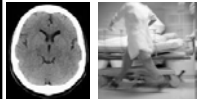



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E. Bradshaw Bunney, MD

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**FERNE/MEMC Session:**

**Treating Ischemic Stroke  
in the 3 – 4.5 Hour Window**




E. Bradshaw Bunney, MD 

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**Disclosures**


- FERNE Board Member
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- Participation on industry-sponsored advisory boards and as lecturer in programs supported by industry
- 2009 MEMC Educational activities supported by an Educational Grant from Alexza Pharmaceuticals

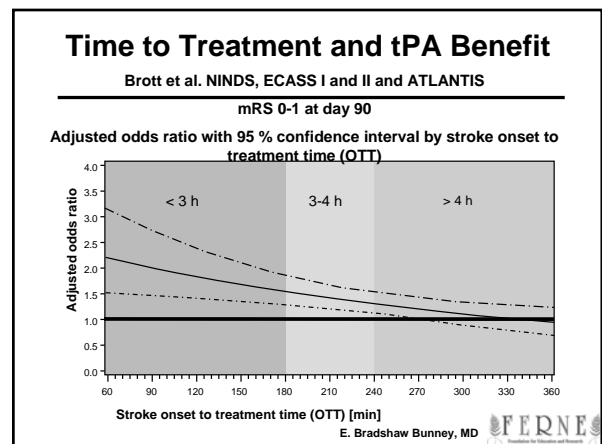
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**Objectives**

- 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**

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- 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 E. Bradshaw Bunney, MD 

**ECASS 3 Criteria**

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- 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**

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- 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**

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- 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**

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- 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**

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- 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: Any hemorrhage not seen on prior CT and suspicion of hemorrhage or 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%

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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 E. Bradshaw Bunney, MD 

### 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 16%, ATLANTIS 21%

Lansberg, Stroke 2009;40:2438-41 E. Bradshaw Bunney, MD 

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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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