Thrombolysis and Beyond: The New Therapeutic Horizons for Acute Ischemic Stroke

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Global Objectives

- Discuss the latest literature and controversy in the use of thrombolysis in stroke
- Discuss options beyond the 3 hour window
- Discuss future therapeutic modalities being studied for the treatment of ischemic stroke

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Clinical History

- 911 call taken by CFD at 2:25 pm
- "My husband is having a stroke and he can not move the left side of his body".
- ALS ambulance arrived at 2:34 pm
- 67-year-old patient to be sitting in a chair with a BP 140/85, pulse 96, respiratory rate 16 and the inability to move his left arm or leg
- His wife also noticed the left side of his face was "flat". He was able to speak.

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Clinical History

- He had a history of hypertension, was on Labetalol and Lasix, with no allergies
- The paramedics noted the time of onset for the symptoms to be 2:15 pm., which was agreed to by both the patient and his wife
- The patient was placed on a cart, an IV was established, oxygen was applied, and glucose was 98
- The patient arrived in the ED at 2:52 pm

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IV Thrombolysis

- The purpose of thrombolysis or clot retrieval in the setting of ischemic stroke is to dissolve or remove the clot
- To preserve the ischemic penumbra and minimize the size of tissue infarct.

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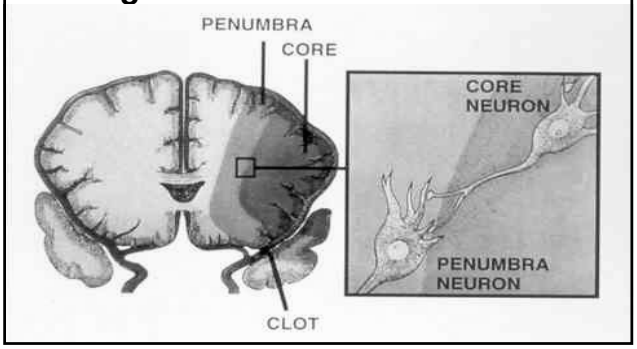
Progression of Ischemic Stroke



IV Thrombolysis

- By minimizing infarct size
- The NIHSS deficit measured acutely (and long-term in clinical trials)
- The MRS and BI disabilities measured long term can be minimized, improving patient outcomes

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NINDS Trial Results

Percentage with favorable outcome

	Placebo	tPA
No. of patients: 312	157	145
Modified Rankin Scale	40%	28%
Glasgow Outcome Scale	43%	32%
NIHSS	34%	20%
Symptomatic ICH (within 36 hr)	6.4%	0.6%
Death (by 90 days)	17%	21%

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IV Thrombolysis

- 14% absolute increase for the best clinical outcomes as measured by an NIHSS of 0-1.
- Benefit = Need to treat eight patients with tPA in order to have one additional patient with this best outcome.
- 6% absolute increase in the number of symptomatic ICH.
- Harm = Will have one symp ICH for every 16 patients treated with tPA.
- 2 patients will have a minimal or no deficit for everyone patient with a symp ICH

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IV Thrombolysis

- In general, tPA should be considered to be optimally useful by reproducing the NINDS protocol
- Studied tPA in patients with a median NIHSS score of 14, signifying a moderate stroke.

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Meta-analyses

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Tale of Meta-analyses

- Wardlaw et al.
- Net benefit despite hazards
- For 1000 treated up to 6hrs, 55 improve, 20 die
- Heterogeneity and wide CI make results unreliable
- Additional trial data required

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Tale of Meta-analyses

- Graham et al., 15 published reports
- ICH rate 5.2%, total death rate 13.4%
- All better than NINDS
- Lysis can be used safely across wide variety of practice settings

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Tale of Meta-analyses

- Hacke et al.
- 6 randomized trials
- Sooner thrombolytics given the greater the benefit
- Particularly when given within 90 min. of onset

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CONTROVERSY: Meta-analysis

- Hoffman and Cooper
- Pooled data can not replace new or confirmatory data
- Meta-analyses did not include streptokinase trials which were negative
- No reason to exclude streptokinase

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Re-analysis

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NINDS Re-analysis

- Does the protocol work?
- Do subgroup imbalances invalidate the entire trial?
- What about BP?

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Baseline NIHSS Imbalance

NIHSS Score		0-5	6-10	11-15	16-20	> 20
No. of patients	Placebo (n=312)	16	83	66	70	77
	t-Pa (n=310)	42	67	65	73	63

Chi-square (4 DF) = 14.8; p = 0.005

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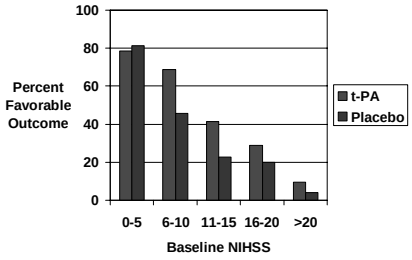
Favorable Outcome Related to Baseline NIHSS - *Modified Rankin Scale*



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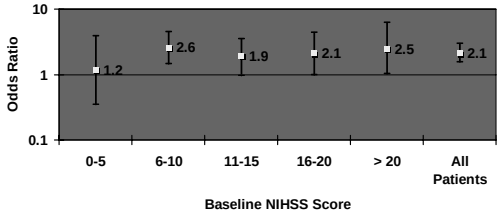
Baseline NIHSS - Specific Odds Ratios



Test for equal ORs: Chi-square (4 DF) = 1.70; p = 0.79
Insufficient evidence was found to a declare a difference in treatment effects (ORs) across the five strata

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OTT Analysis Report

- **Review Committee had concerns about analyzing OTT as a continuous variable**
- **Uncertainty about the exact time of stroke onset.**
- **OTT distribution was nonlinear with 25% of all the patients having OTT values of either 89 or 90 minutes.**

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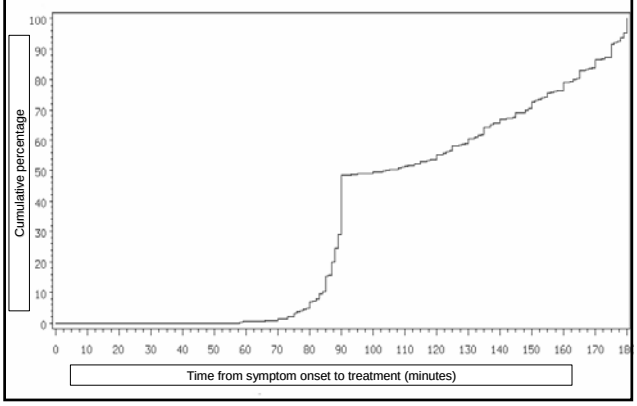

NINDS ICH Analysis

Risk Factors for ICH:
- **Baseline NIHSS > 20**
- **Age > 70 years**
- **Ischemic changes present on initial CT**
- **Glucose > 300 mg/dl (16.7 mmol/L)**

# of Risk Factors	# of patients treated with t-PA (n=310)	# Symptomatic ICHs (# of placebo patients with ICH)	Percentage (%)
0	114	2 (1)	1.8
1	144	7 (1)	4.9
> 1	52	11	21.2

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IV Thrombolysis

- The independent reanalysis of the NINDS tPA clinical trial confirms the results from the initial *NEJM* publication
- Support the use of tPA in stroke patients within three hours of symptom onset
- Number needed to treat calculation based on this reanalysis confirms that approximately 8-10 patients need to be treated with tPA in order to cause one extra patient to have the best clinical outcome.
- 2 patients will improve for every one that develops a symp ICH

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IV Thrombolysis: Conclusion

- tPA has never been demonstrated to be superior or inferior in patients with an acute NIHSS score of 0-5 (mild stroke) or greater than 20 (severe stroke)
- These stroke patients require a more careful assessment of the risks and benefits of tPA
- Since they are less like the patients most commonly treated in the NINDS clinical trial.

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Intra-Arterial Thrombolysis

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IA THROMBOLYSIS

- Two randomized trials – PROACT 1 & 2
- Tested prourokinase vs. heparin <6 hours
- MCA occlusions only
- Recanalization improved with IA
- Mortality identical
- Relative risk reduction for outcome – 60%

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IA Clinical Practice

- Numerous clinical series published
- Basilar artery thrombosis series suggest benefit
- Benefit with basilar may be late (12-24 hrs)
- MRI diffusion/perfusion may aid selection

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IA Thrombolysis

- Within three hours of symptom onset IV tPA is the thrombolytic therapy of choice
- Between three and six hours, there may be a role for intra-arterial tPA in institutions that provide this therapy
- Especially when the stroke is related to occlusion of the middle cerebral artery.

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IA Thrombolysis

- After six hours from stroke symptom onset
- Data suggests that posterior circulation strokes may benefit from attempts to provide intra-arterial thrombolytic therapy
- Data is limited in its scope.

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Future Therapies

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Future Therapies: Neuroprotectants

- First generation failure
- Adverse events
- Lack of efficacy

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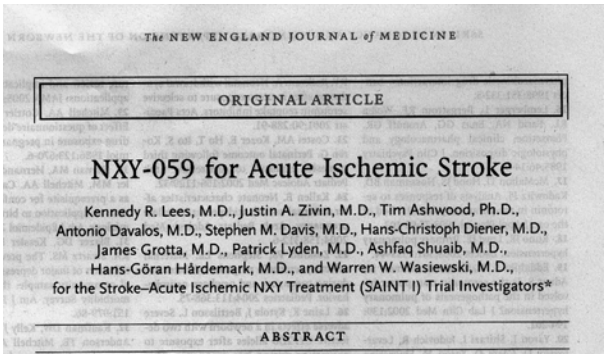

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

NXY-059 for Acute Ischemic Stroke

Kennedy R. Lees, M.D., Justin A. Zivin, M.D., Tim Ashwood, Ph.D., Antonio Davalos, M.D., Stephen M. Davis, M.D., Hans-Christoph Diener, M.D., James Grotta, M.D., Patrick Lyden, M.D., Ashfaq Shuaib, M.D., Hans-Göran Hårdemark, M.D., and Warren W. Wasiewski, M.D., for the Stroke–Acute Ischemic NXY Treatment (SAINT I) Trial Investigators*

ABSTRACT

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NXY – 059: Preclinical

- Traps carbon and oxygen radicals
- Positive trials in animals/primates
- Significant dose response
- Effective after 4 hours of ischemia

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SAINT I Trial

- Placebo controlled trial
- Acute stroke < 6 hours
- 72 hours infusion of NXY-059
- Primary outcome
  - Disability as measured by Modified Rankin
- BENEFIT at 90 days
  - 4.4% increase in rate of no disability
- No significant AE's

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Future Therapies: Neuroprotectants

- NMDA receptor
- New subtypes
- Antagonists in preclinical trials

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Future Therapies: Neuroprotectants

- Serotonin agonists
- Reduce glutamate-induced excitotoxicity
- Repinotan has reduced infarct volume in preclinical trials
- Up to 5 hours after injury
- Early clinical trials = safe
- Serotonin adverse effects = nausea/vomiting

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Future Therapies: Neuroprotectants

- Inflammatory response in microvasculature
- Leukocyte activation/adhesion
- Good preclinical data, no clinical data of efficacy

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Future Therapies: Hypothermia

- Useful adjunct to other therapies
- Known to be neuroprotective for years
- Positive results in 2 studies with global ischemia
- Timing, degree and duration need further study
- Inconvenient to use

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COOL AID

- 18 patients received hypothermia
- Clinical outcomes similar
- MRI outcomes similar
- Appeared to be well tolerated
- Further studies

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Neuroprotectants

- Neuroprotectants are designed to minimize neuronal cell death and limit infarct size through penumbra stabilization
- A recent *NEJM* publication demonstrated benefit in stroke patients with the use of a novel neuroprotectant
- If confirmed in an ongoing second complementary clinical trial, this would represent the first clinically effective neuroprotectant.

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Informed Consent: Documentation

- With tPA, there is a 30% greater chance of a good outcome at 3 months
- With tPA use, there is 10x greater risk of a symptomatic ICH (severe bleeding stroke)
- Mortality rates at 3 months are the same regardless of whether tPA is used
- 2 patients will have a minimal or no deficit for everyone patient with a symp ICH

Informed Consent: Documentation

- Patient was explained risks and benefits of tPA use and was able to understand and provide verbal consent (as able), and signature with L hand.
- Risk/benefit favored tPA given clear onset time, young patient with no significant morbidities or factors that would preclude tPA use, and approx NIHSS that suggests OK use.
- Rapid CT obtained, neurology aware of pt status, agreed with expedited tPA use, to follow.

Documentation

- Just as important
- "The patient is NOT a candidate for tPA because…"

Case Conclusion

Clinical Course

- The patient was met by a nurse, a doctor and an EM tech and taken to the resuscitation room.
- They confirmed the onset time of 2:15pm.
- BP 142/88, P 98, R 16, T 99.2 F. HEENT: EOMI, PERRL, Ears clear, neck supple. Heart, lungs and abdomen were normal.
- Neurological exam: CN mild left facial droop, strength 5/5 R arm and leg, 1/5 L arm and leg, no light touch or pin prick sensation in the L arm and leg. NIHSS=17-18.

Clinical Course

- The stroke team was called at 3:05pm
- Labs were drawn and sent.
- The patient went to CT at 3:20 pm and returned at 3: 41pm.
- The stroke team assessed the patient on return from CT and agreed with the diagnosis of CVA and NIHSS=18.
- Head CT reading was "negative for bleed, normal brain" at 4:03pm.

Clinical Course

- The patient was felt to be a good candidate for thrombolytics.
- The patient was advised of the risks and benefits.
- The patient, along with his wife declined thrombolytic therapy, stating "I want nature to take its course".
- The patient was given 325 mg. of aspirin and admitted to the hospital.
- His 24 hour NIHSS=14.
- On discharge, 5 days later, NIHSS=10.

Key Learning Points

- IV thrombolysis is best when used per the NINDS protocol and in patients similar to the NINDS trial
- IA thrombolysis may allow the window to extend to 6 hours in patients with MCA occlusions or posterior circ stroke
- Neuroprotectants may be proven beneficial in the treatment of patients with ischemic stroke in the near future
- Allow patients to make informed decisions

Questions?

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