

Optimal Emergency Department Neuroprotection Strategies in Acute Ischemic Stroke Patients

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Session Objectives

- Review the current state of neuroprotection strategies that limit the extent of secondary injury following acute ischemic stroke
- Discuss the possible role of neuroprotectants such as NXY-059 in the treatment of ED ischemic stroke patients based on the methods and preliminary results of the SAINT I clinical trials


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Case Presentation...


- A 50 yo male with slurred speech and left sided weakness found by his spouse
- Last known normal 2 hours prior
- Irregular heart rhythm, BP175/101
- Non-compliant with a "strong blood thinner"
- Arrives at the door of a small, rural hospital's ED about 2 ½ hours after last confirmed normal

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Case Presentation...

- Exam confirms slurred speech, facial droop, a right preferential gaze, and 1/5 strength in both his left arm and left leg
- Family wants "everything done possible"
- Non-contrast CT performed shows a dense MCA sign on the right, but is otherwise normal
- Now about 3 hours since the patient last known normal
 - Patient's symptoms could have started anywhere from 1 to 3 hours ago
 - INR is still pending

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Case Presentation...

- A stroke center about 45 minutes away is contacted
- Helicopter sent to get the patient with the hope of performing an endovascular intervention to restore blood flow
- The transferring physician asks the accepting stroke neurologist if there is anything he can give the patient to "buy him some time"

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Clinical Questions

- What are the theoretic and practical goals of neuroprotection strategies in the management of ED ischemic stroke patients?
- What neuroprotection strategies are currently being studied in the management of ischemic stroke patients?

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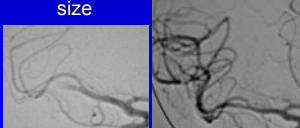
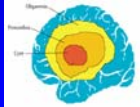
Clinical Questions


- What has the experience to date been with specific neuroprotectants in the treatment of the ischemic penumbra?
- What has been the experience with NXY-059 based on the SAINT I clinical trial?
- What future research might improve our ability to provide neuroprotection to acute ischemic stroke patients in the ED?

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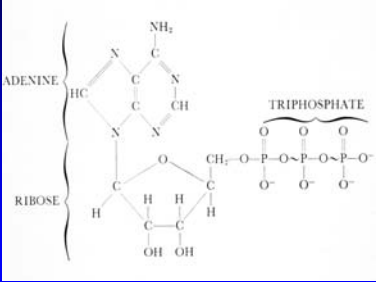
Acute Ischemic Stroke Treatment Strategies


- Reperfusion Therapy**
 - Restores blood flow to tissues before infarction
 - Salvages penumbral tissue, reduces final infarct size
- Neuroprotective Agents**
 - Do not directly restore blood flow
 - Act on ischemic cascade
 - Protects brain tissue from consequences of cerebral ischemia

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Stroke Pathophysiology



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Glutamate Mediated Neuronal Damage

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Glutamate Mediated Neuronal Damage

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Calcium Mediated Cytotoxic Effects

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Stroke Pathophysiology

Calcium Mediated Cytotoxic Effects

GM,
Piracetam
Tirilizad
PEG SOD
PNA
Enlimomab
Citicoline
CX295
Ceresine

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Free Radical Formation

Free Radical Formation

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Free Radical Formation

Free Radical Formation

Tirilizad
Citicoline
Ebselen
NXY-059

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History of Neuroprotection

Trials of Neuroprotection Agents in Stroke: 1955-2000

Neuroprotective Agents Tested	49
RCTs Performed	114
Patients Enrolled	21,445
Trials with Positive Results	0

This year, first positive primary endpoint trial

Kidwell CS et al. Stroke 32(6):1349-59.

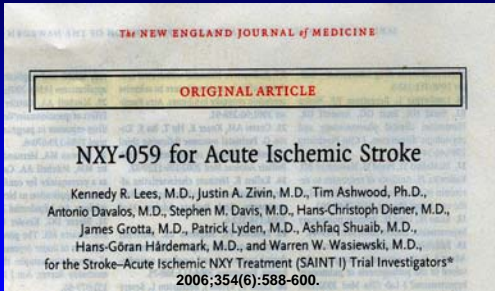
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Why have neuroprotection agents failed in human trials?

- The theoretical concept is wrong
- Treatment initiated too late
- Pathophysiological heterogeneity of stroke
 - Enrolled patients unlikely to respond to drug action
- Doses too low
- Trials underpowered
- Outcome measures analyzed with statistical techniques insensitive to modest, but clinically important, benefits

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NXY-059 (Cerovive)



ORIGINAL ARTICLE


NXY-059 for Acute Ischemic Stroke

Kennedy R. Lees, M.D., Justin A. Zivin, M.D., Tim Ashwood, Ph.D., Antonio Davalos, M.D., Stephen M. Davis, M.D., Hans-Christoph Diener, M.D., James Grotta, M.D., Patrick Lyden, M.D., Ashfaq Shuaib, M.D., Hans-Göran Härdemark, M.D., and Warren W. Wasiewski, M.D., for the Stroke-Acute Ischemic NXY Treatment (SAINT I) Trial Investigators*
 2006;354(6):588-600.

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NXY – 059


- NXY-059 (Cerovive) is an intravenous, nitronone-based, free radical trapping agent
- Preclinical trials positive in rats/primates
- Significant dose response
- Effective after 4 hours of ischemia in animals

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SAINT I Trial

(Stroke – Acute Ischemic – NXY-059 Treatment)


- RCT Design
 - 72 hr treatment window
 - NXY-059 vs placebo
 - Target plasma concentration ~260 µM
 - 158 centers across 24 countries
 - Europe, Asia, Australia, New Zealand, South Africa

Lees KR et al. *N Engl J Med* 2006;354(6):588-600. Andrew Asimos, MD, FACEP 

SAINT I Trial

(Stroke – Acute Ischemic – NXY-059 Treatment)

- Eligibility
 - CT/MR consistent with AIS
 - Previous independence
 - NIHSS ≥6 including limb weakness
 - t-PA permitted
 - < 6hr ictus to treatment
 - Forced allocation to achieve mean time from onset to start of treatment ≤ 4 hrs


Lees KR et al. *N Engl J Med* 2006;354(6):588-600. Andrew Asimos, MD, FACEP 

SAINT I Primary Outcome Variable:

Modified Rankin Scale

At 90 Days


Symptom free	0	Symptom free
Symptomatic, but performing previous activities	1	Able to do all usual activities
Unable to do some previous activities, but independent	2	Able to look after self
Requires some help, but can walk without assistance	3	Able to walk without assistance
Needs assistance with walking and attending to bodily needs	4	Not bedridden
Bedridden, incontinent, requires constant care	5	Bedridden / Death

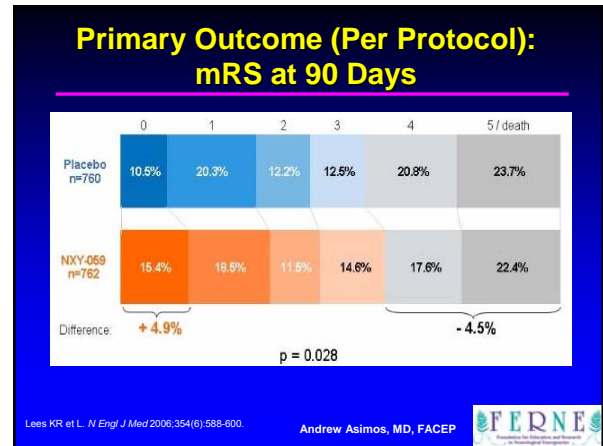
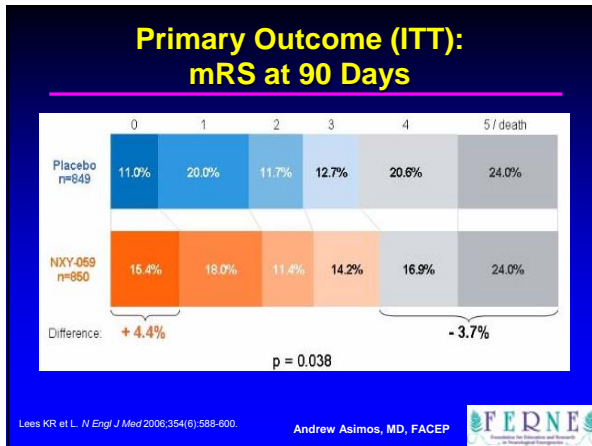
Lees KR et al. *N Engl J Med* 2006;354(6):588-600. Andrew Asimos, MD, FACEP 

SAINT I Secondary Outcome Variables

- mRS at additional time points
 - 7 and 30 days
- NIHSS change from baseline
 - Days 7 and 90
- Barthel Index
 - Days 7, 30, and 90
- Safety
- SIS-16 and Four Domains
- EQ-5D

} Day 90

Lees KR et al. *N Engl J Med* 2006;354(6):588-600. Andrew Asimos, MD, FACEP 



Number Needed to Treat to Benefit from NXY-059 for Using Shift Analysis

Lowest Possible	7.9
Highest Possible	16.7
Expert Panel	9.8
Expert Panel	8.7 – 10.9

Saver J. *UCLA Stroke Center*. Andrew Asimos, MD, FACEP

Number Needed to Treat to Benefit from NXY-059 for Dichotomized Outcomes

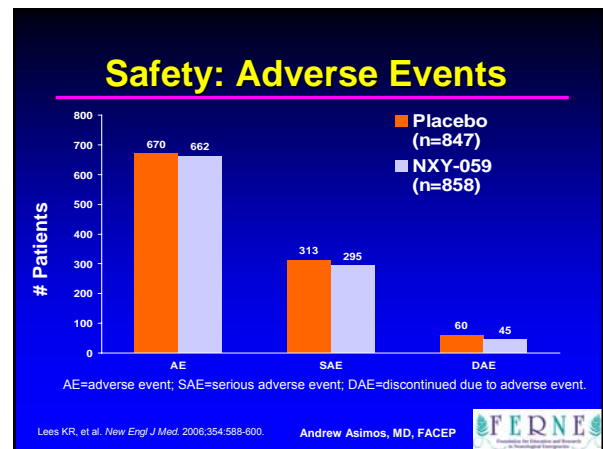
Comparison	mRS	NNT
0 vs 1-6		23
0-1 vs 2-6		42
0-2 vs 3-6		48
0-3 vs 4-6		28

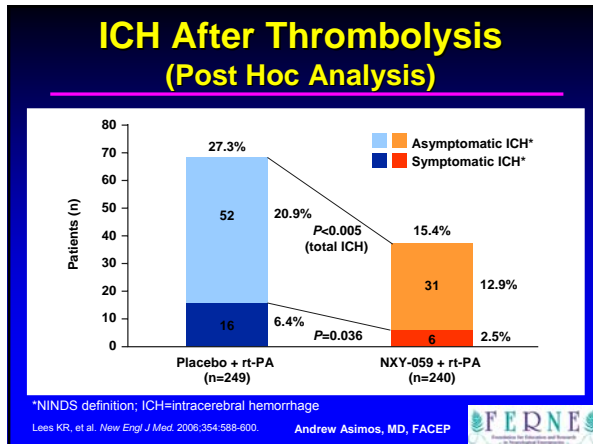
Saver J. *UCLA Stroke Center*. Andrew Asimos, MD, FACEP

SAINT I Endpoints

Endpoint	P Value
Rankin shift	0.038
Rankin dichotomized	0.17
Improvement in NIHSS	0.86
Barthel Index dichotomized	0.14
Stroke Impact Scale	0.08
EuroQOL Index	0.06
QOL Visual Analogue Scale	0.05

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- ### Magnesium
- Blocks NMDA receptor
 - Safe
 - Proven in stroke, MI, and other studies
 - FAST-Mag (Field Administration of Stroke Therapy) Phase III trial ongoing

- ### Hypothermia
- Known to be neuroprotective for years
 - Positive results in 2 studies with global ischemia
 - Multiple mechanisms for neuroprotection-may prevent reperfusion injury
 - CHILI (Controlled Hypothermia in Large Infarction) and NOCSS (Nordic Cooling Stroke Study) are ongoing

- ### Conclusions
- We may be on the verge of neuroprotective therapy
 - Must await the results of SAINT II, CHILI, NOCSS and FAST-MAG
 - The effect of NXY-059 on hemorrhagic risk after t-PA should be further explored

Questions?

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