EUROPEAN RESUSCITATION COUNCIL

RESUSCITATION 2018

New technologies in resuscitation

20 - 22 September • Bologna • Italy

Will this patient recover consciousness after cardiac arrest?

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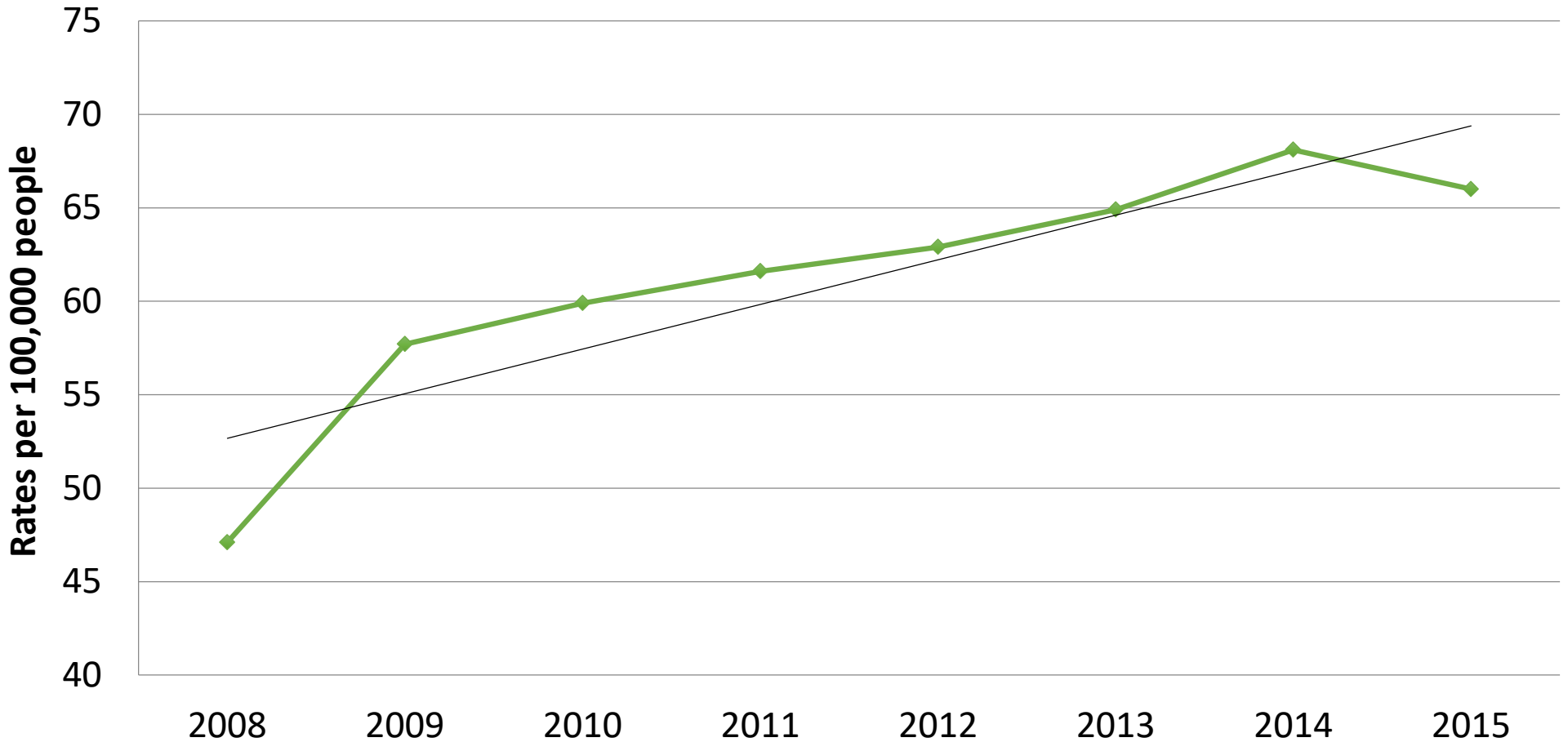
COI

- Intellectual
  - Lead author, ERC-ESICM Advisory Statement on Prognostication After Cardiac Arrest
  - Author, ERC-ESICM Guidelines on Post-Resuscitation Care
  - Deputy Chair, Trauma and Emergency Medicine Section, European Society of Intensive Care Medicine (ESICM)

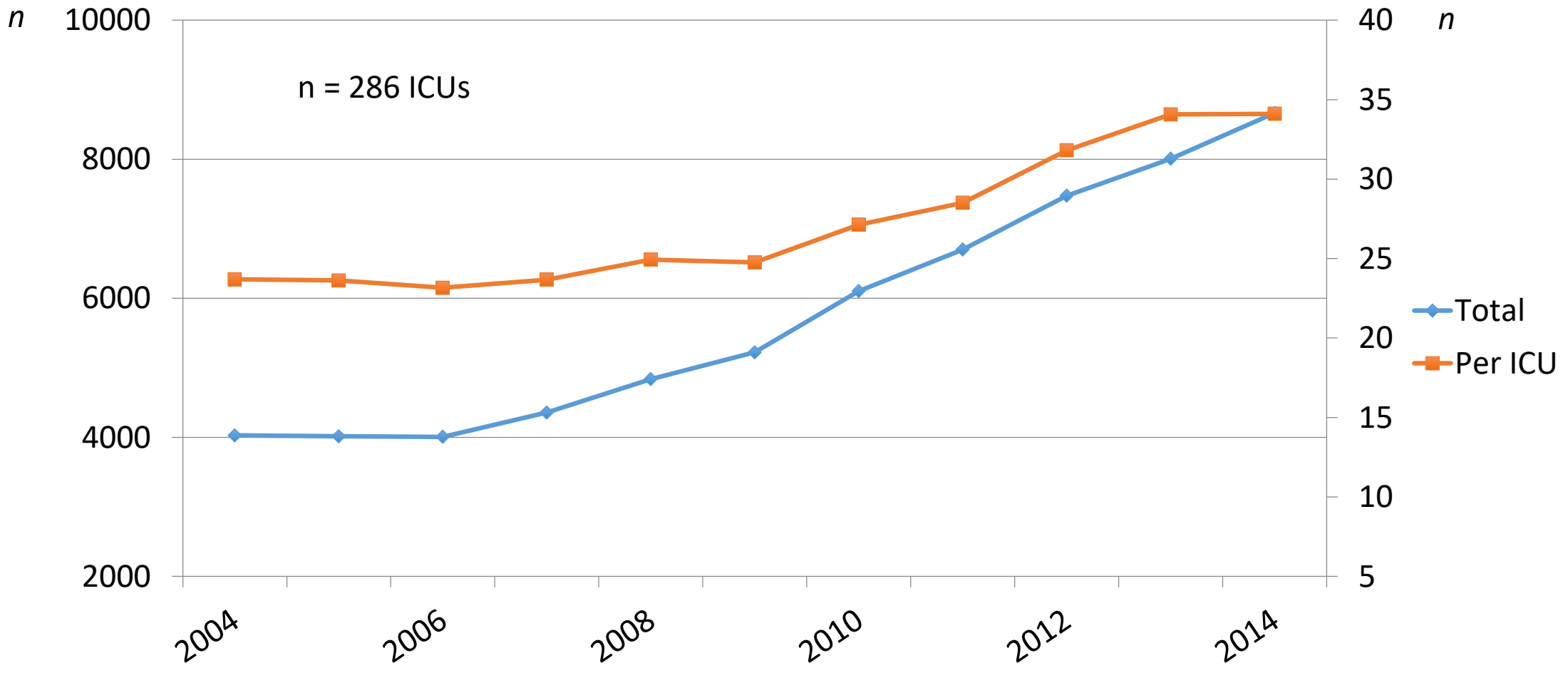

Every minute someone has a cardiac arrest

Incidence of resuscitated OHCA



Data from 9 ROC (Resuscitation Outcomes Consortium) EMS agencies, *unpublished*.

Post-CA admissions in UK, 2004-2014



Nolan et al. Critical Care 2016; 20:219.

Intensive Care Med (2013) 39:1972–1980
DOI 10.1007/s00134-013-3043-4

ORIGINAL

Virginie Lemiale
Florence Dumas
Nicolas Mongardon
Olivier Giovanetti
Julien Charpentier
Jean-Daniel Chiche
Pierre Carli
Jean-Paul Mira
Jerry Nolan
Alain Cariou

Intensive care unit mortality after cardiac arrest: the relative contribution of shock and brain injury in a large cohort

- 1150 comatose survivors of out-of-hospital cardiac arrest (OHCA)
- 768 (66%) died before hospital discharge, of whom

  → 499 (65%) from hypoxic-ischaemic brain injury (**HIBI**)

Lemiale V et al, *Intensive Care Med* 2013; 39: 1972–80

SYSTEMATIC REVIEW

The rate of brain death and organ donation in patients resuscitated from cardiac arrest: a systematic review and meta-analysis

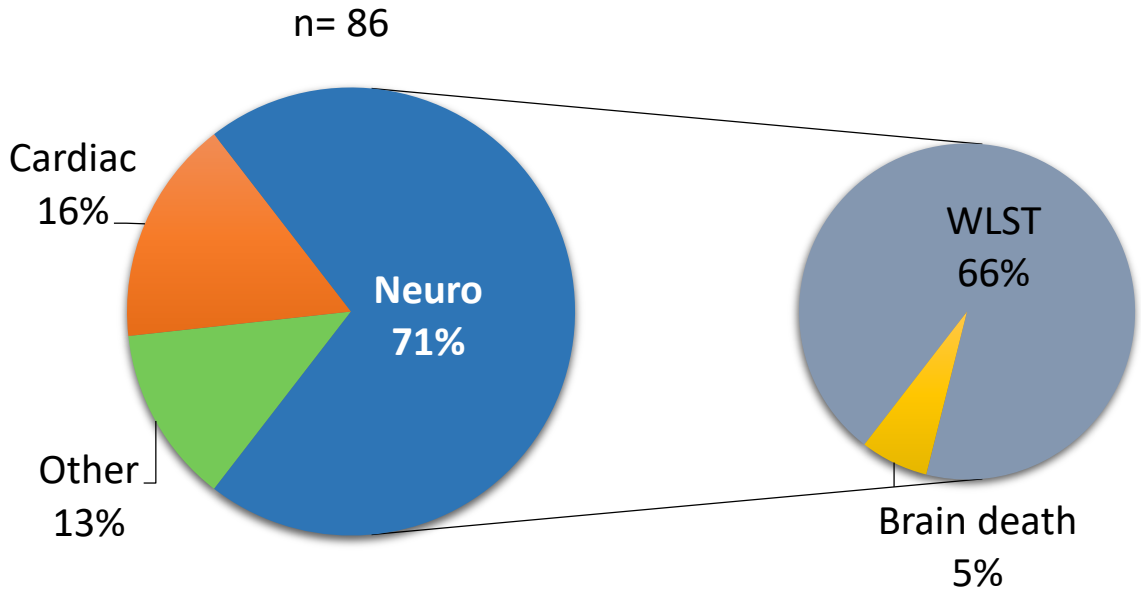
Claudio Sandroni[1*], Sonia D'Arrigo[1], Clifton W. Callaway[2], Alain Cariou[3], Irina Dragancea[4], Fabio Silvio Taccone[5] and Massimo Antonelli[1]

- 23,388 patients in 26 studies
- 1830 brain deaths @ 3.2 ± 0.4 days after ROSC
- Brain death: **12.6** [10.2-15.2]**%** of total deaths

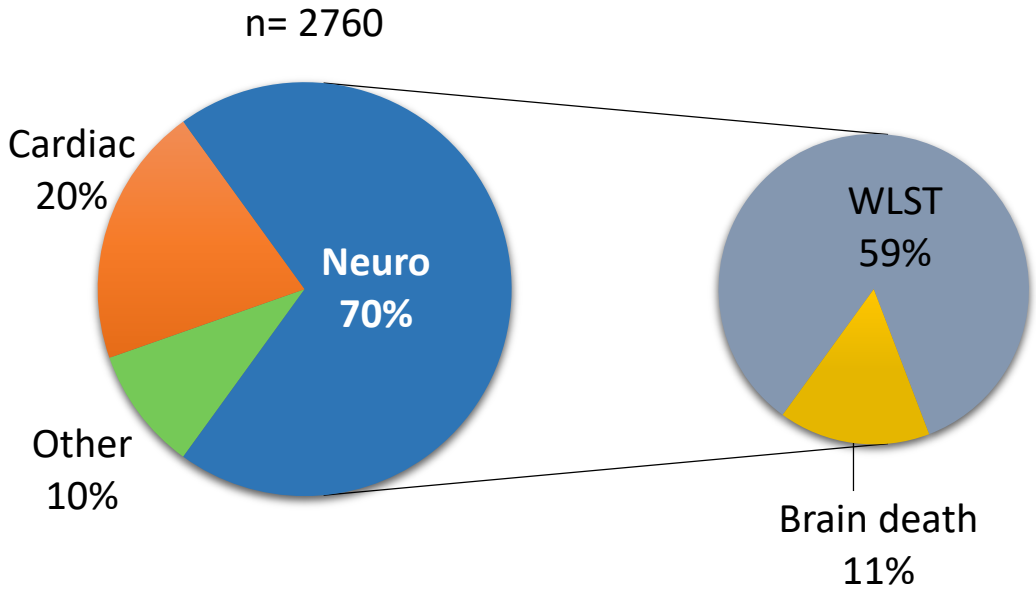
Sandroni et al, Intensive Care Med 2016; 42:1661–1671

Causes of death after resuscitation

- Dragancea 2013, Sweden



- Elmer 2016, USA



WLST = Withdrawal of Life-Sustaining Treatment

Dragancea I et al Resuscitation 2013; 84:337-42

Elmer J et al Resuscitation 2016; 102:127-35

WLST is the main mechanism of death after resuscitation

Prognostic tests

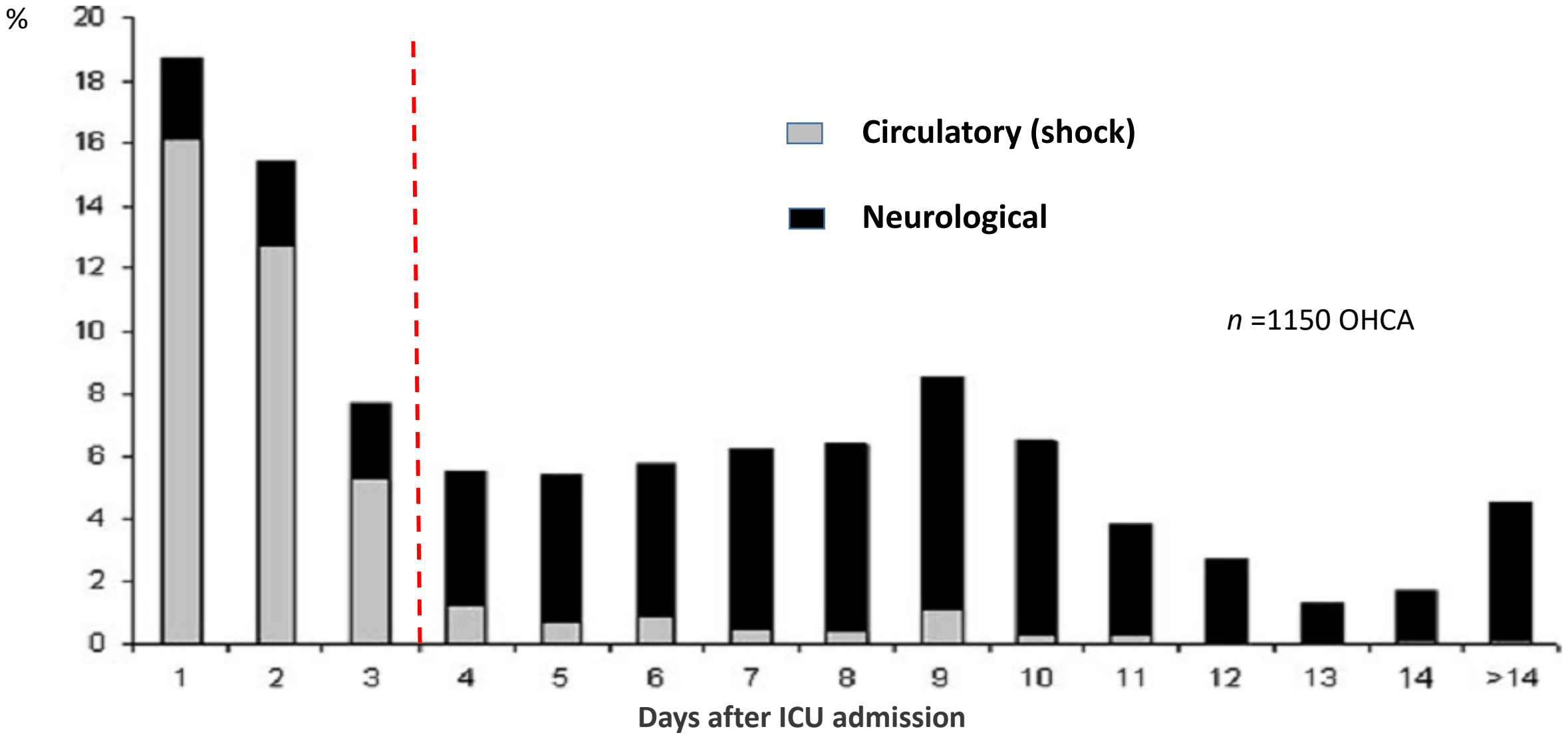
- Prognostication currently means predicting *poor* outcome
- Ideal test:
  - False positive rate (FPR) = 0% = 100% specificity
  - Minimal imprecision = narrow 95% CIs

Prognostication is a time-dependent process

3 reasons for waiting 3 days

1. Cardiovascular instability

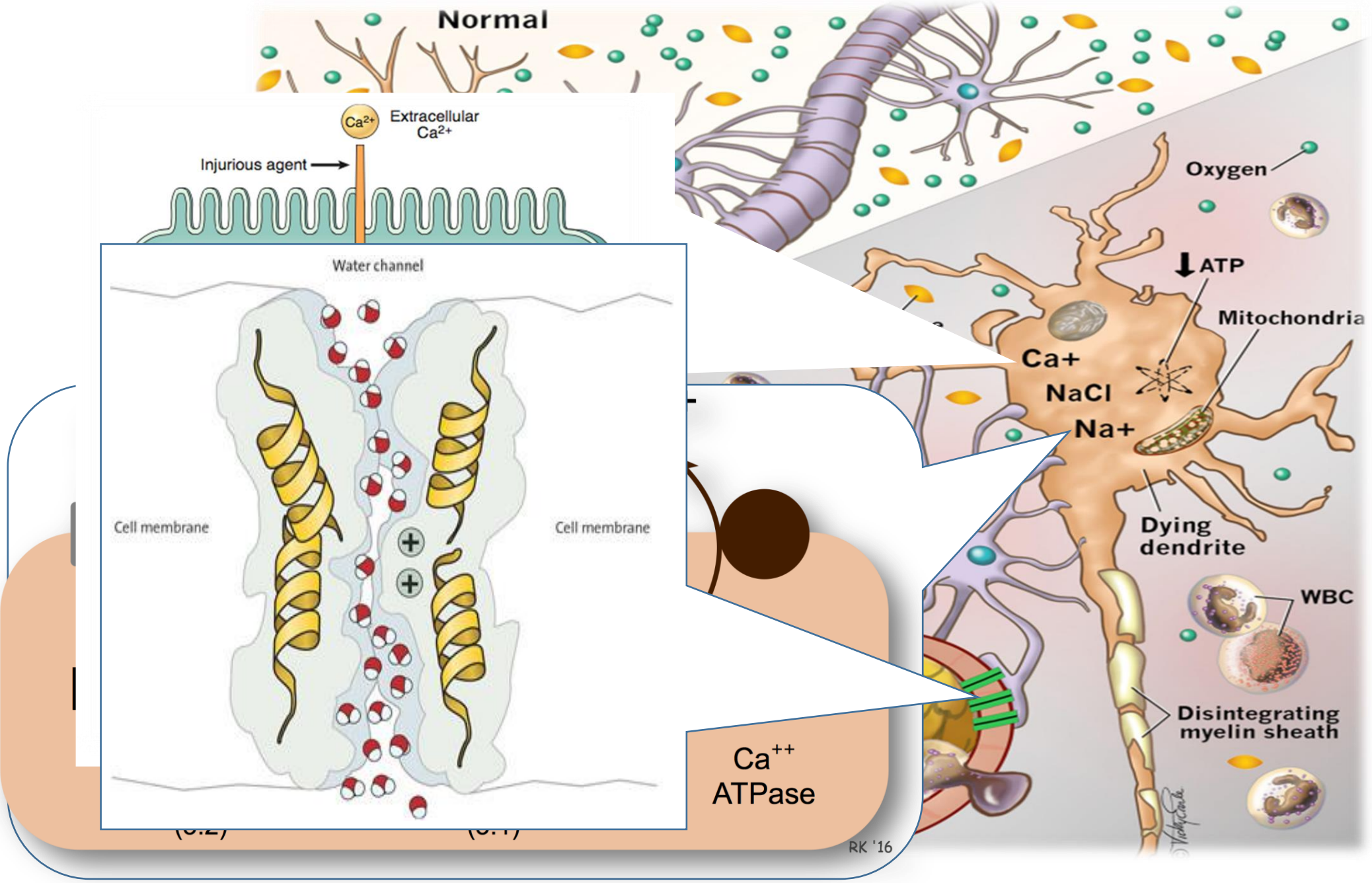
Causes of death after cardiac arrest



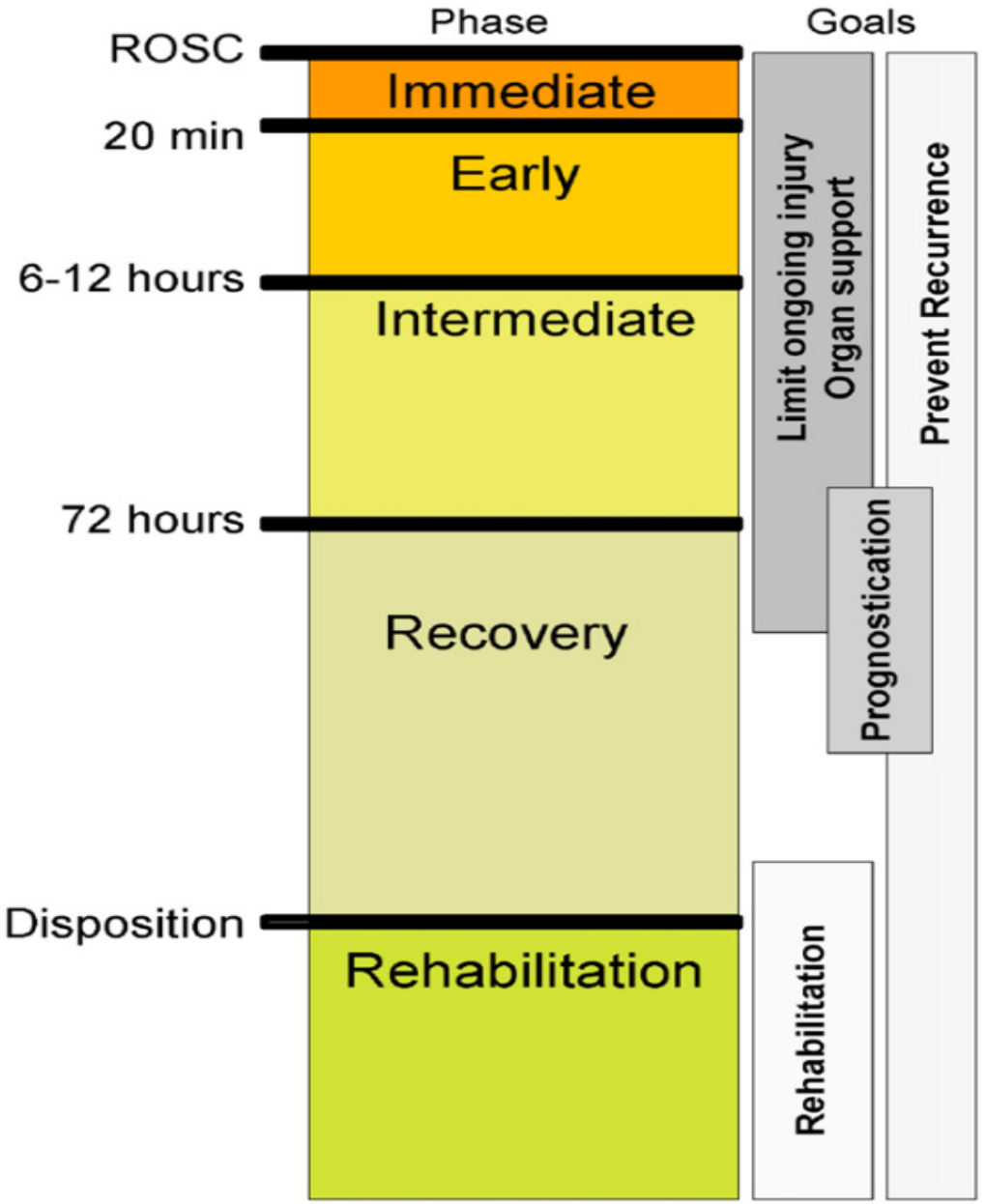
Lemiale V et al, Intensive Care Med 2013; 39: 1972–80

3 reasons for waiting 3 days

1. Cardiovascular instability
2. HIBI develops over time

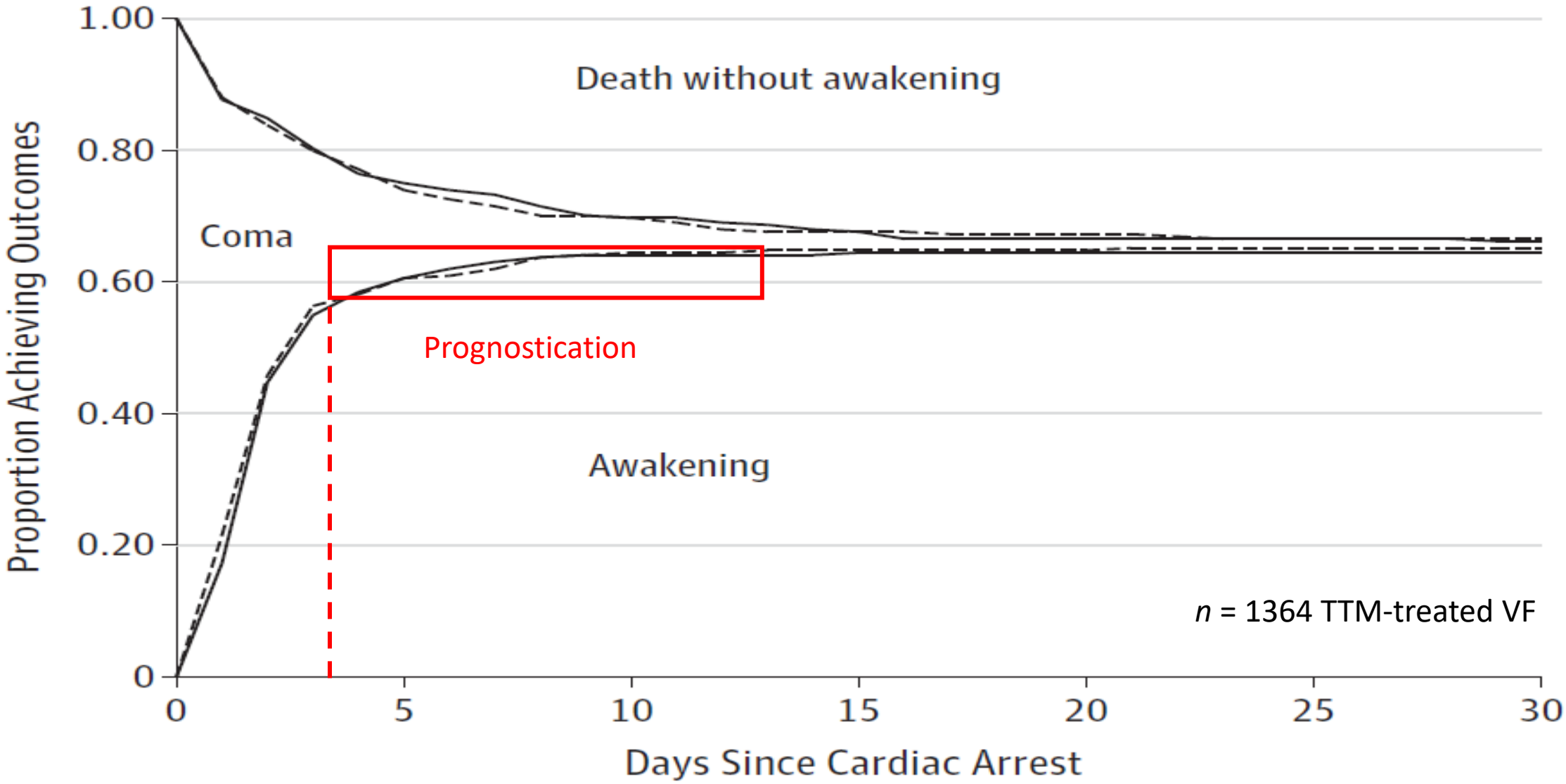

Normal
Ca2+
Extracellular Ca2+
Injurious agent
Water channel
Cell membrane
Cell membrane
Oxygen
ATP
Mitochondria
Ca+
NaCl
Na+
Dying dendrite
WBC
Disintegrating myelin sheath
Ca++ ATPase
RK '16

Post- CA syndrome

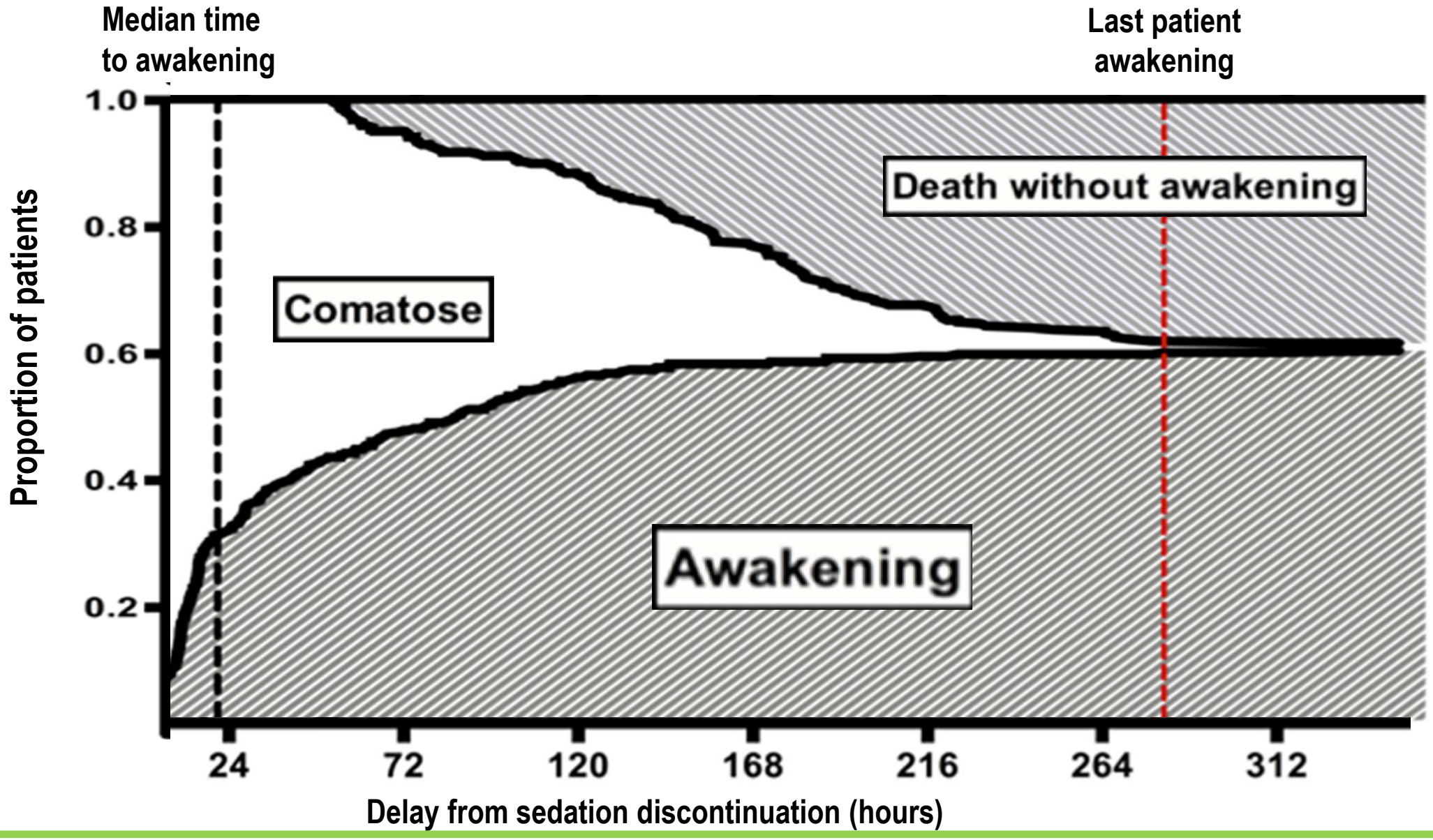


3 reasons for waiting 3 days

1. Cardiovascular instability
2. HIBI develops over time
3. Awakening



Kim et al *JAMA* 2014; 311:45-52

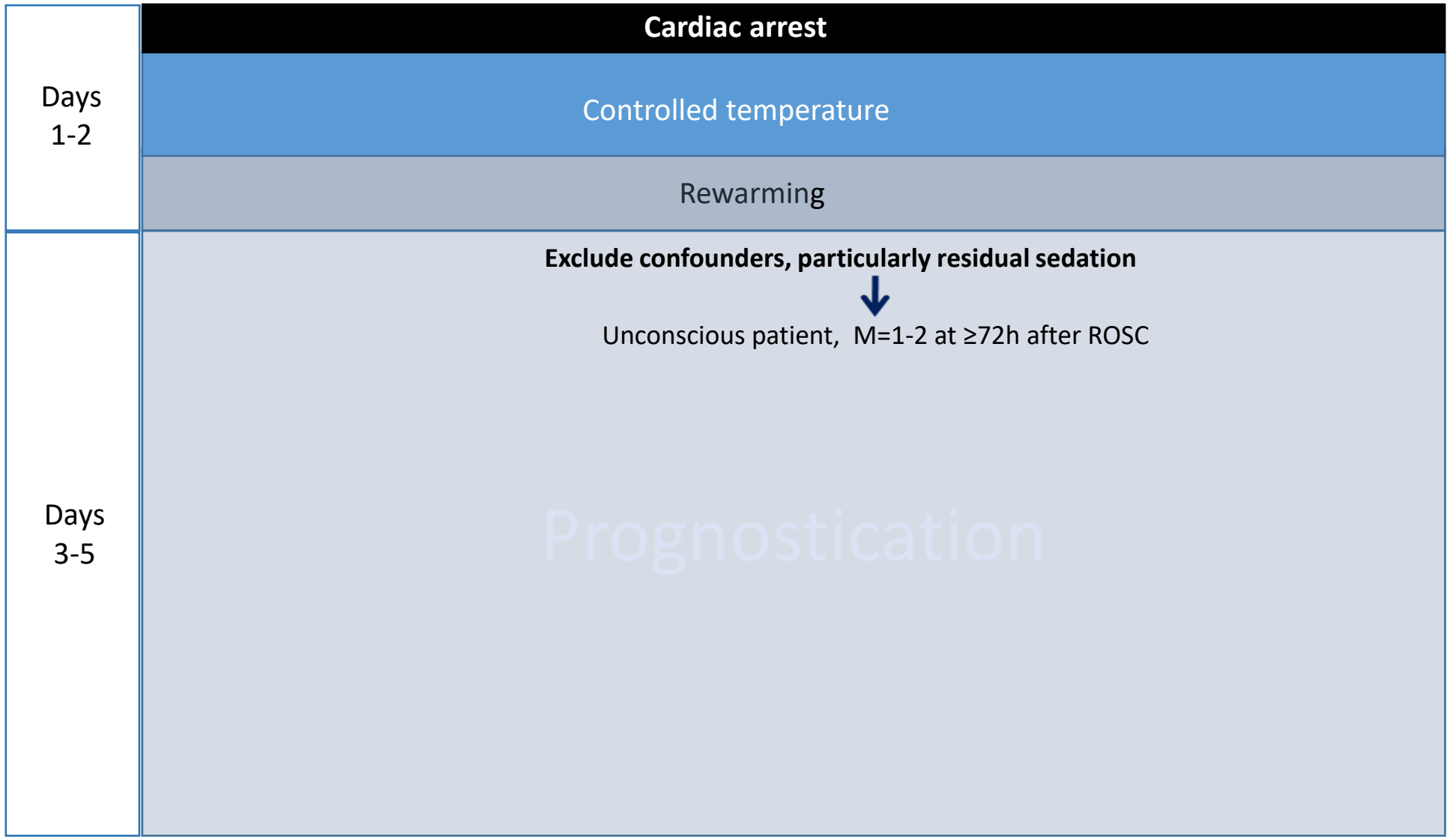


n = 326

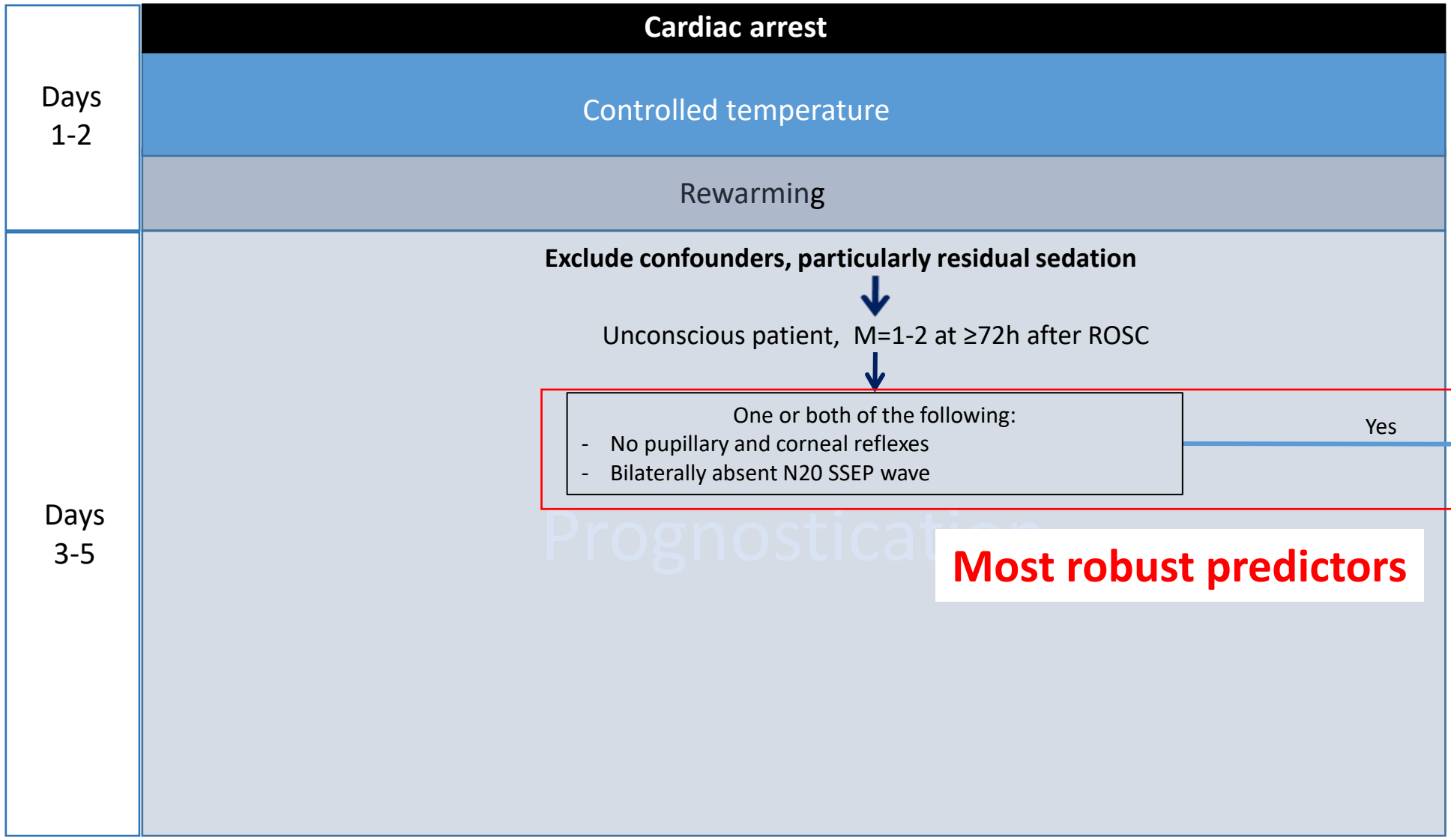
Paul M et al. Intensive Care Med 2016; 42: 1128-1136.

We prognosticate in patients who…

- Do not awaken after a reasonable time after ROSC
  - Major confounders must be excluded
- Have signs of severe cerebral damage
  - GCS = 3-4 (M=1-2)



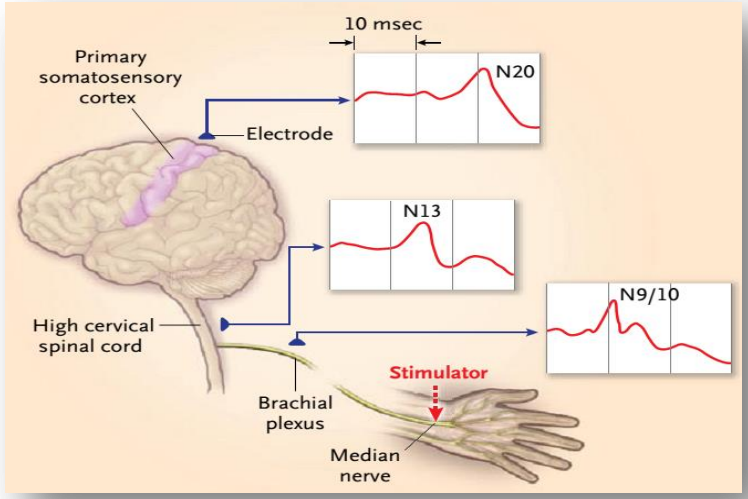
Sandroni C et al., Intensive Care Med 2014; 85:1779-89 - Resuscitation 2014; 40:1816-31.



Sandroni C et al., Intensive Care Med 2014; 85:1779-89 - Resuscitation 2014; 40:1816-31.

Pupillary light response (PLR) and short-latency SSEP at 72 h

- FPR: 0.4 [0-2]%
- Sensitivity: 23 [19-28]%
- Total patients: 546



- FPR: 0.5 [0-3]%
- Sensitivity: 49 [44-54]%
- Total patients: 577

Kamps M, Intensive Care Med 2013;39:1671-82
Sandroni C et al., Resuscitation 2013;84:1324-38

PLR and SSEP: limitations

- Lack of blinding
  - Risk of self-fulfilling prophecy

PLR: limitations

- Lack of standardisation
  - Intensity
  - Duration
  - Distance
  - Environmental light
- Qualitative
  - Interater agreement for reactivity only moderate (κ= 0.40)

Olson et al. Neurocrit Care. 2016 ; 24:251-7

Automated pupillometry

- Standardised
- Quantitative
- Potential for blinded testing

Solari et al. Ann Neurol 2017;81:804–810

Annals of NEUROLOGY

Early Prediction of Coma Recovery after Cardiac Arrest with Blinded Pupillometry

Daria Solari,[1] Andrea O. Rossetti,[3] Laurent Carteron,[1,2,4] John-Paul Miroz,[1,2] Jan Novy,[3] Philippe Eckert,[1] and Mauro Oddo [1,2]

n = 103

Tool	Criterion	Sensitivity	Specificity
Pupillometry	qPLR <13%	61 (48-75)	100 (93-100)
SSEP	Absent N20	52 (37-67)	100 (92-100)

1-y survivors vs. non-survivors

Solari et al. Ann Neurol 2017;81:804–810

Annals of NEUROLOGY

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n = 103

Pupillometry	Non-survivors	Survivors	*p*
Baseline, mm	2.3 (1.4–7.6)	2.2 (1.2–5.3)	0.379
Constriction, %	11 (0–55)	20 (13–41)	<0.001
Constriction velocity, mm/s	0.94 (0.16–4.97)	1.46 (0.85–4.63)	<0.001

Values are expressed as median (range)

Automated pupillometry for coma prognostication after cardiac arrest (NCT02607878)

- Multicentre (#10)
- Blinded
- Comparison with other predictors
- Manuscript in preparation

NIH U.S. National Library of Medicine
ClinicalTrials.gov

PLR and SSEP: limitations

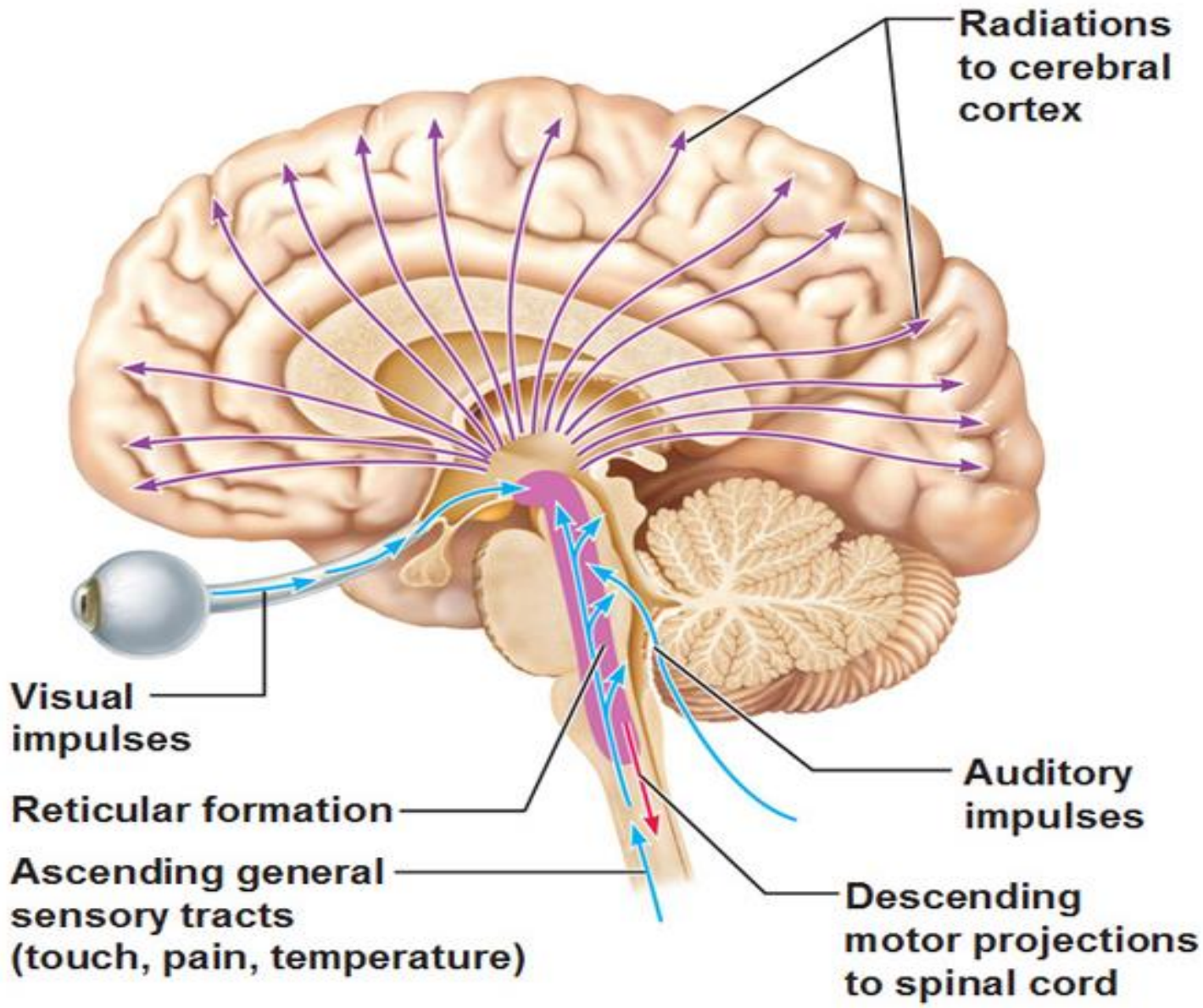
- Lack of blinding
  - Risk of self-fulfilling prophecy
- Low sensitivity
  - 25% PLR, 50% SSEP

Neural correlates of consciousness

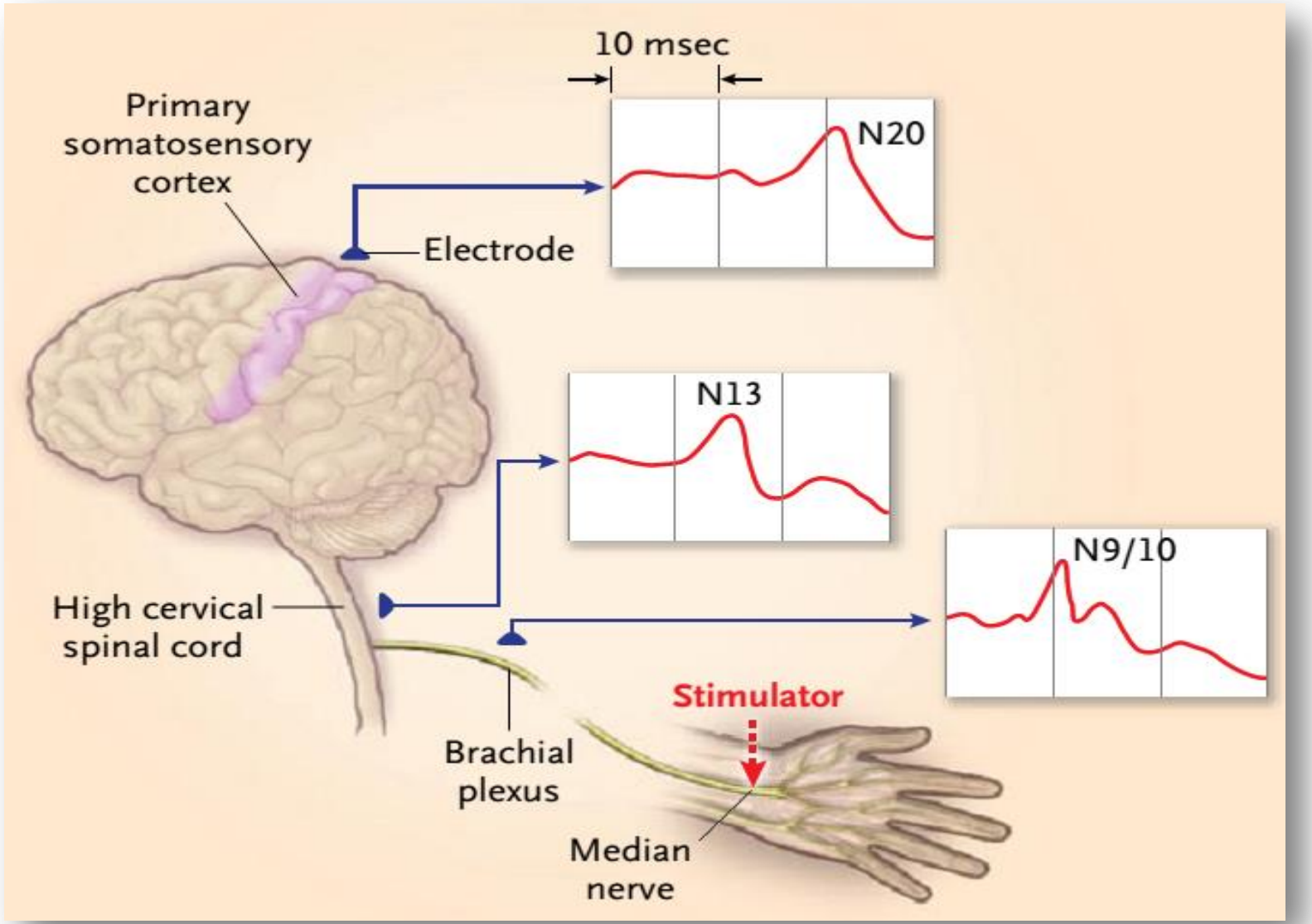
The missing link in neuroprognostication

A test for specifically investigating the circuits that maintain consciousness

Reticular activating system



Short-latency SSEP



Karen Ann Quinlan, 1954-1985

- April 15, 1975: OHCA from overdose
- PVS for > 10 years
- Never regained consciousness

The New England
Journal of Medicine

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Volume 330 MAY 26, 1994 Number 21

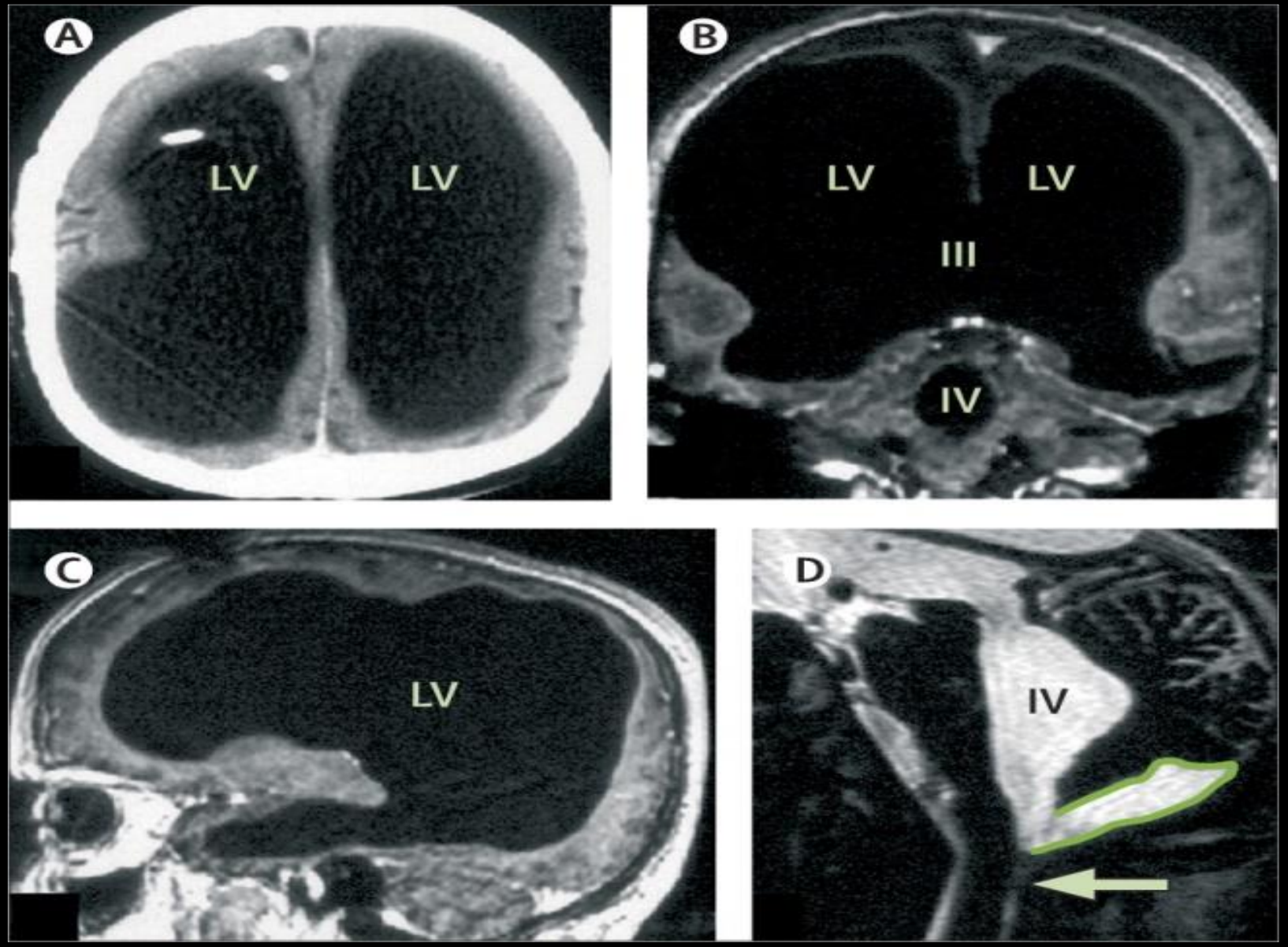
NEUROPATHOLOGICAL FINDINGS IN THE BRAIN OF KAREN ANN QUINLAN

HANNAH C. KINNEY, M.D., JULIUS KOREIN, M.D., ASHOK PANIGRAHY, B.A., PIETER DIKKES, B.A., AND ROBERT GOODE, M.D.

Kinney et al., NEJM 1994; 330:469-75

Massive hydrocephalus

- Male, 44y
- Married
  - Father of 2 children
- White-collar worker

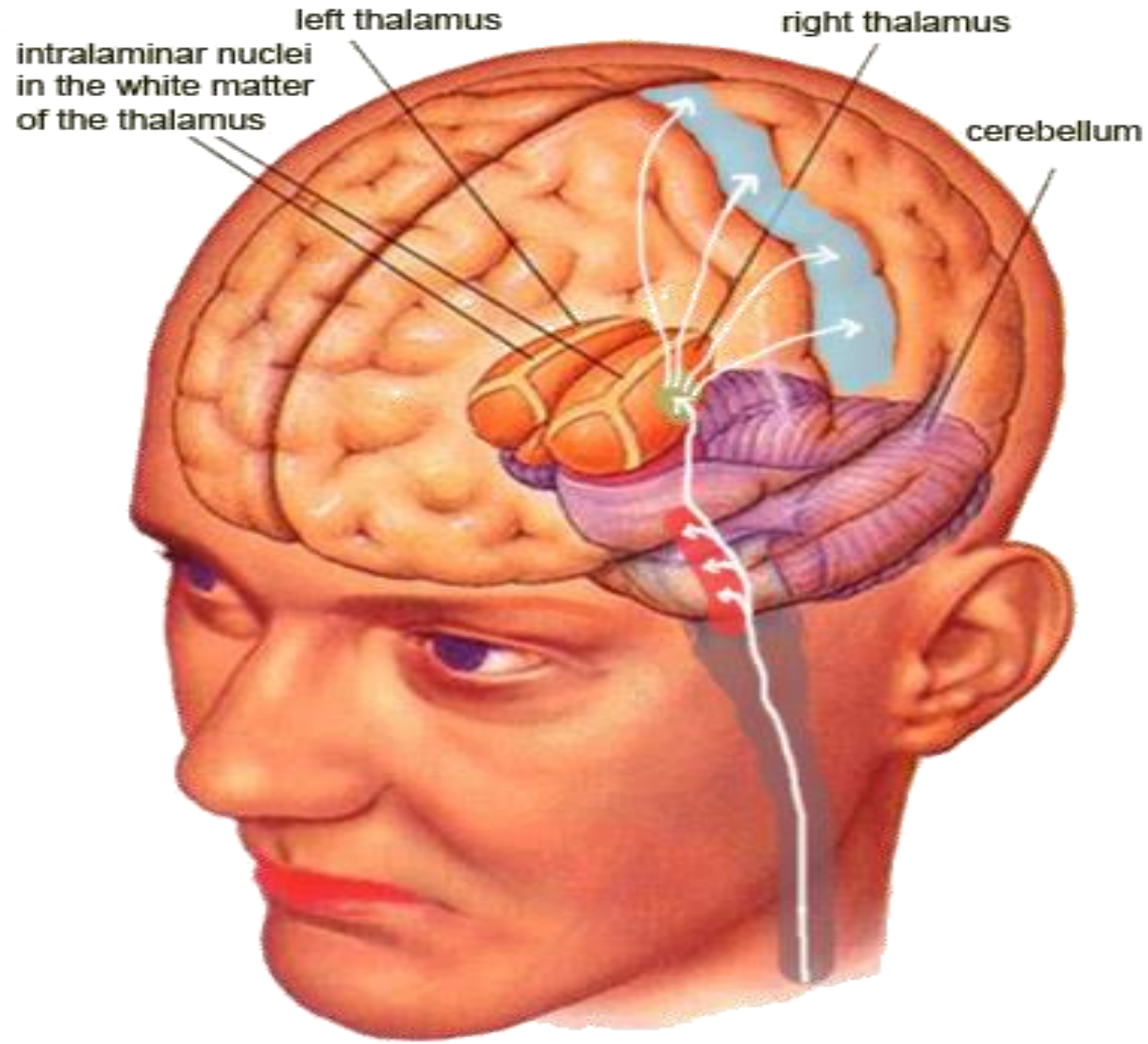


Feuillet et al. Lancet 2007;370(9583):262

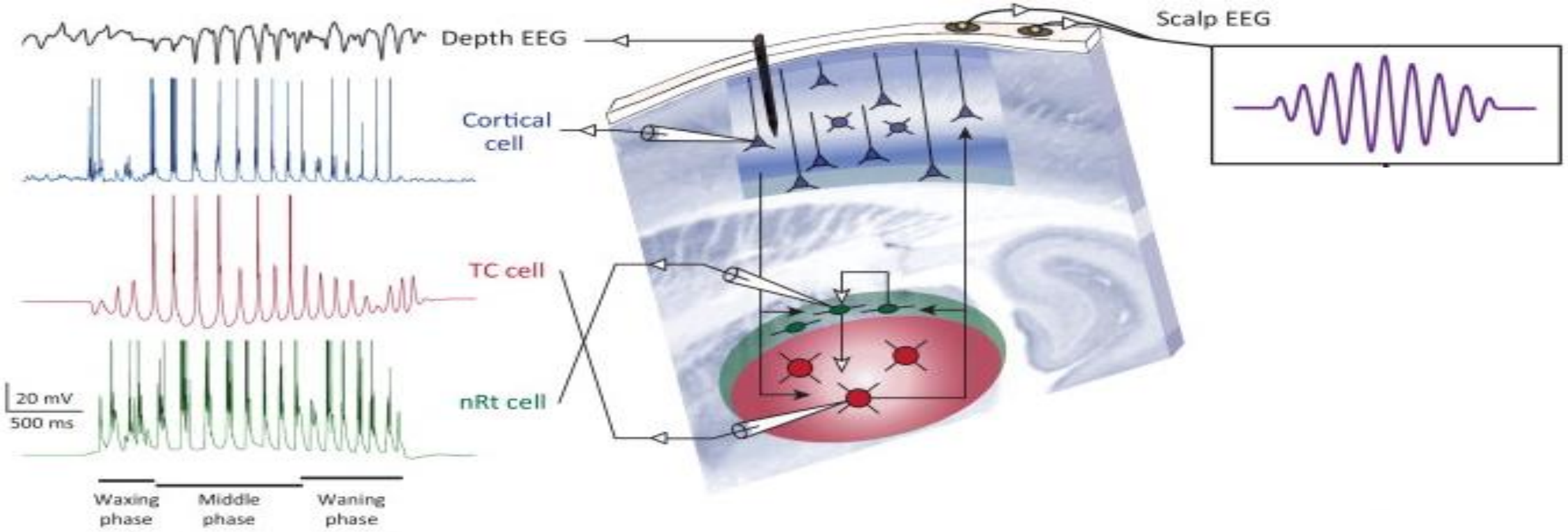
Kinney et al., NEJM 1994; 330:469-75

Is thalamus the key?

Thalamo-reticular connections

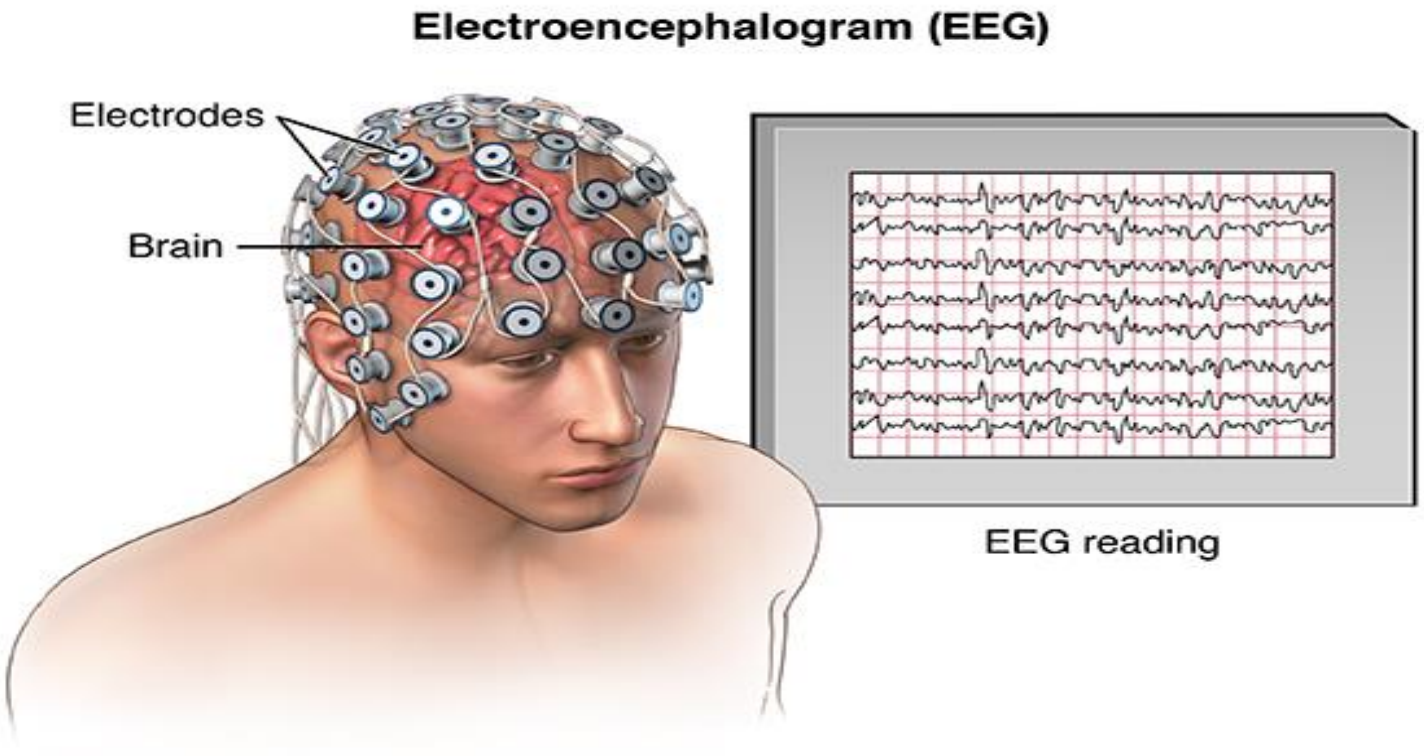


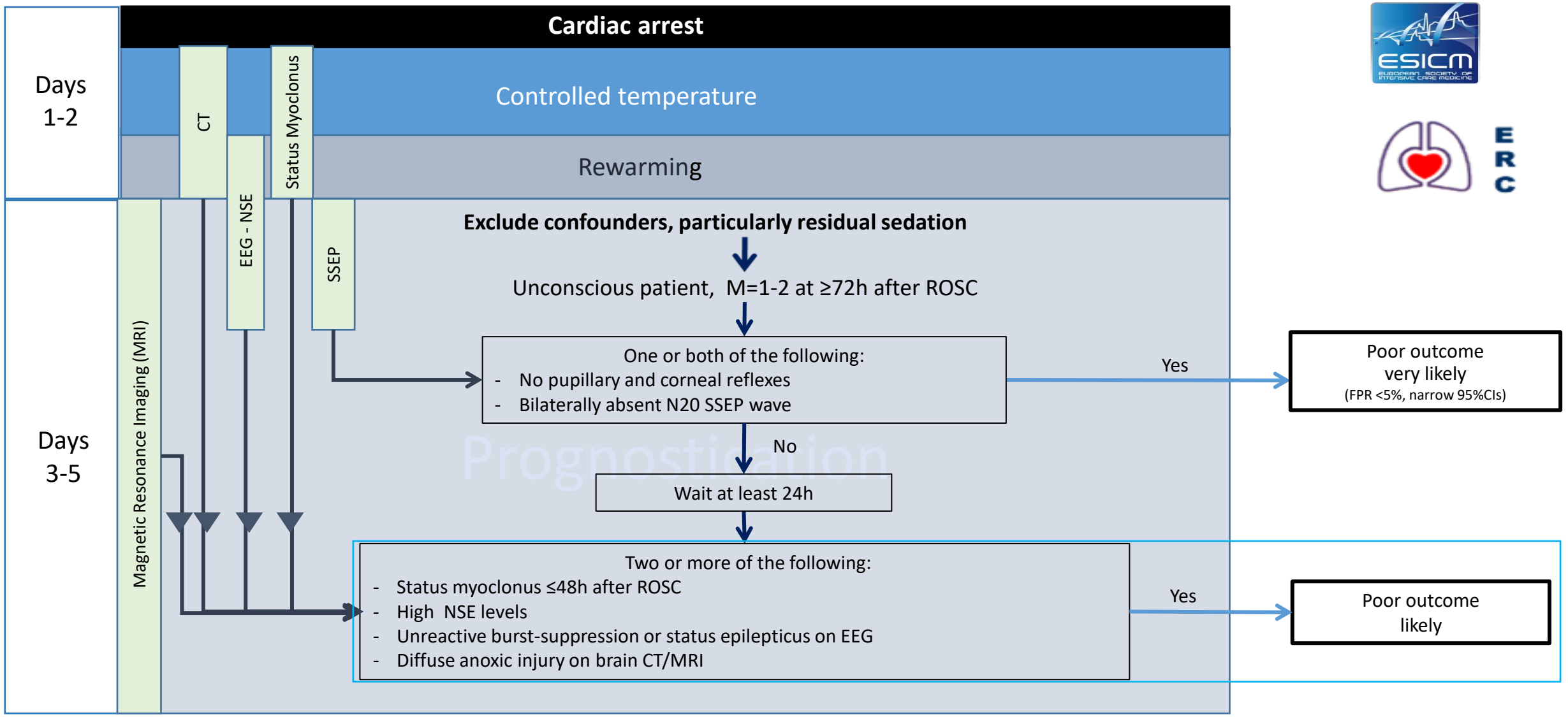
Cortico-thalamic circuits



Astori et al Trends Neurosci 2013; 12:738-48

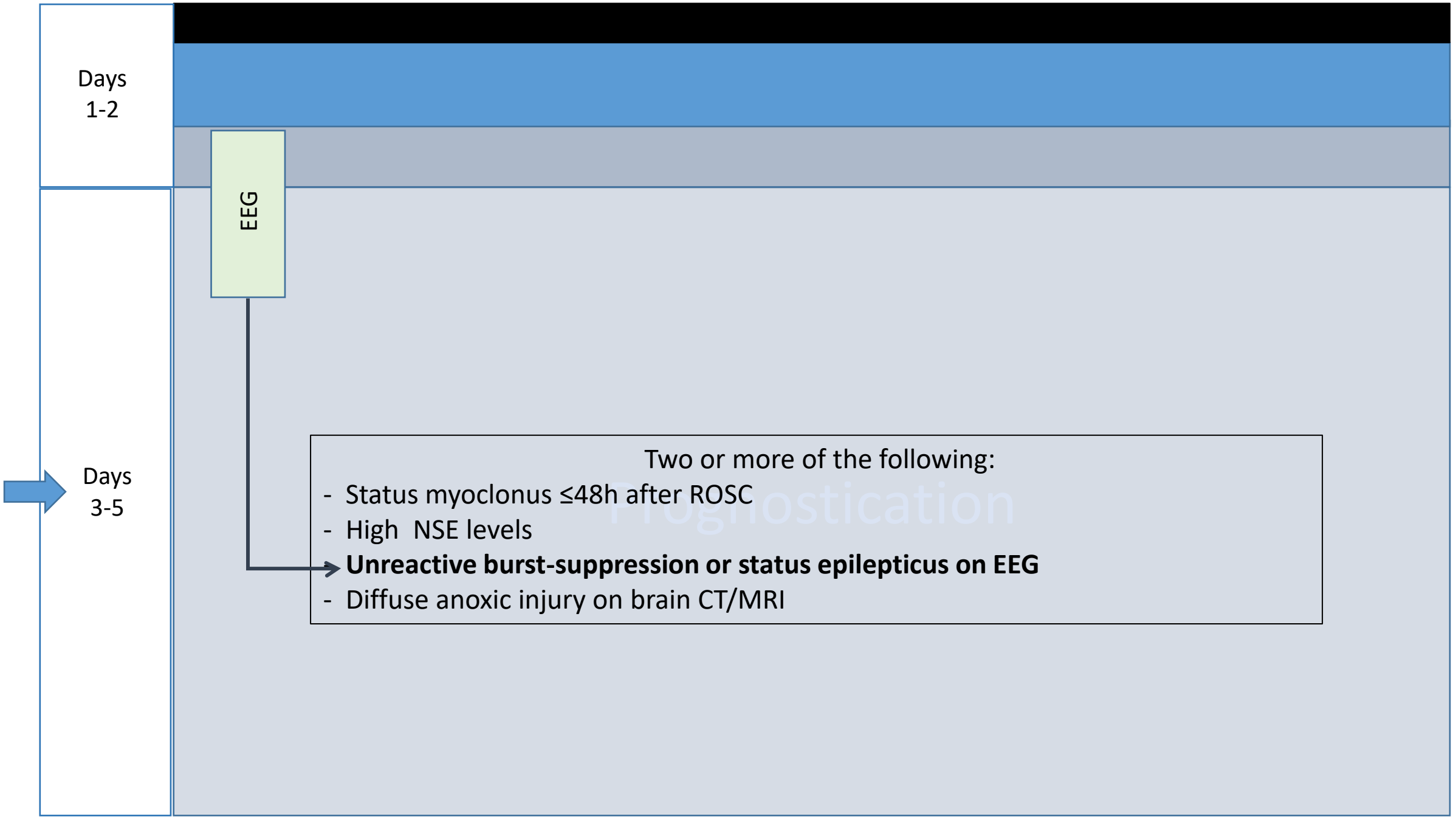
Electroencephalogram (EEG)





Less robust predictors

Sandroni C et al., Intensive Care Med 2014; 85:1779-89 - Resuscitation 2014; 40:1816-31.

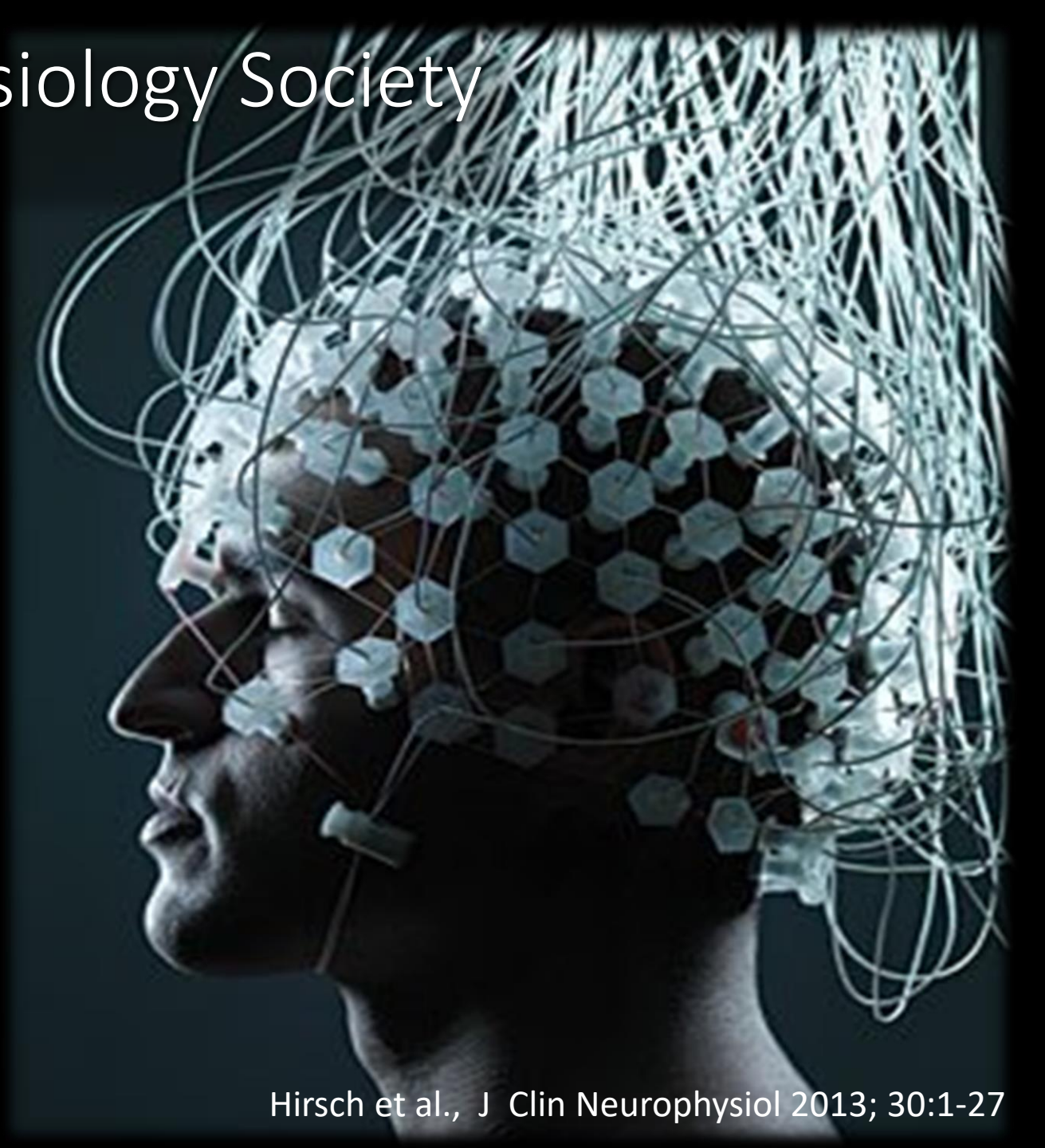

Days
1-2
EEG
Days
3-5
Two or more of the following:
- Status myoclonus ≤48h after ROSC
- High NSE levels
- **Unreactive burst-suppression or status epilepticus on EEG**
- Diffuse anoxic injury on brain CT/MRI

American Clinical Neurophysiology Society (ACNS) terminology

For use in Critical Care

Standard definitions:

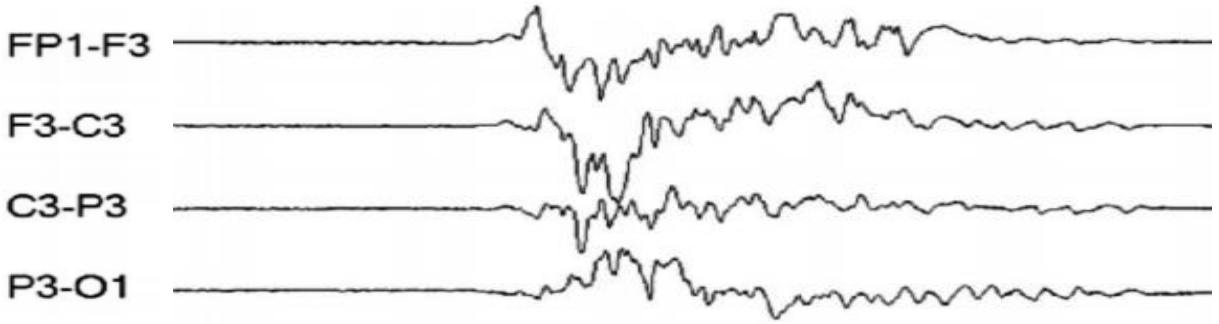
- Voltage
- Burst-suppression
- Epileptiform discharges



Hirsch et al., J Clin Neurophysiol 2013; 30:1-27

Highly malignant EEG patterns in HIBI

Suppressed background
± periodic discharges



Burst-suppression

- N = 103 patients with HIBI
- ACNS definitions
- Substantial interrater agreement (κ = 0.71) among four specialists

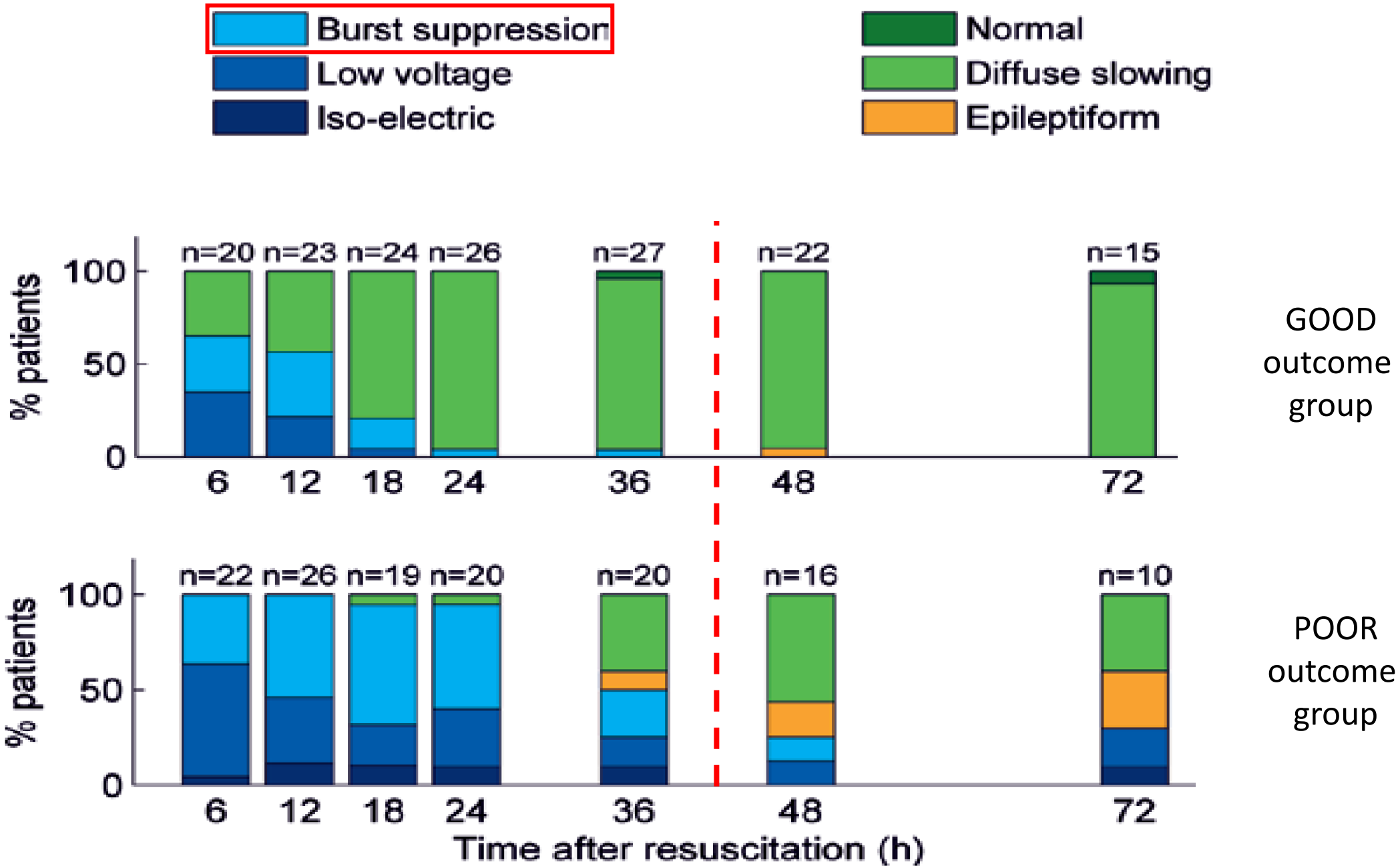
Westhall et al. Clin Neurophysiol 2015; 126:2397-404.

Highly malignant EEG @ 24-72h

Author	n	Timing (h)	Sensitivity	Specificity
Sivaraju 2015	124	24	83 (72-90)	100 (96-100)
Rossetti 2017	367	24-48	69 (61-75)	99 (96- 100)
Westhall 2016	103	48-72	50 (39-61)	100 (91-100)
TOTAL	**584**		**67 (61-72)**	**99 (97-100)**

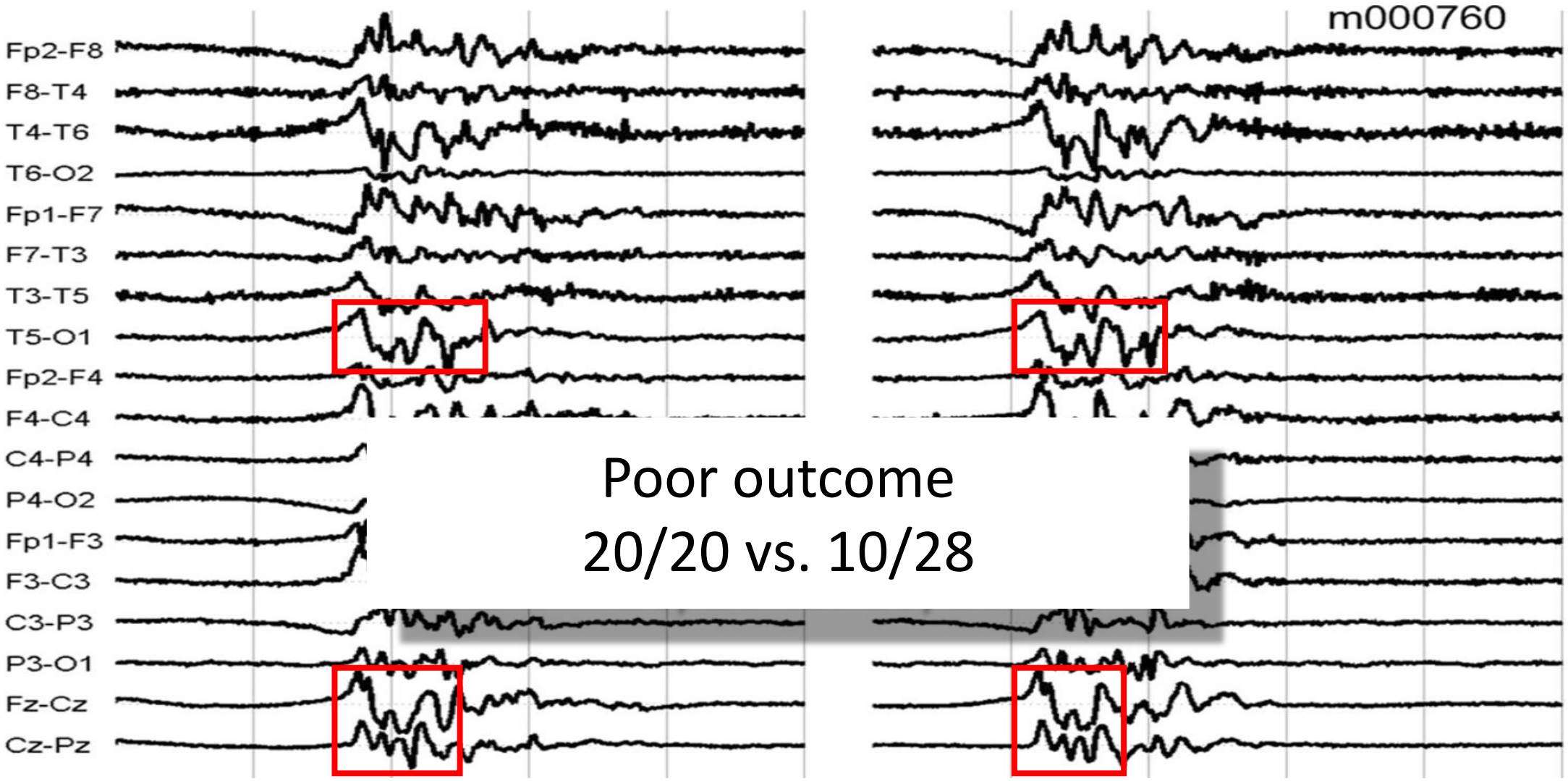
Sivaraju et al, Int Care Med 2015; 41:1264–1272 – Rossetti, Crit Care Med 2017; 45: e674-e682 - Westhall Neurology 2016; 86: 1482-1490

Can EEG predict earlier?



Cloostermans MC Crit Care Med 2012; 40: 2867-75.

Identical bursts at 12-36h



Poor outcome
20/20 vs. 10/28

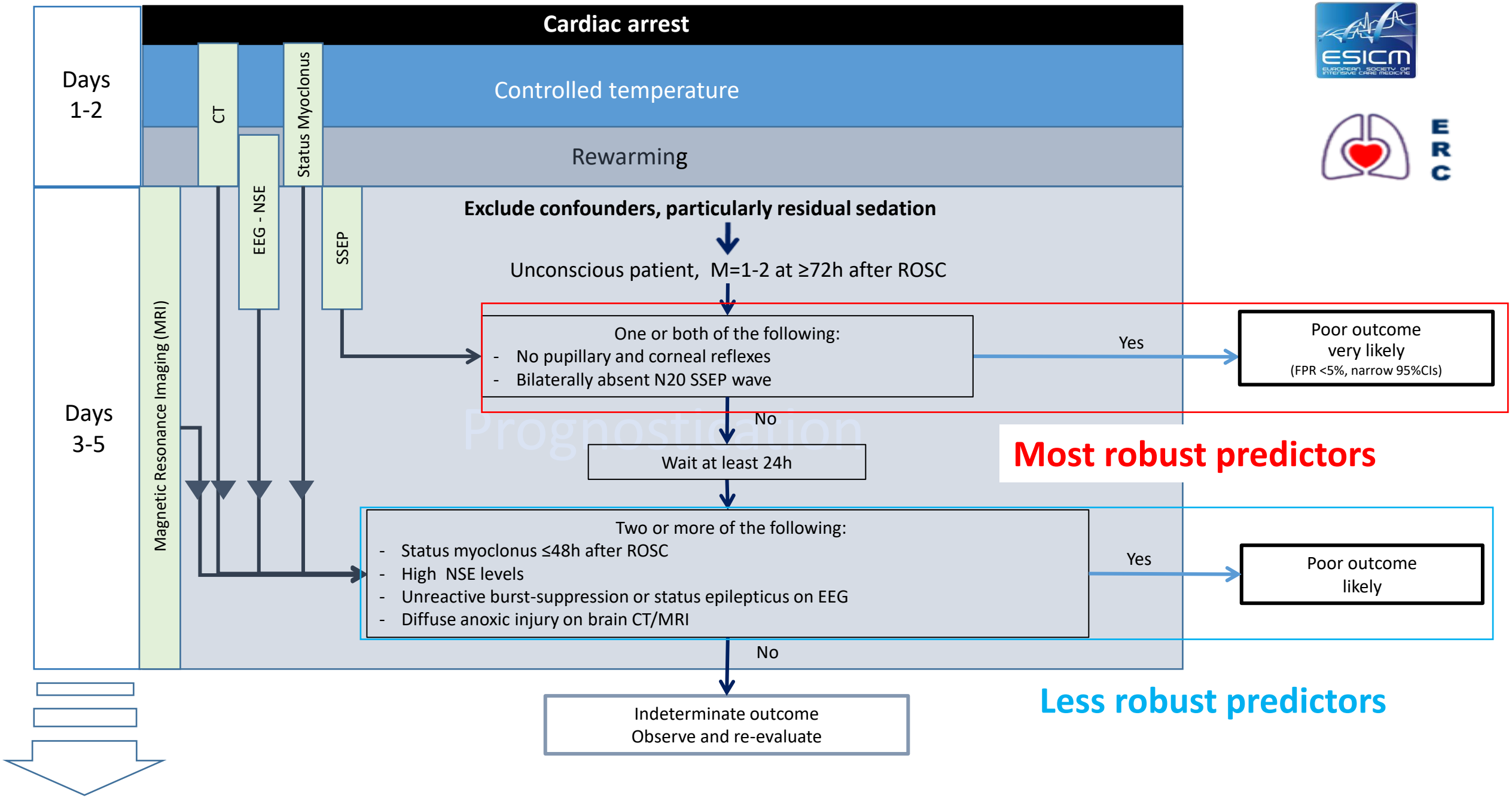
Hofmeijer et al, Clinical Neurophysiology 2014; 125: 947–954

EEG

- Functional
- Standardised
- Available at bedside

Malignant EEG patterns

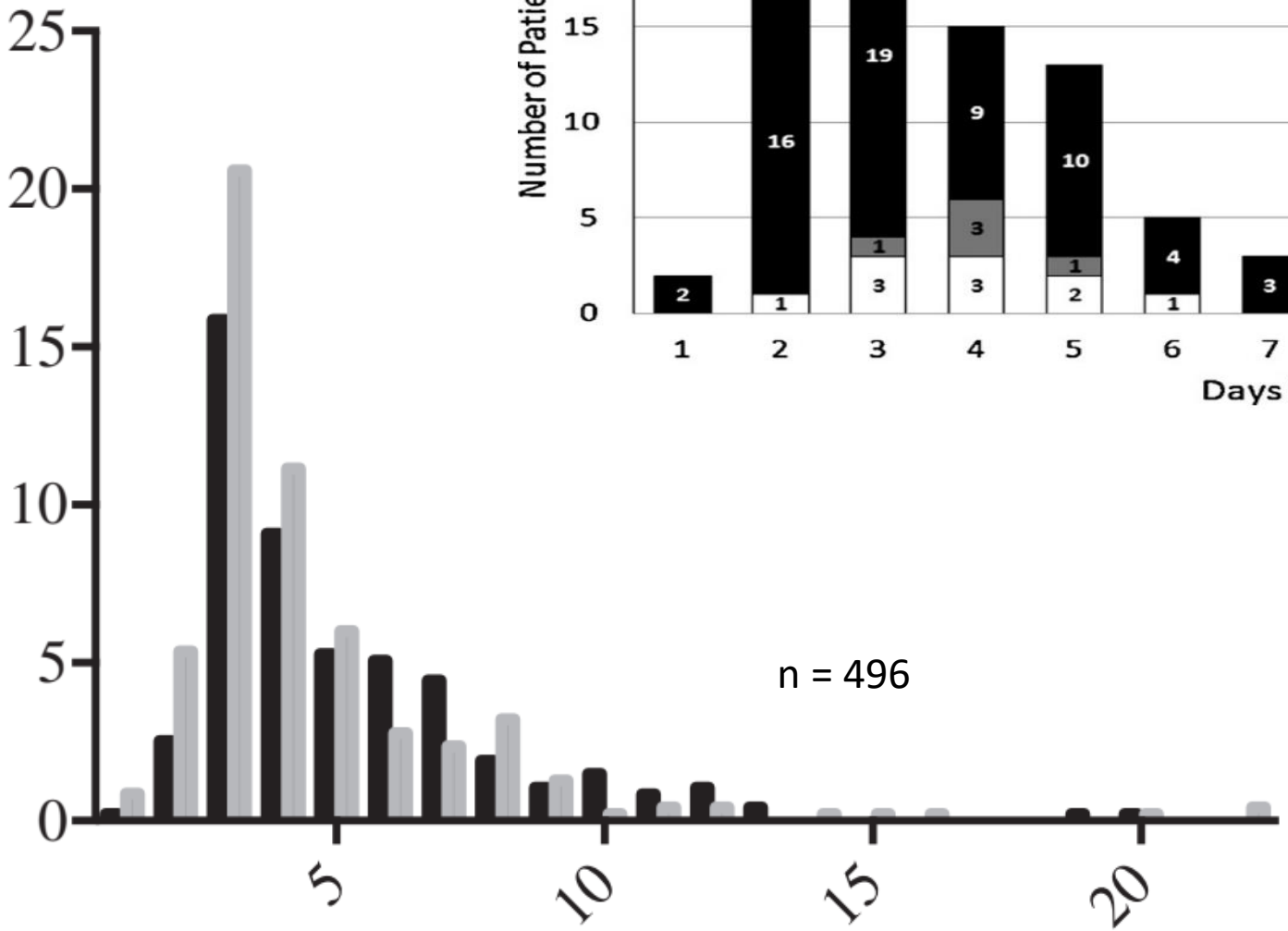
- Need a specialist for their interpretation
- Time-dependent
- Continuous recording probably better



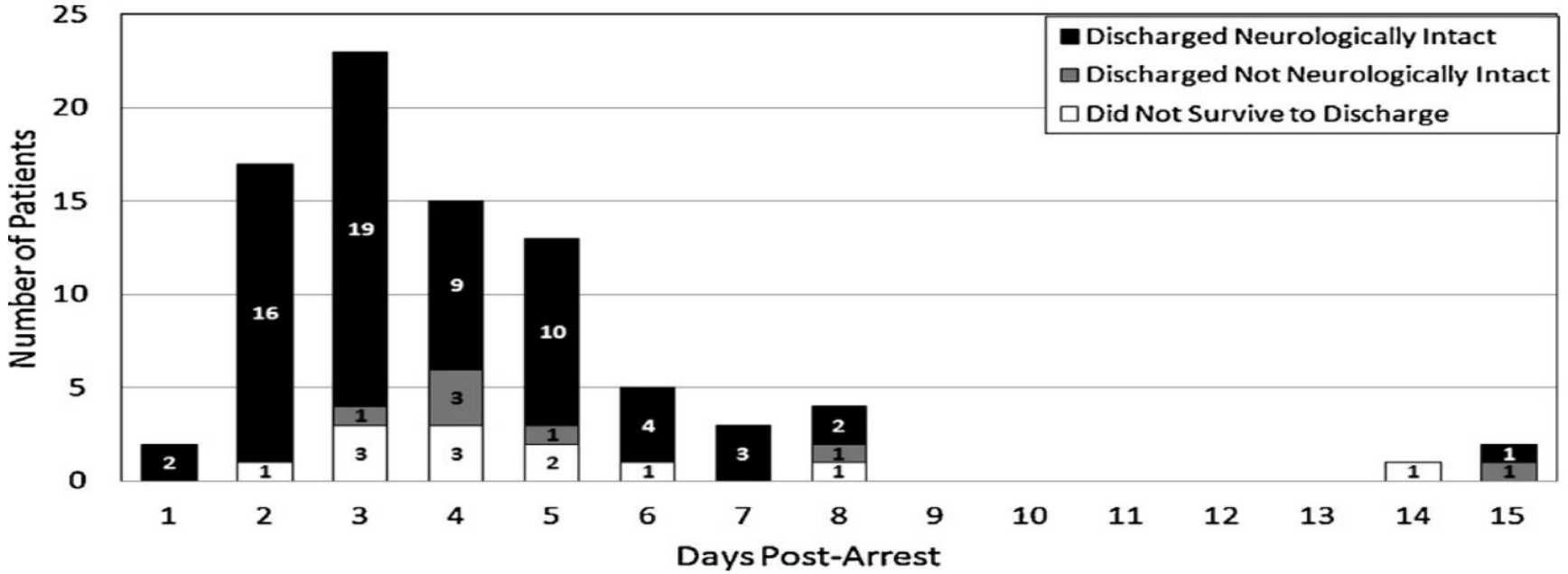
Sandroni C et al., Intensive Care Med 2014; 85:1779-89 - Resuscitation 2014; 40:1816-31.

Late awakeners

%



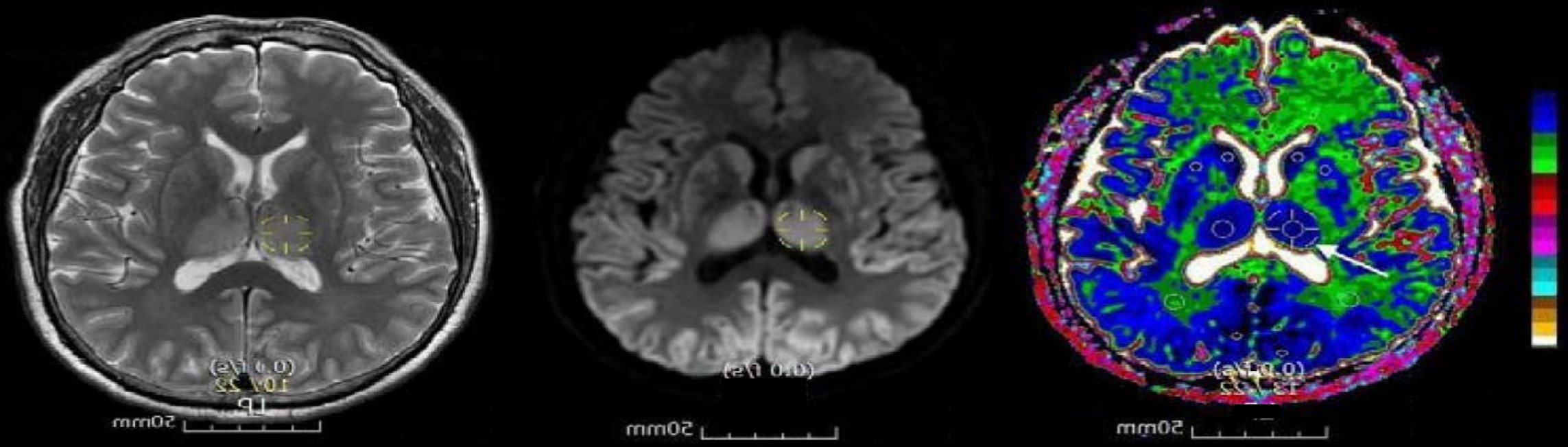
n = 496



Irisawa et al Ann Emerg Med. 2016;-:1-8

Lybeck et al., Resuscitation 2018 126, 166-171

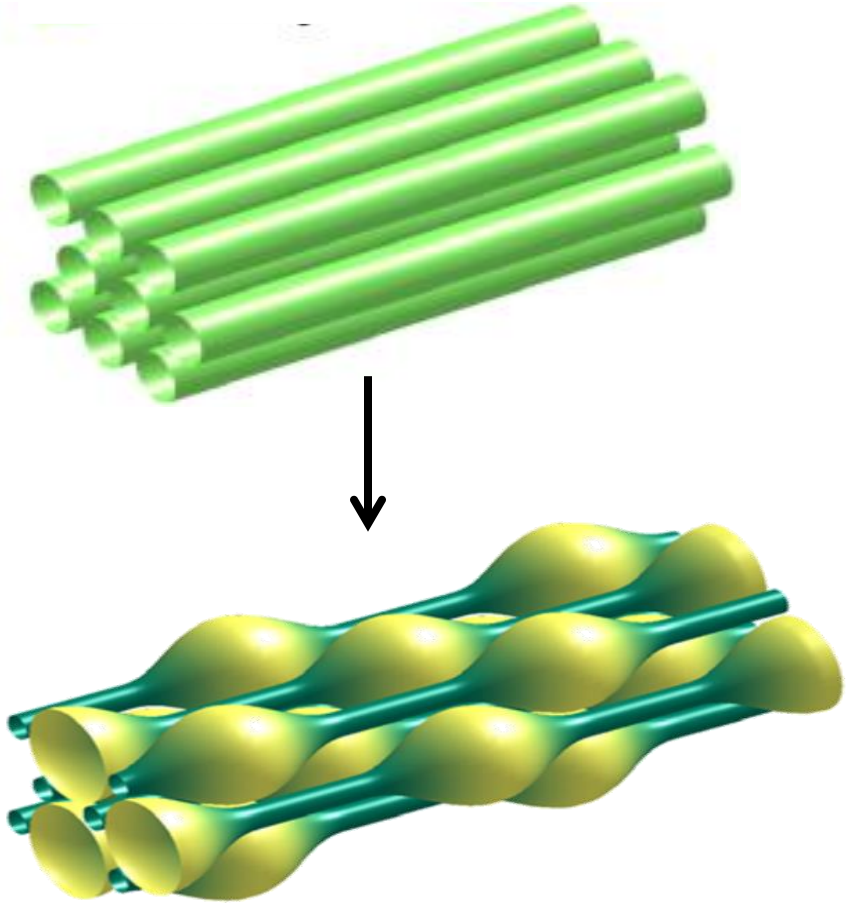
MRI signs of HIBI

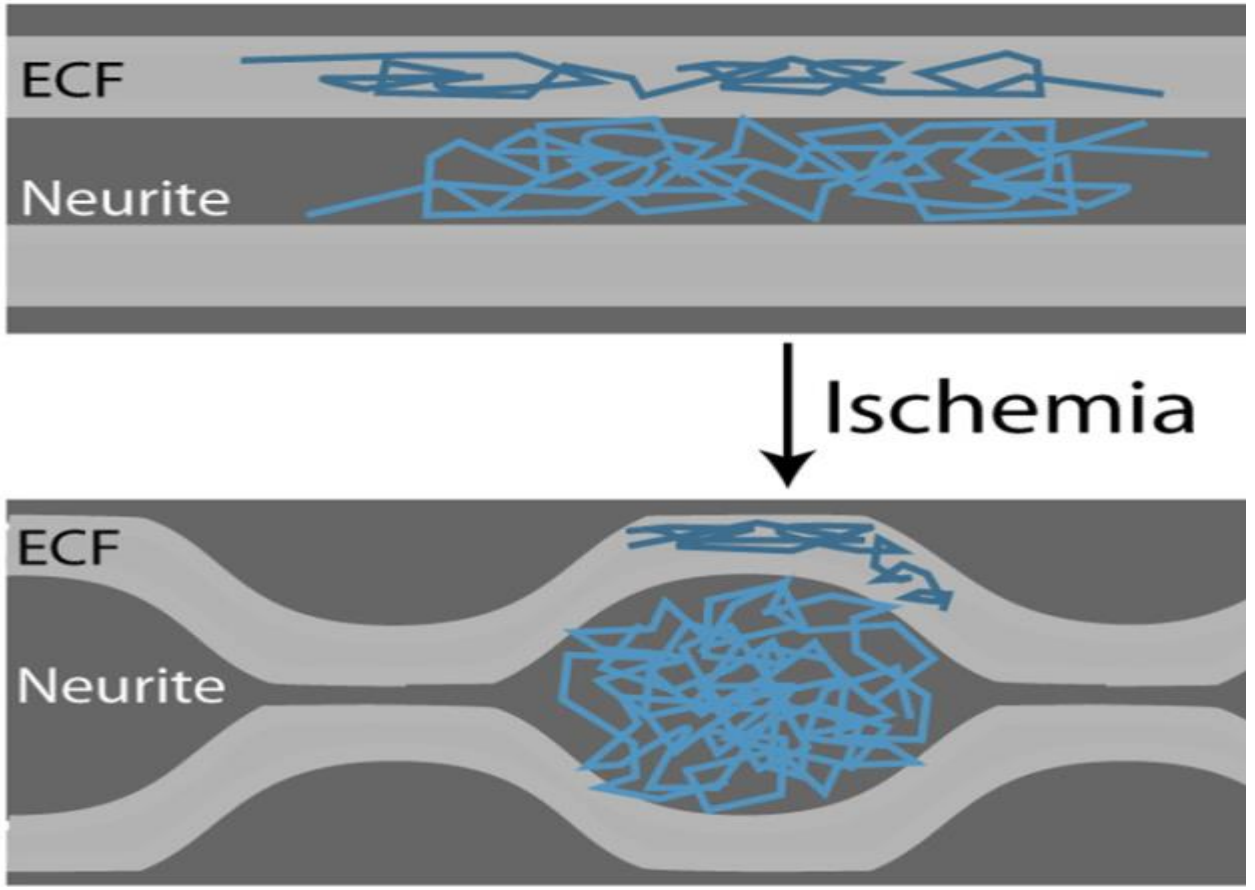


T2W DWI ADC

Choi et al. Critical Care 2010, 14:R17

Axon beading





Baron et al., Stroke. 2015;46:2136-2141

Delayed Neurological Deterioration After Anoxia

FRED PLUM, M.D.
JEROME B. POSNER, M.D.
AND
RAYMOND F. HAIN, M.D.
SEATTLE

It is widely recognized that anoxia produces acute neurological deficits, but many are unaware that severe neurological reactions may sometimes be delayed for days or weeks after anoxic exposure. Between the original anoxic coma and the relapse, intellectual and neurological recovery may seem complete, providing no hint that potentially fatal cerebral reactions have been initiated. The problem is not rare; 10 cases

temporal, and occipital lobes as well as from hippocampus, midbrain, pons, cerebellum, and medulla. Sections were also taken from basal ganglia, thalamus, and the frontal centrum semiovale. Frozen sections were stained for fat; other sections were blocked in paraffin or celloidin and stained for general architecture (hematoxylin and eosin), cellular morphology (Nissl), myelin (Weil or luxol fast blue), axis cylinders (Bodian), and glial fibers (Holzer).

Report of Cases

Plum et all, Arch Intern Med. 1962; 110:18-25

Subacute CNS degeneration after HIBI

- It continues for weeks and months after CA
- It involves mainly the white matter
- It can be detected *in vivo* using MRI with fractional anisotropy

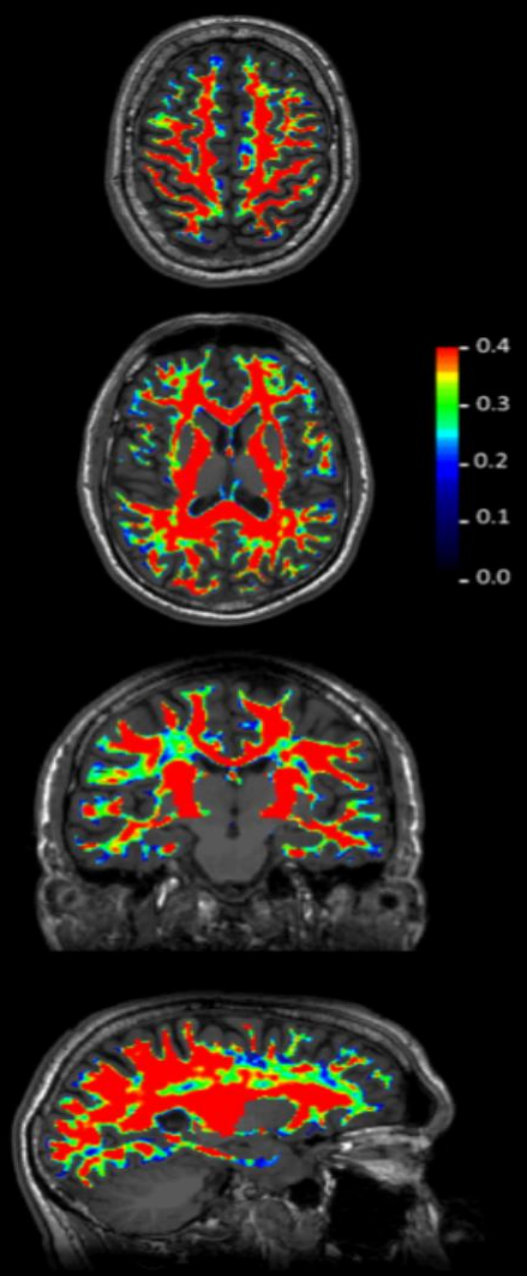
Is white matter the key?

Use of brain diffusion tensor imaging for the prediction of long-term neurological outcomes in patients after cardiac arrest: a multicentre, international, prospective, observational, cohort study

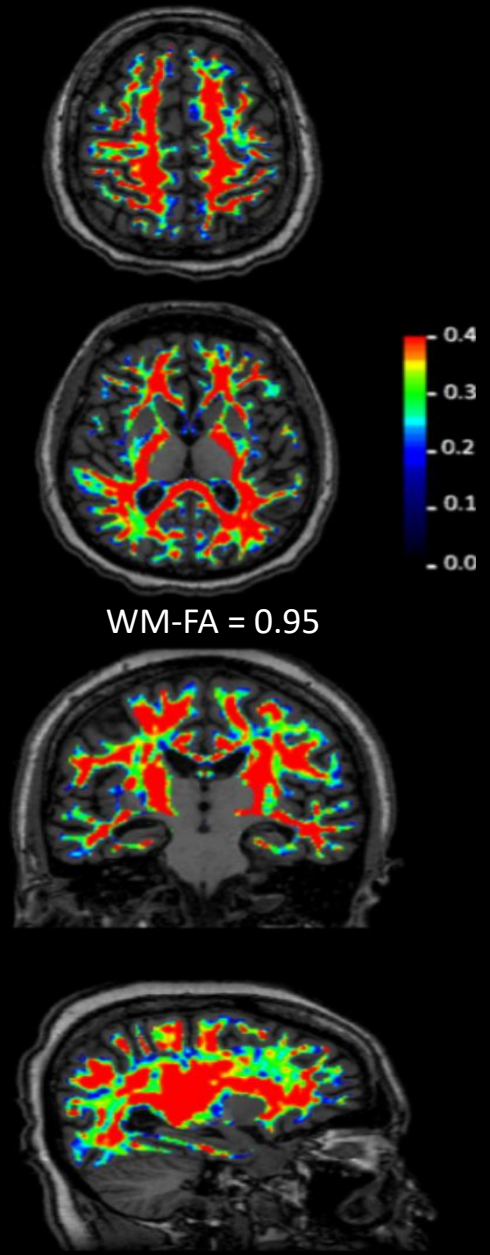
- Post-CA patients (n=150) in a coma >7 days
- MRI (fractional anisotropy) performed @ 7-28 days (median 13)
- Primary outcome best CPC at 6 months

Velly et al. The Lancet Neurology 2018; 17: 317-326

Velly et al. Lancet Neurol. 2018; 17:317-326.

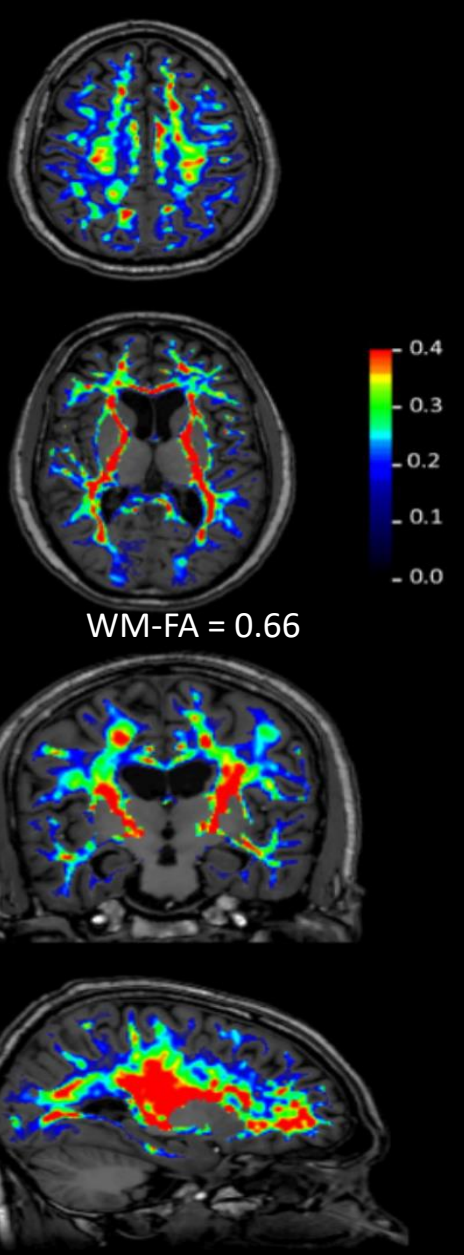


Normal



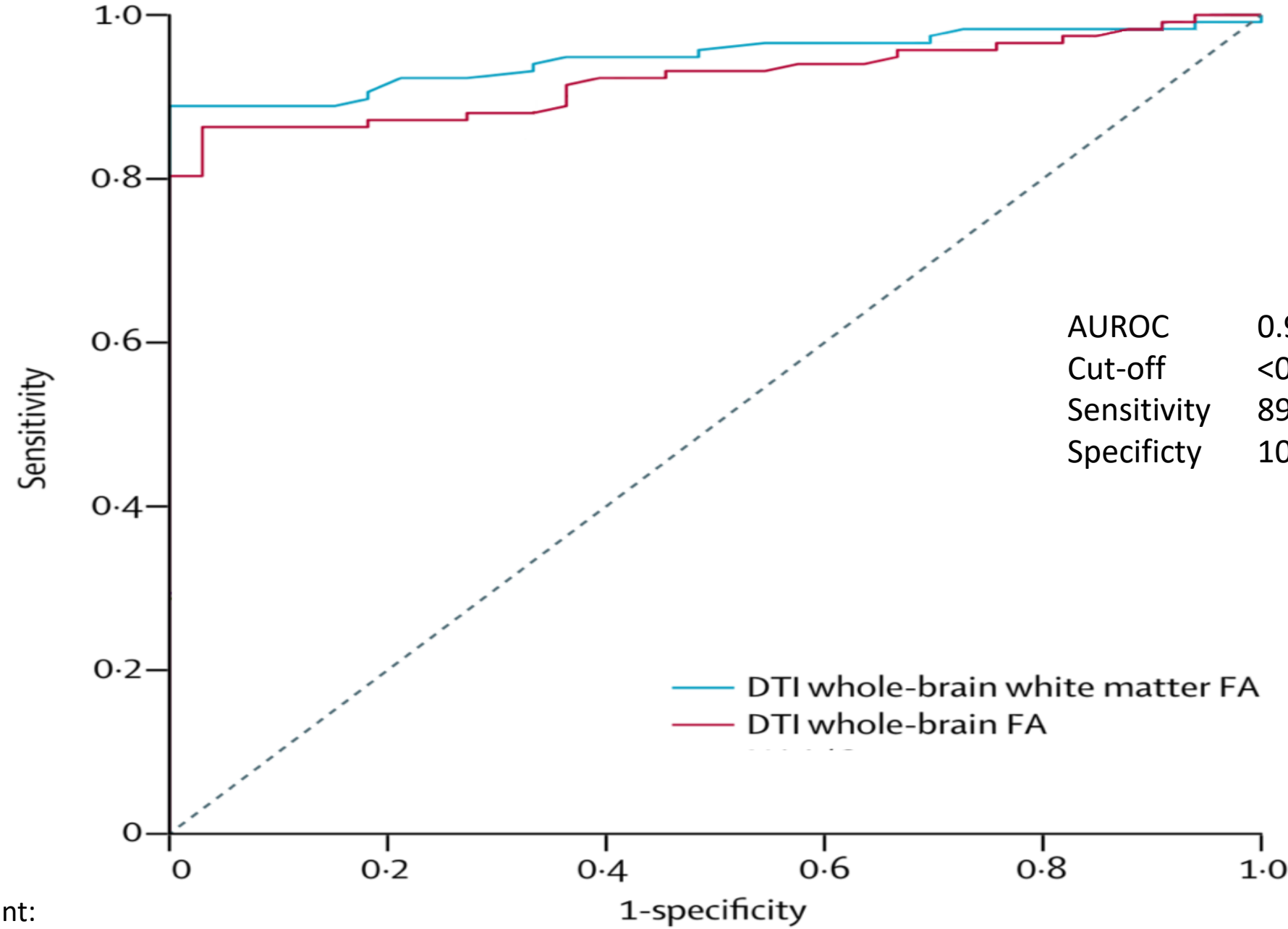
WM-FA = 0.95

Moderately disabled



WM-FA = 0.66

Vegetative



AUROC	0.95
Cut-off	<0.91
Sensitivity	89 [82–94]%
Specificty	100 [89-100]%

Predicted event:
CPC = 3-5 @ 6 months

Velly et al. Lancet Neurol. 2018; 17:317-326.

Conclusions (1)

- Most resuscitated patients die of HIBI
- Prognostication should assess the severity of HIBI
- It is a time-dependent process

Conclusions (2)

- The neural correlates of consciousness are incompletely understood
- The correlation between HIBI, unconsciousness, and prognostic indices are incompletely understood

Conclusions (3)

- Standardisation is now available for important predictors such as PLR and EEG
  - ↑ Consistency, reproducibility, robustness
- Subacute/chronic phase of HIBI deserves investigation
  - White matter most involved
  - Long-term and functional outcomes

"Resuscitation should be looked upon as a neurologic science."

V Negovsky Resuscitation 1995; 29:169-76

Thank you for your attention

claudio.sandroni@unicatt.it

RESUSCITATION 2019

Controversies in Resuscitation

19 - 21 September • Ljubljana • Slovenia