

## T-PA in Treatment of Acute Stroke: What We Know From NINDS 2004 vs 2000

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## OUTLINE

- Benefit and Risk of tPA use in Original NINDS Trial Data Analysis
- Reanalysis of the NINDS Trial
- Benefit and Risk of tPA use in Reanalysis and Metaanalysis
- Combined Trials analysis
- Conclusion

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## NINDS t-PA Acute Ischemic Stroke Treatment 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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## Benefit and Risk of tPA use in Original Analysis of the NINDS

• No.of patients:	Percentage with favorable outcome	
	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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## t-PA Treatment for Acute Ischemic Stroke

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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## t-PA Treatment for Acute Ischemic Stroke

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.*”

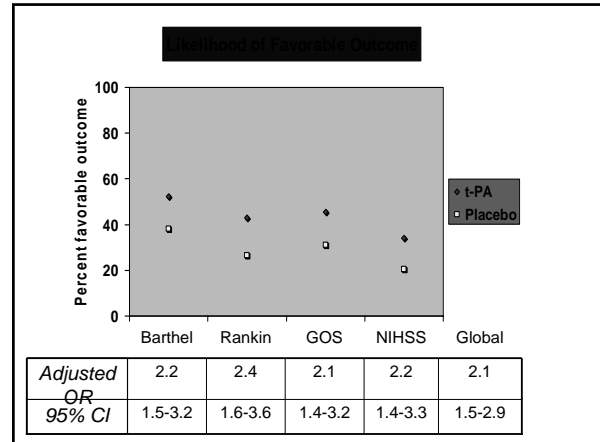
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### Committee Findings

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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### Committee 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

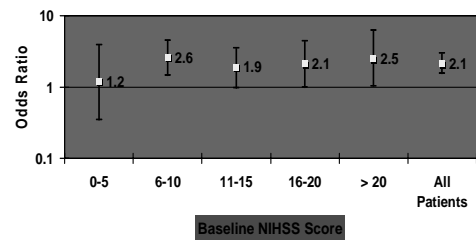
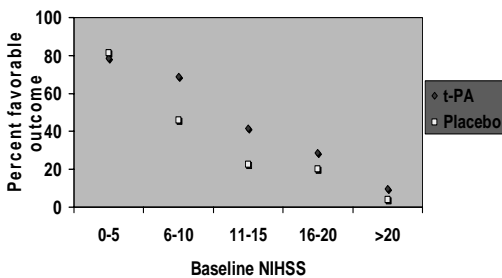
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### Baseline NIHSS Imbalance

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

### Blood Pressure Measurement and Management

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

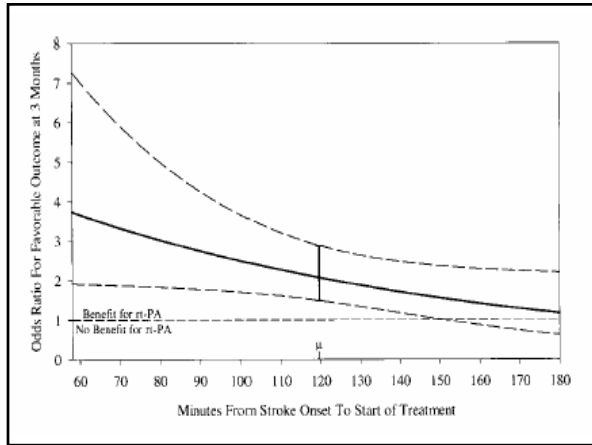
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### Early stroke treatment associated with better outcome

#### The NINDS rt-PA Stroke Study

J.R. Marler, MD, B.C. Tilley, PhD; M. Lu, PhD; T.G. Brett, MD; P.C. Lyden, MD; J.C. Grotta, MD; J.P. Broderick, MD; S.R. Levine, MD; M.P. Frankel, MD; S.H. Heesowit, 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 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 ( $p = 0.08$ ). 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 (1.53 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** 2009;53:1648–1658

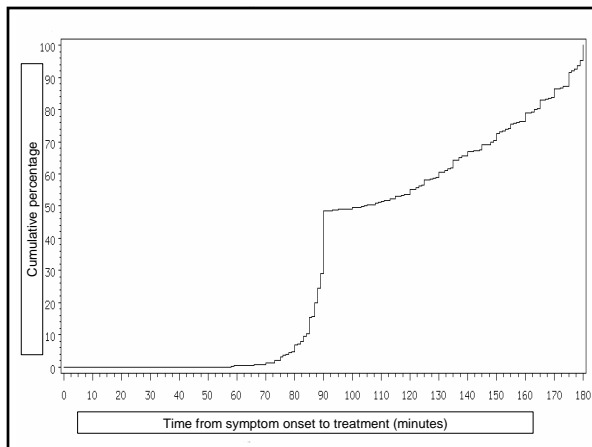


### Time from Stroke Onset to treatment (OTT)

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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### Review Committee OTT Analysis


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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### Review Committee OTT Analysis

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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### Review Committee OTT Analysis

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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### 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)	# of 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

### 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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### 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 occurrence of ICH and a decreased likelihood of having a favorable outcome


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

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### T-PA for Acute Ischemic Stroke: Meta-analysis


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


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


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### TPA use in Patients with Ischemic Stroke in Re-analysis and Meta-analysis

	Re-analysis	Meta-analysis
• Patients, n	312	2639
• Median Baseline 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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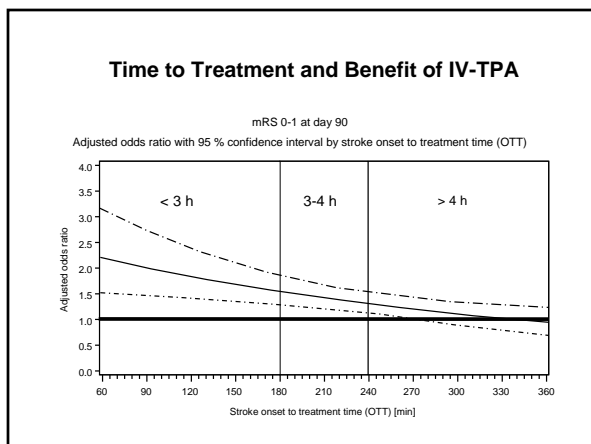
- ### Combined Trials Analysis: NINDS, ATLANTIS and ECASS I, II
- The Greatest Benefit is when rt-PA is given within 90 min of Stroke onset.
  - A Potential Benefit beyond 3 hr, but this Potential might come with some Risks.
  - Trials assessed the Relation of the Interval from Stroke onset to start of Treatment on Favorable 3-month outcome and on the occurrence of clinically relevant Parenchymal Hemorrhage
- Sydney Starkman, MD, FACEP 

- ### Criteria for The Combined Study
- 2776 Patients Randomly selected 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*
- Sydney Starkman, MD, FACEP 

### Pooled NINDS/ECASS/ATLANTIS Analysis 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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### 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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## The Way Forward

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- Reach a consensus that the NINDS trial results are valid when t-PA is administered using the NINDS protocol.
- Use this result as a springboard to:
  - Design further studies to address the unanswered questions
  - Bring together professional bodies representing Neurology, ED, and IM to develop guidelines as to how t-PA should be administered

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## Questions