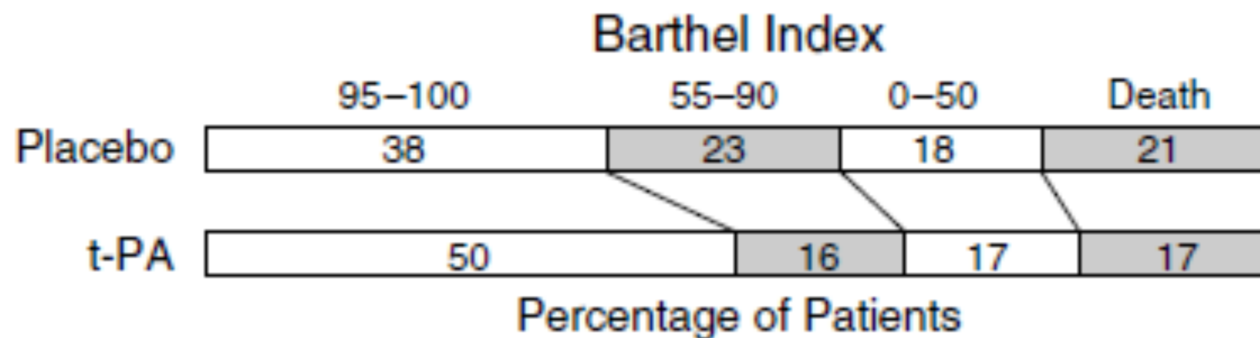
NINDS t-PA Stroke Trials

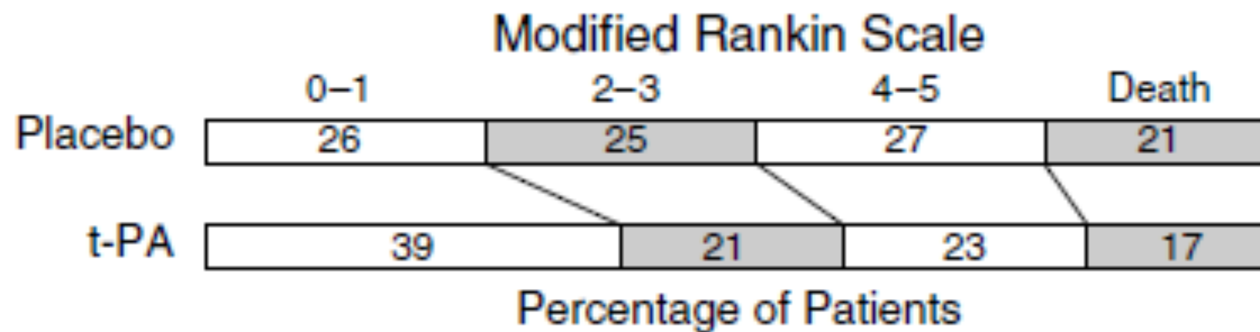
Percentage of patients with minimal or no disability at 3 months



Global comparison of all scales combined RFO 1.34, p = 0.02

Functional Outcomes

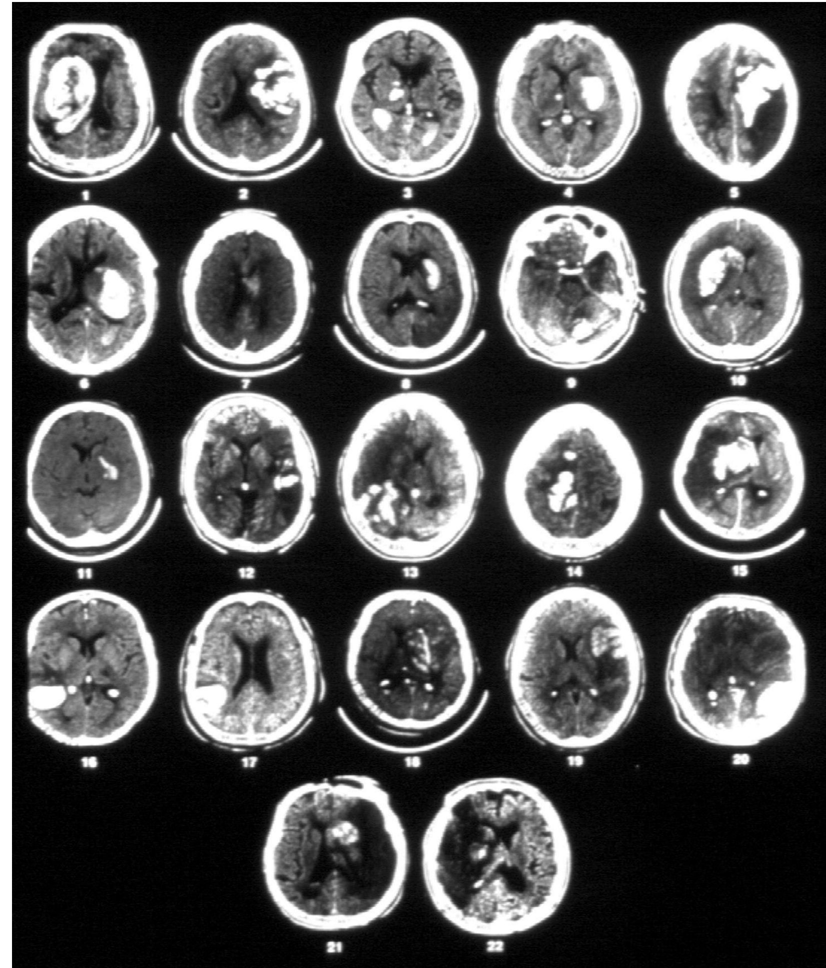




NINDS t-PA Stroke Trials

Computed tomography brain images of all patients in NINDS trials with symptomatic ICH

Symptomatic ICH in first 36 hours	
tPA	6.4%
Control	0.6%



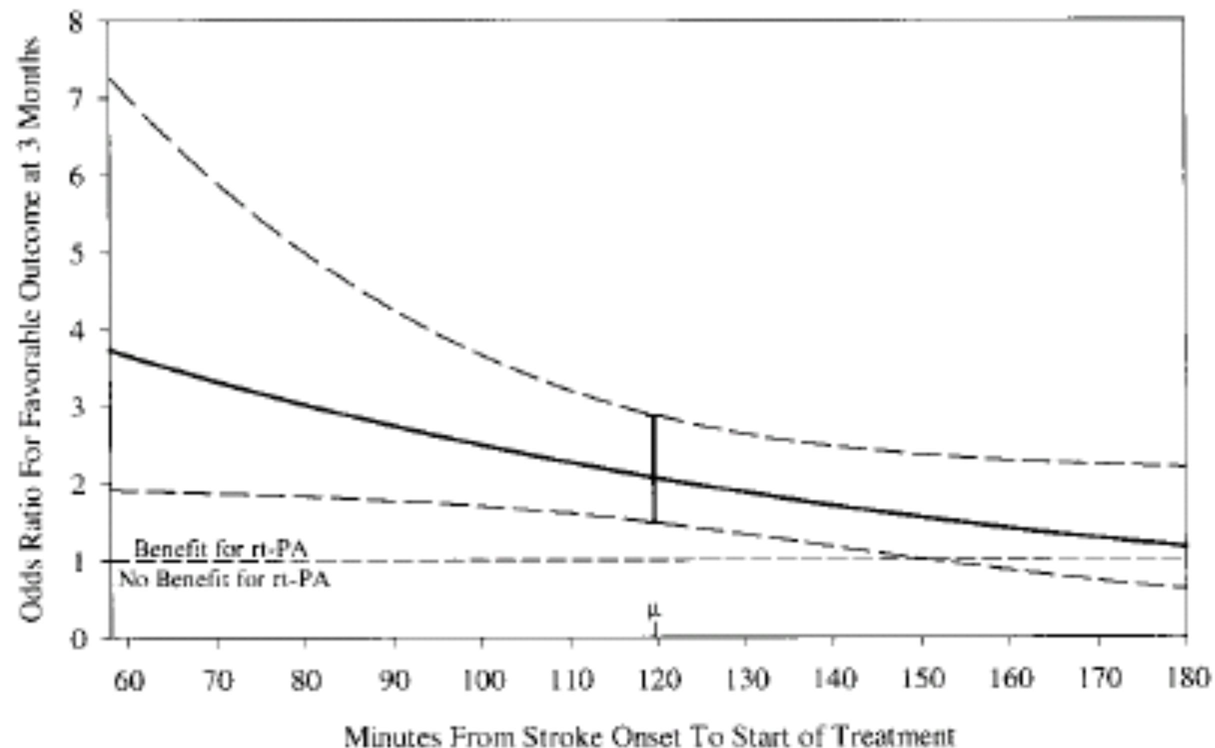
NINDS t-PA Stroke Trials

Summary

- No significant change in neurologic improvement in 24 hours by NIHSS
- Significant functional improvement in t-PA treated group at 90 days (Global odds ratio of favorable outcome 1.7 [95% CI,1.2-2.6])
- t-PA group was 30% more likely to have minimal or no disability at 90 days (by mRS $\leq$ 1)
- Symptomatic ICH significantly more frequent in t-PA treated group (6.4% vs 0.6%, $p < .001$)
- Mortality rates no different at 90 days

NEJM, 333:1581,1995

Early Stroke Treatment Associated with Better Outcome (NINDS trial only)



Marler et al Neurology 2000;55:1649

Time is Brain--Quantified

Estimated Pace of Neural Circuitry Loss in Typical Large Vessel, Supratentorial Acute Ischemic Stroke

	Neurons Lost	Synapses Lost	Myelinated Fibers Lost	Accelerated Aging
Per Stroke	1.2 billion	8.3 trillion	7140 km/4470 miles	36 y
Per Hour	120 million	830 billion	714 km/447 miles	3.6 y
Per Minute	1.9 million	14 billion	12 km/7.5 miles	3.1 wk
Per Second	32 000	230 million	200 meters/218 yards	8.7 h

Stroke 2006;37:263-266

National Use of IV tPA for Ischemic Stroke

- AHA Goal: 1997
  - 20% of all ischemic stroke patients
- Use of IV tPA increased from 2001-2004
- Estimated percentage of US patients with acute ischemic stroke treated in 2004 with IV tPA:

$\sim$ 2 %

Kleindorfer et al Stroke 39:2008

Reasons for Low Rates

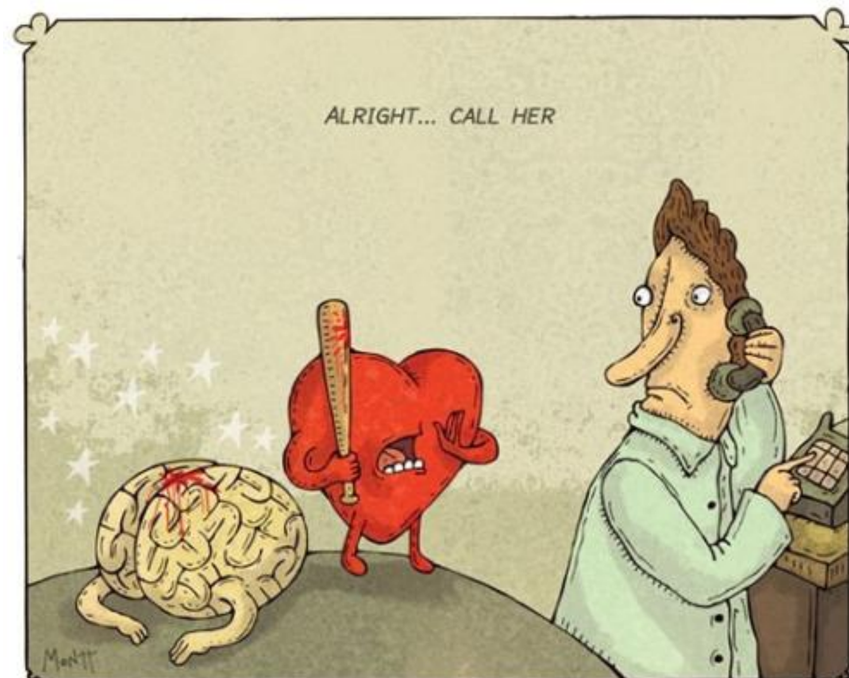
- Low levels of public awareness
- Failure to recognize acute stroke symptoms
- Delays in transfer
- Inadequate infrastructure
- Thrombolytic antipathy

Medical Reasons for Low Rates

- “Do strokes occur in the brain or the heart?”

--anonymous patient

Heart vs Brain



odd.gonzojenny.com

Medical Reasons for Low Rates

Myocardial Infarction	Cerebral Infarction
Usually painful	Usually painless
Limited symptom repertoire	Highly variable presentation
Diagnostic Tests	
Readily available	Limited availability
Quick	Can be delayed
Inexpensive	Expensive
Treat when positive	Treat when negative

Medical Reasons for Low Rates

- Narrow therapeutic window
  - 3 hours for first decade of use
- Chagrin factor
  - Hazards immediate, benefits delayed
- Reliance on time, not tissue
  - Treatment eligibility largely determined by
    - Time of symptom onset
    - *Time when last seen normal*
      - 25% of cases may be “wake-up strokes”

Strategies to Improve Rate of Treatment

- Improve thrombolytic efficacy
  - Bridging trials:
    - Combination of IV thrombolysis and endovascular treatment (IMS III, BASICS)
  - Ultrasound-enhanced thrombolysis
  - Alternative agents
    - Tenecteplase, desmoteplase—both more fibrin-specific, desmoteplase not neural toxic
    - Phase II and III trials ongoing

Strategies to Improve Rate of Treatment

- Penumbral imaging
  - EPITHET—post hoc analysis showing infarct growth attenuated by tPA treatment up to 6 hrs
  - DEFUSE—early reperfusion associated with improved outcome after tPA treatment to 6 hrs
  - EXTEND, DIAS 3 and DIAS 4 ongoing

- Expand time window (ECASS III, IST-3)

European Cooperative Acute Stroke Study (ECASS III)

- RCT comparing IV tpa vs placebo administered between 3 and 4.5 hours after onset of stroke symptoms

- 821 patients treated on average at 3 hours 59 minutes

- Primary outcome: Favorable (0-1 mRS) vs unfavorable (2-6 mRS)

- Global Outcome Score (mRS 0-1, Barthel 95-100, NIHSS 0-1, GOS=1)

NEJM September 2008

European Cooperative Acute Stroke Study (ECASS III)

- Inclusion Criteria
  - Age 18-80 years
  - Symptom onset 3 – 4.5 hours
  - Stable deficit
- Exclusion Criteria
  - NIHSS > 25
  - Combination of prior stroke and DM
  - Oral anticoagulant treatment

NEJM September 2008

European Cooperative Acute Stroke Study (ECASS III)

Modified Rankin Score 0-1
at 90 days

- tPA arm: 52.4%
- Placebo: 45.2%

- OR for favorable outcome 1.34 with IV tPA treatment 3 – 4.5 hrs (p= 0.04)
  - Functional recovery 34% higher with treatment at 90 days
  - Similar findings for Global Outcome (OR 1.28)

NEJM September 2008

European Cooperative Acute Stroke Study (ECASS III)

- Safety Data
  - Symptomatic ICH (2.4% vs 0.2%)
    - NINDS definition (7.9% vs 3.5%)
  - No difference in mortality between groups

NEJM September 2008

European Cooperative Acute Stroke Study (ECASS III)

- Conclusions:
  - Findings consistent with pooled analyses of other tPA trials
  - AHA: Level B evidence that IV tPA can be given safely within the 3-4.5 hour window
  - FDA: No change in labeling to date

Treatment options in extended time window should not delay earlier treatment if possible

NEJM September 2008

Odds Ratio for
Favorable Global Outcome

• 0-90 minutes	2.81
• 91-180 minutes	1.55
• 181-270 minutes	1.34

Pooled Analysis (8 trials): NINDS, ATLANTIS, ECASS, EPITHET

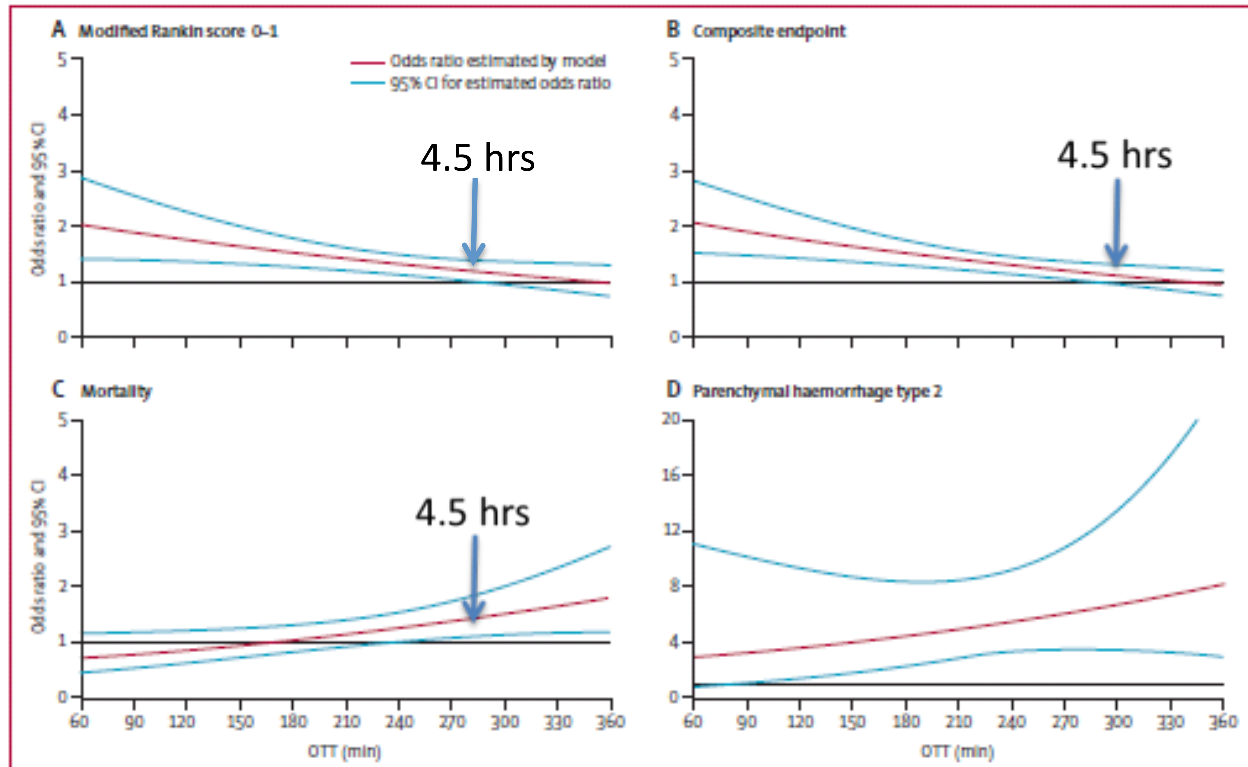
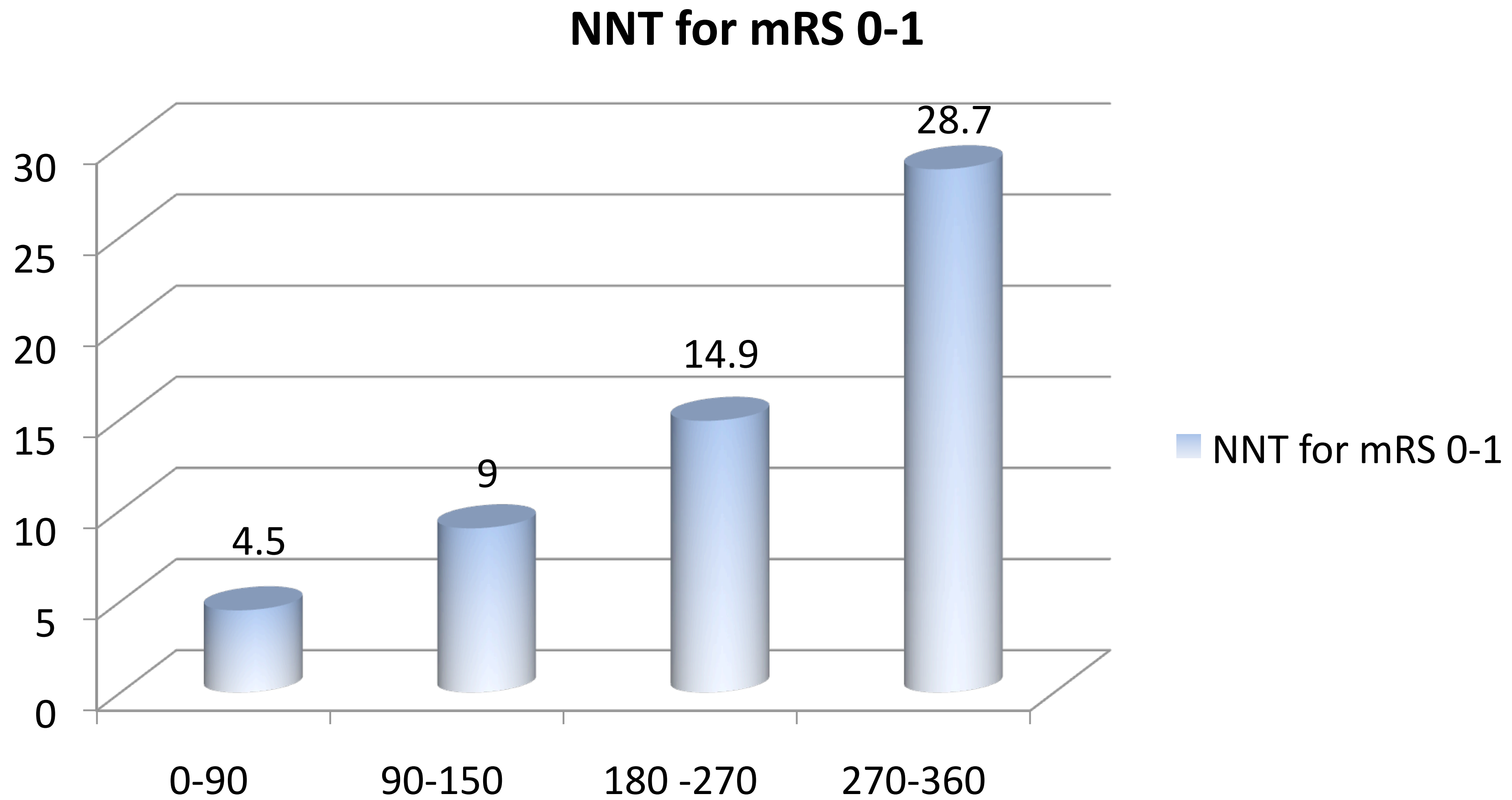


Figure 1: Relation of onset to treatment delay with treatment effect

Relation of stroke onset to start of treatment (OTT) with treatment effect after adjustment for prognostic variables assessed by (A) day 90 modified Rankin score 0–1 versus 2–6 (interaction p=0·0269, n=3530 [excluding EPITHET' data p=0·0116, n=3431]); (B) global test that incorporates modified Rankin score 0–1 versus 2–6, Barthel Index score 95–100 versus 90 or lower and NIHSS score 0–1 versus 2 or more (interaction p=0·0111, n=3535 [excluding EPITHET' data p=0·0049, n=3436]); (C) mortality (interaction p=0·0444, n=3530 [excluding EPITHET' data p=0·0582, n=3431]); and (D) parenchymal haemorrhage type 2 (interaction p=0·4140, n=3531 [excluding EPITHET' data p=0·4578, n=3431]). Thus, for parenchymal haemorrhage type 2, the fitted line is not statistically distinguishable from a horizontal line. For each graph, the adjusted odds ratio is shown with the 95% CIs. CIs from the models will differ from those shown in the tables because the model uses data from all patients treated within 0–360 min whereas the categorised analyses in the tables are based on subsets of patients: the modelled CIs are deemed to be more reliable.

Lancet 375 May 2010

The Earlier, the Better



Practical Steps for Acute Treatment

- Early identification/evaluation, including EMS pre-notification
- “Code Stroke”
- Immediate action
  - CT imaging
  - IV access
  - Lab
- tPA at hand in ED

Post-tPA Treatment

- Admit to ICU
- Supplemental oxygen as needed
- Neuro checks q 30 min x 6 hours, then q 1 hour until 24 hours
- Control serum glucose
- No antithrombotics x 24 hrs
- SCDs
- BP checks q 15 min x 2 hrs, the q 30 min x 6 hours, then q 1 hr x 16 hours
- Treat BP if > 180/105 mmHg
- Avoid unnecessary blood draws

Local Practices

- STAR member institutions:
  – Unity Hospital
  – Rochester General Hospital
  – Highland Hospital
  – Strong Memorial Hospital

- Unique entity on GWTG Data Registry

Discharges—STAR hospitals 2008-2011

2500
2000
1500
1000
500
0

2008 2009 2010 2011

Ischemic stroke
TIA
SAH
ICH
Total

IV tPA Initiated for ED Patients

8.00%
7.00%
6.00%
5.00%
4.00%
3.00%
2.00%
1.00%
0.00%

2008 2009 2010 2011

STAR
NYS
All Hospitals

Any Thrombolytic Therapy

10.00%
9.00%
8.00%
7.00%
6.00%
5.00%
4.00%
3.00%
2.00%
1.00%
0.00%

2008 2009 2010 2011

STAR
NYS
All Hospitals

- Acute ischemic stroke is a treatable condition, with proven therapies
- Rapid treatment improves outcomes
- Opportunities exist for improving *local* care

Stroke Treatment Alliance of Rochester

UNIVERSITY *of* ROCHESTER
MEDICAL CENTER

STRONG MEMORIAL HOSPITAL

HIGHLAND HOSPITAL

ROCHESTER
GENERAL HOSPITAL