







FERNE/EMRA Session:


Treating Ischemic Stroke Patients Using a 3 to 4.5 Hour tPA Window


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Disclosures

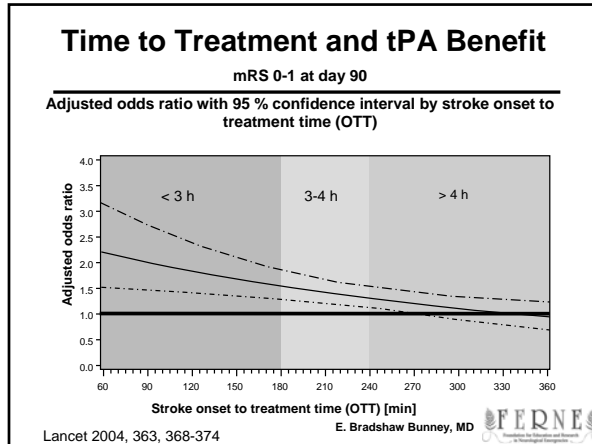
- FERNE Board Member
- FERNE grants by industry
- Participation on industry-sponsored advisory boards and as lecturer in programs supported by industry

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Objectives

- **What does the ECASS 3 study tell us?**
- **How does the ECASS 3 data compare to other studies?**
- **What other data is available regarding treatment in the 3 - 4.5 hour window?**

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ECASS 3

- 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 easily controlled, no IV drips

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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

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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

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ECASS 3 Data


- Primary out come 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%

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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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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, predominant cause of deterioration.**
- **ECASS 2: Same as ECASS 3 without causal requirement**
- **NINDS: Suspicion of hemorrhage or neuro deterioration, and finding hemorrhage not previously there on a subsequent CT.**


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NINDS sICH Definition

	tPA	Placebo
NINDS	6.4%	0.6%
ECASS 3	7.9%	3.5%


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ECASS3 sICH Definition

	tPA	Placebo
NINDS	N/A	N/A
ECASS 3	2.4%	0.2%


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ECASS 3 Conclusions

- **tPA significantly improved clinical outcomes in patients with acute ischemic stroke presenting between 3 – 4.5 hours.**
- **tPA is associated with increased sICH compared to placebo.**

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ECASS 3 Criticisms

- Fewer diabetics compared to NINDS
 - tPA 14.8% v. 22%, placebo 16.6% v. 20%
- Much lower mean NIHSS
 - tPA 10.7 v. 14, placebo 11.6 v. 14
- No history of prior stroke and diabetes allowed

Lyden, NEJM 2008;395:1393-95

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Meta-analysis

- 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 onset to drug 4 hours
- Diabetes similar among ECASS's 16%, ATLANTIS 21%

Lansberg, Stroke 2009;40:2438-41

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Meta-analysis

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

Lansberg, Stroke 2009;40:2438-41

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SITS-ISTR 3 – 4.5 hour

- European data base
- Observational study
- Not randomized controlled trial
- Compare 664 treated 3 – 4.5 h with 11865 treated within 3 h.

Wahlgren, Lancet 2008;372:1303-09

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SITS-ISTR 3 – 4.5 hour

- Median 55 min. later 195 min. v. 140 min.
 - 60% before 200 min.
- 3 years younger 65 v. 68
- NIHSS lower 11 v. 12

Wahlgren, Lancet 2008;372:1303-09

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SITS-ISTR 3 – 4.5 hour

- Independence 58% 3-4.5 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

- **Benefit: To improve by 1 or more mRS**
 - 0 – 3 hours 32.3/100 treated
 - 3 - 4.5 hours 16.4/100 treated
- **Harm: To worsen by 1 or more mRS**
 - 0 – 3 hours 3.3/100 treated
 - 3 – 4.5 hours 2.7/100 treated

Saver, Stroke 2009;40:2433-37

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Number Needed to Treat

- **NNT to benefit by 1 or more mRS is 6**
- **NNT to harm by 1 or more mRS is 37**
- **From ECASS 3 NNT to benefit to mRS of 0 – 1 (best outcome) is 14**

Saver, Stroke 2009;40:2433-37

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Who should be treated in 3 – 4.5 h?

- **Relatively young, 65 +/- 10years old**
- **Less severe strokes, NIHSS < 11 +/- 6, median in tPA group of ECASS 3 was 9**
- **Diabetes??**
- **No one with diabetes and prior stroke**

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Conclusions

- **Meta-analysis and observational studies appear to support the use of tPA beyond the 3 hour window**
- **Extension of the treatment window to 4.5 hours is being endorsed by many**
- **Institutions must modify their protocols to adjust for the population treated in the ECASS 3 trial in the 3 – 4.5 hour window**

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Questions?

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