Early goal-directed hemodynamic optimization in comatose survivors after cardiac arrest:

**The Neuroprotect trial**

Koen Ameloot, MD

For the Neuroprotect investigators
### Background: 2-hit model

<table>
<thead>
<tr>
<th>Pre-hospital</th>
<th>ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>No flow</td>
<td>80% post-anoxic encephalopathy</td>
</tr>
<tr>
<td>Low flow</td>
<td></td>
</tr>
</tbody>
</table>

80% post-anoxic encephalopathy

1. No flow
2. Low flow
3. Hypoperfusion
4. Reperfusion

- **Post-ROSC survival**: 40%
- **Guidelines**
  - TTM 33-36°C (class Ia)
  - MAP > 65mmHg (class Ib)

**Background:** 2-hit model

- **Post-ROSC survival**: 40%
- **Guidelines**
  - TTM 33-36°C (class Ia)
  - MAP > 65mmHg (class Ib)

Meex, resuscitation 2013
Background: optimal MAP post-CA?

Ameloot et al, Resuscitation 2015
Aim

EGDHO
MAP 85-100mmHg
SVO₂ 65-75%

Control
MAP 65mmHg

1. Safe?
2. Improves cerebral oxygenation and perfusion?
3. Reduces anoxic brain damage on DW-MRI?
4. Improves functional outcome at 180 days?

Meex, resuscitation 2013
Neuroprotect: trial design

**Investigator driven**
Ziekenhuis Oost-Limburg, Genk, Belgium
University Hospitals Gasthuisberg, Leuven, Belgium

**Randomized**
Stratified by presence of shockable rhythm

**Parallel group**
EGDHO (MAP 85-100mmHg, SVO₂ 65-75%)
MAP65mmHg

**Open Label**
Responsible ICU team

**Outcome Assessor blinded**
Neurologists (➔ neuroprognostication at day 5)
Radiologist (➔ MRI analysis)
Statisticians

**DSMB**
Fabio Taccone (Chair), Karen Hirsch, Niklas Nielsen

**Sponsored**
IWT grant Flemish government Belgium
## Neuroprotect: study population

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>- <strong>Out-of-hospital CA</strong> of presumed cardiac cause irrespective of the presenting rhythm</td>
<td></td>
</tr>
<tr>
<td>- Unconsciousness (<strong>GCS &lt; 8</strong>) at hospital admission</td>
<td>- <strong>Systolic blood pressure</strong> &lt; 90mmHg ↔ <strong>NE</strong> &gt; 1 mcg/kg/min</td>
</tr>
<tr>
<td>- Age ≥ 18 years</td>
<td>- <strong>ECMO/ECLS</strong></td>
</tr>
<tr>
<td>- <strong>Sustained return of spontaneous circulation</strong> (ROSC) (=when chest compressions have not been required for 20 consecutive minutes)</td>
<td>- Previous major stroke</td>
</tr>
<tr>
<td></td>
<td>- MRI incompatible cardiac or neurosurgical device</td>
</tr>
</tbody>
</table>
Neuroprotect: Endpoints

**Primary**

DW-MRI at day 5: 
% of irreversibly damaged anoxic voxels 
(ADC score < 650.10^{-6} mm^2/s)

- 6%
- 48%

If \( B = 0.80 \) & \( \alpha = 0.05 \)
40% relative reduction

112 patients

**Secondary**

- **Favorable neurological outcome (CPC 1-2)**
  - ICU discharge
  - 180 days

- **ICU endpoints**
  - Length of ICU stay
  - Days on mechanical ventilator
  - Need for tracheostomy

- **Safety endpoints**
  - Re-arrest req ALS
  - Pulmonary edema req diuretics
  - Limb ischemia
  - New onset atrial fibrillation
112 patients randomized

56 to EGDHO
- 4 excluded
  - 2 next of kin refused informed consent
  - 2 asphyxia

52 patients (42 with MRI)
- 1 excluded
  - Aortic dissection

56 to MAP65mmHg
- 1 excluded
  - Asphyxia

55 patients (40 with MRI)
- 4 excluded
  - 3 with GCS 15/15 at ICU admission
  - 1 with pacemaker

FAS
- 52 patients (42 with MRI)

PPS
- 51 patients (42 with MRI)

- 1 excluded
  - Aortic dissection

- 4 excluded
  - 3 with GCS 15/15 at ICU admission
  - 1 with pacemaker

51 patients (37 with MRI)
## Neuroprotect: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>EGDHO</th>
<th>MAP65</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>52</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>64±12</td>
<td>65±13</td>
<td>0.99</td>
</tr>
<tr>
<td>Male</td>
<td>39 (75%)</td>
<td>42 (76%)</td>
<td>0.75</td>
</tr>
<tr>
<td><strong>Arrest characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basic life support</td>
<td>31/52 (60%)</td>
<td>29/53 (55%)</td>
<td>0.45</td>
</tr>
<tr>
<td>Shockable</td>
<td>36/52 (69%)</td>
<td>35/54 (65%)</td>
<td>0.63</td>
</tr>
<tr>
<td>Non-shockable</td>
<td>16/52 (31%)</td>
<td>19/54 (35%)</td>
<td></td>
</tr>
<tr>
<td>Time-to-ROSC (min)</td>
<td>18 (10; 25)</td>
<td>17 (10; 25)</td>
<td>0.42</td>
</tr>
<tr>
<td><strong>Cause of arrest</strong></td>
<td></td>
<td></td>
<td>0.65</td>
</tr>
<tr>
<td>(n)STEMI</td>
<td>29/52 (56%)</td>
<td>33/54 (61%)</td>
<td></td>
</tr>
<tr>
<td>Arrhythmogenic</td>
<td>14/52 (27%)</td>
<td>13/54 (24%)</td>
<td></td>
</tr>
<tr>
<td>Hypoxic</td>
<td>7/52 (13%)</td>
<td>4/54 (7%)</td>
<td></td>
</tr>
<tr>
<td>Other/unclear</td>
<td>2/52 (4%)</td>
<td>4/54 (7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Admission</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>88±21</td>
<td>85±25</td>
<td>0.55</td>
</tr>
<tr>
<td>Corneal reflex (presence)</td>
<td>11/41 (27%)</td>
<td>24/49 (49%)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Angiography</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angio performed</td>
<td>46/52 (88%)</td>
<td>48/53 (91%)</td>
<td>0.73</td>
</tr>
<tr>
<td>PCI performed</td>
<td>27/52 (52%)</td>
<td>30/54 (56%)</td>
<td>0.62</td>
</tr>
</tbody>
</table>

- 56% received BLS
- 33% non-shockable
- 58% (n)STEMI
Neuroprotect: Hemodynamics & Cerebral oxygenation

- **Mean Arterial Pressure (MAP) [mmHg]**
  - P < 0.001

- **Norepinephrine [m/kg/min]**
  - P = 0.02

- **Cerebral saturation [%]**
  - P = 0.04
  - P = 0.30

- **Flow MCA [cm/s]**
  - P < 0.001 (n=10)
Neuroprotect primary endpoint: % anoxic voxels DW-MRI

<table>
<thead>
<tr>
<th></th>
<th>EGDHO</th>
<th>MAP65</th>
<th>Ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>42/52 (81%)</td>
<td>40/55 (73%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Observed</strong></td>
<td>11% (8;18)</td>
<td>11% (8;15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Median, (Q1,Q3))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Imputation</strong></td>
<td>16% (13;21)</td>
<td>12% (9;16)</td>
<td>1.37 (0.95;1.98)</td>
<td>0.09</td>
</tr>
<tr>
<td>(Median, (95% CI))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The % of anoxic voxels (ADC score < 650.10^{-6} mm^2/s) was only a poor predictor of favorable neurological outcome (CPC 1-2) at 180 days (ROC AUC 0.60)

MRI could not be obtained in 23% of the patients and more patients assigned to EGDHO underwent MRI (Bias)
Neuroprotect: favorable neurological outcome (CPC 1-2)

- EGDHO
- MAP65

<table>
<thead>
<tr>
<th>Group</th>
<th>EGDHO</th>
<th>MAP65</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAS</td>
<td>42%</td>
<td>33%</td>
</tr>
<tr>
<td>PPS</td>
<td>43%</td>
<td>27%</td>
</tr>
</tbody>
</table>

p-values:
- FAS: p=0.39
- PPS: p=0.15

ICU discharge
# Neuroprotect secondary endpoints: ICU

<table>
<thead>
<tr>
<th></th>
<th>EGDHO</th>
<th>MAP65</th>
<th>Ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ICU stay (days)</strong> (Median, (Q1,Q3))</td>
<td>7 (5;11)</td>
<td>8 (5;17)</td>
<td></td>
<td>0.13</td>
</tr>
<tr>
<td><strong>Mechanical ventilation (days)</strong> (Median, (Q1,Q3))</td>
<td>5 (3;9)</td>
<td>7 (3;13)</td>
<td></td>
<td>0.31</td>
</tr>
<tr>
<td><strong>Tracheostomy (n, (%))</strong></td>
<td>2/52 (4%)</td>
<td>10/55 (18%)</td>
<td>0.18 (0.04;0.88)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Neuroprotect: safety endpoints

Assessed hourly by study nurses

- Recurrent arrest: 13% (EGDHO) vs 24% (MAP65), RRR 60%
- Limb ischemia: 0% (EGDHO) vs 2% (MAP65)
- New AF: 0% (EGDHO) vs 7% (MAP65)
- Pulmonary edema: 0% (EGDHO) vs 4% (MAP65)
- Any AE: 13% (EGDHO) vs 33% (MAP65), p=0.02

RRR 60%
**Neuroprotect: Conclusions**

1. **Safe:** ↓ Re-arrest & serious adverse events
2. Improves cerebral oxygenation and perfusion
3. **No** reduction anoxic brain damage on DW-MRI
4. **No** improvement functional outcome at 180 days
   - Poor accuracy DW-MRI to predict prognosis
   - Baseline brain damage: too extensive?
   - Brain stem reflexes: more present in the MAP65mmHg arm

Need for future outcome trial
Neuroprotect: Acknowledgements

CCU attendings cardiology
- S. Janssens, MD, PhD
- T. Adriaenssens, MD, PhD
- J. Bennett, MD, PhD
- W. Desmet, MD, PhD
- C. Dubois, MD, PhD
- P. Sinnaeve, MD, PhD
- T. Vanassche, MD, PhD
- Nursing staff CCU
- T. Petit, MD
- P. Nuyens, MD
- M. Vanhaverbeke, MD
- R. Lemmens, MD, PhD, neurology
- P. Demaerel, MD, PhD, radiology
- R. Peeters, radiology

CCU attendings dept of cardiology
- K. Ameloot, MD
- J. Dens, MD, PhD
- B. Ferdinande, MD
- M. Dupont, MD
- PJ. Palmers, MD
- C. De Deyne, MD, PhD
- W. Eertmans, PhD
- J. Maeremans, PhD
- J. Vundelinckx, MD
- Nursing staff CCU

Leuven Coordinating Center, KU-Leuven, BE
- A. Belmans, PhD
- K. Vandenberghe, PhD
- P. Van Rompaey
- A. Luyten, MD, PhD
- M. Beckx
- K. Broos

DSMB
- F. Taccone MD, PhD
- K. Hirsch MD, PhD
- N. Nielsen MD, PhD
THANK YOU!