




  
**FERNE/EMA Session:**  
**Treating Ischemic Stroke  
Patients Using a  
3 to 4.5 Hour tPA Window**


Edward P. Sloan, MD, MPH 

  
**2009 EMA Advanced Emergency  
& Acute Care Medicine  
Conference**


*Atlantic City, NJ  
September 22, 2009*

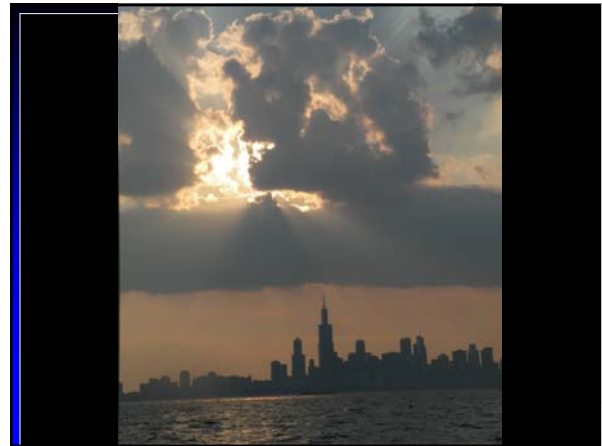
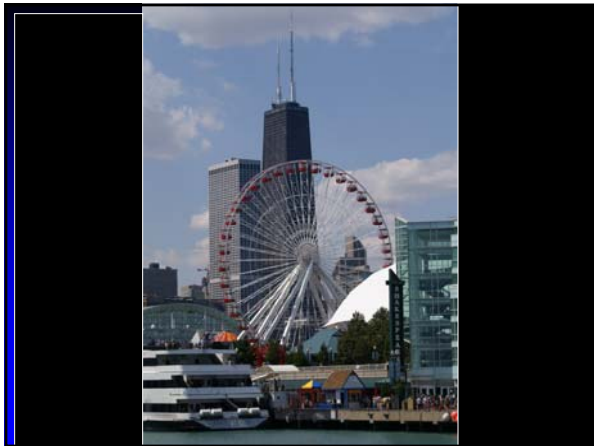
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## Disclosures

- FERNE Chairman and President
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- *Credit to E. Bradshaw Bunney, MD*

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## Global Objectives

- Improve stroke patient care
- Optimize safe tPA use
- Allow EM practitioners to follow best practices
- Reduce stress
- Use resources well

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## Specific Objectives

- Examine rationale for extended tPA treatment window
- Discuss ECASS 3 design and outcome data
- Compare to other tPA studies (NINDS)
- Understand how this data changes our clinical practice
- Determine for whom the new window should cause a change in practice

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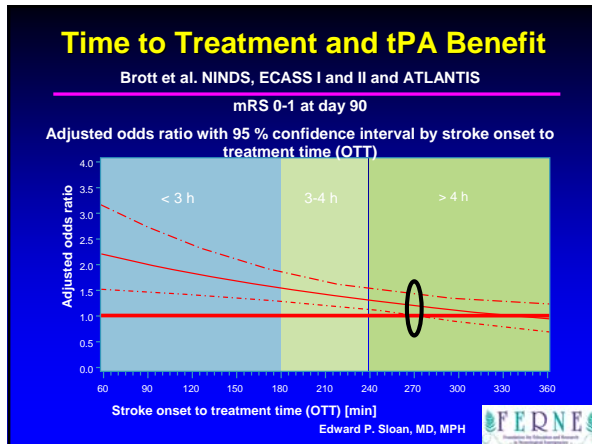


## Background

- When does tPA stop providing benefit?
- What is the rationale for the up to 4.5 hour window?
- Where are we at with this new window in September 2009?
- Why?

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### ECASS 3 Study

- Prospective, randomized, placebo controlled, study
- Is tPA efficacious in the treatment of ischemic stroke in the 3 – 4.5 hour window?
- Primary outcome = mRS 0 - 1 at 90 days
- Study mandated by the European Medicines Agency (EMA), pharmaceutical approval agency

Hacke, NEJM 2008;359:1317-29

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### ECASS 3 Criteria

- Inclusion
  - 18 – 80 years old
  - Symptoms > 30 min.
- Exclusion
  - NIHSS > 25
  - Prior stroke *and* Diabetes
  - Oral anticoagulation use
  - Seizure at onset of symptoms
  - BP > 185/110 not controlled (no IV drips)

Hacke, NEJM 2008;359:1317-29

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### ECASS 3 Data

- N = 821
- 43 tPA and 48 placebo excluded
  - Did not treat, age, CT criteria
- Median time to treat = 3:59

Hacke, NEJM 2008;359:1317-29

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### ECASS 3 Data

- Differences between tPA and placebo groups
  - NIHSS 10.7 v. 11.6 p=0.003
  - History of stroke 7.7 v. 14.1 p=0.03
- tPA treated group had fewer pts with baseline stroke history

Hacke, NEJM 2008;359:1317-29

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### ECASS 3 Data

- Primary outcome mRS 0-1
- tPA 219/418 (52.4%)
- Placebo 182/403 (45.2%)
- p = 0.04
  - OR 1.34 (CI 1.02 – 1.76)
  - Absolute improvement 7.2%

Hacke, NEJM 2008;359:1317-29

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## ECASS 3 Data

- Secondary outcomes
  - mRS
  - Barthel Index
  - NIHSS
  - Glasgow Outcome Scale
- Global odds ratio 1.28

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## Intra-cerebral Hemorrhage

- Intra-cerebral hemorrhage complicates tPA use
- Rationale for not using tPA
- What occurred vs. what was caused by the therapy and the treating physician

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## Types of ICH

- HI 1 = small petechiae along margin of infarct
- HI 2 = more confluent petechiae without mass effect
- PH 1 = parenchymal ICH
- PH 2 = clot exceeding 30% of infarct area with mass effect

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## Symptomatic ICH Definitions

- ECASS 3: Any hemorrhage with neurological deterioration, increase of 4 or more NIHSS, and predominant cause of deterioration.
- ECASS 2: Same as ECASS 3 without causal requirement
- NINDS: Any hemorrhage not seen on prior CT or suspicion of hemorrhage and neuro deterioration

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## ECASS 3 ICH

- Intra-cerebral hemorrhage
  - tPA 27% v. placebo 17%
- Symptomatic ICH
  - ECASS 3 criteria tPA 2.4% v. placebo 0.2%
  - Predominant cause of neuro deterioration
  - NINDS criteria tPA 7.9% v. placebo 3.5%
- ICH 2x more common with tPA use
- Sx ICH 12x more common (NINDS 10x)

Hacke, NEJM 2008;359:1317-29

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## ECASS 3 Conclusions

- tPA significantly improved clinical outcomes in patients with acute ischemic stroke presenting between 3 and 4.5 hours.
- tPA is associated with increased symptomatic ICH when compared to placebo.
- Improved outcome despite increased ICH risk and occurrence.

Hacke, NEJM 2008;359:1317-29

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### ECASS 3 Criticisms

- Fewer diabetics vs. NINDS
  - tPA 14.8% vs. 22%, placebo 16.6% vs. 20%
- Lower mean NIHSS
  - tPA 10.7 vs. 14, placebo 11.6 vs. 14
- No patients with a history of prior stroke and DM included in study

Leyden, NEJM 2008;395:1393-95

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### Meta-analysis: tPA Window

- ECASS 1, ECASS 2, ECASS 3, ATLANTIS
- Patients in 3 - 4.5 hour window
- Mean age 65
- Mean NIHSS 2 - 3 points less in ECASS 3
- Mean stroke onset to tPA: 4 hours
- DM similar: ECASS 16%, ATLANTIS 21%

Lansberg, Stroke 2009;40:2438-41

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### Meta-analysis: tPA Window

- mRS 0 – 1, OR 1.31
- Global outcome
  - mRS
  - NIHSS
  - Barthel Index
  - OR 1.31
- Mortality the same, OR 1.04

Lansberg, Stroke 2009;40:2438-41

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### SITS-ISTR 3-4.5 Hour Window

- European data base
- Observational study
- Not a randomized, controlled trial
- Compared 664 patients treated 3 to 4.5 hours with 11,865 treated within 3 hours

Wahlgren, Lancet 2008;372:1303-09

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### SITS-ISTR 3-4.5 Hour Window

- Median tPA time: 55 minutes later
- 195 min. (3' 15") vs. 140 min.
- 60% before 200 minutes (3'20")
- Younger: 65 v. 68 years age
- NIHSS lower: 11 v. 12

Wahlgren, Lancet 2008;372:1303-09

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### SITS-ISTR 3-4.5 Hour Window

- 3 to 4.5 hour tPA treated patients
- Independence: 58% v. 56%
- sICH: 2.2% v. 1.6%
- Mortality: 12.7% v. 12.2%

Wahlgren, Lancet 2008;372:1303-09

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## Number Needed to Treat

- So how many times do we have to use tPA in order to impart benefit (or harm)?
- What is the ratio of benefit to harm?
- Recall that with tPA use in the NINDS clinical trials, NNT for benefit = 8, NNT for harm (Sx ICH) = 16
- Ratio = 2 to 1, benefit to harm

Saver, Stroke 2009;40:2433-37

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## NNT Analysis from ECASS 3

- For Benefit
  - To improve by 1 or more mRS
    - 0 - 3 hours: 32.3/100 treated (1/3)
    - 3 - 4.5 hours: 16.4/100 treated (1/6)
- For Harm
  - To worsen by 1 or more mRS
    - 0 - 3 hours: 3.3/100 treated (1/30)
    - 3 - 4.5 hours: 2.7/100 treated (1/33)

Saver, Stroke 2009;40:2433-37

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## ECASS 3 NNT Data

- NNT to benefit by >1 mRS: 6
- NNT to harm by >1 mRS: 37
- Ratio = 6 to 1, benefit to harm
- Analysis of mRS, not Sx ICH
- NNT to achieve mRS of 0 - 1 (best outcome): 14

Saver, Stroke 2009;40:2433-37

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## Who to Rx in Up to 4.5 Hr Window?

- Relatively young, 65 ± 10 years old
- Less severe strokes
- NIHSS: 11 ± 6,
- tPA group median was 9 in ECASS 3
- Diabetes??
- No one with diabetes *and* prior stroke
- Shortly after 3 hours is likely OK

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## Conclusions

- Meta-analysis and observational studies support the use of tPA beyond 3 hours
- NNT data suggests potential for benefit outweighs risk in select patients
- Must be aware of optimal population for this Rx, the protocol, and other options
- Extension of the treatment window to 4.5 hours that is being endorsed by many is based on relatively sound data in adequate samples, and has been reproduced

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## Recommendations: *These studies*

- Know the ECASS 3 protocol so that you can reproduce it

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**Recommendations: *These studies***

- Know the ECASS 3 protocol so that you can reproduce it
- Know exactly what type of patients were treated with tPA in the ECASS 3 study so that you can treat similar patients in your clinical practice

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**Recommendations: *These studies***

- Know the ECASS 3 protocol so that you can reproduce it
- Know exactly what type of patients were treated with tPA in the ECASS 3 study so that you can treat similar patients in your clinical practice
- Have a journal club to explore these studies in more detail

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**Recommendations: *What to do?***

- Know your own opinion

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**Recommendations: *What to do?***

- Know your own opinion
- Know what the ASA and others endorse regarding tPA use window

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**Recommendations: *What to do?***

- Know your own opinion
- Know what the ASA and others endorse regarding tPA use window
- Discuss with your neurologists and stroke consultants off-line

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**Recommendations: *What to do?***

- Know your own opinion
- Know what the ASA and other endorse regarding tPA use window
- Discuss with your neurologists and stroke consultants off-line
- Know the alternatives to tPA during the extended window time (3-4.5 hr)

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**Recommendations: How to proceed?**

- Develop a group policy that takes into account individual hospital capabilities

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**Recommendations: How to proceed?**

- Develop a group policy that takes into account individual hospital capabilities
- Revise consent as needed

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**Recommendations: How to proceed?**

- Develop a group policy that takes into account individual hospital capabilities
- Revise consent as needed
- Know the exact data that will be in the actual script (or include this information in the consent)

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**Recommendations: Documentation**

- Document well the data discussed, with whom, and how the decision was made regarding tPA use

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**Recommendations: Documentation**

- Document well the data discussed, with whom, and how the decision was made regarding tPA use
- Relate the exact Risk / Benefit assessment, especially when tPA is not being used

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**Recommendations: Clinical Practice**

- Realize that we are all going to be somewhat uneasy as we now sail in uncharted waters

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**Recommendations: *Clinical Practice***

- Realize that we are all going to be somewhat uneasy as we now sail in uncharted waters
- Understand that the data is likely as good as was the NINDS clinical trials data, and that outcomes have been generally OK

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**Recommendations: *Clinical Practice***

- Realize that we are all going to be somewhat uneasy as we now sail in uncharted waters
- Understand that the data is likely as good as was the NINDS clinical trials data, and that outcomes have been generally OK
- Do the right thing for the patient

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**Questions?**

[www.FERNE.org](http://www.FERNE.org)

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