

tPA in Acute Ischemic Stroke: The NINDS Reanalysis & Meta-analysis Data

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Lecture Outline

- Benefit/risk of tPA use in original NINDS trial data analysis & reanalysis
- Meta-analysis of phase IV safety data
- Pooled data analysis from randomized tPA trials
- Conclusions

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A Clinical Case

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Clinical History

- 46 year old Emergency Physician
- 20 years of ED experience
- Aware of the medical literature
- Knows of the NINDS clinical trial
- Has utilized tPA in stroke
- Has read statement from EM societies
- Understands medical & legal risks
- Wants to understand tPA use in 2005

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ED Presentation

- Pt presents with acute ischemic stroke
- What needs to happen for successful tPA use?
- How closely does the NINDS protocol need to be followed?
- What does the most recent data suggest regarding its use?

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Why Do This Exercise?

- Ischemic stroke is a common disease
- tPA is the industry standard
- Benefit/risk profile suggests need for deliberate, efficacious tPA use
- Legal risk most often associated with lack of tPA use, not complicated use

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Key Clinical Questions

- What are the benefits and risks of tPA for acute ischemic stroke from:
 - The original NINDS trial?
 - The reanalysis of the NINDS trial data?

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Key Clinical Questions

- What does the reanalysis of the NINDS data tell us regarding:
 - Stroke severity imbalances by Rx group
 - Blood pressure management
 - Symptomatic ICH risk factors
 - Subgroup analysis for a more likely favorable outcome as a result of tPA therapy?

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Key Clinical Questions

- How does the meta-analysis of the safety data in post approval use of tPA for acute stroke reports compare with the NINDS trial?
- What can be learned from the report of the pooled analysis of the randomized, placebo controlled tPA trials for acute stroke?

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NINDS Trial Study Design

- A two part, double blind study with 624 acute stroke patients randomized to treatment with either t-PA or placebo stratified on center and time from symptom onset to treatment (0-90 and 91-180 minutes)
- "Favorable outcome" defined as normal or near normal at 90 days using four outcome measures: Barthel Index, Modified Rankin Scale, Glasgow Outcome Scale, National Institute of Health Stroke Scale (NIHSS)

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NINDS Trial Results

Percentage with favorable outcome

No. of patients:	t-PA	Placebo
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 %


NEJM 1995; 333:1581-7

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NINDS NEJM Results


December 1995: NEJM article reported a positive treatment effect for the use of IV t-PA in the treatment of acute ischemic stroke patients within 3 hours of symptom onset.

- From Part 2, the adjusted t-PA to placebo global OR for favorable outcome was **1.7 (95%CI,1.2-2.6)**

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NINDS Reanalysis Rationale


May 2002: NINDS appointed a committee to address *“whether there is concern that eligible stroke patients may not benefit from t-PA given according to the protocol used in the trials, and whether the subgroup imbalance invalidates the entire trial as claimed by some of the critics.”*

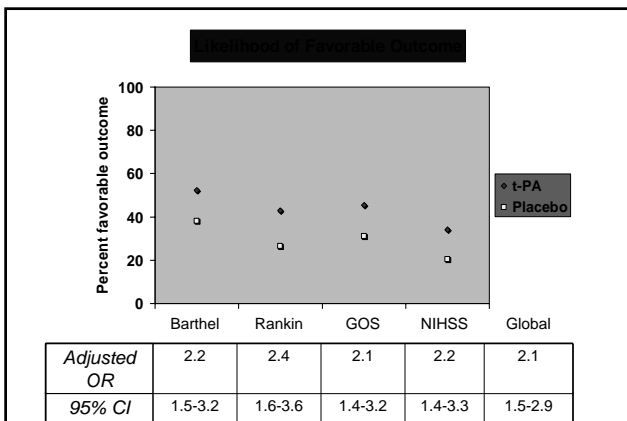
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Reanalysis Findings

The committee concluded, despite an increased incidence of symptomatic intracerebral hemorrhage in t-PA treated patients, there was a statistically significant benefit of t-PA treatment measured by an adjusted t-PA to placebo global odds ratio of 2.1 (95% CI: 1.5-2.9) for a favorable clinical outcome at three months

The analysis was adjusted for center, time to treatment, study part, age, baseline NIHSS, diabetes, pre-existing disability, and the interaction between age and baseline NIHSS.


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Reanalysis Methods

The following issues were assessed:

- Baseline NIHSS imbalance
- Blood pressure measurement and management
- Time from symptom onset to treatment
- Risk factors for intracerebral hemorrhage
- Predictors of favorable outcome

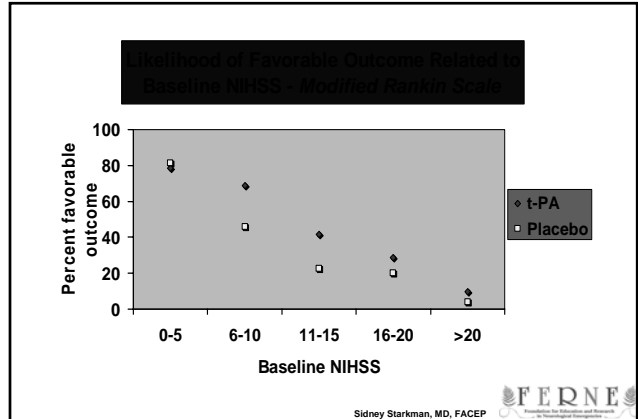
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Baseline NIHSS Imbalance

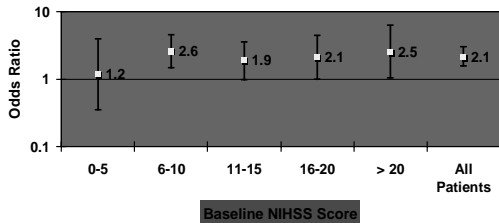
NIHSS Score		0-5	6-10	11-15	16-20	> 20
No. of patients	Placebo (n=312)	16	83	66	70	77
	t-PA (n=310)	42	67	65	73	63

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

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

BP Rx: Committee Report

We concluded that a number of problems preclude the use of the study's blood pressure information in either statistical analyses or clinical management.

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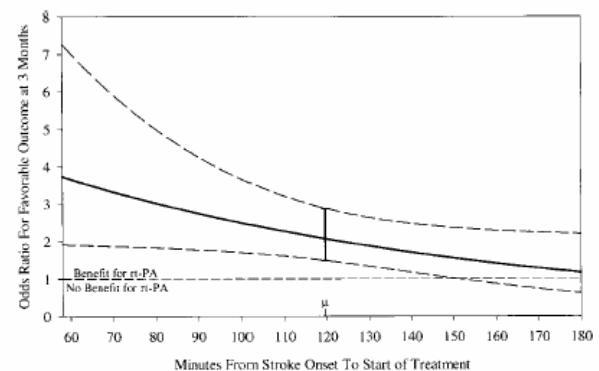
Early stroke treatment associated with better outcome

The NINDS rt-PA Stroke Study

J.R. Marler, MD; E.C. Tilley, PhD; M. Lu, PhD; T.G. Brott, MD; P.C. Lyden, MD; J.C. Grotta, MD; J.P. Broderick, MD; S.R. Levine, MD; M.P. Frankel, MD; S.H. Horowitz, MD; E.C. Haley, Jr., MD; C.A. Lewandowski; and T.P. Kwiatkowski, MD, for the NINDS rt-PA Stroke Study Group*

Article abstract—Background: The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study showed a similar percentage of intracranial hemorrhage and good outcome in patients 3 months after stroke treatment given 0 to 90 minutes and 91 to 180 minutes after stroke onset. At 24 hours after stroke onset more patients treated 0 to 90 minutes compared to 91 to 180 minutes after stroke onset had improved by four or more points on the NIH Stroke Scale (NIHSS). The authors performed further analyses to characterize the relationship of onset-to-treatment time (OTT) to outcome at 3 months, early improvement at 24 hours, and intracranial hemorrhage within 36 hours. **Methods:** Univariate analyses identified potentially confounding variables associated with OTT that could mask an OTT-treatment interaction. Tests for OTT-treatment interactions adjusting for potential masking confounders were performed. An OTT-treatment interaction was considered significant if $p \leq 0.10$, implying that treatment effectiveness was related to OTT. **Results:** For 24-hour improvement, there were no masking confounders identified and there was an OTT-treatment interaction ($p = 0.06$). For 3-month favorable outcome, the NIHSS met criteria for a masking confounder. After adjusting for NIHSS as a covariate, an OTT-treatment interaction was detected ($p = 0.09$); the adjusted OR (95% CI) for a favorable 3-month outcome associated with recombinant tissue-type plasminogen activator (rt-PA) was 2.11 (1.23 to 3.35) in the 0 to 90 minute stratum and 1.69 (1.09 to 2.62) in the 91 to 180 minute stratum. In the group treated with rt-PA, after adjusting for baseline NIHSS, an effect of OTT on the occurrence of intracranial hemorrhage was not detected. **Conclusions:** If the NINDS rt-PA Stroke Trial treatment protocol is followed, this analysis suggests that patients treated 0 to 90 minutes from stroke onset with rt-PA have an increased odds of improvement at 24 hours and favorable 3-month outcome compared to patients treated later than 90 minutes. No effect of OTT on intracranial hemorrhage was detected within the group treated with rt-PA, possibly due to low power.

NEUROLOGY 2000;55:1649-1655

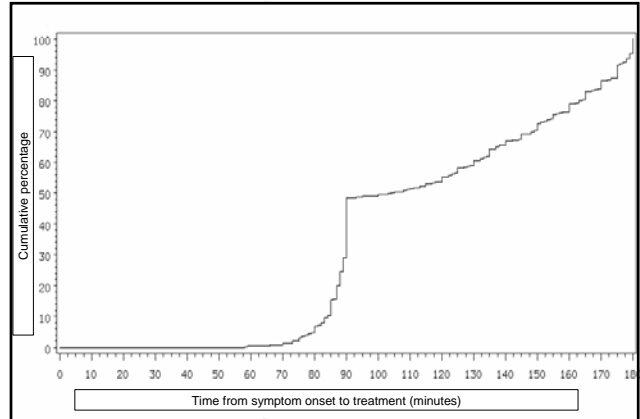


Stroke Onset to Treatment (OTT)

This analysis was conducted with OTT as a continuous variable:

- After adjusting for baseline NIHSS, a significant OTT*t-PA interaction was found indicating that time from stroke onset to treatment modified the t-PA treatment effect such that earlier treatment with t-PA was associated with a greater chance of having a favorable outcome.

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OTT Analysis Report

The t-PA Review Committee had concerns about analyzing OTT as a continuous variable:

- Uncertainty about the exact time of stroke onset leads to imprecision in the individual OTT estimates.
- OTT distribution was nonlinear with almost a quarter of all the patients having OTT values of either 89 or 90 minutes.

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OTT Committee Report

“Based on our analyses, and the observation that the distribution of the OTT values was substantially nonlinear, the Review Committee concluded there was no evidence that the effectiveness of t-PA treatment decreased as the time from stroke onset increased.”

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OTT Analysis: A Retrospective

The differences in the findings of the OTT analyses performed by the NINDS investigators and the Review Committee are a good example of the hazards involved in interpreting exploratory analyses from a study that was not designed to determine if there was a differential effect of t-PA treatment associated with the time from stroke onset.

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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

NINDS Conclusions (I)

Despite an increased incidence of symptomatic intracerebral hemorrhage in t-PA treated patients and subgroup imbalances in baseline stroke severity subgroup imbalances, the adjusted analysis demonstrated a statistically significant, and clinically important, benefit for treating acute ischemic stroke patients with IV t-PA within three hours of symptom onset.

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NINDS Conclusions (II)

- Age, baseline NIHSS, and the interaction between the two, were related to a decreased likelihood of having a favorable outcome.
- A risk factor score using combinations of age, baseline NIHSS, admission glucose, and CT scan findings predicted the ICH occurrence and a decreased likelihood of a favorable outcome.

This information must be utilized very cautiously in the management of individual patients.

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Phase IV Meta-analysis

- Performed analysis of all open-label reports of t-PA for acute ischemic stroke published through April 2003 (15 studies)
- Followed approved indications and guidelines in a non-selected patient population
- Postapproval data support the safety of intravenous thrombolytic therapy with tPA for acute ischemic stroke, when established treatment guidelines are followed

Graham G, MD, PhD. Stroke. 2003;34:2847-2850

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Phase IV vs. NINDS Data

Re-analysis and Meta-analysis

	Re-analysis	Meta-analysis
• Patients, n	312	2639
• Median NIHSS	14	14
• Very Favorable Outcome %	39.0	37.1
• Symptomatic ICH,%	6.4	5.2
• Death %	12.8	13.0

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Combined tPA Trials Data: NINDS, ATLANTIS and ECASS I, II

- The greatest benefit is when rt-PA is given within 90 min of Stroke onset.
- A potential benefit beyond 3 hr, but this potential might come with some risks.
- Trials assessed the relation of the interval from stroke onset to start of treatment on favorable 3-month outcome and on the occurrence of clinically relevant parenchymal hemorrhage

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Combined tPA Studies Data

- 2776 pts randomized for tPA or placebo
- Median Age: 68 years
- Median Baseline NIHSS: 11
- Median OTT (Stroke onset to Treatment): 243 min

Lancet 2004; 363: 768-74

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Pooled NINDS/ECASS/ATLANTIS Data

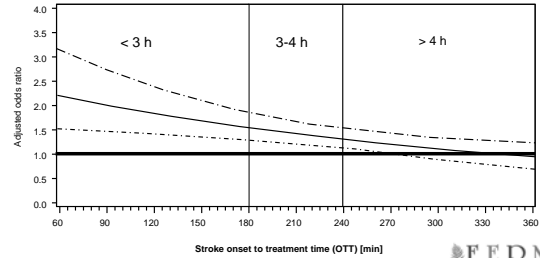
Time to Treatment and Benefit of tPA in Achieving Favorable Outcome (Rankin 0-1)

Time	Odds Ratio	95% CI
0 - 90	2.8	1.8-9.5
91 - 180	1.5	1.1-2.1
181 - 270	1.4	1.1-1.9
271 - 360	1.2	0.9-1.5

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Time to Treatment and tPA Benefit

mRS 0-1 at day 90
Adjusted odds ratio with 95 % confidence interval by stroke onset to treatment time (OTT)



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Frequency of Parenchymal Haematoma between 0 and 360 min after Treatment

(Combined Trials Analysis)

OTT(min)	Placebo		rt-PA	
	n*	Patients with parenchymal haematoma (90%,95% CI)	n*	Patients with parenchymal haematoma(90%,95% CI)
0-90	150	0 (0,.....)	161	15 (3.1, 1.6-5.6)
91-180	315	3 (1.0, 0.4-2.0)	302	17 (5.6, 3.9-7.9)
181-270	411	7 (1.7, 1.0-2.0)	390	23 (5.9, 4.3-8.0)
271-360	508	5 (1.0, 0.5-1.8)	538	37 (6.9, 5.3-8.7)

Lancet 2004; 363: 768-74

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Key Learning Points

- The NINDS tPA Acute Stroke Trial:
 - NEJM, 1995
 - 624 patients
 - Half were randomly treated with tPA
 - Rx within 3 hours of stroke onset
- The tPA group demonstrated an absolute benefit (favorable outcome) of 12% (OR 1.7)
- A symptomatic ICH rate of 6.4% (10x placebo)

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Key Learning Points

- A reanalysis of NINDS was conducted
- Done to address baseline imbalances
- Attempted to address study validity
- Stroke, 2004: The NINDS Re-analysis
- “A clinically important and statistically significant benefit of tPA therapy was identified (adjusted OR of a favorable outcome of 2.1)”

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Key Learning Points

- Stroke, 2004: The NINDS Re-analysis
- “Benefit...despite baseline stroke severity imbalances and an increased incidence of symptomatic intracerebral hemorrhage.”
- “The NINDS trial was not powered to detect any subgroup differences.”

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Key Learning Points

- Meta-analysis of safety data from 15 published reports of post-approval tPA use in 2639 acute stroke patients
- *Stroke*, 2003
- The symptomatic ICH rate was 5.2%
- The total death rate was 13.4%
- Both slightly < the NINDS trial data.

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Key Learning Points

- A pooled analysis of tPA therapy
- Six randomized acute stroke trials
- *Lancet*, 2004
- The sooner tPA therapy was given, the greater the benefit,
- Especially true if tPA started within 90 minutes of stroke symptom onset.

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Case Outcome

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ED Management Approach

- The emergency physician learned more.
- “tPA can be used *per the NINDS protocol*.”
- A collaborative approach was developed.
- A protocol was established off-line.
- tPA is now used when feasible.
- Patient outcomes are expected to match those found in the NINDS trial.

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The Way Forward

- Reach a consensus that the NINDS trial results are valid.
- Agree that when tPA is administered using the NINDS protocol, it is effective.
- Use ED tPA per the NINDS protocol
- Attempt to use tPA within 90 minutes of stroke symptom onset

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The Way Forward

- Use this agreed upon approach as a springboard to:
 - Design further studies to address the unanswered questions
 - Bring together professional bodies representing Neurology, EM, and IM to develop guidelines as to how tPA can be more broadly and safely administered

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Questions??

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