Multimodal monitoring to prognosticate in anoxic brain injury

Eyal Golan, MD FRCPC PhD(c)
Critical Care & Neurosciences Critical Care Medicine
Interdepartmental Division of Critical Care and Department of Medicine
University of Toronto
Conflicts of interest

Financial  None (unfortunately)

Academic  Research program
Guideline development
  (ILCOR, AHA-ECC, CCCTG-CNCS)
Evidence reviewer for ILCOR
• Neuroprognostication... things to consider

• ILCOR review

• New guidelines
Case presentation

65M collapses at home while watching game 6 of the Blue Jays in Kansas

- Bystander CPR is performed by his wife
- EMS arrives at scene and perform ACLS
- Time to ROSC 30min
- Patient is brought to ER
Family asks “what’s the prognosis”
Day 1

- Patient is admitted to the ICU and receives TTM intervention (cooling & sedation)
- On exam, patient is decerebrate (GCS-M = 2)
- Myoclonic jerks are seen intermittently
- EEG performed showing “encephalopathy”
- CT head at 2hr post-ROSC
  - Mild loss of GM/WM differentiation
- Biomarkers sent
  - Neuron-specific enolase 24hrs = 30
Day 2

• TTM intervention is completed
• Best motor exam still decerebrate (GCS-M = 2)
• cEEG is placed – no seizures
• Pupils 3mm and sluggish
• Biomarkers sent
  – Neuron-specific enolase 48hrs = 40
Day 3 (72hr after ROSC)

• No myoclonic jerks
• cEEG – no change
• Brainstem testing - no change (sluggish pupils & decerebrate)
• Repeat CT head - slightly worse GM/WM differentiation; edema R>L
• SSEP – absent on R-side
• TCDs performed – suggestive of hyperemia +/- ischemia
Day 5 (72hr after return to normothermia)

- No myoclonic jerks
- EEG – no change
- Brainstem testing
  - bilaterally absent pupillary reflex
- SSEP – bilaterally absent
- Biomarkers sent
  - Neuron-specific enolase = 80
- Optic nerve ultrasound
  - ONSD 6.2 mm bilaterally
Family asks “what’s the prognosis”

Likely poor neurological outcome with near certainty (FPR near 0% with narrow confidence interval)

Basis of recent guideline recommendations from
- ILCOR
- AHA
- ERC
- CCCTG-CNCS
We just performed “appropriate multimodal prognostication”

- Continued aggressive management until minimum time from ROSC attained
- Avoided self-fulfilling prophecies
- Applied >2 recognized modes
- Time from ROSC for each mode taken into account
- Trends in results taken into account (ex. biomarkers & imaging)
Prognostication after cardiac arrest

• Key topic in resuscitation research

• With the advancement of neurocritical care, studies now examining invasive and non-invasive prognostic tests

• Newly released guidelines with a focus on an appropriate multimodal approach

Howes DJ et al, Resuscitation. 2015 Sep 28. pii: S0300-9572(15)
Factors to consider

1. Our predictions are important
2. Self-fulfilling prophecies
3. Dichotomous outcomes
4. Targeted temperature management
5. Selective memory
6. Diagnostic test accuracy
Factors to consider

1. Our predictions are important
2. Self-fulfilling prophecies
3. Dichotomous outcomes
4. Targeted temperature management
5. Selective memory
6. Diagnostic test accuracy
Termination of life support is the most common way that patients die during ICU

Physician prediction of poor outcome is the strongest predictor of termination of life support

We’re just not very good at it.... Clinicians are generally poor at subjectively predicting survival, functional outcome and quality after critical illness

Factors to consider

1. Our predictions are important
2. Self-fulfilling prophecies
3. Dichotomous outcomes
4. Targeted temperature management
5. Selective memory
6. Diagnostic test accuracy
You know, hot chocolate, you're scared of the unknown, so you never try things, so things stay unknown, and you stay scared of it all.

It's called a self-fulfilling prophecy....

Well...whatever it's called....

It's a system that works.
Self-fulfilling prophecies

Problems clinically
Physicians become falsely reassured

Problems for research
Most studies do not prevent physicians from stopping life support in response to clinical predictors

Newer trials aim to prevent “early” withdrawal

Geocadin et al. Neurology 2006; 67:105
Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest

Niklas Nielsen, M.D., Ph.D., Jørn Wetterslev, M.D., Ph.D., Tobias Cronberg, M.D., Ph.D.,
High rate of protocol violation
37% early WLST
20% death due to early WLST
Factors to consider

1. Our predictions are important
2. Self-fulfilling prophecies
3. Dichotomous outcomes
4. Targeted temperature management
5. Selective memory
6. Diagnostic test accuracy
Emphasis is on predicting poor, not good outcomes.

Patients may still wish to base decisions to withdraw life support on intermediate outcomes.

Spectrum of outcomes between disability and complete neurological recovery.
Neuroprognostication after cardiac arrest in Europe

Fig. 1. CPC thresholds for poor neurological outcome in 87 prognostication studies, 1974–2014. CPC = Cerebral Performance Categories.
Factors to consider

1. Our predictions are important
2. Self-fulfilling prophecies
3. Dichotomous outcomes
4. Targeted temperature management
5. Selective memory
6. Diagnostic test accuracy
Coma

Exclude major confounders

No brain stem reflexes at any time (pupil, cornea, oculocephalic, cough)

Or

Day 1 Myoclonus Status Epilepticus

Or

Day 1-3 SSEP absent N20 responses*

Or

Day 1-3 Serum NSE >33 μg/L*

Or

Day 3 Absent pupil or corneal reflexes; extensor or absent motor response

Yes

Brain Death testing

FPR 0% (0-8.8)

FPR 0.7% (0-3.7)

FPR 0% (0-3)

Poor outcome

Poor outcome

Poor outcome

Indeterminate outcome
The Targeted Temperature Management (TTM) Trial

- Box A: 4 h Achievement of target temperature
- Box B: 24 h Maintenance of target temperature
- Box C: 8 h Rewarming to normothermia

CT of neck/head, coronary angiography, PCI, and other diagnostics and interventions when indicated

Start of intervention as soon as possible after sustained ROSC

Sedation mandatory
The Targeted Temperature Management (TTM) Trial

**Box A:** 4 h
Achievement of target temperature

**Box B:** 24 h
Maintenance of target temperature

**Box C:** 8 h
Rewarming to normothermia.

CT of neck/head, coronary angiography, PCI, and other diagnostics and interventions when indicated

Start of intervention as soon as possible after sustained ROSC

Sedation mandatory
TTM changes the accuracy of our clinical predictors

- Confounding due to sedating/paralyzing medications used to induce and maintain hypothermia
- May change accuracy of predictors used for neuroprognostication by attenuating degree of brain injury
- Does prognostication change with different levels of cooling?
TTM changes the accuracy of our clinical predictors

• Confounding due to sedating/paralyzing medications used to induce and maintain hypothermia

• May change accuracy of predictors used for neuroprognostication by attenuating degree of brain injury

• Does prognostication change with different levels of cooling?
Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest

Niklas Nielsen, M.D., Ph.D., Jørn Wetterslev, M.D., Ph.D., Tobias Cronberg, M.D., Ph.D.

Clinical Paper
Neurological prognostication after cardiac arrest and targeted temperature management 33°C versus 36°C: Results from a randomised controlled clinical trial

Irina Dragancea,a,b Janneke Horn,b Michael Kuiper,c Hans Friberg,d Susann Ullén,e Jørn Wetterslev,e Jules Cranshaw,c Christian Hassagerb, Niklas Nielsen,d Tobias Cronberg,a,b, the TTM trial investigators

* Department of Clinical Sciences, Division of Neurology, Lund University, Lund, Sweden

Editorial
Neurological outcome prediction in the new era of targeted temperature management: Is 36°C different from 33°C?

Golan E, Resuscitation; 2015 Aug;93:A9-10
No difference in diagnostic test accuracies

$36^\circ C = 33^\circ C$ for prognostication
Factors to consider

1. Our predictions are important
2. Self-fulfilling prophecies
3. Dichotomous outcomes
4. Targeted temperature management
5. Selective memory
6. Diagnostic test accuracy
Reversible brain death after cardiopulmonary arrest and induced hypothermia*

- “A 55-yr-old man presented with cardiac arrest... spontaneous perfusion restored, and therapeutic hypothermia provided”
- “Death was pronounced and the family consented to organ donation”
- “24 hrs after brain death, on arrival to the operating room for organ procurement, the patient was found to have regained corneal reflexes, cough reflex, and spontaneous respirations”

Webb and Samuels, CCM 2011
Factors to consider

1. Our predictions are important
2. Self-fulfilling prophecies
3. Dichotomous outcomes
4. Targeted temperature management
5. Selective memory
6. Diagnostic test accuracy
The confidence problem

No consensus on the PRECISION that should be obtained for predicting poor outcomes

How precise is precise enough?

How wide should confidence intervals around ZERO be?

Prognostication after Cardiac Arrest and Hypothermia
A Prospective Study

Andrea O. Rossetti, MD,¹ Mauro Oddo, MD,² Giancarlo Logroscino, MD, PhD,³ and Peter W. Kaplan, MBBS, FRCP¹,⁴

• 111 cardiac arrests treated with hypothermia
• Neurological examination 36-72 HOURS
  – EEG
  – SSEP
  – All measurements during normothermia and off sedation
• CPC assessed at 3 to 6 months
<table>
<thead>
<tr>
<th>Variable</th>
<th>FPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-VF CA (asystole or PEA)</td>
<td>0.15 (0.06–0.29)</td>
</tr>
<tr>
<td>ROSC ≥25 minutes</td>
<td>0.24 (0.13–0.40)</td>
</tr>
<tr>
<td>≥1 brainstem reflexes absent&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.04 (0.01–0.15)</td>
</tr>
<tr>
<td>Motor response worse than flexion</td>
<td>0.24 (0.13–0.40)</td>
</tr>
<tr>
<td>Early myoclonus</td>
<td>0.03 (0.00–0.11)</td>
</tr>
<tr>
<td>Epileptiform activity on first EEG</td>
<td>0.09 (0.02–0.21)</td>
</tr>
<tr>
<td>Unreactive EEG background</td>
<td>0.07 (0.01–0.18)</td>
</tr>
<tr>
<td>Bilaterally absent N20 on SSEP</td>
<td>0.00 (0.00–0.08)</td>
</tr>
<tr>
<td>Variable</td>
<td>FPR</td>
</tr>
<tr>
<td>----------------------------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Non-VF CA (asystole or PEA)</td>
<td>0.15 (0.06–0.29)</td>
</tr>
<tr>
<td>ROSC &gt;25 minutes</td>
<td>0.24 (0.13–0.40)</td>
</tr>
<tr>
<td>≥1 brainstem reflexes absent^a</td>
<td>0.04 (0.01–0.15)</td>
</tr>
<tr>
<td>Motor response worse than flexion</td>
<td>0.24 (0.13–0.40)</td>
</tr>
<tr>
<td>Early myoclonus</td>
<td>0.03 (0.00–0.11)</td>
</tr>
<tr>
<td>Epileptiform activity on first EEG</td>
<td>0.09 (0.02–0.21)</td>
</tr>
<tr>
<td>Unreactive EEG background</td>
<td>0.07 (0.01–0.18)</td>
</tr>
<tr>
<td>Bilaterally absent N20 on SSEP</td>
<td>0.00 (0.00–0.08)</td>
</tr>
<tr>
<td>Variable</td>
<td>FPR</td>
</tr>
<tr>
<td>----------------------------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Non-VF CA (asystole or PEA)</td>
<td>0.15 (0.06–0.29)</td>
</tr>
<tr>
<td>ROSC &gt;25 minutes</td>
<td>0.24 (0.13–0.40)</td>
</tr>
<tr>
<td>≥1 brainstem abnormality</td>
<td>0.04 (0.01–0.15)</td>
</tr>
<tr>
<td>Motor flexion absent</td>
<td>0.24 (0.13–0.40)</td>
</tr>
<tr>
<td>Early first EKG</td>
<td>0.03 (0.00–0.11)</td>
</tr>
<tr>
<td>Epileptic background</td>
<td>0.09 (0.02–0.21)</td>
</tr>
<tr>
<td>Unrealized background</td>
<td>0.07 (0.01–0.18)</td>
</tr>
<tr>
<td>Bilaterally absent N20 on SSEP</td>
<td>0.00 (0.00–0.08)</td>
</tr>
</tbody>
</table>
Predicting Neurologic Outcome After Targeted Temperature Management for Cardiac Arrest: Systematic Review and Meta-Analysis*

Eyal Golan, MD, PhDC1,2; Kali Barrett, MD1; Aziz S. Alali, MD2; Abhijit Duggal, MD3; Draga Jichici, MD4; Ruxandra Pinto, PhD5; Laurie Morrison, MD, MSc2,6,7,8; Damon C. Scales, MD, PhD4,29,10

Contents lists available at SciVerse ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Review article

Predictors of poor neurological outcome in adult comatose survivors of cardiac arrest: A systematic review and meta-analysis.
Part 2: Patients treated with therapeutic hypothermia

Claudio Sandroni a, *, Fabio Cavallaro a, Clifton W. Callaway b, Sonia D'Arrigo a, Tommaso Sanna c, Michael A. Kuiper d, Matteo Biancone e, Giacomo Della Marca e, Alessio Farcomeni f, Jerry P. Nolan g

a Department of Anaesthesiology and Intensive Care, Catholic University School of Medicine, Rome, Italy
b Department of Emergency Medicine, University of Pittsburgh, United States
c Department of Cardiovascular Sciences, Catholic University School of Medicine, Rome, Italy
d Department of Intensive Care, Medical Center Leeuwarden, Leeuwarden, The Netherlands
e Department of Neurology, Catholic University School of Medicine, Rome, Italy
f Department of Public Health and Infectious Disease, Statistics Section, Sapienza University of Rome, Italy
g Department of Anaesthesia and Intensive Care Medicine, Royal United Hospital, Bath, UK
2015 ILCOR EVIDENCE EVALUATION RESULTS
Achieving Consensus regarding Resuscitation Science

The American Heart Association and other member councils of International Liaison Committee on Resuscitation (ILCOR) complete a review of resuscitation science every five years.
2015 CoSTR DEVELOPMENT Timeline

CoSTR and Guidelines Published October 2010

- ILCOR December Porto
- ILCOR November Orlando

Evidence Evaluation Reviews

- ILCOR April Melbourne
- ILCOR March Banff

ILCOR November Vienna

Public Comment

- ILCOR November Chicago
- CoSTR and Guidelines Published October, 2015

International Consensus February Dallas
International Evidence Evaluation Process

- 165 scientific evidence reviews
- February 2015 Consensus Conference
  - 232 professional participants
  - 46% from outside the US
  - 34 countries represented
- Management of potential COI throughout process
Part 8: Post–Cardiac Arrest Care

2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

Clifton W. Callaway, Chair; Michael W. Donnino; Ericka L. Fink; Romerathyko G. Geocadin; Eyal Golan; Karl B. Kern; Marion Leary; William J. Meurer; Mary Ann Peberdy; Trevonne M. Thompson; Janice L. Zimmerman
Part 8: Post–Cardiac Arrest Care

2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

Clifton W. Callaway, Chair; Michael W. Donnino; Ericka L. Fink; Romergryko G. Geocadin; Eyal Golan; Karl B. Kern; Marion Leary; William J. Meurer; Mary Ann Peberdy; Trevonne M. Thompson; Janice L. Zimmerman
Outcome dichotomized to good neurological outcome (CPC 1-2) vs poor neurological outcome (CPC 3-5)
Clinical Examination... timing is crucial

- Pupillary reflex
- Corneal reflex
- GCS-motor response
- Myoclonus
Clinical Examination

- **Bilaterally absent pupillary light reflex** at 72 to 108 hours after cardiac arrest predicted poor outcome, with an FPR of 1% (95% CI, 0%–3%)

- **Bilaterally absent corneal reflexes** at 72 to 120 hours after cardiac arrest predicted poor outcome, with a 2% FPR (95% CI, 0%–7%)

- Extensor posturing or no **motor response** to pain at 36 to 108 hours after cardiac arrest predicted poor outcome, with a **10% FPR** (95% CI, 7%–15%)
Updated 2015 recommendations

- In comatose patients who are treated with TTM, the absence of pupillary reflex to light at 72 hours or more after cardiac arrest is useful to predict poor neurologic outcome (FPR, 1%; 95% CI, 0%–3%; Class I, LOE B-NR)

- Given their unacceptable FPRs, the findings of either absent motor movements or extensor posturing should not be used alone for predicting a poor neurologic outcome (FPR, 10%; 95% CI, 7%–15% to FPR; Class III: Harm, LOE B-NR)
Myoclonus and status myoclonus

• In 2015, new distinction between myoclonus and status myoclonus (continuous, repetitive myoclonic jerks lasting more than 30 minutes)
• The presence of any myoclonus is not a reliable predictor of poor functional recovery
• But status myoclonus within 72 to 120 hours after ROSC predicted poor outcome, with a 0% FPR (95% CI, 0%–4%).
Myoclonus and status myoclonus

• In 2015, new distinction between myoclonus and status myoclonus (continuous, repetitive myoclonic jerks lasting more than 30 minutes)

• The presence of any myoclonus is not a reliable predictor of poor functional recovery

• But **status myoclonus** within 72 to 120 hours after ROSC predicted poor outcome, with a 0% FPR (95% CI, 0%–4%).
Updated 2015 Recommendations

• We recommend that the presence of myoclonus, which is distinct from status myoclonus, should not be used to predict poor neurologic outcomes because of the high FPR (FPR, 5%; 95% CI, 3%–8% to FPR, 11%; 95% CI, 3%–26%; Class III: Harm, LOE B-NR).

• In combination with other diagnostic tests at 72 or more hours after cardiac arrest, the presence of status myoclonus during the first 72 to 120 hours after cardiac arrest is a reasonable finding to help predict poor neurologic outcomes (FPR, 0%; 95% CI, 0%–4%; Class IIa, LOE B-NR).
Electrophysiology modalities

- SSEP considered default “gold standard” in many studies
  - **BUT** may artificially inflate the accuracy estimates

- EEG or cEEG are suggested, with caveat
  - EEG and cEEG are used routinely for prognostication but no standardized terminology
  - Difficult to attain in real time, or sometimes even at a reasonable time
Consistently unreliable...
Consistently unreliable... NOT recommended

- Low voltage EEG
- Low bispectral index
- EEG grades
Updated 2015 Recommendations

• **Persistent absence of EEG reactivity** to external stimuli at 72 hours after cardiac arrest, and **persistent burst suppression** on EEG after rewarming, predict a poor outcome (FPR, 0%; 95% CI, 0%–3%; Class IIb, LOE B-NR)

• **Intractable and persistent (more than 72 hours) status epilepticus** in the absence of EEG reactivity to external stimuli may be reasonable to predict poor outcome (Class IIb, LOE B-NR)
ERC-ESICM guidelines
(combining unreactivity + BS/SE)

Canadian guidelines
(“malignant” EEG; 1 of 4 definitions)
Imaging modalities

• Attractive modality

• CT or MRI can define structural brain injury, detect focal injury, and edema

• Edema can theoretically be quantified
  – CT (quantified as GWR in Hounsfield units; Normal = 1.3, and decreases with edema)
  – MRI (quantified by apparent diffusion coefficient; Normal ADC= 700-800 Å~ 10−6 mm2/s and decrease with edema)
## Evidence profile table

<table>
<thead>
<tr>
<th>CT Index</th>
<th>Timing from ROSC</th>
<th>Risk of bias</th>
<th>Indirectness</th>
<th>Inconsistency</th>
<th>Imprecision</th>
<th>Quality of evidence</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>Sensitivity [95%CI]</th>
<th>FPR [95%CI]</th>
<th>LR+ [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>GWR BG &lt;1.22</td>
<td>&lt; 1 h</td>
<td>Very serious</td>
<td>Serious</td>
<td>Very serious</td>
<td>Very low</td>
<td>TP</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>100 [55-100]</td>
<td>0 [0-63]</td>
<td>7 [1-99]</td>
</tr>
<tr>
<td>Average GWR &lt;1.14 (BG/cerebrum)</td>
<td>&lt;1 h</td>
<td>Very serious</td>
<td>No</td>
<td>Very serious</td>
<td>Very low</td>
<td>4</td>
<td>0</td>
<td>26</td>
<td>21</td>
<td>13 [4-31]</td>
<td>0 [0-13]</td>
<td>6 [0-113]</td>
<td></td>
</tr>
<tr>
<td>GWR CN/PIC &lt;1.10</td>
<td>≤2 h</td>
<td>Serious</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>16</td>
<td>0</td>
<td>66</td>
<td>60</td>
<td>20 [12-30]</td>
<td>0 [0-5]</td>
<td>24 [1-396]</td>
<td></td>
</tr>
<tr>
<td>GWR P/CC &lt;1.17</td>
<td>≤2 h</td>
<td>Serious</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>43</td>
<td>0</td>
<td>39</td>
<td>60</td>
<td>52 [41-64]</td>
<td>0 [0-5]</td>
<td>64 [4-1018]</td>
<td></td>
</tr>
<tr>
<td>GWR CN/IC ≤1.18</td>
<td>&lt; 1 h</td>
<td>Very Serious</td>
<td>No</td>
<td>Very serious</td>
<td>Very low</td>
<td>51</td>
<td>1</td>
<td>12</td>
<td>11</td>
<td>81 [69-90]</td>
<td>8 [0-38]</td>
<td>10 [1-64]</td>
<td></td>
</tr>
<tr>
<td>Global cerebral oedema</td>
<td>Median day 1 (1-7)</td>
<td>Serious</td>
<td>No</td>
<td>Serious</td>
<td>Low</td>
<td>11</td>
<td>0</td>
<td>34</td>
<td>57</td>
<td>24 [13-40]</td>
<td>0 [0-5]</td>
<td>29 [2-479]</td>
<td></td>
</tr>
</tbody>
</table>

BG = Basal ganglia; CC= Corpus callosum; CN = Caudate nucleus; PIC = Posterior limb of the internal capsule; P = Putamen
# Evidence profile table

<table>
<thead>
<tr>
<th>MRI Index</th>
<th>Timing from ROSC</th>
<th>Risk of bias</th>
<th>Indirectness</th>
<th>Inconsistency</th>
<th>Imprecision</th>
<th>Quality of evidence</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>Sensitivity [95%CI]</th>
<th>FPR [95%CI]</th>
<th>LR+ [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extensive cortical lesion pattern</td>
<td>80H (IQR 55-117)</td>
<td>Very serious</td>
<td>No</td>
<td>Very serious</td>
<td>Very low</td>
<td>9 [55-100]</td>
<td>9</td>
<td>1</td>
<td>1</td>
<td>10</td>
<td>9 [0-41]</td>
<td>10 [2-65]</td>
<td></td>
</tr>
<tr>
<td>DWI changes in BG</td>
<td>80H (IQR 55-117)</td>
<td>Very serious</td>
<td>No</td>
<td>Very serious</td>
<td>Very low</td>
<td>8 [44-97]</td>
<td>9</td>
<td>1</td>
<td>2</td>
<td>10</td>
<td>9 [0-41]</td>
<td>9 [1-58]</td>
<td></td>
</tr>
<tr>
<td>DWI changes in BS</td>
<td>80H (IQR 55-117)</td>
<td>Very serious</td>
<td>No</td>
<td>Very serious</td>
<td>Very low</td>
<td>3 [7-65]</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>11</td>
<td>0 [0-24]</td>
<td>8 [0-132]</td>
<td></td>
</tr>
<tr>
<td>Changes in cortex + BG</td>
<td>74h (IQR 61-86)</td>
<td>Serious</td>
<td>Serious</td>
<td>Very serious</td>
<td>Very low</td>
<td>11 [33-80]</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>3</td>
<td>0 [0-63]</td>
<td>5 [0-63]</td>
<td></td>
</tr>
<tr>
<td>Changes in cortex + BG</td>
<td>&lt; 5 days</td>
<td>Very serious</td>
<td>No</td>
<td>Very serious</td>
<td>Very low</td>
<td>5 [55-100]</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0 [0-63]</td>
<td>7 [1-99]</td>
<td></td>
</tr>
</tbody>
</table>

BG = Basal ganglia; BS = Brainstem
# Evidence profile table

<table>
<thead>
<tr>
<th>MRI Index</th>
<th>Timing from ROSC</th>
<th>Risk of bias</th>
<th>Indirectness</th>
<th>Inconsistency</th>
<th>Imprecision</th>
<th>Quality of evidence</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>Sensitivity [95%CI]</th>
<th>FPR [95%CI]</th>
<th>LR+ [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC &lt; 650 • 10^-6 mm²/sec in &gt;10% of brain volume</td>
<td>49-108 h</td>
<td>Serious</td>
<td>No</td>
<td>Very serious</td>
<td>Very low</td>
<td>10</td>
<td>0</td>
<td>3</td>
<td>9</td>
<td>77 [46-95]</td>
<td>0 [0-28]</td>
<td>15 [1-227]</td>
<td></td>
</tr>
<tr>
<td>Occipital cortex ADC &lt; 616 • 10^-6 mm²/sec</td>
<td>45.8 (IQR 36.8-52.4)</td>
<td>Very serious</td>
<td>No</td>
<td>Very serious</td>
<td>Very low</td>
<td>29</td>
<td>0</td>
<td>3</td>
<td>11</td>
<td>91 [75-98]</td>
<td>0 [0-24]</td>
<td>21 [1-324]</td>
<td></td>
</tr>
<tr>
<td>Putamen ADC &lt; 590 • 10^-6 mm²/sec</td>
<td>Very serious</td>
<td>No</td>
<td>Very serious</td>
<td>Very low</td>
<td>25</td>
<td>0</td>
<td>7</td>
<td>11</td>
<td>78 [60-91]</td>
<td>0 [0-24]</td>
<td>19 [1-281]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalamus ADC &lt; 660 • 10^-6 mm²/sec</td>
<td>Very serious</td>
<td>No</td>
<td>Very serious</td>
<td>Very low</td>
<td>20</td>
<td>0</td>
<td>12</td>
<td>11</td>
<td>63 [44-79]</td>
<td>0 [0 24]</td>
<td>15 [1-228]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADC = Apparent Diffusion Coefficient
But...

- Acquisition and interpretation of imaging studies have **not** been fully standardized and are subject to interobserver variability.

- In addition, the recommendations are made with the **assumption** that images are performed in centers with expertise in this area.
Updated 2015 Recommendations

• In patients who are comatose after resuscitation, it may be reasonable to use the presence of a marked reduction of the GWR on brain CT obtained within 2 hours after cardiac arrest to predict poor outcome (Class IIb, LOE B-NR)

• It may be reasonable to consider extensive restriction of diffusion on brain MRI at 2 to 6 days after cardiac arrest in combination with other established predictors to predict a poor neurologic outcome (Class IIb, LOE B-NR)
Biomarkers

• **No threshold values** that enable prediction of poor outcome with confidence were identified.

• Laboratory **standards vary** between centers for the two most common markers, NSE and S-100B.

• The **kinetics have not been studied**, particularly during or after TTM in cardiac arrest patients.

• Importantly, **NSE and S-100B are not specific to neuronal damage** (can be produced by hemolysis, neuroendocrine tumors, myenteric plexus, muscle, and adipose tissue breakdown).

• Confirmatory > predictive.
Updated 2015 Recommendations

• Given the possibility of high FPRs, blood levels of NSE and S-100B should not be used alone to predict a poor neurologic outcome (Class III: Harm, LOE C-LD)

• When performed with other prognostic tests at 72 hours or more after cardiac arrest, it may be reasonable to consider high serum values of NSE at 48 to 72 hours after cardiac arrest to support the prognosis of a poor neurologic outcome (Class IIb, LOE B-NR), especially if repeated sampling reveals persistently high values (Class IIb, LOE C-LD)
Part 8: Post–Cardiac Arrest Care

2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

Clifton W. Callaway, Chair; Michael W. Donnino; Ericka L. Fink; Romergrkyo G. Geocadin; Eyal Golan; Karl B. Kern; Marion Leary; William J. Meuer; Mary Ann Peberdy; Trevonne M. Thompson; Janice L. Zimmerman
Achieving Consensus regarding Resuscitation Science
Canadian Guidelines for the use of targeted temperature management (therapeutic hypothermia) after cardiac arrest: A joint statement from the Canadian Critical Care Society (CCCS), Canadian Neurocritical Care Society (CNCCS), and the Canadian Critical Care Trials Group (CCCTG)

At ≥24h after ROSC in patients not treated with targeted temperature, see text for details.

Poor outcome very likely (FPR <5%, narrow 95%CIs)

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

One or both of the following:
- No pupillary and corneal reflexes
- Bilaterally absent N20 SSEP wave

Indeterminate outcome

Use multimodal prognostication whenever possible

(1) At ≥24h after ROSC in patients not treated with targeted temperature
(2) See text for details.

...So what’s your suggestion...
...So what’s your suggestion...

• Apply a protocol based strategy

• Rule out confounders

• Wait

• Use ≥ 2 modes
...So what’s your suggestion...

• Apply a protocol based strategy
  – Recognize and avoid self-fulfilling prophecy (aggressiveness and WLST)
  – Family involvement

• Rule out confounders

• Wait

• Use ≥ 2 modes
...So what’s your suggestion...

• Apply a protocol based strategy

• Rule out confounders

• Wait

• Use ≥ 2 modes
...So what’s your suggestion...

• Apply a protocol based strategy

• Rule out confounders
  – Rule out confounders to your diagnostic tests
  – Do not attempt neuroprognostication until sedatives, paralytics have worn off, hypotension is treated

• Wait

• Use ≥ 2 modes
...So what’s your suggestion...

- Apply a protocol based strategy
- Rule out confounders
- Wait
- Use ≥ 2 modes
...So what’s your suggestion...

- Apply a protocol based strategy
- Rule out confounders
- Wait
  - ≥ 72hrs post-NT for clinical examination
  - ≥ 72hrs post-arrest for electrophysiology
  - CT/MRI at specific points, in specific centers
- Use ≥ 2 modes
...So what’s your suggestion...

- Apply a protocol based strategy
- Rule out confounders
- Wait
- Use $\geq 2$ modes
Thank you!
Questions...

eyal.golan@uhn.ca
<table>
<thead>
<tr>
<th>Predictor (studies)</th>
<th>Timing</th>
<th>Risk of bias</th>
<th>Indirectness</th>
<th>Inconsistency</th>
<th>Imprecision</th>
<th>Quality of evidence</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>Sensitivity [95%CI]</th>
<th>FPR [95%CI]</th>
<th>LR+ [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Corneal reflex (4)</strong></td>
<td>At 72-120h</td>
<td>Very serious</td>
<td>No</td>
<td>Serious</td>
<td>Serious</td>
<td>Very low</td>
<td>43</td>
<td>3</td>
<td>132</td>
<td>123</td>
<td>25 [18-32]</td>
<td>2 [0-7]</td>
<td>9 [2-29]</td>
</tr>
<tr>
<td><strong>Pupillary reflex (5)</strong></td>
<td>at 72-108h</td>
<td>Very serious</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>42</td>
<td>1</td>
<td>180</td>
<td>160</td>
<td>19 [14-25]</td>
<td>1 [0-3]</td>
<td>5 [1-32]</td>
</tr>
<tr>
<td><strong>GCS Motor 1-2 (6)</strong></td>
<td>At 36-108h</td>
<td>Very serious</td>
<td>No</td>
<td>No</td>
<td>very serious</td>
<td>very low</td>
<td>257</td>
<td>28</td>
<td>111</td>
<td>239</td>
<td>70 [65-74]</td>
<td>10 [7-15]</td>
<td>6 [4-9]</td>
</tr>
<tr>
<td><strong>Myoclonus (5)</strong></td>
<td>At 24-72h</td>
<td>Very serious</td>
<td>No</td>
<td>Serious</td>
<td>serious</td>
<td>very low</td>
<td>193</td>
<td>18</td>
<td>300</td>
<td>334</td>
<td>39 [35-44]</td>
<td>5 [3-8]</td>
<td>6 [4-10]</td>
</tr>
<tr>
<td><strong>Status myoclonus (3)</strong></td>
<td>≤72h</td>
<td>Very serious</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>26</td>
<td>0</td>
<td>137</td>
<td>78</td>
<td>16 [11-22]</td>
<td>0 [0-4]</td>
<td>6 [4-10]</td>
</tr>
</tbody>
</table>
## Evidence profile table

<table>
<thead>
<tr>
<th>Predictor (studies)</th>
<th>Timing</th>
<th>Risk of bias</th>
<th>Indirectness</th>
<th>Inconsistency</th>
<th>Imprecision</th>
<th>Quality of evidence</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>Sensitivity [95%CI]</th>
<th>FPR [95%CI]</th>
<th>LR+ [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent N20 SSEP (4)</td>
<td>During TTM</td>
<td>Serious</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Moderate</td>
<td>63</td>
<td>3</td>
<td>164</td>
<td>194</td>
<td>28 [22-34]</td>
<td>2 [0-4]</td>
<td>24 [6-98]</td>
</tr>
<tr>
<td>Unreactive EEG (3)</td>
<td>During TTM</td>
<td>Very serious</td>
<td>No</td>
<td>No</td>
<td>Serious</td>
<td>Very low</td>
<td>80</td>
<td>3</td>
<td>46</td>
<td>120</td>
<td>63 [54-72]</td>
<td>2 [1-7]</td>
<td>18 [5-61]</td>
</tr>
<tr>
<td>Unreactive EEG (3)</td>
<td>After RW</td>
<td>Very serious</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>85</td>
<td>0</td>
<td>52</td>
<td>86</td>
<td>62 [53-70]</td>
<td>0 [0-3]</td>
<td>33 [7-163]</td>
</tr>
<tr>
<td>Burst-suppression EEG (1)</td>
<td>After RW</td>
<td>Serious</td>
<td>no</td>
<td>very serious</td>
<td>No</td>
<td>Very low</td>
<td>7</td>
<td>0</td>
<td>31</td>
<td>57</td>
<td>18 [8-34]</td>
<td>0 [0-5]</td>
<td>22 [1-379]</td>
</tr>
<tr>
<td>Predictor (studies)</td>
<td>Timing</td>
<td>Risk of bias</td>
<td>Indirectness</td>
<td>Inconsistency</td>
<td>Imprecision</td>
<td>Quality of evidence</td>
<td>TP</td>
<td>FP</td>
<td>FN</td>
<td>TN</td>
<td>Sensitivity [95%CI]</td>
<td>FPR [95%CI]</td>
<td>LR+ [95%CI]</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>-----------------------------</td>
<td>--------------</td>
<td>---------------</td>
<td>---------------</td>
<td>-------------</td>
<td>---------------------</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>---------------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>EEG seizures, nonreactive</td>
<td>During TTM</td>
<td>Very serious</td>
<td>No</td>
<td>-</td>
<td>Very serious</td>
<td>Very low</td>
<td>10</td>
<td>0</td>
<td>23</td>
<td>28</td>
<td>30 [16-49]</td>
<td>0 [0-10]</td>
<td>18 [1-293]</td>
</tr>
<tr>
<td>EEG seizures</td>
<td>After RW</td>
<td>Very serious</td>
<td>No</td>
<td>-</td>
<td>Very serious</td>
<td>Very low</td>
<td>9</td>
<td>0</td>
<td>17</td>
<td>12</td>
<td>35 [17-56]</td>
<td>0 [0-22]</td>
<td>9 [1-145]</td>
</tr>
<tr>
<td>EEG seizures</td>
<td>During TTM and RW</td>
<td>Very serious</td>
<td>No</td>
<td>-</td>
<td>Serious</td>
<td>Very low</td>
<td>5</td>
<td>0</td>
<td>16</td>
<td>33</td>
<td>24 [8-47]</td>
<td>0 [0-9]</td>
<td>17 [1-292]</td>
</tr>
<tr>
<td>Status epilepticus</td>
<td>During TTM</td>
<td>Very serious</td>
<td>no</td>
<td>-</td>
<td>no</td>
<td>Low</td>
<td>5</td>
<td>0</td>
<td>34</td>
<td>12</td>
<td>13 [4-27]</td>
<td>0 [0-22]</td>
<td>4 [0,2-60]</td>
</tr>
<tr>
<td>Status epilepticus</td>
<td>After RW</td>
<td>Very serious</td>
<td>no</td>
<td>-</td>
<td>serious</td>
<td>Very low</td>
<td>4</td>
<td>0</td>
<td>5</td>
<td>21</td>
<td>44 [14-79]</td>
<td>0 [0-13]</td>
<td>20 [1-334]</td>
</tr>
<tr>
<td>Status epilepticus (2)</td>
<td>≤72h</td>
<td>Very serious</td>
<td>No</td>
<td>serious</td>
<td>Very serious</td>
<td>Very low</td>
<td>43</td>
<td>2</td>
<td>131</td>
<td>31</td>
<td>25[18-32]</td>
<td>6 [1-20]</td>
<td>3 [0-23]</td>
</tr>
</tbody>
</table>
## Evidence profile table

<table>
<thead>
<tr>
<th>CT Index</th>
<th>Timing from ROSC</th>
<th>Risk of bias</th>
<th>Indirectness</th>
<th>Inconsistency</th>
<th>Imprecision</th>
<th>Quality of evidence</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>Sensitivity [95%CI]</th>
<th>FPR [95%CI]</th>
<th>LR+ [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GWR BG &lt;1.22</strong></td>
<td>&lt; 1 h</td>
<td>Very serious</td>
<td>Serious</td>
<td>Very serious</td>
<td>Very low</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>100</td>
<td>[55-100]</td>
<td>0 [0-63]</td>
<td>7 [1-99]</td>
</tr>
<tr>
<td><strong>Average GWR &lt;1.14 (BG/cerebrum)</strong></td>
<td>&lt;1 h</td>
<td>Very serious</td>
<td>No</td>
<td>Very serious</td>
<td>Very low</td>
<td>4</td>
<td>0</td>
<td>26</td>
<td>21</td>
<td>13</td>
<td>[4-31]</td>
<td>0 [0-13]</td>
<td>6 [0-113]</td>
</tr>
<tr>
<td><strong>GWR CN/PIC &lt;1.10</strong></td>
<td>≤2 h</td>
<td>Serious</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>16</td>
<td>0</td>
<td>66</td>
<td>60</td>
<td>20</td>
<td>[12-30]</td>
<td>0 [0-5]</td>
<td>24 [1-396]</td>
</tr>
<tr>
<td><strong>GWR P/CC &lt;1.17</strong></td>
<td>≤2 h</td>
<td>Serious</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>43</td>
<td>0</td>
<td>39</td>
<td>60</td>
<td>52</td>
<td>[41-64]</td>
<td>0 [0-5]</td>
<td>64 [4-1018]</td>
</tr>
<tr>
<td><strong>GWR CN/IC ≤1.18</strong></td>
<td>&lt; 1 h</td>
<td>Very Serious</td>
<td>No</td>
<td>Very serious</td>
<td>Very low</td>
<td>51</td>
<td>1</td>
<td>12</td>
<td>11</td>
<td>81</td>
<td>[69-90]</td>
<td>8[0-38]</td>
<td>10 [1-64]</td>
</tr>
<tr>
<td><strong>Global cerebral oedema</strong></td>
<td>Median day 1 (1-7)</td>
<td>Serious</td>
<td>No</td>
<td>Serious</td>
<td>Low</td>
<td>11</td>
<td>0</td>
<td>34</td>
<td>57</td>
<td>24</td>
<td>[13-40]</td>
<td>0 [0-5]</td>
<td>29 [2-479]</td>
</tr>
</tbody>
</table>

BG = Basal ganglia; CC= Corpus callosum; CN = Caudate nucleus; PIC = Posterior limb of the internal capsule; P = Putamen
<table>
<thead>
<tr>
<th>MRI Index</th>
<th>Timing from ROSC</th>
<th>Risk of bias</th>
<th>Indirectness</th>
<th>Inconsistency</th>
<th>Imprecision</th>
<th>Quality of evidence</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>Sensitivity [%95CI]</th>
<th>FPR [%95CI]</th>
<th>LR+ [%95CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extensive cortical lesion pattern</td>
<td>80H (IQR 55-117)</td>
<td>Very serious</td>
<td>No</td>
<td>Very serious</td>
<td>Very low</td>
<td>9</td>
<td>1</td>
<td>1</td>
<td>10</td>
<td></td>
<td>90 [55-100]</td>
<td>9 [0-41]</td>
<td>10 [2-65]</td>
</tr>
<tr>
<td>DWI changes in BG</td>
<td>80H (IQR 55-117)</td>
<td>Very serious</td>
<td>No</td>
<td>Very serious</td>
<td>Very low</td>
<td>8</td>
<td>1</td>
<td>2</td>
<td>10</td>
<td></td>
<td>80 [44-97]</td>
<td>9 [0-41]</td>
<td>9 [1-58]</td>
</tr>
<tr>
<td>DWI changes in BS</td>
<td>80H (IQR 55-117)</td>
<td>Very serious</td>
<td>No</td>
<td>Very serious</td>
<td>Very low</td>
<td>3</td>
<td>0</td>
<td>7</td>
<td>11</td>
<td></td>
<td>30 [7-65]</td>
<td>0 [0-24]</td>
<td>8 [0-132]</td>
</tr>
<tr>
<td>Changes in cortex + BG</td>
<td>74h (IQR 61-86)</td>
<td>Serious</td>
<td>Serious</td>
<td>Very serious</td>
<td>Very low</td>
<td>11</td>
<td>0</td>
<td>8</td>
<td>3</td>
<td></td>
<td>58 [33-80]</td>
<td>0 [0-63]</td>
<td>5 [0-63]</td>
</tr>
<tr>
<td>Changes in cortex + BG</td>
<td>&lt; 5 days</td>
<td>Very serious</td>
<td>No</td>
<td>Very serious</td>
<td>Very low</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td></td>
<td>100 [55-100]</td>
<td>0 [0-63]</td>
<td>7 [1-99]</td>
</tr>
</tbody>
</table>

BG = Basal ganglia; BS = Brainstem
## Evidence profile table

<table>
<thead>
<tr>
<th>MRI Index</th>
<th>Timing from ROSC</th>
<th>Risk of bias</th>
<th>Indirectness</th>
<th>Inconsistency</th>
<th>Imprecision</th>
<th>Quality of evidence</th>
<th>Sensitivity [95%CI]</th>
<th>FPR [95%CI]</th>
<th>LR+ [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC &lt; $650 \times 10^{-6}$ mm$^2$/sec in &gt;10% of brain volume</td>
<td>49-108 h</td>
<td>Serious</td>
<td>No</td>
<td>Very serious</td>
<td>Very low</td>
<td>10 0 3 9</td>
<td>77 [46-95]</td>
<td>0 [0-28]</td>
<td>15 [1-227]</td>
</tr>
<tr>
<td>Occipital cortex ADC &lt; $616 \times 10^{-6}$ mm$^2$/sec</td>
<td>45.8 (IQR 36,8-52,4))</td>
<td>Very serious</td>
<td>No</td>
<td>Very serious</td>
<td>Very low</td>
<td>29 0 3 11</td>
<td>91 [75-98]</td>
<td>0 [0-24]</td>
<td>21 [1-324]</td>
</tr>
<tr>
<td>Putamen ADC &lt; $590 \times 10^{-6}$ mm$^2$/sec</td>
<td>45.8 (IQR 36,8-52,4))</td>
<td>Very serious</td>
<td>No</td>
<td>Very serious</td>
<td>Very low</td>
<td>25 0 7 11</td>
<td>78 [60-91]</td>
<td>0 [0-24]</td>
<td>19 [1-281]</td>
</tr>
<tr>
<td>Thalamus ADC &lt; $660 \times 10^{-6}$ mm$^2$/sec</td>
<td>45.8 (IQR 36,8-52,4))</td>
<td>Very serious</td>
<td>No</td>
<td>Very serious</td>
<td>Very low</td>
<td>20 0 12 11</td>
<td>63 [44-79]</td>
<td>0 [0-24]</td>
<td>15 [1-228]</td>
</tr>
</tbody>
</table>

ADC = Apparent Diffusion Coefficient
## Biomarkers - Evidence profile

<table>
<thead>
<tr>
<th>Predictor, timing, studies</th>
<th>Threshold (mcg.L⁻¹)</th>
<th>Risk of bias</th>
<th>Indirectness</th>
<th>Inconsistency</th>
<th>Imprecision</th>
<th>Quality of evidence</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>Sensitivity [95%CI]</th>
<th>FPR [95%CI]</th>
<th>LR+ [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSE 48 h (13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>Very serious</td>
<td>no</td>
<td>very serious</td>
<td></td>
<td>Very low</td>
<td>2</td>
<td>0</td>
<td>7</td>
<td>24</td>
<td>22 [3-60]</td>
<td>0 [0-12]</td>
<td>13 [1-238]</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>Serious</td>
<td>No</td>
<td>S</td>
<td></td>
<td>Serious</td>
<td>122</td>
<td>11</td>
<td>107</td>
<td>191</td>
<td>53 47-60]</td>
<td>5 [3-10]</td>
<td>9 [5-16]</td>
</tr>
<tr>
<td></td>
<td>44.3</td>
<td>Very serious</td>
<td>no</td>
<td>-</td>
<td>Very serious</td>
<td>Very low</td>
<td>19</td>
<td>0</td>
<td>3</td>
<td>7</td>
<td>86 [64-97]</td>
<td>0 [0-34]</td>
<td>14 [1-209]</td>
</tr>
<tr>
<td></td>
<td>52.7</td>
<td>Very serious</td>
<td>no</td>
<td>-</td>
<td>No</td>
<td>Low</td>
<td>49</td>
<td>0</td>
<td>33</td>
<td>60</td>
<td>60 [48-70]</td>
<td>0 [0-5]</td>
<td>73 [5-1157]</td>
</tr>
<tr>
<td></td>
<td>54.5</td>
<td>Very serious</td>
<td>no</td>
<td>Very serious</td>
<td></td>
<td>Very low</td>
<td>14</td>
<td>0</td>
<td>10</td>
<td>9</td>
<td>10]0-45]</td>
<td>0 [0-28]</td>
<td>12 [1-176]</td>
</tr>
<tr>
<td></td>
<td>59.25</td>
<td>Very serious</td>
<td>No</td>
<td>Very serious</td>
<td></td>
<td>Very low</td>
<td>1</td>
<td>0</td>
<td>9</td>
<td>20</td>
<td>10 [0-45]</td>
<td>0 [0-14]</td>
<td>6 [0-129]</td>
</tr>
<tr>
<td></td>
<td>81.8</td>
<td>Serious</td>
<td>No</td>
<td>Np</td>
<td>Moderate</td>
<td>29</td>
<td>0</td>
<td>130</td>
<td>151</td>
<td>18</td>
<td>18 [13-25]</td>
<td>0 [0-2]</td>
<td>56 [3-909]</td>
</tr>
<tr>
<td></td>
<td>112.4</td>
<td>Very Serious</td>
<td>No</td>
<td>Serious</td>
<td></td>
<td>Very low</td>
<td>9</td>
<td>0</td>
<td>21</td>
<td>33</td>
<td>30 [15-49]</td>
<td>0 [0-9]</td>
<td>21 [1-343]</td>
</tr>
<tr>
<td></td>
<td>151.5</td>
<td>Very Serious</td>
<td>No</td>
<td>Serious</td>
<td></td>
<td>Very low</td>
<td>14</td>
<td>0</td>
<td>48</td>
<td>41</td>
<td>23 [13-35]</td>
<td>0 [0-7]</td>
<td>19 [1-343]</td>
</tr>
</tbody>
</table>
## Biomarkers - Evidence profile

<table>
<thead>
<tr>
<th>Predictor, timing</th>
<th>Threshold (mcg L⁻¹)</th>
<th>Risk of bias</th>
<th>Indirectness</th>
<th>Inconsistency</th>
<th>Imprecision</th>
<th>Quality of evidence</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>Sensitivity [95%CI]</th>
<th>FPR [95%CI]</th>
<th>LR+ [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSE 72h (4)</td>
<td>33</td>
<td>Serious</td>
<td>No</td>
<td>-</td>
<td>Very serious</td>
<td>Very low</td>
<td>18</td>
<td>4</td>
<td>6</td>
<td>14</td>
<td>75 [53-90]</td>
<td>22 [6-48]</td>
<td>3 [1-8]</td>
</tr>
<tr>
<td></td>
<td>57.2</td>
<td>Very serious</td>
<td>No</td>
<td>-</td>
<td>Very serious</td>
<td>Very low</td>
<td>11</td>
<td>0</td>
<td>13</td>
<td>9</td>
<td>46 [26-67]</td>
<td>0 [0-28]</td>
<td>9 [1-142]</td>
</tr>
<tr>
<td></td>
<td>65.4</td>
<td>Very serious</td>
<td>No</td>
<td>-</td>
<td>Serious</td>
<td>Very low</td>
<td>23</td>
<td>0</td>
<td>7</td>
<td>33</td>
<td>77 [58-90]</td>
<td>0 [0-9]</td>
<td>52 [3-813]</td>
</tr>
<tr>
<td></td>
<td>78.9</td>
<td>Very serious</td>
<td>no</td>
<td>Serious</td>
<td></td>
<td>Very low</td>
<td>21</td>
<td>0</td>
<td>23</td>
<td>53</td>
<td>48 [32-63]</td>
<td>0 [0-6]</td>
<td>52 [3-828]</td>
</tr>
</tbody>
</table>
# Biomarkers - Evidence profile

<table>
<thead>
<tr>
<th>Predictor, timing, studies</th>
<th>Threshold (mcg L⁻¹)</th>
<th>Risk of bias</th>
<th>Indirectness</th>
<th>Inconsistency</th>
<th>Imprecision</th>
<th>Quality of evidence</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>Sensitivity [95%CI]</th>
<th>FPR [95%CI]</th>
<th>LR+ [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSE 24 h (6)</td>
<td>31.2</td>
<td>Very serious</td>
<td>no</td>
<td>-</td>
<td>very serious</td>
<td>very low</td>
<td>2</td>
<td>1</td>
<td>8</td>
<td>24</td>
<td>20 [3-56]</td>
<td>4 [0-20]</td>
<td>5 [1-49]</td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>Serious</td>
<td>no</td>
<td>-</td>
<td>very serious</td>
<td>very low</td>
<td>7</td>
<td>2</td>
<td>32</td>
<td>48</td>
<td>18 [8-34]</td>
<td>4 [0-14]</td>
<td>4 [1-20]</td>
</tr>
<tr>
<td></td>
<td>49.6</td>
<td>Very serious</td>
<td>no</td>
<td>-</td>
<td>very serious</td>
<td>very low</td>
<td>20</td>
<td>0</td>
<td>5</td>
<td>9</td>
<td>80 [59-93]</td>
<td>0 [0-29]</td>
<td>15 [1-229]</td>
</tr>
<tr>
<td></td>
<td>52.4</td>
<td>Very serious</td>
<td>no</td>
<td></td>
<td>very serious</td>
<td>very low</td>
<td>1</td>
<td>0</td>
<td>9</td>
<td>20</td>
<td>10 [0-45]</td>
<td>0 [0-14]</td>
<td>6 [0,3-129]</td>
</tr>
<tr>
<td></td>
<td>80.8</td>
<td>Serious</td>
<td>no</td>
<td></td>
<td>Moderate</td>
<td>Moderate</td>
<td>22</td>
<td>0</td>
<td>60</td>
<td>60</td>
<td>27 [18-37]</td>
<td>0 0-4]</td>
<td>33 [2-535]</td>
</tr>
<tr>
<td></td>
<td>151.4</td>
<td>Very serious</td>
<td>No</td>
<td></td>
<td>Very serious</td>
<td>Very low</td>
<td>8</td>
<td>0</td>
<td>54</td>
<td>41</td>
<td>13 [6-24]</td>
<td>0 [0-7]</td>
<td>11 [1-191]</td>
</tr>
</tbody>
</table>
Reversible brain death after cardiopulmonary arrest and induced hypothermia*

- “A 55-yr-old man presented with cardiac arrest... spontaneous perfusion restored, and therapeutic hypothermia provided”
- “Death was pronounced and the family consented to organ donation”
- “24 hrs after brain death, on arrival to the operating room for organ procurement, the patient was found to have regained corneal reflexes, cough reflex, and spontaneous respirations”

Webb and Samuels, CCM 2011.
YOU DIDN'T COME HERE TO MAKE THE CHOICE, YOU'VE ALREADY MADE IT.

YOU'RE HERE TO UNDERSTAND *WHY*
The most likely outcome in adult out-of-hospital cardiac arrest patients that survive to hospital discharge

1. Minimal disability
2. Moderate disability
3. Severe disability
4. Vegetative state
The most likely outcome in adult out-of-hospital cardiac arrest patients that survive to hospital discharge

1. Minimal disability
2. Moderate disability
3. Severe disability
4. Vegetative state

More than two thirds of patients will have minimal to no disability

Aufderheide T et al. NEJM 2011;365:798-806
Predicting good neurological outcome in adult cardiac arrest survivors that receive targeted temperature management

Golan E, Scales DC, Morrison LM; 2015 (unpublished data)
Predicting good neurological outcome in adult cardiac arrest survivors that receive targeted temperature management

78% of patients that survived to hospital discharge experienced a very good neurological outcome as defined by a CPC 1 (431/550 patients)

Golan E, Scales DC, Morrison LM; 2015 (unpublished data)
The majority (79%) of surviving patients who underwent TH after cardiac arrest in this series had preserved cognitive function and were able to return to work.
<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Time post-ROSC, hours</th>
<th>Patients tested, n</th>
<th>Number of studies, n</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>FPR</th>
<th>Positive LR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Simple proportions</td>
<td>Continuity correction</td>
<td></td>
</tr>
<tr>
<td>Corneal reflex</td>
<td>≤ 72</td>
<td>240</td>
<td>3</td>
<td>0.32 (0.22-0.44)</td>
<td>0.98 (0.92-1.00)</td>
<td>0.97 (0.90-0.99)</td>
<td>0.02 (0.00-0.08)</td>
</tr>
<tr>
<td></td>
<td>&gt; 72</td>
<td>127</td>
<td>2</td>
<td>0.20 (0.12-0.31)</td>
<td>1.00 (0.94-1.00)</td>
<td>0.95 (0.36-1.00)</td>
<td>0.00 (0.00-0.06)</td>
</tr>
<tr>
<td>Pupillary reflex</td>
<td>≤ 72</td>
<td>305</td>
<td>3</td>
<td>0.27 (0.19-0.36)</td>
<td>0.99 (0.96-1.00)</td>
<td>0.98 (0.94-1.00)</td>
<td>0.01 (0.00-0.04)</td>
</tr>
<tr>
<td></td>
<td>&gt; 72</td>
<td>133</td>
<td>2</td>
<td>0.18 (0.10-0.28)</td>
<td>1.00 (0.94-1.00)</td>
<td>0.96 (0.54-1.00)</td>
<td>0.00 (0.00-0.06)</td>
</tr>
<tr>
<td>Motor score (M1 or M2)</td>
<td>≤ 72</td>
<td>583</td>
<td>5</td>
<td>0.63 (0.43-0.80)</td>
<td>0.90 (0.86-0.93)</td>
<td>0.90 (0.85-0.93)</td>
<td>0.10 (0.07-0.14)</td>
</tr>
<tr>
<td></td>
<td>&gt; 72</td>
<td>208</td>
<td>3</td>
<td>0.59 (0.26-0.86)</td>
<td>0.96 (0.90-0.99)</td>
<td>0.95 (0.89-0.98)</td>
<td>0.04 (0.01-0.1)</td>
</tr>
<tr>
<td>Clinical status myoclonus</td>
<td>≤ 72</td>
<td>410</td>
<td>5</td>
<td>0.27 (0.19-0.38)</td>
<td>0.98 (0.93-1.00)</td>
<td>0.95 (0.88-0.98)</td>
<td>0.02 (0.01-0.07)</td>
</tr>
<tr>
<td>Unfavorable EEG</td>
<td>≤ 72</td>
<td>465</td>
<td>8</td>
<td>0.57 (0.32-0.79)</td>
<td>0.96 (0.92-0.99)</td>
<td>0.94 (0.88-0.97)</td>
<td>0.04 (0.01-0.08)</td>
</tr>
<tr>
<td></td>
<td>&gt; 72</td>
<td>87</td>
<td>3</td>
<td>0.80 (0.70-0.88)</td>
<td>1.00 (0.75-1.00)</td>
<td>0.90 (0.61-0.98)</td>
<td>0.06 (0.03-0.12)</td>
</tr>
<tr>
<td>SSEP</td>
<td>≤ 72</td>
<td>417</td>
<td>6</td>
<td>0.40 (0.25-0.57)</td>
<td>1.00 (0.97-1.00)</td>
<td>0.98 (0.94-0.99)</td>
<td>0.01 (0.00-0.03)</td>
</tr>
<tr>
<td></td>
<td>&gt; 72</td>
<td>157</td>
<td>2</td>
<td>0.44 (0.29-0.59)</td>
<td>1.00 (0.83-1.00)</td>
<td>0.94 (0.68-0.99)</td>
<td>0.00 (0.00-0.17)</td>
</tr>
<tr>
<td>NSE &gt; 33</td>
<td>≤ 72</td>
<td>507</td>
<td>4</td>
<td>0.51 (0.46-0.57)</td>
<td>0.89 (0.84-0.93)</td>
<td>0.88 (0.77-0.94)</td>
<td>0.11 (0.07-0.16)</td>
</tr>
</tbody>
</table>

Golan E et al, CCM 2014 Oct;42(10):2235-43
<table>
<thead>
<tr>
<th>Predictor (studies)</th>
<th>Timing</th>
<th>Risk of bias</th>
<th>Indirectness</th>
<th>Inconsistency</th>
<th>Imprecision</th>
<th>Quality of evidence</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>Sensitivity [95%CI]</th>
<th>FPR [95%CI]</th>
<th>LR+ [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flat</td>
<td>During TTM</td>
<td>Serious</td>
<td>No</td>
<td>-</td>
<td>Very serious</td>
<td>Very low</td>
<td>10</td>
<td>21</td>
<td>26</td>
<td>17</td>
<td>31 [38-71]</td>
<td>46 [32-59]</td>
<td></td>
</tr>
<tr>
<td>Flat or low-voltage</td>
<td>During TTM</td>
<td>Serious</td>
<td>No</td>
<td>-</td>
<td>Very serious</td>
<td>Very low</td>
<td>9</td>
<td>8</td>
<td>0</td>
<td>12</td>
<td>26 [19-64]</td>
<td>0 [0-11]</td>
<td></td>
</tr>
<tr>
<td>Flat</td>
<td>After RW</td>
<td>Serious</td>
<td>No</td>
<td>-</td>
<td>Serious</td>
<td>Very low</td>
<td>5</td>
<td>6</td>
<td>3</td>
<td>32</td>
<td>54 [6-31]</td>
<td>5 [1-15]</td>
<td></td>
</tr>
<tr>
<td>BIS=0</td>
<td>During TTM</td>
<td>Very serious</td>
<td>no</td>
<td>-</td>
<td>Very serious</td>
<td>Very low</td>
<td>14</td>
<td>0</td>
<td>14</td>
<td>17</td>
<td>50 [31-69]</td>
<td>0 [0-16]</td>
<td>18 [1-284]</td>
</tr>
<tr>
<td>Lowest mean BIS≤ 5,5</td>
<td>During TTM</td>
<td>Very serious</td>
<td>no</td>
<td>-</td>
<td>Very serious</td>
<td>Very low</td>
<td>29</td>
<td>7</td>
<td>5</td>
<td>34</td>
<td>85 [69-95]</td>
<td>17 [7-32]</td>
<td>5 [3-10]</td>
</tr>
<tr>
<td>Lowest BIS=0</td>
<td>During TTM</td>
<td>Very serious</td>
<td>No</td>
<td>-</td>
<td>Very serious</td>
<td>Very low</td>
<td>26</td>
<td>4</td>
<td>8</td>
<td>37</td>
<td>76 [59-89]</td>
<td>10 [3-23]</td>
<td>8 [3-30]</td>
</tr>
</tbody>
</table>
# Precision of the diagnostic tests

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Patients tested, n</th>
<th>Number of studies, n</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>FPR</th>
<th>Positive LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corneal reflex</td>
<td>367</td>
<td>5</td>
<td>0.28 (0.21-0.37)</td>
<td>0.96 (0.91-0.99)</td>
<td>0.04 (0.01-0.09)</td>
<td>6.8 (2.52-18.38)</td>
</tr>
<tr>
<td>Pupillary reflex</td>
<td>438</td>
<td>5</td>
<td>0.24 (0.19-0.31)</td>
<td>0.98 (0.94-0.99)</td>
<td>0.02 (0.01-0.06)</td>
<td>10.45 (3.37-32.43)</td>
</tr>
<tr>
<td>Motor score (M1 or M2)</td>
<td>791</td>
<td>8</td>
<td>0.61 (0.44-0.76)</td>
<td>0.91 (0.87-0.94)</td>
<td>0.09 (0.06-0.13)</td>
<td>7.11 (5.01-10.08)</td>
</tr>
<tr>
<td>Clinical status myoclonus</td>
<td>513</td>
<td>6</td>
<td>0.29 (0.22-0.38)</td>
<td>0.95 (0.89-0.98)</td>
<td>0.05 (0.02-0.11)</td>
<td>5.58 (2.56-12.16)</td>
</tr>
<tr>
<td>Unfavorable EEG</td>
<td>552</td>
<td>11</td>
<td>0.66 (0.47-0.82)</td>
<td>0.93 (0.88-0.96)</td>
<td>0.07 (0.04-0.12)</td>
<td>8.85 (4.87-16.08)</td>
</tr>
<tr>
<td>SSEP</td>
<td>620</td>
<td>9</td>
<td>0.43 (0.33-0.53)</td>
<td>0.97 (0.93-0.99)</td>
<td>0.03 (0.01-0.07)</td>
<td>12.79 (5.35-30.62)</td>
</tr>
<tr>
<td>NSE &gt; 33</td>
<td>507</td>
<td>4</td>
<td>0.51 (0.46-0.57)</td>
<td>0.88 (0.77-0.94)</td>
<td>0.12 (0.06-0.23)</td>
<td>4.14 (1.82-9.42)</td>
</tr>
</tbody>
</table>

Golan E et al, CCM 2014 Oct;42(10):2235-43
What about real life data?

- Consecutive OHCA patients that received TTM and survived to 72hrs post-arrest
- Multicentre (n=34 hospitals) in Southwestern Ontario from 2011-2014
- N= 982

Golan E et al, Data not yet published
## Results

### Neuroprognostic tests

<table>
<thead>
<tr>
<th>Neuroprognostic tests</th>
<th>Unadjusted OR (95%CI)</th>
<th>Unadjusted OR (95%CI)</th>
<th>Adjusted OR (95%CI)</th>
<th>Adjusted OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilaterally absent corneal reflex at 48 to 72 hours</td>
<td>28.33 (8.15-98.52)</td>
<td>&lt;0.001</td>
<td>7.34 (1.10-49.22)</td>
<td>0.040</td>
</tr>
<tr>
<td>Bilaterally absent pupillary reflex at 48 to 72 hours</td>
<td>23.79 (11.97-47.28)</td>
<td>&lt;0.001</td>
<td>7.71 (3.26-18.23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bilateral Glasgow coma motor score of 1-2 at 48 to 72 hours</td>
<td>18.36 (12.90-26.12)</td>
<td>&lt;0.001</td>
<td>15.95 (9.58-26.56)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Clinical diagnostic test

<table>
<thead>
<tr>
<th>Clinical diagnostic test</th>
<th>False positive rate (percentage; 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilaterally absent corneal reflex at 48 to 72 hours</td>
<td>5.1 (1.4-12.8)</td>
</tr>
<tr>
<td>Bilaterally absent pupillary reflex at 48 to 72 hours</td>
<td>4.5 (2.2-8.1)</td>
</tr>
<tr>
<td>Bilateral Glasgow coma motor score of 1-2 at 48 to 72 hours</td>
<td>15.9 (12.8-19.5)</td>
</tr>
</tbody>
</table>

Golan E et al, Data not yet published
Do we stop too early?
Timing of neuroprognostication in postcardiac arrest therapeutic hypothermia

Sarah M. Perman, MD, MS; James N. Kirkpatrick, MD; Angelique M. Reitsma, MD; David F. Gaieski, MD; Bonnie Lau, MD; Thomas M. Smith, RN; Marion Leary, RN; Barry D. Fuchs, MD; Joshua M. Levine, MD; Benjamin S. Abella, MD, MPhil; Lance B. Becker, MD; Raina M. Merchant, MD, MS
The PremaTOR Study
(Preventing Premature Termination Of Resuscitation)