
**Case Studies in
Cerebrovascular
Emergencies Research:**

Edward P. Sloan, MD, MPH



***Current International
Clinical Trials in
Ischemic and
Hemorrhagic Stroke***

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**SIMEU / ACEP
Emergency Medicine
Congress**

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Disclosures

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A Special Welcome To...

William Barsan, MD FACEP
Jonathan Edlow, MD, FACEP
J. Stephen Huff, MD, FACEP
Andrew Jagoda, MD, FACEP
Our Italian hosts.

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Today's Agenda

- Present the current clinical situation
- Review two articles and editorials
- Consider the research impact
- Consider the clinical care impact
- Project future work and collaboration

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Clinical Cases

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Ischemic Stroke Patient

- 67 year old male
- Pt experiences L sided weakness
- Occurs during breakfast
- Slurred speech
- Arrives by EMS to the ED in 30 min
- Accucheck 300


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Hemorrhagic Stroke Pt

- 58 year old female
- Pt with a change in mental status
- Headache, not feeling well
- Went back to bed
- Found by family less responsive
- Arrives by EMS to the ED in 15 min
- Blood pressure 228/126


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Learning Objectives and Key Clinical Questions

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Session Objectives

- Discuss the impact of the negative SAINT II trial of NXY-059 on the development of an effective neuroprotectant for the treatment of ischemic stroke patients.
- Review the current status of the clinical trials of Factor VIIa in the treatment of intracerebral hemorrhage and the differences between these clinical trials and those of NXY-059.

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Session Objectives

- Determine how the data from these large international trials can improve the care of acute stroke patients even if the results of the clinical trials do not identify a new effective therapy.
- Consider how the NETT research consortium might enhance CNS emergencies clinical trials research in the US and internationally.

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Key Clinical Questions

- What can be learned from the international clinical trials of NXY-059 and Factor VIIa regarding neurological emergencies clinical trial design and conduct?

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Key Clinical Questions

- How can the data from these clinical trials be successfully analyzed so that the story can be told of how acute ischemic and hemorrhagic stroke patients can be optimally managed in the 21st century, especially in the area of tPA use in ischemic stroke?

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Key Clinical Questions

- How can the formation of NETT in the US be leveraged to enhance international research and collaboration in the area of acute neurological emergencies patient management?

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Key Clinical Questions

- What are the best next steps to be taken by leaders in the field of neurological emergencies research, patient management, clinical trials design, clinical policy formation, patient advocacy, and public health?

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NXY-059: Clinical and Research Data

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NXY-059 Clinical Data

- Neuroprotectant
- Remains intravascular
- Does not cross blood brain barrier
- Protects neurons

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NXY-059 Research Data

- SAINT I positive phase III trial
- 1722 patients
- Improved outcome using mRS
- Reduced tPA significant ICH rate
- SAINT II confirmatory trial: 3000 pts
- SAINT II phase III trial negative

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NXY-059 Publications

- NEJM Feb 2006 article
- Lees *et al*
- Multinational phase III clinical trial

- NEJM Feb 2006 editorial
- del Zoppo
- “Stroke & Neurovascular Protection”

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Key Clinical Questions

- Clinical trials often will generate different results given differences in patient populations and standard therapies.

- What should be done if one trial is positive and the other neutral?

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Key Clinical Questions

- The FDA requires paired phase III clinical trials in order for efficacy to be demonstrated.

- Should paired trials be required for all drugs in development?

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Key Clinical Questions

- What is a possible explanation of these two clinical trials not having the same results?

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Key Clinical Questions

- Emergency physicians utilize many therapies that provide neuroprotection: airway, blood pressure, and ICP/cerebral perfusion control being the most important.

- Is neuroprotection possible using a specific neuroprotectant?

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Key Clinical Questions

- The proposed number needed to treat in the SAINT I trial was approximately 24.
- The NNT in the tPA clinical trials was approximately 8.
- What does this suggest about the efficacy of IV tPA in ischemic stroke?

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Factor VIIa: Clinical and Research Data

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Factor VIIa Clinical Data

- Anticoagulant
- Final common pathway agent
- Used to treat hemophilia patients
- Reduces hemorrhage volume in ICH patients volume via hemostasis

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Factor VIIa Research Data

- Positive phase III trial
- 399 patients
- Reduced hemorrhage volume
- Improved outcome using mRS
- Increased thromboembolic events
- Confirmatory trial taking place

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Factor VIIa Publications

- NEJM Feb 2005 article
- Mayer *et al*
- Multinational phase III clinical trial

- NEJM Feb 2006 editorial
- Brown and Morgenstern
- “Stopping the Bleeding in ICH”

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Key Clinical Questions

- What is the number needed to treat with this therapy in order to provided the best clinical outcome?

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Key Clinical Questions

- What can be learned about the use of the modified Rankin Scale in the clinical trials and treatment of stroke patients?

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Key Clinical Questions

- This drug is already FDA approved and can and is already being used by clinicians for ICH patients.
- How can this situation be optimally managed?

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Key Clinical Questions

- What will happen if the second confirmatory trial is neutral and clinicians already are used to including this therapy in the management of ICH patients?

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Clinical Trials Data: Providing Maximal Benefit

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Key Clinical Questions

- How can we best access and publish data from industry sponsored clinical trials?

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Key Clinical Questions

- What might be learned from the tPA data contained within the NXY-059 clinical trials, especially with regards to tPA use in the ED?

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Key Clinical Questions

- What might be learned about the clinical practice of Emergency Medicine and the resuscitation of acute stroke patients from these clinical trials?

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Key Clinical Questions

- What can be learned about outcome measures such as the modified Rankin Scale and their use in clinical trials research?

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Coordinated Research & NETT: How Can This Opportunity Be Leveraged Internationally?

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Key Clinical Questions

- How can the detailed clinical trials conducted by industry be performed by NETT?

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Key Clinical Questions

- What role for NETT is envisioned for the development of clinical trials that answer important stroke patient care questions?

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Key Clinical Questions

- Could a research network such as NETT be developed in Italy in order to enhance clinical care, research, and the specialty of Emergency Medicine?

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Key Clinical Questions

- Could a research network such as NETT be developed in the EU in order to enhance clinical care, research, and the specialty of Emergency Medicine?

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Conclusions

- Important neurological emergencies research being conducted by industry
- Much can be learned from these protocols and the patients treated in the context of this clinical trials research
- It is an opportunity for emergency physicians to better understand our clinical practice
- Opportunities for international work exist

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Recommendations

- We should closely monitor the outcomes of these clinical trials
- A concerted effort to analyze all aspects of these clinical trials should be made
- Collaboration with industry and government should be enhanced
- Examination of opportunities abroad should be made

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Questions?

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