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**ED Ischemic Stroke Patient  
Neuroprotection:**  
*What neuroprotection  
strategies do we utilize and  
what might be the role of  
NXY-059?*

Edward Sloan, MD, MPH, FACEP




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**2006 Advanced Emergency  
& Acute Care Medicine and  
Technology Conference**

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**Emergency Medicine  
Associates**  
  
**Atlantic City, NJ  
September 26-27, 2006**

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**Edward P. Sloan, MD, MPH  
FACEP**

*Professor*

*Department of Emergency Medicine  
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**Attending Physician  
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*University of Illinois Hospital  
Our Lady of the Resurrection Hospital*

**Chicago, IL**

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**Disclosures**

- NovoNordisk, King Pharmaceuticals, UCB Pharma Advisory Boards
- Eisai Speakers' Bureau
- ACEP Clinical Policies Committee
- ACEP Scientific Review Committee
- Executive Board, Foundation for Education and Research in Neurologic Emergencies

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## Global Objectives

- Maximize patient outcome
- Utilize health care resources well
- Optimize evidence-based medicine
- Enhance ED practice

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## Sessions Objectives

- State key questions and concepts
- Why perform neuroprotection?
- What global neuroprotections?
- What specific therapies?
- What lies ahead?

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## Case Presentation...

- 64 year old presents to ED
- Trouble using L hand and speech
- Symptoms for last 90 minutes
- No headache or trauma
- History of TIA x 1, similar symptoms
- Hx DM, smoker
- No recent illness

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## ED Neuroprotection: *Key Concepts*

- Outcome related to infarct volume
- Need to limit infarct size
- Aggressively Rx ischemic penumbra
- ED MD is the best neuroprotectant
- Specific neuroprotectants tested
- SAINT-I clinical trial showed benefit
- Specific questions to be addressed

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## ED Neuroprotection: *Key Concepts*

- Outcome related to infarct volume

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## Stroke Volume and Outcome

- Vessel occlusion
- Infarct core
- Ischemic penumbra
- How large is the core in the ED?
- What is the penumbra conversion?
- Do ED therapies limit infarct growth?

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## ED Neuroprotection: Key Concepts

- Outcome related to infarct volume
- Need to limit infarct size

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## Limiting Stroke Volume

- Enhance perfusion
- Treat hypoxia, hypotension
- Limit ischemic cascade effects
- Prevent complications

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## ED Neuroprotection: Key Concepts

- Outcome related to infarct volume
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## Aggressively Rx Ischemic Penumbra

- Maximize cerebral perfusion
- Provide optimal substrates, O<sub>2</sub>
- Avoid cell death
- Maintain intact blood brain barrier

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## Cerebral Perfusion

- $CPP = MAP - ICP$
- Cerebral perfusion pressure
- Mean arterial pressure
- Intracranial pressure

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## Cerebral Perfusion

- $CPP = MAP - ICP$
- If  $MAP = 110 \text{ mmHg}$ ,  $ICP = 10 \text{ mmHg}$
- $CPP$  then equals  $100 \text{ mmHg}$
- Cerebral blood flow auto-regulation
- $CPP$  maintained over range of  $MAPs$
- Pathological  $ICP$  elevations limited

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## Mean Arterial Pressure

- 120 / 75 MAP = 90 mmHg
- 210 / 120 MAP = 150 mmHg
- 180 / 110 MAP = 97 mmHg
- How much MAP therapy is OK?
- What agents provide best Rx?
- How to avoid watershed infarct?

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## Watershed Infarct

wa-ter-shed (wô t r-sh d) *n.*

1. A ridge of high land dividing two areas that are drained by different river systems. Also called *water parting*.
2. The region draining into a river, river system, or other body of water.
3. A critical point that marks a division or a change of course; a turning point:

watershed infarction *n.*  
Infarction of the cerebral cortex  
in an area of blood supply  
between two major cerebral  
arteries.



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## ED Neuroprotection: Key Concepts

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## ED MD: Best Neuroprotectant



## ED MD: Best Neuroprotectant

- Available 24/7

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## ED MD: Best Neuroprotectant

- Available 24/7
- Effectively able to diagnose infarct

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## ED MD: Best Neuroprotectant

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- Available 24/7
- Effectively able to diagnose infarct
- Systems expert; able to make things happen quickly

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## ED MD: Best Neuroprotectant

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- Available 24/7
- Effectively able to diagnose infarct
- Systems expert; able to make things happen quickly
- Focus on acute interventions

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## ED MD: Best Neuroprotectant

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- Available 24/7
- Effectively able to diagnose infarct
- Systems expert; able to make things happen quickly
- Focus on acute interventions
- Know our limitations

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## ED MD: Best Neuroprotectant

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- Available 24/7
- Effectively able to diagnose infarct
- Systems expert; able to make things happen quickly
- Focus on acute interventions
- Know our limitations
- We can be trained

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## ED MD Neuroprotection

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- Manage the airway

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## ED MD Neuroprotection

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- Manage the airway
- ETI, rapid sequence induction

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## ED MD Neuroprotection

- Manage the airway
- ETI, rapid sequence induction
- Manage hypotension

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## ED MD Neuroprotection

- Manage the airway
- ETI, rapid sequence induction
- Manage hypotension
- Manage hypertension

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## ED MD Neuroprotection

- Manage the airway
- ETI, rapid sequence induction
- Manage hypotension
- Manage hypertension
- Treat metabolic abnormalities

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## ED MD Neuroprotection

- Manage the airway
- ETI, rapid sequence induction
- Manage hypotension
- Manage hypertension
- Treat metabolic abnormalities
- Diagnose and lower elevated ICP

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## ED MD Neuroprotection

- Manage the airway
- ETI, rapid sequence induction
- Manage hypotension
- Manage hypertension
- Treat metabolic abnormalities
- Diagnose and lower elevated ICP
- Prevent and treat seizures

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## ED MD Neuroprotection

- Manage the airway
- ETI, rapid sequence induction
- Manage hypotension
- Manage hypertension
- Treat metabolic abnormalities
- Diagnose and lower elevated ICP
- Prevent and treat seizures
- We first do no harm

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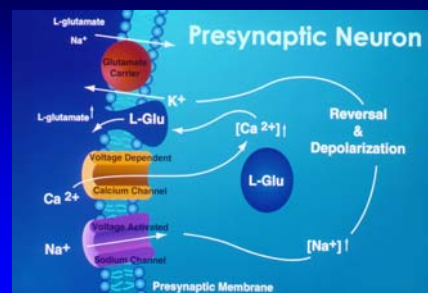
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## Stroke Pathophysiology, Neuroprotectants

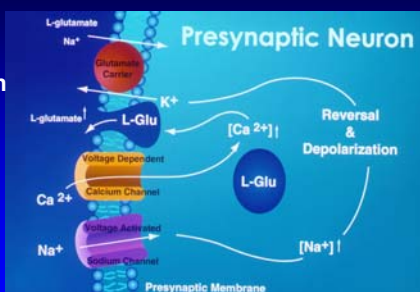


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## Stroke Pathophysiology, Neuroprotectants

- Lubeluzole
- Fosphenytoin
- Sipatrigine
- Riluzole
- Lamotrigine
- Lofarizine
- Maxipost

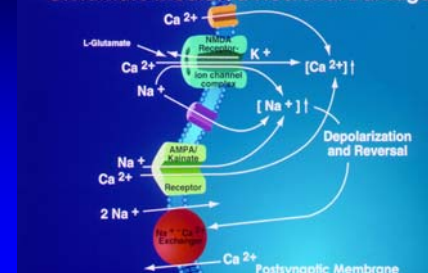


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## Stroke Pathophysiology, Neuroprotectants

### Glutamate Mediated Neuronal Damage



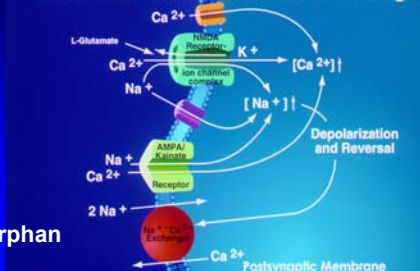
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## Stroke Pathophysiology, Neuroprotectants

- Aptiganel
- Selfotel
- GV-150526
- CP-101606
- Eliprofil
- ACPG
- ACEA 1021
- Dizocilpine
- Dextromethorphan
- NBQX
- Magnesium

### Glutamate Mediated Neuronal Damage

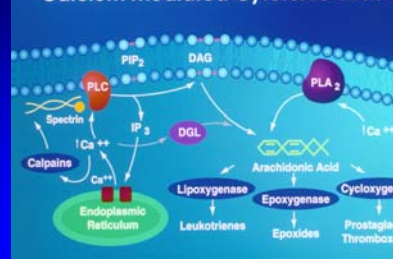


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## Stroke Pathophysiology, Neuroprotectants

### Calcium Mediated Cytotoxic Effects

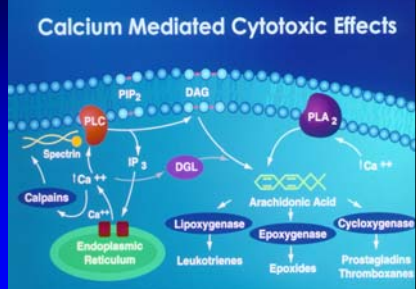


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## Stroke Pathophysiology, Neuroprotectants

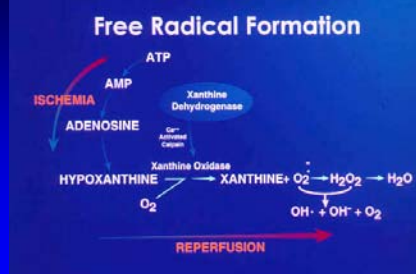
GM<sub>1</sub>  
Piracetam  
Tirilizad  
PEG SOD  
PNA  
Enlimomab  
Citicoline  
CX295  
Ceresine



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## Stroke Pathophysiology: Free Radical Formation



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## Stroke Pathophysiology: Free Radical Formation

Tirilizad  
Citicoline  
Ebselen  
NXY-059



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## Neuroprotection 1955-2000

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?

- Wrong theoretical concept
- Treatment initiated too late
- Stroke heterogeneity
- Wrong drug action
- Doses too low
- Trials underpowered
- Wrong outcome measures
- Insensitive statistical techniques

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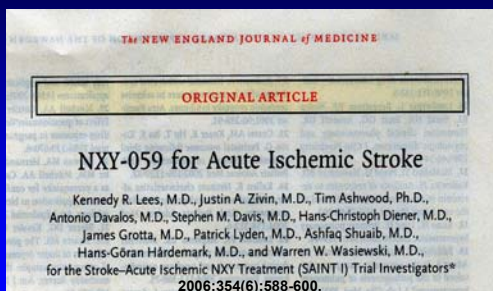
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## NXY-059 (Cerovive)



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## NXY – 059 Characteristics

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

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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  $\mu$ M
  - 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.

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## SAINT I Trial

(Stroke – Acute Ischemic – NXY-059 Treatment)

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

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

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## SAINT I Primary Outcome Variable: Change in Modified Rankin Scale

Symptom free	0	Symptom free	At 90 Days	
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.

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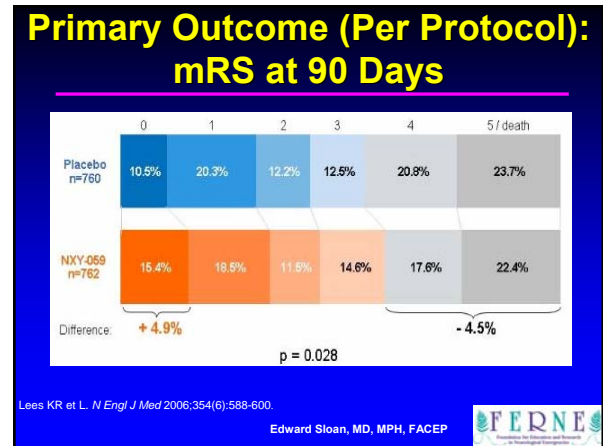
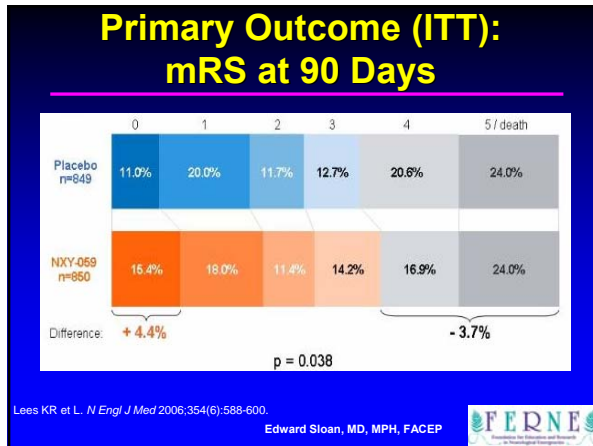
## SAINT I Secondary Outcome Variables

- mRS at 7 and 30 days
- NIHSS change on days 7 and 90
- Barthel Index on days 7, 30, and 90
- Safety
- Day 90 SIS-16 and Four Domains
- Day 90 EQ-5D

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

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### NXY-059 Number Needed to Treat: Benefit Using mRS 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*. Edward Sloan, MD, MPH, FACEP

### NXY-059 Number Needed to Treat: Benefit Using Outcome Dichotomy

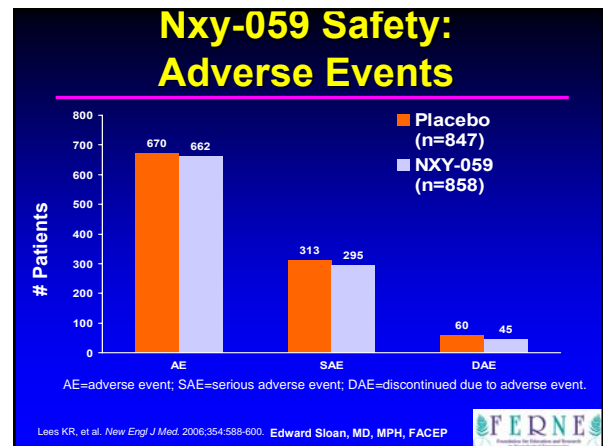
mRS	NNT
0 vs 1-6	23
0-1 vs 2-6	42
0-2 vs 3-6	48
0-3 vs 4-6	28

Saver J. *UCLA Stroke Center*. Edward Sloan, MD, MPH, FACEP

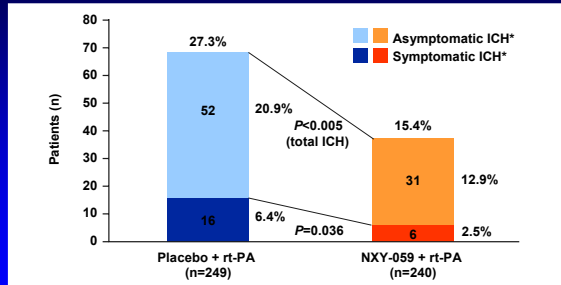
### SAINT I Clinical Endpoints

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
Euro QOL Index	0.06
QOL Visual Analogue Scale	0.05

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## ICH After IV tPA Thrombolysis: (SAINT –I Post Hoc Analysis)



Lees KR, et al. *New Engl J Med*. 2006;354:588-590. Edward Sloan, MD, MPH, FACEP



## ED Neuroprotection: Key Concepts

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## Neuroprotectant Questions

- Will SAINT-II reproduce results?

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- Will the tPA / ICH data compare?

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## Neuroprotectant Questions

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- Will SAINT-II reproduce results?
- Will the NNT be comparable?
- Will safety data be comparable?
- Will the tPA / ICH data compare?
- How to explain BBB information?

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## Neuroprotectant Questions

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- Will SAINT-II reproduce results?
- Will the NNT be comparable?
- Will safety data be comparable?
- Will the tPA / ICH data compare?
- How to explain BBB information?
- What cost will the results justify?

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## Conclusions

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- We provide neuroprotection
- Neuroprotection reduces infarct volume, complications
- New neuroprotection data
- Interesting data related to IV tPA
- Ischemic stroke care enhanced
- Patient outcomes improved

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## Questions?

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