

Post-Ischemic Neuroprotection: *Past, Present and Future*

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CARDIAC ARREST

- Sudden cardiac death occurs 700/day, 255,000 annually
- 50% of deaths due to ASHD are sudden
- Long term survival in large cities = 1-2 % (infrequent bystander CPR, long transport)
 - NYC 26/2,329 (1.1%) survived to D/C
 - Kellerman: 3,400 unsuccessful pre-hospital arrests 0.47% survived to D/C

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Post-Ischemic Cerebral Reperfusion

- CPR restores ROSC in about 70,000 patients a year in the US
- 60% of these die from neurologic complications
- Only 3-10% of resuscitated patients are able to resume their former lifestyles

Krause GS, Kumar K, White BC, Aust SD, Wiegstein JG. Ischemia, resuscitation, and reperfusion: Mechanisms of tissue injury and prospects for protection. Am Heart J 1986; 111:768-80.

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Neuronal Viability

- Viability is flow dependant & regional
 - Functional loss as flow decreases:
 - Normal > 60 ml/100gm/min
 - protein synthesis < 55 ml/100gm/min
 - anaerobic glycolysis < 35 ml/100gm/min
 - neurotransmitter release < 20 ml/100gm/min
 - anoxic depolarization < 15 ml/100gm/min
 - Selectively vulnerable neuronal zones:
 - Hippocampus CA_{1&4}, Cerebral cortex 3-5, Cerebellar purkinje cells

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Neuronal Viability

- **Penumbra:** neurons which are functionally silent but energy metabolism is preserved
 - fundamentally salvageable
- Normal Neurons threatened at:
 - < 15 ml/100gm/min
 - CPP < 30 mmHg
 - CPP = MAP - ICP
 - Cerebral venous PO₂ < 20 torr.

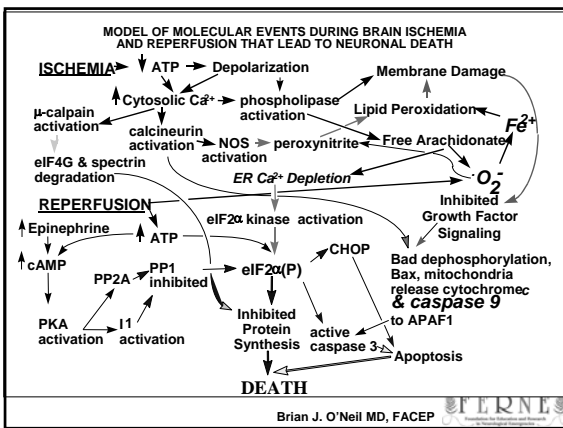
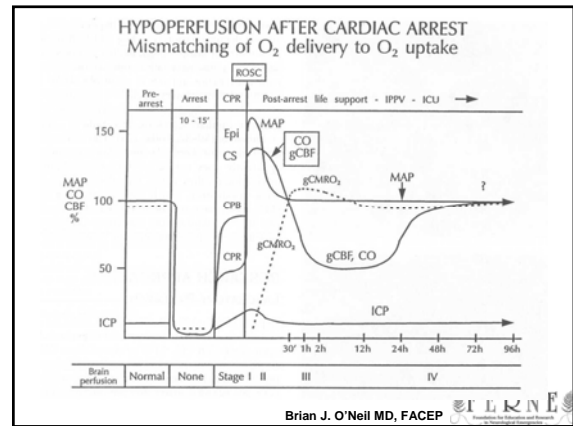
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Post-Arrest Encephalopathy

- Brain ATP depletion, ion pumps and tissue pH- restored rather quickly
- perfusion failure
 - vasoconstriction, platelet aggregation, precapillary cellular edema, abnormal calcium ion fluxes
- re-oxygenation injury
- extracerebral organ dysfunction
- blood derangements due to stasis
- post- arrest inflammatory process

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ED Neuroprotection: Key Concepts

- Outcome related to infarct volume
- Save Viable tissue: Rx ischemic penumbra
- Therapeutic window is short
- Primarily selective neuroprotectants tested
- Fundamental questions still need to be addressed

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Stroke Pathophysiology, Neuroprotectants

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Stroke Pathophysiology, Neuroprotectants: Glutamate

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Stroke Pathophysiology, Neuroprotectants

GM₁
Piracetam
PNA
Enlimomab
Citicoline
CX295
Ceresine
Magnesium

Calcium Mediated Cytotoxic Effects

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Stroke Pathophysiology: Free Radical Formation

Tirilazad
PEG-SOD
Citicoline
Ebselen
NXY-059

Free Radical Formation

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Neuroprotection 1955-2000

Trials of Neuroprotection Agents in Stroke:

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

Kidwell CS et al. *Stroke* 32(6):1349-59. Brian J. O'Neil MD, FACEP

NXY-059 (Cerovive)

THE NEW ENGLAND JOURNAL of MEDICINE

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 Characteristics

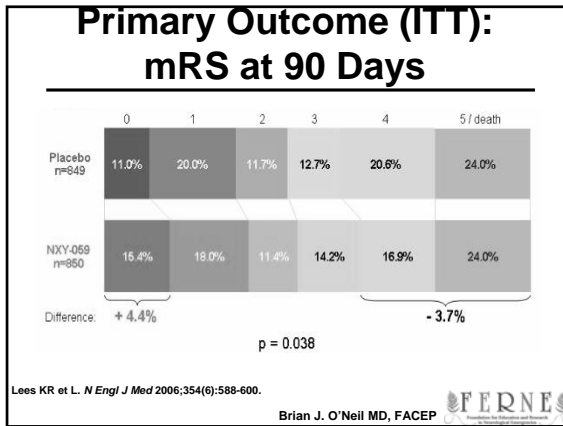
- NXY-059 (Cerovive) is an intravenous, nitrone-based, free radical trapping agent
- Preclinical trials positive in rats/primates
- Effective after 4 hours of ischemia
- Significant dose response

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SAINT I Trial (Stroke – Acute Ischemic – NXY-059 Treatment)

- **RCT Design**
 - 72 hr treatment window
 - NXY-059 vs placebo
- **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

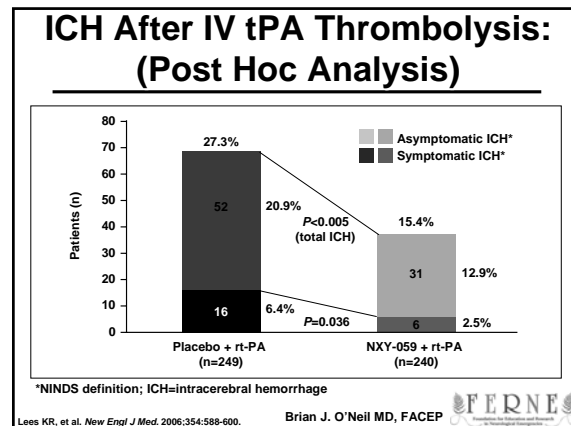
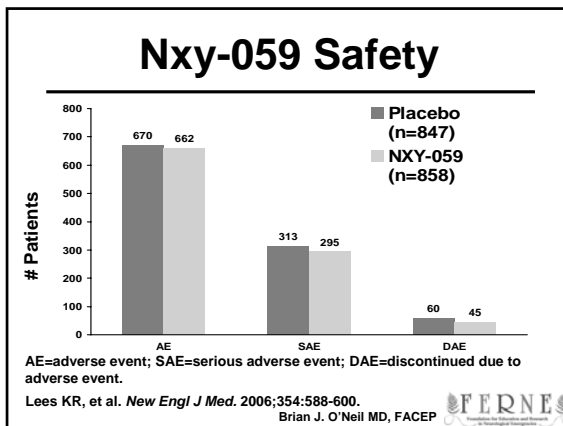
Lees KR et L. *N Engl J Med* 2006;354(6):588-600. Brian J. O'Neil MD, FACEP



NXY-059 Number Needed to Treat:

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*
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SAINT II

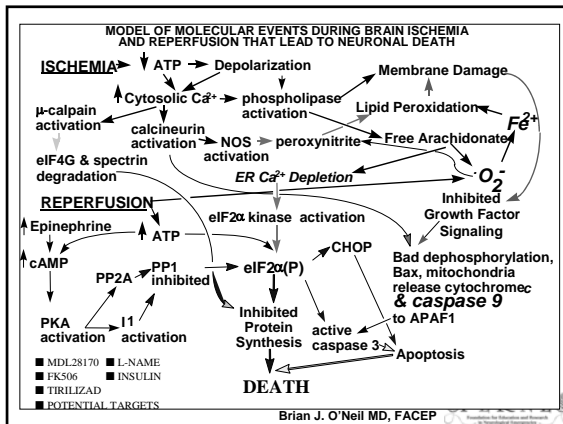
- NXY-059 failed to meet the primary outcome of significant reduction in stroke-related disability
 - modified Rankin Scale (mRS) (p=0.33, odds ratio 0.94)
 - National Institutes of Health Stroke Scale (NIHSS) (p=0.70)
- No evidence of lowering the incidence of symptomatic ICH with rt-PA (p=0.56).

Mortality and adverse events were similar to placebo.
 "AstraZeneca plans no further development of NXY-059 in acute ischemic stroke."
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Why have neuroprotection agents failed?

- Wrong theoretical concept
- Treatment initiated too late
- Stroke heterogeneity
- Inadequate Dosing
- Trials underpowered
- Wrong outcome measures
- Insensitive statistical techniques

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What can we do now?

- Correct base deficit to < 5 mEq/L
- NaHCO₃ produces transient worsening of myocardial hypercapnea
- best buffer ?
- NaHCO₃-causes mild transient hypercarbia that appears harmless to heart and head if with hyperventilation

What can we do now?

- Brief hypertensive bout to SBP 150-200, MAP of 130mmHg at ROSC
 - at little as five minutes abolishes the no-reflow phenomenon
 - brief hypertension correlates with good outcome, hypotension portends a poor prognosis.
 - most patients with good recoveries do this on their own
- then normotensive to mild hypertension, normocarbia, normoxia

What Can We Do Now?

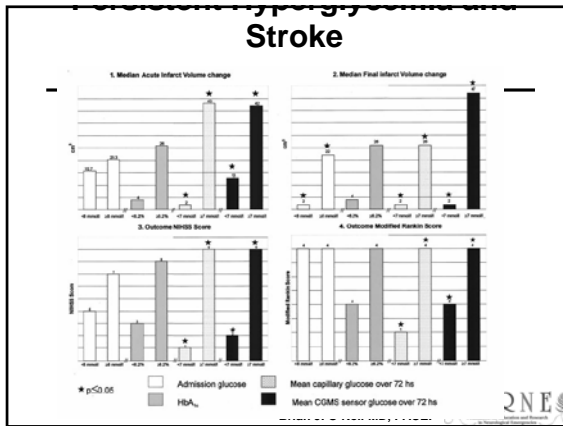
- Monitor temperature: Avoid hyperthermia
- Relaxing doses of paralytics
- sedate with benzodiazepines / barbituates
- seizure prophylaxis phenytoin / ativan

What Else Can We Do Now?

- HCT around 30-35%
- Normalize electrolytes
- Serum Osm 280-330 mOsm/L
- Elevated head 30 degrees
- Stress Dose steroids
 - Hydrocortisone 100 mg
- Neuro ICUs

Hyperglycemia in stroke

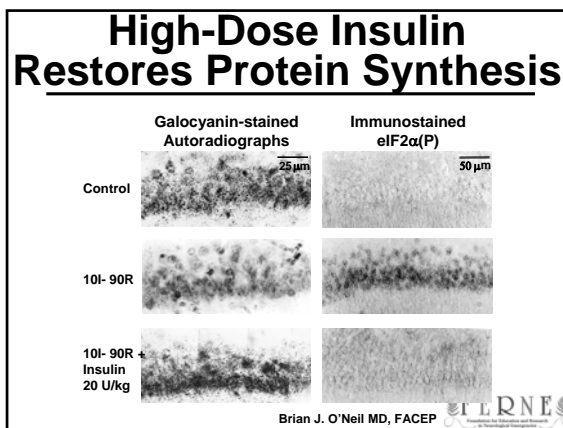
- ↑ initial Glucose non diabetic CVAs
 - 3.3 times more likely to die (Cape meta-analysis)
- Toast study: initial hyperglycemia predicts outcome from CVA
- Potential mechanisms:
 - ↑ catecholamines, i.e. worse stress
 - Increased cerebral acidosis and lactate
- Parson's et al by MRI and MR spectroscopy: proved a mechanistic link between hyperglycemia and increased infarct volume and lactate production



So What Else?

- Hamilton and Auer: Normalization of glucose levels with insulin ameliorates neuronal damage
- Insulin use in Diabetics with AMI decrease morbidity and mortality
- Strict glucose control with insulin decreased ICU mortality from 8% to 4.6% ($p < 0.04$)
- Whether due to euglycemia or neuroprotective effects is unknown

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Historical Observations

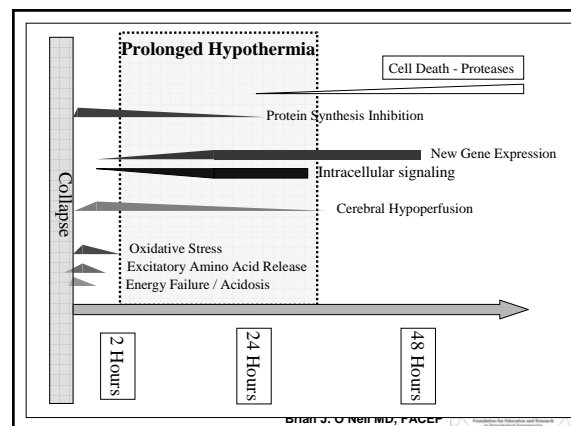
- Not Dead till Warm and Dead
 - Cold patients would wake up in the Morgue
- Kids / Hockey Players- fall through ice, long rescue times, but good recovery
- Hibernation: state of low oxygen, acidosis, low energy supply
- Basic science animal research showed promising results

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Hypothermia: Potential Mechanisms


- 6% ↓ in metabolic rate per 1° C reduction in brain temperature
- CMR declined to 50% after brain cooling to 32 degrees C (CBF & CMR coupled)
- blocks release of excitatory amino acid
- reduces early calcium rise
- reduces calpain specific and cytoskeletal damage

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Clinical Hypothermia

- Bernard et al (77 pts)
 - external cooling, ice bags, initiated by EMS at ROSC
 - 33.5 C within two hours ROSC cooled for 12 hours
 - Good outcome = 49% v 26%

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Clinical Hypothermia


- The European group, 136 pts,
 - VF arrest, comatose, stable hemodynamics
 - external cooling device,
 - 8 hours = median time to target Temp (32-34 C)
 - 14.4% did not reach target T°
 - Cooling for a mean of 24 hours
 - Good outcome = 55% v 39%

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Hypothermia: The Beaumont Experience

INCLUSION


- Patients with witnessed out of hospital cardiac arrest of presumed cardiac origin
- any initial rhythm that had ACLS within 15 minutes
- restoration of spontaneous circulation, (ROSC) within 60 mins of collapse
- able to obtain informed consent by representative/family member were enrolled

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Hypothermia: The Beaumont Experience

EXCLUSION

- temperature was < 35°C on admission
- pregnant
- had a purposeful response to verbal commands
- hypotension (MAP<60) for more than 30 mins
- oxygen saturation < 86% despite

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Methods

- Patients cooled to 33.5°C for 24 hours
- Gradually rewarmed to 36.0°C over 12 hours
- Outcomes CPC upon hospital discharge
- Hypothermic patients were compared to historical case matched normothermic controls from the OOHCA database maintained at WBH
 - Compared using witnessed arrest and GCS < 8, then by initial rhythm, bystander CPR, and age within 5 years



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Table 1: Baseline Characteristics

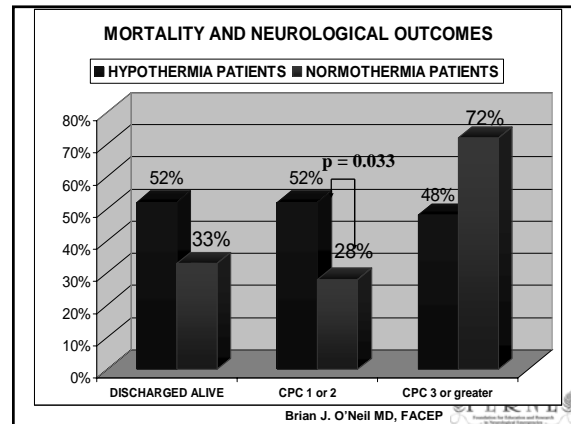
	HYPOTHERMIA PATIENTS	NORMOTHERMIA PATIENTS
DATES	5/05-9/06	1/97-2/06
TOTAL PTS	23	80
AGE AVG	65.8	67.9
Bystand CPR	13 (56%)	45 (56%)
INITIAL RHYTHM		
vfib	14 (61%)	62 (78%)
pea	4 (17%)	5 (6%)
asystole	5 (22%)	13 (16%)
ROSC AVG	21	14

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Patients Discharged Alive


	HYPOTHERM	NORMOTHERM	Chi Square
DISCHARGE ALIVE	12 (52%)	26 (33%) ^a	P = 0.085
AGE AVG (yrs)	62.5	59.9	
AGE RANGE (yrs)	16-90	40-85	
ROSC AVG (min)	14.7	11.2	

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CONCLUSION

- Patients who receive induced hypothermia after OOHCA have a significant increase in good neurological outcome when compared to normothermic case matched controls.

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What the Future Holds


- NMDA/ AMPA receptor antagonist and phase II trials have recently shown some efficacy in CHI
- Estradiols and Progesterone
- L-Name
- Coronary Bypass/ CPR on way to PCI
- Hypertensive, hemodilution, heparinization
- Hypothermia during resuscitation

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What the Future Holds

Opioid receptor antagonists:


- δ-, DADLE, κ opioid receptor, BRL-52537
- proteins trigger hibernation
 - opiate antagonists reverse hibernation
- pre-conditioning protein
 - myocytes and neurons
- mechanisms: ATP-K⁺ channels, PKC, free radicals
 - increases ERK and bcl-2

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What the Future Holds


Cannabinoids:

- most potent antioxidants known, (dexamabinol)
- Many receptor similarities to opioids
- Receptors in hippocampus, Basal ganglia and cerebellum
- Affect glutamate, GABA, Norepinephrine and dopamine release

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CONCLUSIONS


- If you do not learn from history you are doomed to repeat their mistakes
- There are no silver bullets
 - Multiple pathways : multiple therapies
 - Single therapy with multiple effects
- Make them euboxic
- Tight glucose control
- Optimize supply and demand
- Stress Dose Steroids
- Strongly Consider Hypothermia

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COOL-MI Study Objective

To evaluate:

the safety and effectiveness of cooling as an adjunctive therapy to primary PCI for acute myocardial infarction compared to PCI alone

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Study Design


Acute MI < 6 hours
 Anterior MI
 Inferior MI with reciprocal changes

Primary PCI Primary PCI & Endovascular Cooling

Infarct size 30-days (SPECT)
 MACE 30-days

Major Exclusion Criteria:

- Previous MI within one month
- Cardiogenic shock
- Hypersensitivity to hypothermia, buspirone, or meperidine
- IVC filter in situ

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Endovascular Cooling Protocol


Cooling (ER or Cath Lab) Primary PCI Re-warming started

Target Temp = 33°C
 3-hours 1°C/hr

Meperidine infusion 25-30 mg/hr*
 Forced Air Blanket (BairHugger)

Buspirone 60mg oral Meperidine 50-75mg initial
 25-50mg at 15 minutes

*Meperidine bolus 12.5-25mg for shivering

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Study Population

Total (n=421)

Randomized (n=392)
 193 T / 199 C

Roll-in (n=29)

ITT Failures (n=35)
 16 T / 19 C


ITT* (n=357)
 177 T / 180 C

Death (n=10)
 6 T / 4 C

No SPECT (n=22)
 4 T / 18 C

With SPECT (n=325)
 167 T / 158 C


* ITT Group = PCI performed; Cooling attempted

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Anterior MI Subgroup Stratified by Temperature

Infarct Size (% LV)

Group	n	Infarct Size (% LV)
All Cool	61	17.9
<35 C	16	9.3
>35 C	38	21.9
Control	59	18.2

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Questions?

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