Stroke Talk:

TPA 2012: It's Not for Everyone

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Disclosures

- No Financial Disclosures

Disclosures Continued

- The opinions conveyed in this talk are not necessarily a representation of my views
- The color scheme of this talk was also not my preference
- Consider me Wayne Clark's Avatar for the day

Outline

- Introduction
- IV tPA beyond 3 hours
  - Is statistical significance always clinically important?
- IV tPA use in the elderly
- IV tPA in mild strokes

TPA Spectrum of Opinion

TPA Zealots — Many ER MDs

Wayne

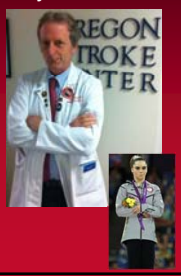
Very safe
TX late, mild, mimics, elderly and wake-ups
Treat all

Very Dangerous
NINDS not enough
Need another trial
Treat none

TPA Spectrum of Opinion

TPA Zealots — Many ER MDs

Me Wayne



Stroke Talk:

IV rt-PA beyond three hours?

ASA science advisory committee recommends TPA between 3-4.5 hours

But

The FDA did not approve it beyond 3 hours

No randomized trial with US patients has shown a TPA benefit > 3 hours

Here are some points to consider in deciding whether to use it past three hours

The Lost Study of ATLANTIS

ATLANTIS STUDY: IV 3-5 hrs

Wayne Clark, Atlantis study group

JAMA Dec 1999

- 3-5 hour window
- NIHSS ≥ 4
- Exclusion > 1/3 MCA on CT
- Drug company sponsored and analyzed (+ bias!)
- 550 patients; 140 US sites; OHSU 15% patients

ATLANTIS Part B Results

90 Day %	Placebo	rt-PA	
BL NIHSS	12	12	NS
Rankin 0,1	41	41	NS
NIHSS 0,1	34	34	NS
Barthel ≥ 95	53	53	NS
Death day 90	7.0%	10.8%	NS
Symp ICH	0.7%	7.2%	0.001

ATLANTIS STUDY: Additional

- Every endpoint negative; very well matched at baseline.
- Started as 3-6 hours; shorten to 5 hours after 15% SICH in 5-6 hour group.
- 82 patients (15%) of entire trial enrolled here in Oregon- therefore these results represent "our" type of patients that we would be be treating in our local ERs.

ECASS III Statistical Baseline Luck

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ECASS III STUDY: IV tPA 3-4.5hrs

Werner Hacke, ECASS III study group

NEJM Sept 2008

- 3-4.5 hour window
- Near identical I/E to NINDS and ATLANTIS
- Exclusion > 1/3 MCA on CT
- Drug company sponsored and analyzed
- 821 patients; 130 sites in Europe

ECASS III Results

90 Day %	Placebo	rt-PA	
BL NIH	10	9	p = 0.03
Rankin 0,1	45	52 (7% Abs improve)	p = 0.04
NIHSS 0,1	43	50	p = 0.04
Barthel ≥ 95	58	63	NS
Death day 90	8%	8%	NS
Symp ICH	4%	8%	p < 0.01

ECASS III STUDY: Additional

Werner Hacke, ECASS III study group

NEJM Sept 2008

- Baseline milder strokes in TPA group may have led to a type II error (false positive) in the trial.
- No US patients in trial- limits generalizability to our local population
- "Placebo" appears to be a very effective treatment in this study (ie these were mild stroke patients)

IV tPA> 3 hours Meta-analysis

Lansberg (Stroke) 1600 patients E123 A

MR 0/1 OR 1.07-1.59 p 0.01

In this and other recent meta-analysis the majority of patients are from ECASS III; the baseline imbalance is not corrected; the false positive ECASS III effect is driving the "positive results" seen.

Statistical Significance may not be Clinically Important

Criteria to consider

- For a dangerous or expensive surgery or medical treatment there should be at least a 10% absolute improvement/reduction.
- This infers that the number needed to treat for a good outcome needs to be 10 or less.
- So do our stroke trials results meet this?

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NINDS tPA Study Results

	tPA (%)	Placebo (%)	
Favorable outcome at 3 mos			
Barthel	51	38	
Rankin	45	25	✓
Glasgow	47	30	
NIHSS	34	21	
Symptomatic hemorrhage	6.4	0.6	
Mortality	17	21	

PROACT II Study Results

IA Pro-Urokinase vs Placebo within 6 hours of onset of MCA occlusion

	ProUK	Placebo	p	
MR 0,1,2	40%	25%	< 0.05	✓
SICH	10.2%	1.8%	<0.01	
Death	24%	27%		

Symptomatic Carotids: CEA

NASCET STUDY: TIA/CVA 120 days
Angio confirmed stenosis; % ipsilateral CVA

	ASA	CEA	NNT	p	
70-99%	24%	7%	8	0.0005	✓
50-70%	22%	16%	15	0.045	

< 50% CEA not better than ASA

Major complication rate for CEA 6.7%
> 50% TX indicated Urgently

ECASS III Results

90 Day %	Placebo	rt-PA	
Baseline NIHSS	10	9	p = 0.03
Rankin 0,1	45 (7% Abs improve)	52	p = 0.04 ☹
NIHSS 0,1	43	50	p = 0.04
Barthel ≥ 95	58	63	NS
Death day 90	8%	8%	NS
Symptomatic ICH	4%	8%	p < 0.01

ECASS III Results: NNT

Number of patients needed to treat for favorable outcome over placebo:

- NINDS TPA 0-90 min 4 ✓
- NINDS TPA 90-180 min 8 ✓
- ECASS 3 TPA 3-4.5hr (if it was real) 14 ☹

For every 13 patients treated 3-4.5 hr, 1 will have a symptomatic ICH

IST-3 Results: 0-6hr window N = 3035

6 Mo Good Out.	Placebo	rt-PA	
Baseline NIHSS	11.6	11.6	p = NS
OHS 0,1,2	35% (2% Abs improve)	37%	p = 0.18 ☹☹
sICH	1%	7%	p < 0.01

IST-3 Group, Lancet June 2012

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Other TPA Considerations

TPA use in the elderly

- Only 42 patients in randomized NINDS trial Age > 80
- VISTA Archive:1200 patients ≥ 80 Outcome @ 3 Mo
- Good Recovery (MR 0-2) tPA 23% Placebo 20% (0.02) ☹
- (ie treat 33 patients to improve outcome in 1) ☹
- Cost: Helicopter $20K tPA $7,000*; Hosp $10-15K*+; MDs $9,000 so up to ~$50,000 extra per case

Just because you could treat doesn't mean you should treat

*Boudreau, Guzauskas, et al. Ann Emerg Med, May 2012

TPA use in Mild Strokes

- Control groups in Neuroprotective trials in the 1990s found that patients with < 8 points on the NIHSS had a up to 77% chance of an excellent recovery at three months.[1,2] (Barthel Index>95)
- Another study saw that 45% patients with NIHSS <8 were functionally normal (NIHSS 0-1) in 48hrs[3]

So is the cost and risk of TPA worth it if they have a 77% chance of an excellent recovery anyway?

1. Clark WM. et al. Stroke. Dec 1999
2. Clark WM. Raps EC. Tong DC. Kelly RE. Stroke. June 2000
3. DeGraba T, Hallenbeck J, et al Stroke. June 1999

Conclusion

- I am not saying that we should never use IV tPA as a treatment for ischemic stroke
- IV tPA is indicated for moderate to severe strokes presenting under three hours who meet inclusion/exclusion criteria
- For other patients, are you really treating the patient or just treating them because you want to do something (i.e. treating yourself)?

Thank You