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ERC-ESICM multimodal algorithm: PRO

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COI

- Member, Advanced Life Support Working Group
  - European Resuscitation Council (ERC)
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  - European Society of Intensive Care Medicine (ESICM)
- Lead author, ERC-ESICM Advisory Statement on prognostication in comatose survivors of cardiac arrest (ASPAC)

Pros of ERC-ESICM Guidelines - 1

It overcomes the limitations of previous prognostication models:

- Based on evidence in non-TTM-treated patients
- Important biases were not addressed
- Inconsistent definition of important accuracy measures, as false positive rate

Pros of ERC-ESICM Guidelines - 2

ASPAC rates predictors based on:

1. The level of their accuracy and precision
2. The quality of supporting evidence, evaluated using the GRADE methodology

Accuracy of predictors

- Currently used indices predict poor outcome
- Ideally, false positive rate (FPR) should be 0% (=no patient is mistakenly predicted as having a poor outcome)
- We adopted FPR as the main measure of accuracy

Accuracy and precision

- Accuracy = how much the prediction is confirmed by study results
  - FPR, sensitivity, specificity
- Precision = how confident are we that the results of the predictive test are reproducible
  - Confidence interval (CI)
  - Upper bound of 95% confidence interval for FPR <5% to define good precision

Quality of evidence

- GRADE - Grading of Recommendations Assessment, Development and Evaluation
  - 2012-2014 version
- First-time use for prognostic accuracy studies

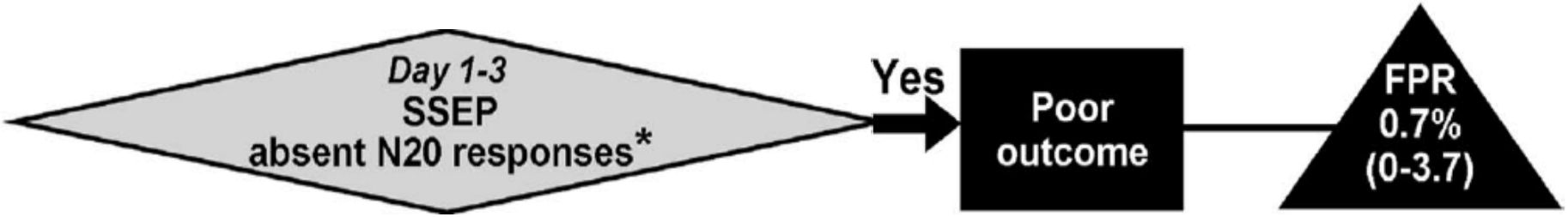
Quality of evidence (GRADE)

- Biases and flaws in literature
  - Self-fulfilling prophecy
  - Inconsistent definition of FPR
  - Inconsistent definition of poor neurological outcome

Quality of evidence (GRADE)

- Biases and flaws in literature
  - **Self-fulfilling prophecy**
  - Inconsistent definition of FPR
  - Inconsistent definition of poor neurological outcome

Bilaterally absent SSEP N20 wave ≤72 h



N° studies	N° patients	Sensitivity	False positive rate (%)
12	577	49 [44-54]	0.5 [0-3]

→ In 10/12 studies (551/577 pts) SSEP had been used as a criterion for withdrawal of life-sustaining treatments

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

Quality of evidence (GRADE)

- Biases and flaws in literature
  - Self-fulfilling prophecy
  - **Inconsistent definition of FPR**
  - Inconsistent definition of poor neurological outcome

Papers with a non-standard definition of false positive rate

- PROPAC Neurology 2006;66:62–68
  - Multicentre study, 407 patients
  - PROPAC 2006 definition:

$$\frac{\text{false positives}}{\text{patients with abnormal test result}}$$

  - Standard definition:

$$\frac{\text{false positives}}{\text{patients with favourable outcome}}$$

Absent or extensor motor response (M= 1-2) at 72h

- FPR (PROPAC 2006 definition)

$$\frac{FP(7)}{FP(7)+TP(207)} = 3\%[1-6]$$

- FPR (standard definition)

$$\frac{FP(7)}{FP(7)+TN(13)} = 35\%[12-58]$$

Quality of evidence (GRADE)

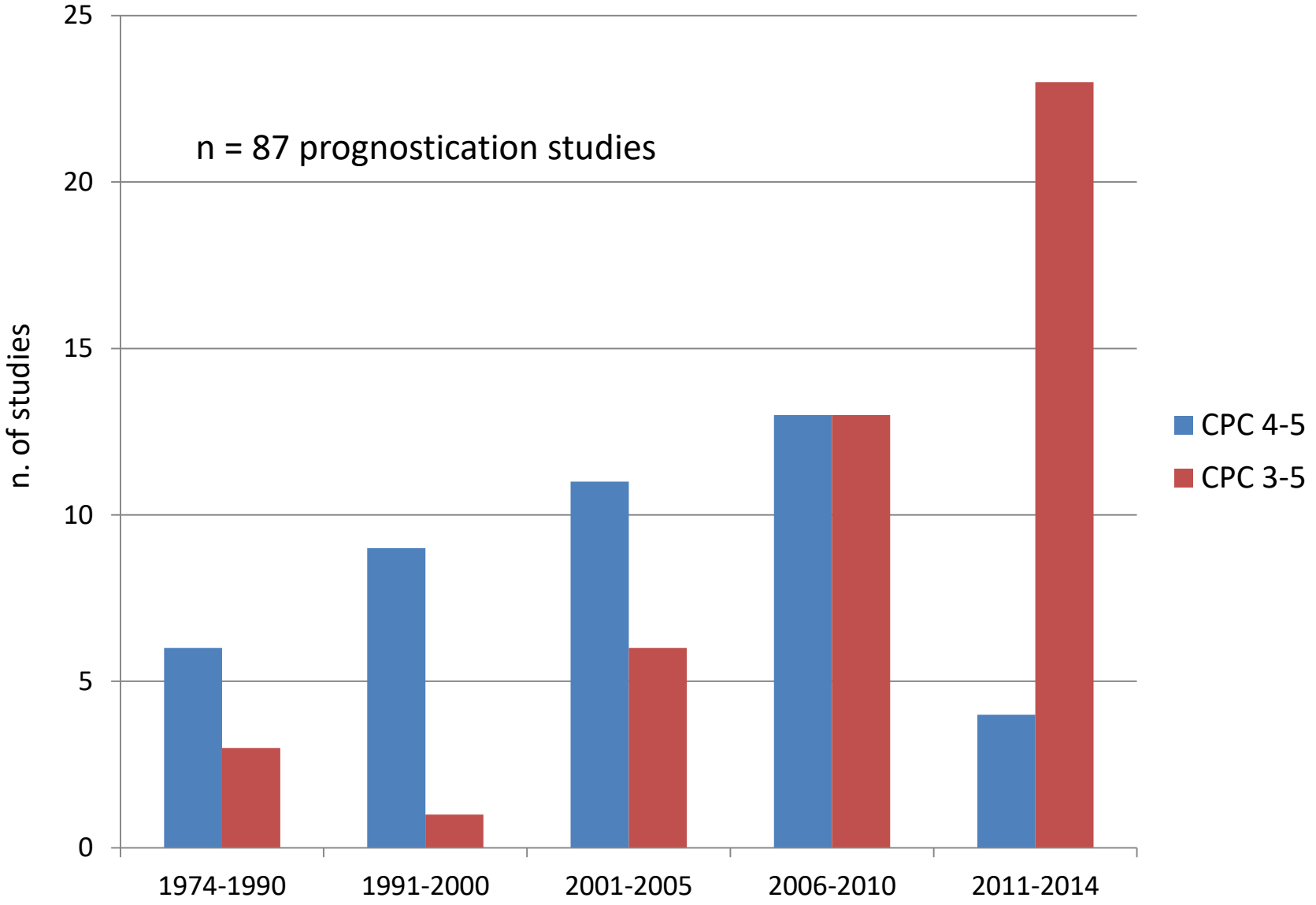
- Biases and flaws in literature
  - Self-fulfilling prophecy
  - Inconsistent definition of FPR
  - **Inconsistent definition of poor neurological outcome**

Cerebral performance categories

CPC	Neurological status
1	Conscious, independent, no or minor neurological deficits
2	Conscious, independent, moderate neurological deficits
3	Conscious, dependent, major neurological deficits
4	Unconscious, dependent (vegetative)
5	Dead

Poor neurological outcome = CPC 3, 4 or 5

CPC thresholds for poor neurological outcome



Sandroni C., Nolan JP, Resuscitation 2015; 90: A4-5.

Pros of ERC-ESICM Guidelines - 3

- It includes predictive indices that were not considered in previous guidelines:
  - EEG
  - Imaging (brain CT, MRI)
- They are recommended as a standard for outcome assessment in patients who remain comatose after cardiac arrest

Consensus statement from the American Heart Association.
Circulation 2011; 124: 2158-77

Techniques used for prognostication: a European Survey

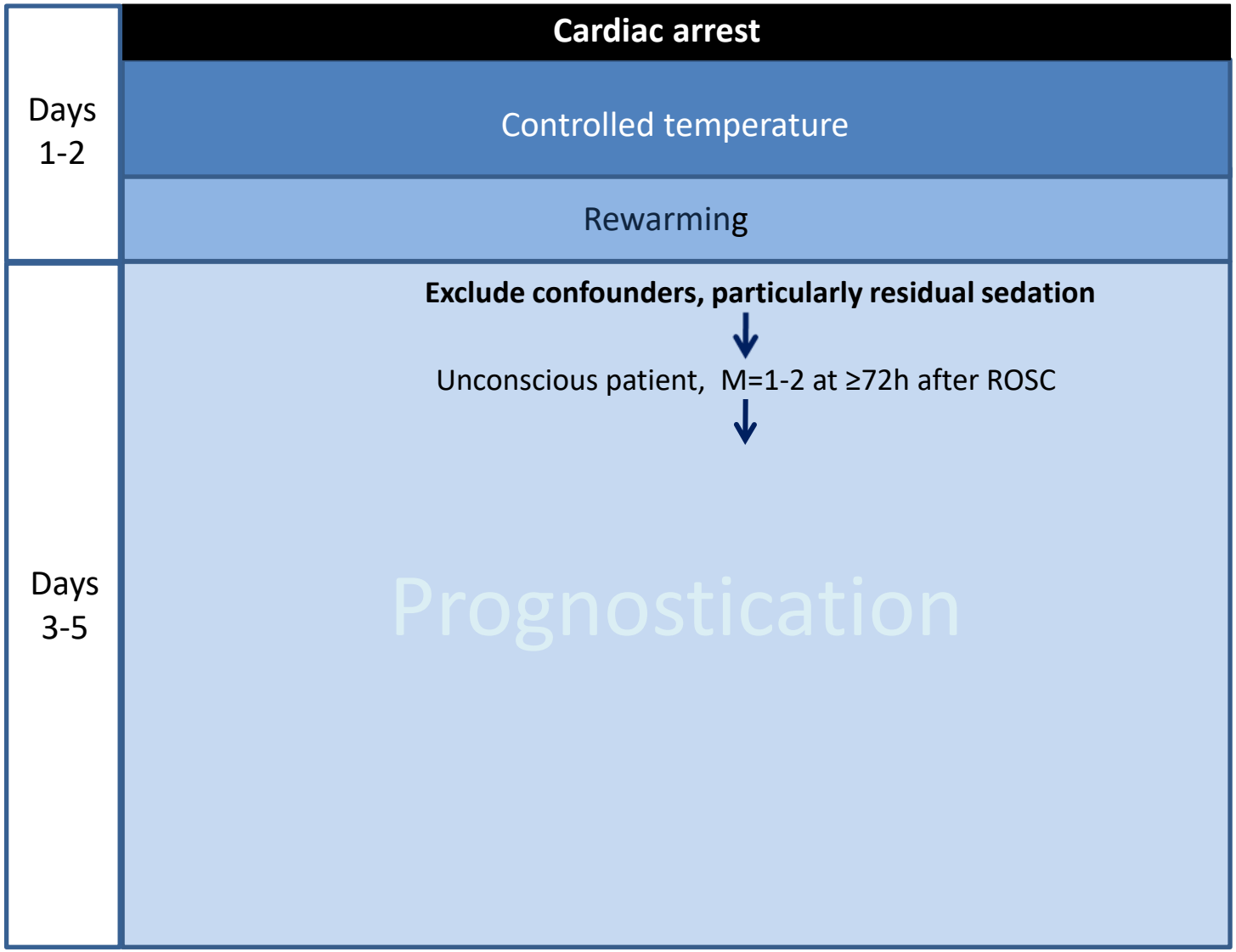
Total 1025 responses (80% Europe)

EEG, intermittent	617 (63%)
Neuroimaging (CT-scan)	576 (58%)
Evoked potentials	351 (36%)
Neuroimaging (MRI)	390 (40%)
Biomarkers, NSE	187 (19%)
EEG, continuous	113 (11%)
Biomarkers, S-100B	48 (5%)
Other	42 (4%)

Friberg H et al Resuscitation 90 (2015) 158–162

Pros of ERC-ESICM Guidelines - 4

- It accounts for interference from sedation and TTM on clinical examination
- Predictors are applied according to a time line based on the timing of TTM and subsequent recovery

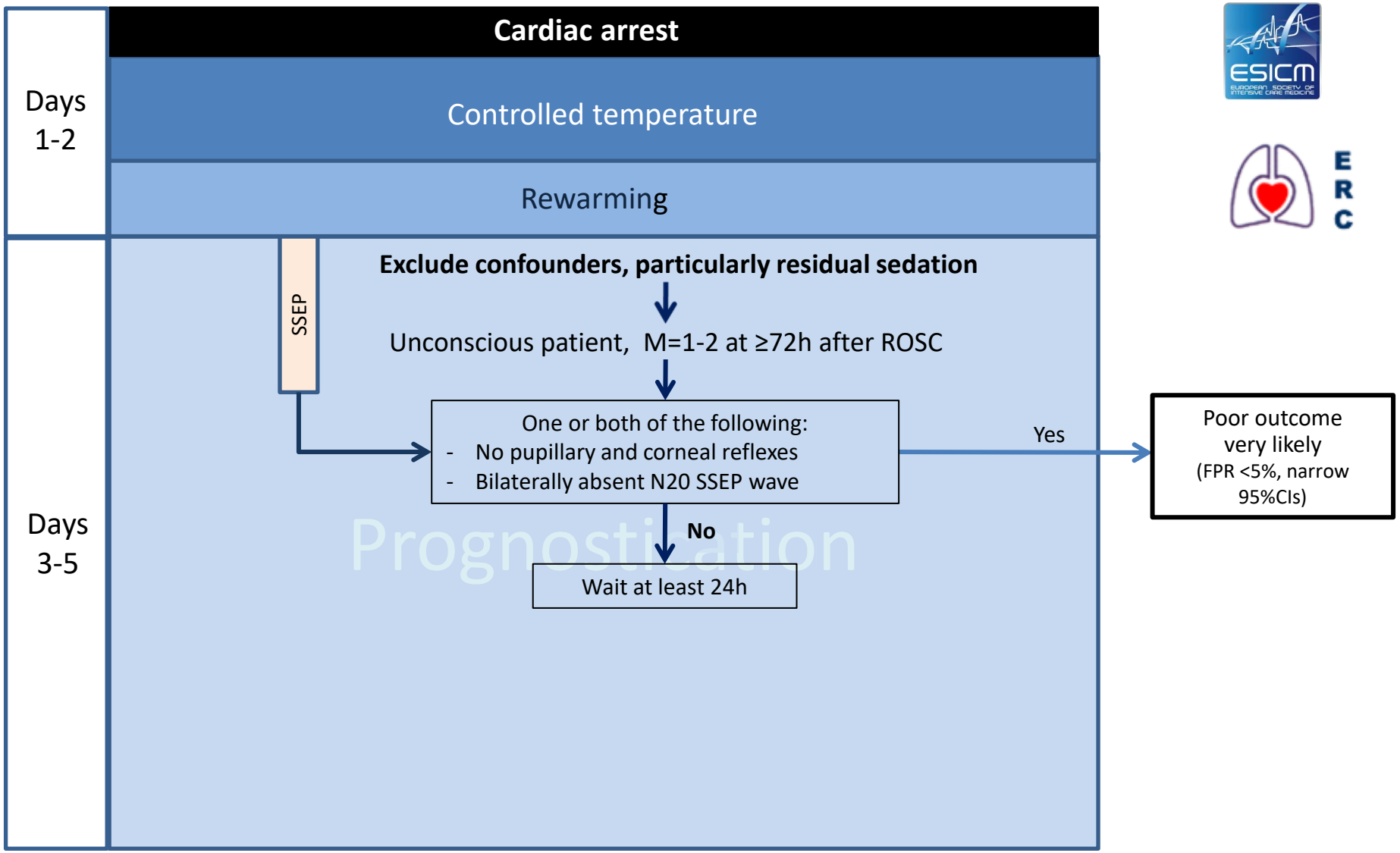

Cardiac arrest
Days 1-2
Controlled temperature
Rewarming
Days 3-5
Exclude confounders, particularly residual sedation
Unconscious patient, M=1-2 at ≥72h after ROSC
Prognostication

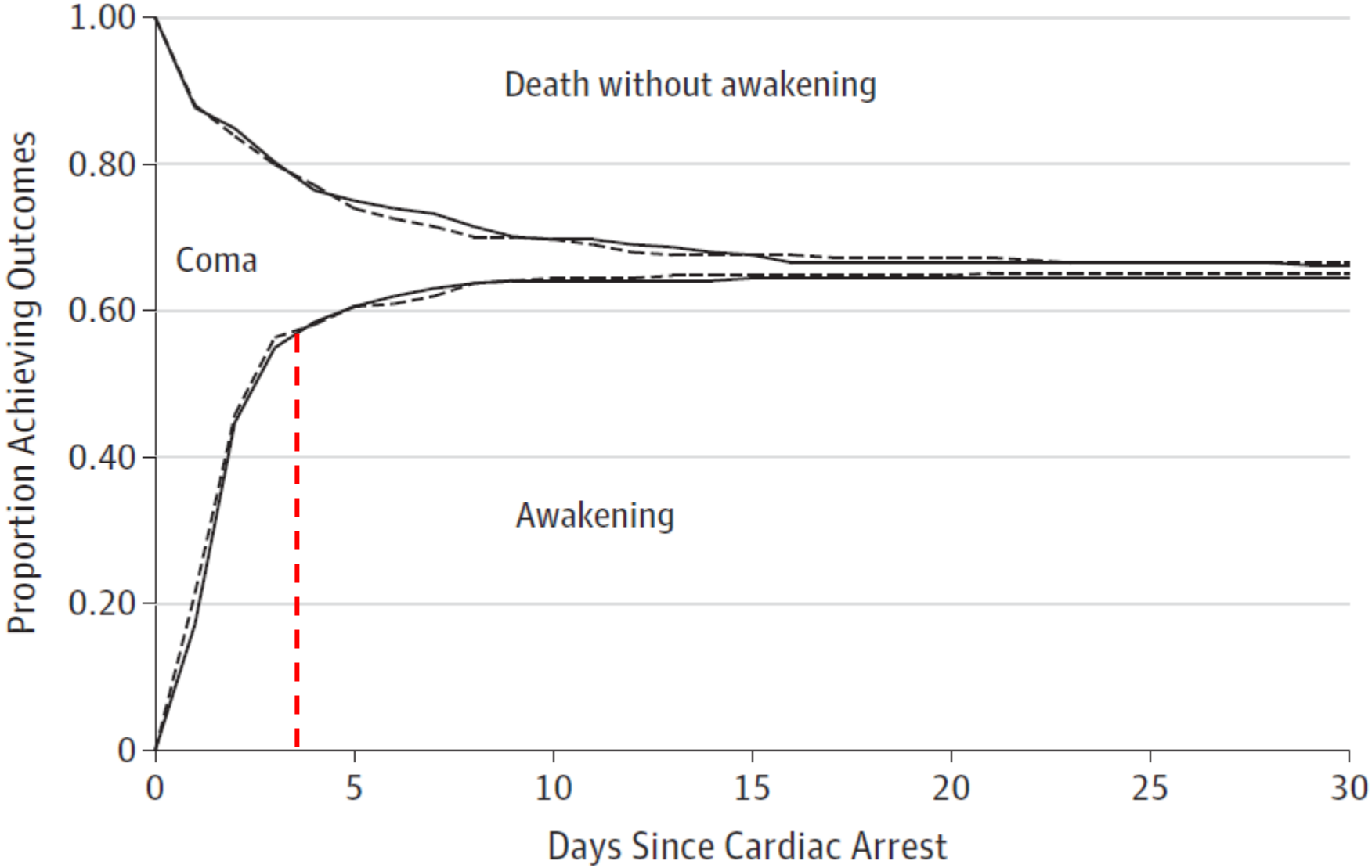
Pros of ERC-ESICM Guidelines - 4

- It accounts for interference from sedation and TTM on clinical examination
- Predictors are applied according to a time line based on the timing of TTM and subsequent recovery
- Predictors are stratified according to their robustness

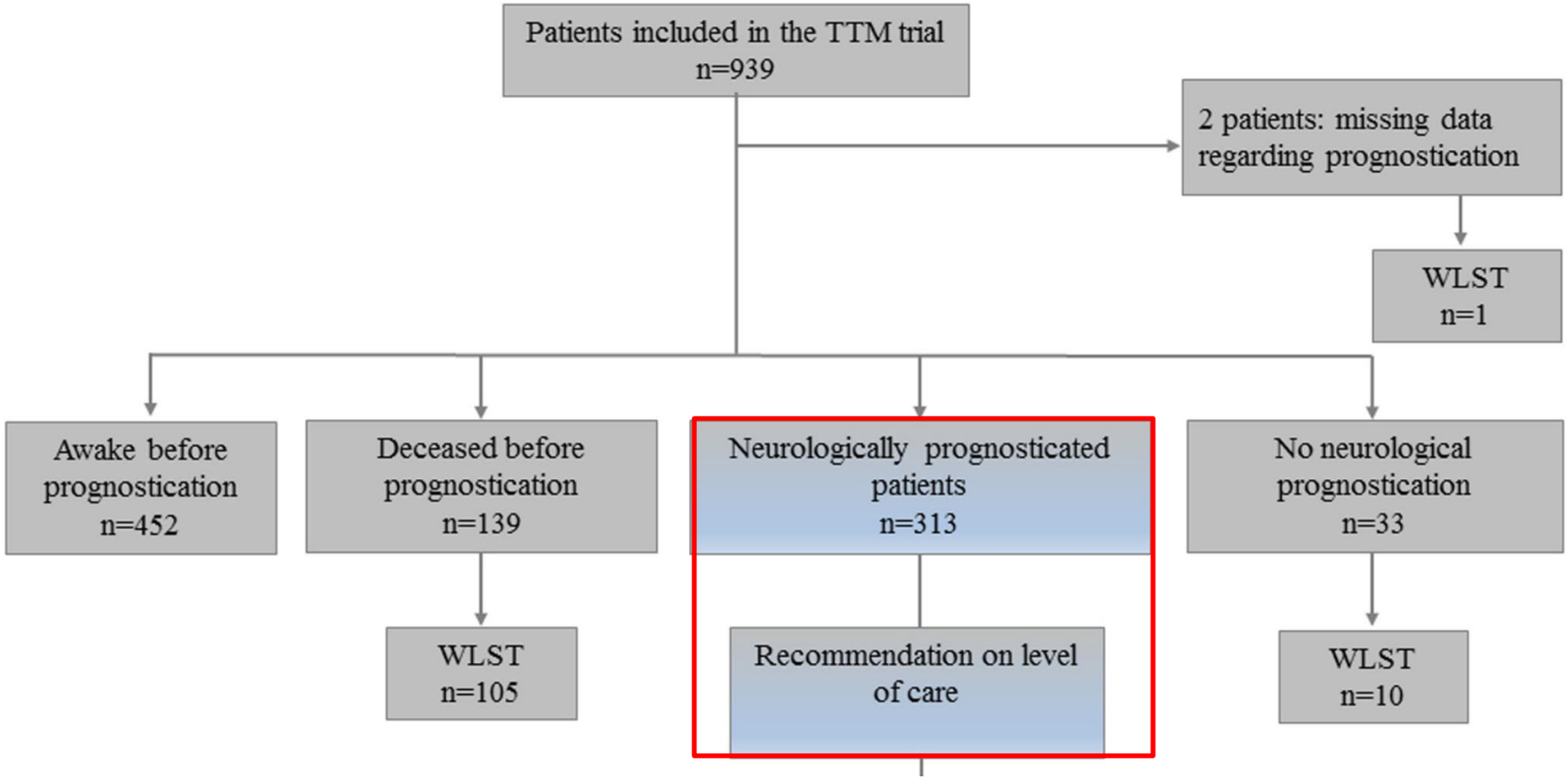
Strength of predictors

- Most robust
  - Ocular reflexes
  - SSEPs
- Characteristics:
  - FPR <5%, 95%CIs <5% in TTM-treated patients
  - documented in ≥5 studies
  - at least 3 different groups of investigators


Cardiac arrest
Days 1-2
Controlled temperature
Rewarming
Days 3-5
SSEP
Exclude confounders, particularly residual sedation
Unconscious patient, M=1-2 at ≥72h after ROSC
One or both of the following:
- No pupillary and corneal reflexes
- Bilaterally absent N20 SSEP wave
Yes
Poor outcome very likely
(FPR <5%, narrow 95%CIs)
No
Wait at least 24h
Prognostication



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

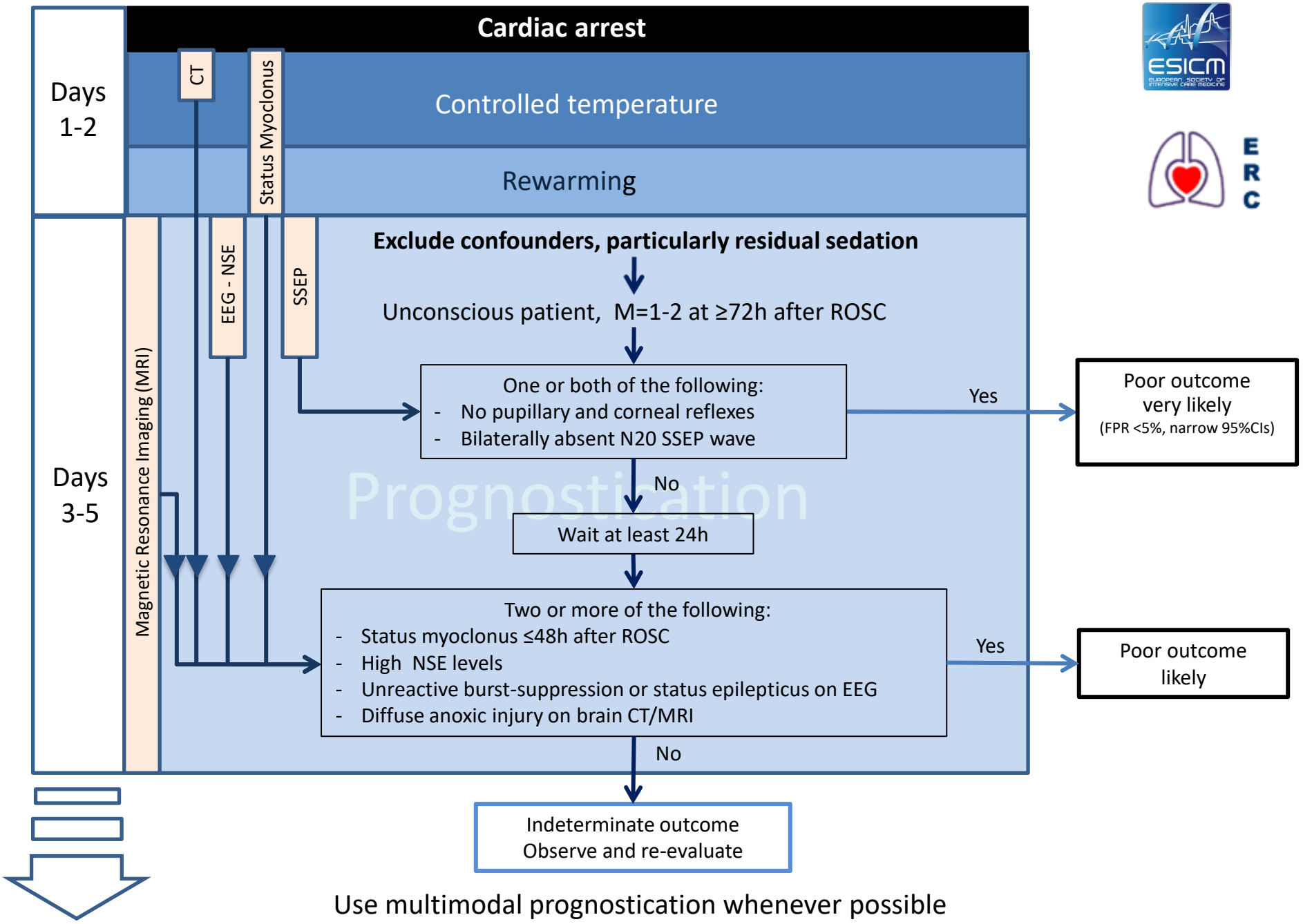


Recommendation on level-of-care in 313/939 (33%) prognosticated patients

Dragancea I et al., Resuscitation 2017; 117:50-7

Less robust predictors

- Include:
  - Status myoclonus
  - EEG
  - Biomarkers
  - Neuroimaging
- Characteristics:
  - FPR <5% but wider 95% CIs
  - and/or inconsistent definition/threshold

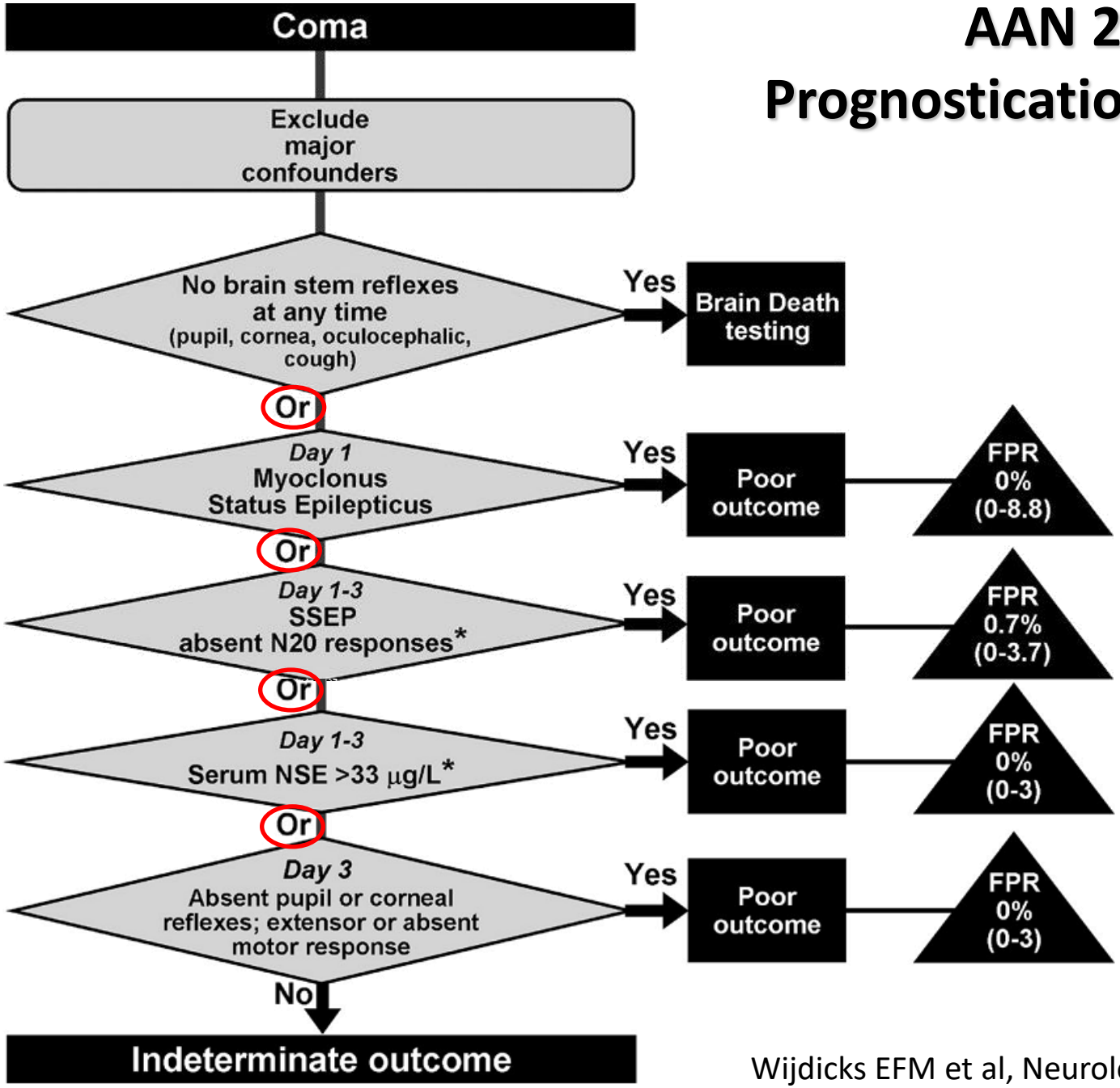


Use multimodal prognostication whenever possible

Pros of ERC-ESICM Guidelines - 5

- Multimodal approach
- Even the most robust predictors do not ensure 100% specificity
  - Important when WLST is considered

AAN 2006
Prognostication algorithm



Wijdicks EFM et al, Neurology 2006; 67:203–210.

5 - Pros of multimodality

- Predictors of good neurological outcome can be considered to counterbalance false-negative predictions
- Parisian OHCA registry (2016)
  - 4/194 patients with an eventually good outcome had an apparent bilaterally absent pupillary reflex (FPR 2%).
  - All of these patients had a reactive EEG

Paul M. et al Intensive Care Med 2016; 42:1128-36.

Pros of ERC-ESICM Guidelines - 6

- Flexible design
- Continuous evidence evaluation
- Planned update every 5 years
  - ILCOR evidence review for resuscitation guidelines
  - Interim statements allowed

ERC-ESICM algorithm: limitations

1. Combinations of predictors need to be validated prospectively
   - Tetsou et al Neurocrit Care 2017, *in press.*
2. Predictors need an unbiased confirmation in populations with no or late WLST
   - Studies ongoing
3. Other EEG predictors need to be included
   - Using consistent definitions (ACNS)
   - Timing of EEG will need revision

Causes of death

- CPC and mRS only report death regardless of underlying cause
- Death from direct “neurological” mechanism uncommon
- CPC5b, CPC5w, CPC5c….

Sandroni C. et al. Intensive Care Med 2016; 42: 1661-7.

Future developments

1. Evaluation of multiple prediction models
   - Using appropriate evidence evaluation measures
2. Inclusion of predictors of good neurological outcome

Thank you for your attention!

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IMPEGNO PER L'ECCELLENZA

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