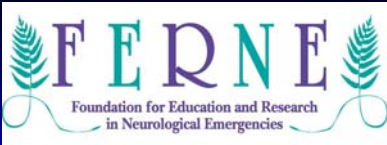



**FERNE / MEMC IV Brain Illness and Injury Course:  
tPA in Ischemic Stroke  
Joseph Lex, MD, FAAEM**



**tPA in Stroke:  
What's All the  
Fuss?**



**FERNE Brain Illness  
and Injury Course**

The Fourth  
Mediterranean Emergency Medicine Congress (MEMC IV)  
Sorrento, Italy  
15-19 September 2007




**4<sup>th</sup> Mediterranean  
Emergency Medicine  
Congress  
Sorrento, Italy  
17 September 2007**

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**Disclosures**

**None**

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## Objectives

- Review the results of the NINDS clinical trials
- Discuss Phase Four clinical data on clinical use of tPA for stroke
- Describe an appropriate informed consent for use of tPA in stroke

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## In the Beginning...

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## NINDS Trial Results

	tPA	Placebo
Number of patients	157	145
•Modified Rankin Scale	40% (63)	28% (41)
•Glasgow Outcome Scale	43% (68)	32% (46)
•NIH Stroke Score	34% (53)	20% (29)
Symptomatic ICH in 36 hours	6.4% (10)	0.6% (1)
Death by 90 days	17% (27)	21% (30)

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## IV Thrombolysis: Up Side

- Rankin: 12% absolute benefit
- Glasgow: 11% absolute benefit
- NIHSS: 14% absolute benefit
- Conclusion: treat 7 – 8 patients with t-PA to have one additional patient with better outcome

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## NINDS Trial Results


	tPA	Placebo
Number of patients	157	145
•Modified Rankin Scale	40% (63)	28% (41)
•Glasgow Outcome Scale	43% (68)	32% (46)
•NIH Stroke Score	34% (53)	20% (29)
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### IV Thrombolysis: Down Side

- 6% absolute increase in number of symptomatic intracranial hemorrhages
- Conclusion: treat 16 patients with tPA to have one additional symptomatic intracranial hemorrhage

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### IV Thrombolysis: Summary

So if you treat 1000 patients who meet t-PA criteria...  
...120 will have an absolute benefit, but...  
...60 will have symptomatic intracranial haemorrhage

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### IV Thrombolysis: Summary


Two patients will have minimal or no deficit for every one patient with symptomatic intracranial hemorrhage

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### NINDS: Design Issues


Patients were excluded if...

- ...blood pressure > 185/110 mm Hg
- ...required “aggressive treatment” of blood pressure
- ...anti-coagulated within 48 hours
- ...anti-platelet treatment within 24 hours

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### And then...

- ...Jeff Mann and
- ...Jerome Hoffman and
- ...Jeanne Lenzer and
- ...several others looked more closely at the data.

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Baseline NIHSS	% tPA (n=153)	% placebo (n=167)
0 – 5	19.0% (29)	4.2% (7)
6 – 10	24.2% (37)	27.5% (46)
11 – 15	17.0% (26)	21.0% (35)
16 – 20	21.6% (33)	19.8% (33)
>20	18.3% (28)	27.5% (46)


Baseline NIHSS	% tPA (n=153)	% placebo (n=167)
0 – 5	19.0% (29)	4.2% (7)
6 – 10	24.2% (37)	27.5% (46)
11 – 15	17.0% (26)	21.0% (35)
16 – 20	21.6% (33)	19.8% (33)
>20	18.3% (28)	27.5% (46)

### NINDS Baseline Imbalance

Corrected	0 – 90 minutes	91 – 180 minutes	0 – 180 minutes
tPA	32%	39%	36%
Placebo	33%	32%	32%

Simple random assignment accounted for 4% of the absolute reduction

Wardlaw JM, Lindley RI, Lewis S. Thrombolysis for acute ischemic stroke: still a treatment for the few by the few. West J Med. 2002 May;176(3):198-9. Joseph Lex, MD




### IV Thrombolysis: Summary

So if you treat 1000 patients who meet t-PA criteria...

- ...80 will have an absolute benefit, but...
- ...60 will have symptomatic intracranial haemorrhage


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### NINDS in Clinical Practice

- Must consider tPA, but patient selection very difficult
- Must maximize risk/benefit ratio
- Must avoid haemorrhage, if possible
- Need adequate severity, but not too severe
- <2% of stroke patients meet criteria

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# Phase IV

## Post-Marketing Studies


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### Phase IV tPA Use

- Many later publications
- Mix of community and academic centers
- 37 to 389 patients (312 in NINDS trials) at one to 57 hospitals
- Treatment given to 1.8% - 22% of eligible patients

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## Phase IV t-PA trials

Author	Patients receiving tPA(%)	Mean time to Rx	Favorable outcome	% ICH	% Symptomatic ICH	% Protocol deviation
NINDS	312		31-54%	10.9%	6.4%	
Chiu	30(2.9%)	2'37"	63%	10%	6.6%	
Tanne	189	>2'		9%	5.8%	30%
Wang	57(6.3%)	2'28"	44-54%	9%	5%	9%
Buchan	68(4.4%)		95%	31%	9%	16%
Albers	389	2'44"	35-43%	11.5%	3.3%	33%
Katzan	70(1.8%)			22%	15.7%	50%
Chapman	46(1.6%)	2'45"	30-48%	9%	2.2%	17%
Grotta	269(16%)	2'17"	33%		4.5%	13%
Bravata	63			17%	6%	67%
Total	928(5.8%)	2'25"	33-95%	9.6%	5.2%	13-67%

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## Phase IV vs NINDS

Age: 63 – 71 years old

NINDS = 68 years

Median NIHSS: 10 – 15

NINDS = 14

Median time to treatment: 126 – 165 minutes

NINDS = 89 minutes

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## Phase IV vs NINDS

Good outcome: 30 – 95%

NINDS = 31 – 54%

Mortality: 5.3 – 25% (Mean: 14%)

NINDS = 17%

Symptomatic ICH: 3.3 – 15.7%  
(Mean: 5.2%)

NINDS = 6.4%

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## Phase IV: Deviations

In 1.3 – 67% of patients

Treatment beyond 180 min: 0 – 22%

Anti-coagulant use: 2.2 – 37%

BP not controlled: 3 – 7%

Baseline coagulopathy: 1.5 – 10%

CT showed large stroke: 2 – 15%

CT edema or mass effect: 2 – 10%  
(NINDS 3-5%)

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## Phase IV tPA: Overall

- Time to treatment near 180 minute window
- Many protocol violations
- Most common protocol violation: giving tPA >180 minutes after symptom onset
- NINDS population and results can be duplicated

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## Cochrane Database

- Randomised trials of any thrombolytic agent compared with control in patients with definite ischaemic stroke
- 18 trials including 5727 patients
  - Not all trials looked at each outcome
  - Sixteen trials were double-blind

Wardlaw JM, Zoppo G, Yamaguchi T, Berge E.  
Thrombolysis for acute ischaemic stroke.  
Cochrane Database Syst Rev. 2003;(3):CD000213.

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## Cochrane Database

Lytic administered up to 6 hours after ischaemic stroke significantly reduced proportion of patients who were dead or dependent (modified Rankin 3 to 6) at 3 to 6 month follow-up (OR 0.84, 95% CI 0.75 to 0.95)

Wardlaw JM, Zoppo G, Yamaguchi T, Berge E. Thrombolysis for acute ischaemic stroke. Cochrane Database Syst Rev. 2003;(3):CD000213.

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## Cochrane Database

In lytic groups there was significant increase in...

...odds of death within first 10 days (OR 1.81, 95% CI 1.46 to 2.24), the main cause of which was fatal intracranial haemorrhage (OR 4.34, 95% CI 3.14 to 5.99)

Wardlaw JM, Zoppo G, Yamaguchi T, Berge E. Thrombolysis for acute ischaemic stroke. Cochrane Database Syst Rev. 2003;(3):CD000213.

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## Cochrane Database

In lytic groups there was significant increase in...

...symptomatic intracranial haemorrhage (OR 3.37, 95% CI 2.68 to 4.22)

...death at end of 3 to 6 month follow-up (OR 1.33, 95% CI 1.15 to 1.53)

Wardlaw JM, Zoppo G, Yamaguchi T, Berge E. Thrombolysis for acute ischaemic stroke. Cochrane Database Syst Rev. 2003;(3):CD000213.

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## Cochrane Database

- If treated within 3 hours of stroke, lytics appeared more effective in reducing death or dependency (OR 0.66, 95% CI 0.53 to 0.83) with no statistically significant adverse effect on death (OR 1.13, 95% CI 0.86 to 1.48)

Wardlaw JM, Zoppo G, Yamaguchi T, Berge E. Thrombolysis for acute ischaemic stroke. Cochrane Database Syst Rev. 2003;(3):CD000213.

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## Cochrane Database

### Conclusion

- Net benefit despite real hazards
- Heterogeneity and wide CI make results unreliable
- Additional trial data required

Wardlaw JM, Zoppo G, Yamaguchi T, Berge E. Thrombolysis for acute ischaemic stroke. Cochrane Database Syst Rev. 2003;(3):CD000213.

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# Informed Consent

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### What Do We Tell the Patient?

- “If we do nothing, there is a 40% chance you’ll have good recovery.”
- “If we give you tPA, there is a 52% chance you will have good recovery after 3 months.”
- “That means there is a one in eight chance that the drug will help.”

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### Explain to Patient / Family

- “There is no evidence that tPA will make any difference before 3 months, so we won’t know right away if it’s working.”
- “If we use tPA, there is a one in sixteen chance that you will develop bleeding in your brain.”

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### Explain to Patient / Family

- “Despite this increase in brain bleeding, your risk of being dead at 3 months is about the same with or without tPA.”

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## Conclusions

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### Clinical Considerations

- Patient selection difficult
- Histories unreliable: must have exact time of onset
- Hypodense area on CT: may be old stroke, older than 180 minutes
- Old habits: tendency not to intervene
- First do no harm

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### Overall Conclusions

- Data supports use of IV t-PA when NINDS protocol strictly followed
- Outcomes similar to NINDS can be achieved
- Sooner may be better
- Narrow therapeutic window

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## **Overall Conclusions**

- In practice, relatively few patients receive tPA treatment
- Document decision-making well on all patients, t-PA or not

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## **Questions?**

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