TTM and post-arrest care: clinical trials and recent evidence

Survival in cardiac arrest

Reperfusion injury pathways

Key RCTs from 2001-2002

**Speaker disclosures**

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American Heart Association

Honoraria/consulting: Velomedix
Stryker Medical Corp
CR Bard

Medical Advisory Board: HeartSine
CardioReady

Equity: Reuscor LLC

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**Survival in cardiac arrest**

<table>
<thead>
<tr>
<th>Time</th>
<th>% Surviving</th>
</tr>
</thead>
<tbody>
<tr>
<td>arrest</td>
<td></td>
</tr>
<tr>
<td>CPR</td>
<td></td>
</tr>
<tr>
<td>ROSC</td>
<td>52%</td>
</tr>
<tr>
<td>hospital discharge</td>
<td>18%</td>
</tr>
</tbody>
</table>

**Reperfusion injury**

Damage observed after restoration of blood flow to ischemic tissues

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**Reperfusion injury pathways**

- ischemia → reperfusion
- reactive oxygen species (ROS) → inflammatory cascades
- mitochondrial dysfunction
- vascular dysfunction/hypotension
- apoptosis – organ dysfunction
- cerebral edema

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**Key RCTs from 2001-2002**

- HACA, 2002
- Bernard, 2002
- Idrissi, 2001

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### Concept of post-arrest TTM

![Graph showing bladder temperature vs. time](image)

**Bladder temperature, °C**

- 39
- 38
- 37
- 36
- 35
- 34
- 33
- 32

**Time in hours**

- 0
- 6
- 12
- 18
- 24
- 30
- 36
- 40

### More RCT details

<table>
<thead>
<tr>
<th>Multicenter?</th>
<th>Main site</th>
<th>pt rhythm</th>
<th>pt location</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>HACA</td>
<td>YES</td>
<td>Austria</td>
<td>VF</td>
<td>OOH</td>
</tr>
<tr>
<td>Bernard</td>
<td>YES</td>
<td>Australia</td>
<td>VF</td>
<td>OOH</td>
</tr>
<tr>
<td>Idrissi</td>
<td>NO</td>
<td>Belgium</td>
<td>OPE/asytole</td>
<td>OOH</td>
</tr>
</tbody>
</table>

### HACA temperature curves

**Cold maintenance**

- Cooling (8-12 hr)
- Rewarming (24 hr)

### HACA temperature curves

- HACA, 2002

### RCT outcomes

<table>
<thead>
<tr>
<th>Hypothermia (%)</th>
<th>Normothermia (%)</th>
<th>RR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive at hospital discharge with favourable neurological recovery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HACA</td>
<td>72/136 (53%)</td>
<td>50/137 (36%)</td>
<td>1.51 (1.14-1.89)</td>
</tr>
<tr>
<td>Bernard</td>
<td>21/43 (49%)</td>
<td>9/34 (26%)</td>
<td>1.75 (0.99-2.43)</td>
</tr>
<tr>
<td>Idrissi</td>
<td>4/16 (25%)</td>
<td>1/17 (6%)</td>
<td>4.25 (0.70-53.83)</td>
</tr>
</tbody>
</table>

### AHA guidelines

**Comatose out-of-hospital VF:**

- Class Ia recommendation
- 2010: Changed to Class I

**In-hospital arrest, other rhythms:**

- Class IIb recommendation
- 2010: Still Class IIb
Cooling intervention with historical controls
Survivors of out-of-hospital arrest (n=109)
Cooling initially via ice bags, then cooling mattress
Target temperature 33°C, maintained for 24 hrs
All post-arrest ST elevations received cardiac cath

Retrospective study at one hospital in Switzerland

Oddo M et al, 2006

Outcome at discharge for out-of-hospital VF arrest

Baseline
CPC5 64% CPC3 19% CPC2 12% CPC1 14%

Cooling
CPC5 40% CPC3 5% CPC2 14% CPC1 42%

CPC 5              .CPC3    CPC2       CPC1
40%                  5%     14%                    42%

Outcome at discharge for out-of-hospital asystole arrest

Baseline
CPC5 89% CPC3 11%

Cooling
CPC5 83% CPC1 17%

CPC5                        CPC1
83%                                               17%

Hypothermia clinical benefit is robust (consistent across Numerous studies)

Meta-analysis of hypothermia for non-shockable Rhythms (non-VF/VT)

Kim Y et al, 2012

Nielsen et al, 2009

Bradydardia (13%)
Significant bleed (4%)
TTM and the cath lab

Usefulness of Cooling and Coronary Catheterization to Improve Survival in Out-of-Hospital Cardiac Arrest

Grossestreuer, 2013

Less than 40% of patients had STEMI; yet huge survival benefits when OHCA patients cathed

Comparing TTM devices

No study has shown significant outcome or adverse event differences between devices

Prehospital cooling?

Induction of Therapeutic Hypothermia by Paramedics After Resuscitation From Out-of-Hospital Ventricular Fibrillation Cardiac Arrest

A Randomized Controlled Trial

Prehospital cooling? (part 2)

The 2013 TTM trial (Nielsen et al)

Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest

Benjamin Abella, MD
CARES webinar August 2014
**Details of the TTM trial**

- 950 patients randomized
- 36 hospitals
- 10 countries
- Europe and Australia

Funded by:
- Swedish Heart Lung Foundation
- LUA-research foundation, Sweden
- Swedish Research Council
- Governmental and regional funding within the Swedish National Health System
- Tryg Foundation, Denmark
- Jonge, Knippel, Thom-Cedersson, Trox-hakelius foundation, Sweden

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**Characteristics of each group**

**Baseline characteristics**

<table>
<thead>
<tr>
<th></th>
<th>33°C</th>
<th>36°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>473</td>
<td>466</td>
</tr>
<tr>
<td>Age</td>
<td>64±11</td>
<td>64±11</td>
</tr>
<tr>
<td>Male sex</td>
<td>63%</td>
<td>79%</td>
</tr>
<tr>
<td>Arrest in place of residence</td>
<td>57%</td>
<td>55%</td>
</tr>
<tr>
<td>Arrest in public place</td>
<td>25%</td>
<td>40%</td>
</tr>
<tr>
<td>Circulatory shock</td>
<td>69%</td>
<td>73%</td>
</tr>
<tr>
<td>Shockable rhythm</td>
<td>79%</td>
<td>81%</td>
</tr>
<tr>
<td>Arrest to ROSC (min)</td>
<td>28 (15–41)</td>
<td>26 (14–40)</td>
</tr>
<tr>
<td>Circulatory shock</td>
<td>10%</td>
<td>14%</td>
</tr>
<tr>
<td>Lactate on ICU</td>
<td>6.7±4.2</td>
<td>6.7±4.0</td>
</tr>
<tr>
<td>Invasive ventilation</td>
<td>48%</td>
<td>47%</td>
</tr>
<tr>
<td>GCS</td>
<td>3±1–4</td>
<td>3±1–4</td>
</tr>
</tbody>
</table>

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**Outcomes in the TTM trial**

![Survival](image)

\[P=0.51\]

**TTM subgroup analyses**

- Nielsen et al
- Bernard et al

![Temperature curve comparison](image)

**Temperature curve comparison**

- HACA study: ~37.6°C
- Bernard et al: ~37.3°C

**Key question raised by TTM trial**

![Key question raised by TTM trial](image)

**How can this be?**

- No cooling
- 33°C
- 36°C
- 36°C
- 33°C

- HACA
- Bernard
- TTM

**Large difference in maintenance temperatures**
2013 TTM trial: key point

2013 TTM trial does not test the same hypothesis as the HACA, Bernard trials

36°C arm in the trial is still active management of temperature

Overview of post-arrest outcomes

<table>
<thead>
<tr>
<th>Degree of post-arrest injury</th>
<th>Poor outcome with any TTM</th>
<th>Good outcome with any TTM</th>
</tr>
</thead>
<tbody>
<tr>
<td>severe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild / none</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

dose of TTM (33°C v 36°C, e.g.) affects outcome

Rationale for our approach

Given that:

1. TTM trial was neutral (no differences in benefit or harms)
2. Cooling to 33°C is based on extensive laboratory evidence and two RCTs (HACA, 2002; Bernard et al, 2002)
3. We can’t tell who will have significant post-arrest injury based on current technology and clinical factors
4. The chance to modify neurologic injury is in the acute care of post-arrest patients – and we don’t get a second chance

Our consensus approach

Therefore:

- It is reasonable to not change current practice based on the TTM trial, but rather continue to treat comatose post-arrest patients with a TTM goal temperature of 33°C.

However, the TTM trial provides evidence that a more flexible approach is possible – for patients intolerant of 33°C (marked bradycardia, increased bleeding, marked QT prolongation, e.g.) or for patients that clinicians feel uncomfortable with treating to 33°C for other clinical factors, it is acceptable to treat with higher TTM temperature goals, up to 36°C.

Other key part of our approach

ALL comatose post-arrest patients should at least receive TTM with a maximum temp goal of 36°C – "normothermia" as defined by lack of any temperature control is not supported by the growing body of literature.

In addition to TTM management in the acute phase (12-24 hours of either 33°C or 36°C TTM), all post arrest patients should receive comprehensive best-practice post arrest care, including aggressive avoidance of fever for up to 48-72 hours following rewarming and avoidance of care withdrawal for at least 72 hours post arrest, as supported in the current AHA guidelines and the TTM trial.

Post-arrest care is multimodal

Requires a critical care “bundle”:

- Therapeutic hypothermia
- Careful hemodynamic management
- Coronary intervention if STEMI or high probability of coronary cause
- Neurology consultation and assessment
Post-arrest hypothermia: an implementation problem

Many hospitals aren’t using the therapy; other hospitals underuse it

Practical training in post-arrest care

Hypothermia and Resuscitation Training (HART) course at Penn

Philadelphia – next course October, 2014

Intensive two day CME course in hypothermia methods, protocols, and applications

Designed for critical care, cardiology or emergency medicine physicians and nurse leaders – i.e., local champions

Offers “hypothermia certification”

Workshop design – small course size – held quarterly

Preparing the future of resuscitation

Hands on simulations

Honoring survivors and rescuers

Expert faculty proctors

Interactive learning

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