

# 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

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



Wayne

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  $\geq 4$
- ❑ 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 $\geq 95$	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 treating in our local ERs.

## ECASS III Statistical Baseline Luck

# Stroke Talk:

## 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?

# Stroke Talk:

## NINDS tPA Study Results

	tPA (%)	Placebo (%)
<b>Favorable outcome at 3 mos</b>		
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	p
Baseline NIHSS	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
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	p
Baseline NIHSS	11.6	11.6	p = NS
OHS 0,1,2	35%	37% (2% Abs improve)	p = 0.18 ☹️☹️
sICH	1%	7%	p < 0.01

IST-3 Group, Lancet June 2012

# Stroke Talk:

## 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.<sup>1,2</sup> (Barthel Index>95)
- Another study saw that **45%** patients with NIHSS <8 were functionally normal (NIHSS 0-1) in 48hrs<sup>3</sup>

**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

