The Great Debate: Hypothermia for In-hospital Cardiac Arrest. A Critique
E Hessel, II, MD, FACS

Strive to Revive: Overcoming Challenges of Resuscitation
American Heart Association and UK HealthCare Gill Heart Institute
Lexington, KY

May 16, 2013

Revised May 16, 2013; 0710 EDST; April 11, 2013; 0955 EDST; June 28, 2012; 0735 EDST
This afternoon I feel a little like Daniel in the Lions Den!!
Disclosures

• I have no financial or other conflicts related to this subject...

• And I don’t expect any hypothermia device companies will be knocking on my door (at least not with friendly intentions.)

• E-mail address: ehessel@uky.edu

• I was a member of the University of Washington team that introduced use of DHCA to conduct open heart surgery in infants in 1965
Use of Rheomacrodex and Hyperventilation in Prolonged Circulatory Arrest under Deep Hypothermia Induced by Surface Cooling

Method for Open Heart Surgery in Infants

Seattle, Washington

Correction of Total Anomalous Pulmonary Venous Drainage in Infancy Utilizing Deep Hypothermia with Total Circulatory Arrest

August 20, 1965;
5 mo, 3.7 Kg with Total Anomalous Pulmonary Venous Drainage
Introduction

• Moderate therapeutic hypothermia (TH) has been mainly advocated for survivors of out-of-hospital (OOH) cardiac arrest (CA) due to “shockable rhythms” (VF or pulseless VT).

• It is less strongly advocated following CA due non-shockable rhythms and following in-hospital (IH) CA, for either of which there is no high-level evidence.
Therapeutic Hypothermia After Cardiac Arrest: An Advisory Statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation


Summary: ILCOR Recommendations

On the basis of the published evidence to date, the ILCOR ALS Task Force has made the following recommendations:

- Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32°C to 34°C for 12 to 24 hours when the initial rhythm was VF.
- Such cooling may also be beneficial for other rhythms or in-hospital cardiac arrest.
European Resuscitation Council Guidelines for Resuscitation 2005
Section 4. Adult advanced life support

Jerry P. Nolan, Charles D. Deakin, Jasmeet Soar, Bernd W. Böttiger, Gary Smith

Unconscious adult patients with spontaneous circulation after out-of-hospital VF cardiac arrest should be cooled to 32–34°C. Cooling should be started as soon as possible and continued for at least 12–24 h.\textsuperscript{368–374} Induced hypothermia might also benefit unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest from a non-shockable rhythm, or cardiac arrest in hospital. Treat shivering by ensuring ade-
In summary, we recommend that comatose (i.e., lack of meaningful response to verbal commands) adult patients with ROSC after out-of-hospital VF cardiac arrest should be cooled to 32°C to 34°C (89.6°F to 93.2°F) for 12 to 24 hours (Class I, LOE B). Induced hypothermia also may be considered for comatose adult patients with ROSC after in-hospital cardiac arrest of any initial rhythm or after out-of-hospital cardiac arrest with an initial rhythm of pulseless electric activity or asystole (Class IIb, LOE B). Active rewarming should be avoided in comatose patients who spontaneously develop a mild degree of hypothermia (>32°C [89.6°F]) after resuscitation from cardiac arrest during the first 48 hours after ROSC. (Class III, LOE C).
Introduction, continued

• The use of therapeutic hypothermia following in-hospital cardiac arrest is based upon
  
  – The laudable effort to improve its poor prognosis (death and poor neurologic function)

  and

  – Extrapolation of the data supporting its use for OOH-CA

  Unfortunately, as I will show, even that evidence is weak!

• I believe we should not use TH following in-hospital CA and I will try to convince you of this point of view during my presentation.
Why do I have the audacity to challenge the recommendations of these professional organizations?

• **First**, because their recommendations are largely based on expert opinion and low quality and level of evidence
Why do I have the audacity to challenge the recommendations of these many professional organizations?

• **Second**, this would **not be the first time** that **guidelines generated by prestigious societies** have been **wrong**.

Some examples include:

– Prophylactic perioperative beta-blockers
– Prophylactic aprotinin to reduce bleeding post cardiac surgery
– Intensive insulin therapy
– Use of activated protein C (Xigris™) in severe sepsis

*But more on this later*
Then why has Therapeutic Hypothermia been so rapidly and widely adopted?

• Strong desire to do something to improve the poor outcome after resuscitation from cardiac arrest

• Enthusiasm and strong conviction of many investigators

• Practitioner and hospital competition

• Promotion by the “Medical-industrial complex”
Here is an example of promotion in our own Region.
Therapeutic Hypothermia for Resuscitated Cardiac Arrest

Floyd Memorial physicians utilize hypothermia to dramatically improve survival rates by Jennifer S. Newton

In medicine, most new therapies years of slow, methodical research often face at least a moderate amount of resistance before actually being adopted. In the case of therapeutic hypothermia, a striking increase in survival rates was accompanied by remarkably rapid acceptance and implementation, especially in the United States. Studies published in major medical journals in the late 1990s and early 2000s demonstrated that judicious application of therapeutic hypothermia for patients who do not initially respond to return of spontaneous circulation (ROSC), meaning they were resuscitated from cardiac arrest but did not return to consciousness, significantly improved outcome. In 2005, the American Heart Association incorporated therapeutic hypothermia into its guidelines for adult cardiac arrest management. However, the marked results prompted a wider consideration of therapeutic hypothermia in the medical community. If implemented appropriately, therapeutic hypothermia can improve outcomes for patients suffering cardiac arrest.

Srin Madhav, MD, a cardiologist with Cardiovascular Associates of Southern Indiana, explains the physiology behind the method. "With therapeutic hypothermia, the result is better neurological function and better quality of life at discharge. This is called "Spin.""

Interventional cardiologist Srin Madhav, MD, says therapeutic hypothermia is a wonderful concept where each specialist or care provider does their part.

Emergency room physician Thomas Harris, MD, says therapeutic hypothermia is all about improving survival rates and neurologic recovery after cardiac arrest.

Research and anecdotal evidence demonstrate that prior to hypothermia treatment, patients may have survived but would have more likely had severe neurological impairment. With therapeutic hypothermia, the result is better neurological function and better quality of life at discharge. This is called "Spin."
The Role of “Spin”

Misrepresentation of Randomized Controlled Trials in Press Releases and News Coverage: A Cohort Study

Amélie Yavchitz¹,²,³, Isabelle Boutron¹,²,³, Aida Bafeta¹,²,³, Ibrahim Marroun⁴, Pierre Charles⁴, Jean Mantz⁵, Philippe Ravaud¹,²,³


Conclusion: “Spin” was identified in about half of press releases and media coverage. In multivariable analysis, the main factor associated with “spin” in press releases was the presence of “spin” in the article abstract conclusion.
What Do These Findings Mean? These findings show that "spin" in press releases and news reports is related to the presence of "spin" in the abstract of peer-reviewed reports of RCTs and suggest that the interpretation of RCT results based solely on press releases or media coverage could distort the interpretation of research findings in a way that favors experimental treatments. This interpretation shift is probably related to the presence of "spin" in peer-reviewed article abstracts, press releases, and news items and may be partly responsible for a mismatch between the perceived and real beneficial effects of new treatments among the general public. Overall, these findings highlight the important role that journal reviewers and editors play in disseminating research findings. These individuals, the researchers conclude, have a responsibility to ensure that the conclusions reported in the abstracts of peer-reviewed articles are appropriate and do not over-interpret the results of clinical research.
Therapeutic Hypothermia post CA

Scientific Hypothesis

• Post arrest ischemia-reperfusion results in further neurologic injury and cerebral edema

• Post ischemic hypothermia may minimize these adverse effects.

• Animal experimental data:
  – Strongly support benefits of prophylactic (i.e., pre arrest) hypothermia.  But...

Delhaye C etal. JACC 2012; 59: 197-10
Therapeutic Hypothermia post CA

Scientific Hypothesis

• Animal experimental data:
  – **However** data are weaker and conflicting as to whether *post arrest* hypothermia is beneficial
    • Some studies indicate that a delay of implementation of only 15-30 minutes may minimize or eliminate any benefit
  – Furthermore: Are the effects in normal animals applicable to “sick” patients, often with vascular disease?
  – Finally, animal data are low on the pyramid of evidence used to support clinical care
Pyramid of Evidence for Evidence Based Medicine

Level I
- Randomized Controlled Double Blind Studies

Level II
- Randomized Controlled Studies
- Cohort Studies
- Case Control Studies
- Case Series
- Case Reports
- Ideas, Editorials, Opinions

Level III
- Animal Research
- In vitro (‘test tube’) research

• First let us examine the clinical evidence that supports the use of therapeutic hypothermia for Out-of-Hospital (OOH) cardiac arrest.
What is the Evidence Supporting the use of Therapeutic Hypothermia post out-of-hospital Shockable rhythms (VR/PVT)?

According to the AHA 1010 Guidelines*

• Level B
  – One good RCT (HACA. NEJM 2002)
  – One pseudorandomized trial (Bernard. NEJM 2002)
  – Two studies with historical controls
    • Belliard, 2007; Castrejon, 2009)

*Peabody MA, etal. Circulation 2010; 122: page S-771
But let us examine the evidence further.
Therapeutic Hypothermia for OOH Cardiac Arrest

The body of evidence
[Walters JH, et al. (Systematic Review) Resuscitation 2011; 82:508-16]

- 77 studies evaluating effects in humans
  - 40 uncontrolled observational studies
  - 15 non-randomized trials utilizing historical controls
  - 9 non-randomized trials utilizing concurrent controls
  -- Only 5 independent RCTs
    *(and I have found no more since this study was published)*
  
  - There have also been 6 meta-analyses including some or all of these 5 RCTs!
Therapeutic Hypothermia for OOH Cardiac Arrest

All of the five RCTs have some limitations

- Relatively small number of patients randomized
  - 275, 77, 54, 42, and 30
- Studies varied regarding details
  - CA rhythms included
  - How and when cooled
  - Depth and duration of cooling
  - Primary outcome examined
- The second largest (77) actually only employed pseudo-randomization
- One was only published as an abstract >12 years ago
- All had methodological problems
- All had substantial risk of bias
- And in all the care teams were obviously un-blinded
Therapeutic Hypothermia for OOH Cardiac Arrest

**Meta-analyses**

- The 6 Meta-analyses:
  - Holzer, Bernard, et al., 2005*
  - Cheung, et al., 2006
  - Arrich, Holzer and Mullner, 2009 **
  - Nielsen, et al., 2011
  - Walters, et al., 2011
  - Arrich J, Holzer AJ, Mullner HC and Herkner H, 2012**

- Evaluated data from some or all of the same 5 RCTs
  - Three included all 5 RCTs
  - One included 4 of these RCTs
  - One included 3 of these RCTs
  - One included only 2 of these RCTs

*Two of the authors (Holzer and Bernard) were the investigators involved in two of the RCTs
**One of the authors (Holzer) was the investigator involved in one of the RCTs
Two Major RCTs (2002)
Therapeutic Hypothermia post out-of-hospital CA due to VF/PVT

- **European study** (HACA study group. NEJM 2002; 346: 549-56)
  - 273 patients
  - Favorable neurological outcome (55% vs 39%, RR 1.4, NNT = 6; P = 0.009)
  - Favorable 6 months survival (Deaths 41 versus 55%, RR 0.74, NNT = 7; P = 0.02)

- **Australian study** (Bernard SA, etal. NEJM 2002; 346: 557-63)
  - Pseudo-randomization
  - 77 patients
  - Greater good neurologic outcome (49 versus 26%, RR 1.85, NNT = 4; P = 0.046)
  - Lower mortality at discharge (51 versus 68%, RR 0.76, NNT = 6; P = 0.145)

- But let us examine these in more detail...
The best and the largest RCT was a multicenter (9) European study from the Hypothermia after Cardiac Arrest (HACA) study group.

**TABLE 2. NEUROLOGIC OUTCOME AND MORTALITY AT SIX MONTHS.**

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>NORMOTHERMIA</th>
<th>HYPOTHERMIA</th>
<th>RISK RATIO (95% CI)*</th>
<th>P VALUE†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable neurologic outcome‡</td>
<td>54/137 (39)</td>
<td>75/136 (55)</td>
<td>1.40 (1.08–1.81)</td>
<td>0.009</td>
</tr>
<tr>
<td>Death</td>
<td>76/138 (55)</td>
<td>56/137 (41)</td>
<td>0.74 (0.58–0.95)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*The risk ratio was calculated as the rate of a favorable neurologic outcome or the rate of death in the hypothermia group divided by the rate in the normothermia group. CI denotes confidence interval.

†Two-sided P values are based on Pearson’s chi-square tests.

‡A favorable neurologic outcome was defined as a cerebral-performance category of 1 (good recovery) or 2 (moderate disability). One patient in the normothermia group and one in the hypothermia group were lost to neurologic follow-up.

HACA study group (Holzer, et al.) NEJM 2002; 346:549-56
Figure 2. Cumulative Survival in the Normothermia and Hypothermia Groups. Censored data are indicated by tick marks.

HACA study group. NEJM 2002; 346:549-56
But...
Therapeutic Hypothermia for OOH Cardiac Arrest

The best RCT: The HACA Trial (2002) Had Limitations
[ Nielsen and Friberg, Resuscitation 2011; 82: 501-2]

- Baseline differences between the groups
- Not all outcomes reported
- Undefined withdrawal policy, not standardized and therefore risk of bias
- The study was prematurely terminated without pre defined criteria
- Baseline coma not reported
- Highly selective: Only included 7% of those screened.
- Didn’t limit hyperthermia in the control group
Figure 1. Bladder Temperature in the Normothermia and Hypothermia Groups.
The T bars indicate the 75th percentile in the normothermia group and the 25th percentile in the hypothermia group. The target temperature in the hypothermia group was 32°C to 34°C, and the duration of cooling was 24 hours. Only patients with recorded temperatures were included in the analysis.
Figure 1. Bladder Temperature in the Normothermia and Hypothermia Groups.
The T bars indicate the 75th percentile in the normothermia group and the 25th percentile in the hypothermia group. The target temperature in the hypothermia group was 32°C to 34°C, and the duration of cooling was 24 hours. Only patients with recorded temperatures were included in the analysis.
Testori C et al. (A retrospective cohort study) Resuscitation 2011; 82: 1162-7
Testori C et al. (A retrospective cohort study) Resuscitation 2011; 82: 1162-7
Hyperthermia after cardiac arrest is associated with an unfavorable Neurologic outcome

• Prospective observational study of 151 with ROC following Cardiac Arrest.

• 49% had favorable neurologic recovery at 6 months

• Favorable recovery associate with lower highest temperature during first 48 hours (37.7° vs 38.3°)

• For each degree Celsius higher than 37° the risk of unfavorable neurologic recovery increases with an odds ratio of 2.6x (95% CI 1.2-4.1)
The Other Major RCT
Australian study (Bernard SA, et al. NEJM 2002)

- Limitations
  - Pseudo-randomization i.e., assignment based on day of the week, i.e., even day received one management, odd day the other.
  - Very small (77 patients total)
  - Obviously unblinded
  - Unequal number of patients in two groups (43 hypothermia, versus 34 controls) (explanation not provided by authors)
  - Interim analysis conducted led to extension of study because of initial difference in outcome not statistically significant.
  - Barely statistically significant greater good neurologic outcome (49 versus 26%, RR 1.85, NNT = 4) but very fragile
  - Statistically insignificant lower mortality at discharge (51 versus 68%, RR 0.76, NNT = 6)
“Fragility” of Small RCTs

• As PJ Devereaux (Departments of clinical epidemiology and Biostatistics, McMaster University) pointed out at the Evidence-Based Decision Making symposium at the recent 2013 IARS Annual meeting (San Diego, May 4, 2013), small RCTs are at risk of being “fragile”.

• He recommends considering the **Absolute Fragility Index** in assessing the reliability of small RCTs.

• The fragility index is the minimum number of patient outcomes required to change in a trial to move the result of the trial from being statistically significant to non-significant, i.e., to increase the P value to >0.05.

• “If your trial is hinging on one or two events you should be very humble about the results.”
**Australian Trial**

**Fragility**

- **Neurologic outcome**

<table>
<thead>
<tr>
<th>Patients</th>
<th>“Good” Neurologic outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothermia</td>
<td>43</td>
</tr>
<tr>
<td>Control</td>
<td>34</td>
</tr>
</tbody>
</table>

*p = 0.046 [per authors]*

*p = 0.061 [per my calculation of Fisher’s Exact Test (Graph Pad ™)]*

**Fragility index = 1**

i.e., If change outcome by 1 in EITHER one group, p > 0.09
## Australian Trial

### Fragility

#### Mortality

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Died</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothermia</td>
<td>43</td>
<td>22 (51%)</td>
</tr>
<tr>
<td>Control</td>
<td>34</td>
<td>23 (68%)</td>
</tr>
</tbody>
</table>

_\( p = 0.145 \) [per authors]_

_\( p = 0.168 \) [per my calculation of Fisher’s Exact Test (Graph Pad™)]_

i.e., not statistically significant
We conclude that induced hypothermia improves outcomes in patients who are comatose after resuscitation from out-of-hospital cardiac arrest. However, treatment assignment was not blinded, and there is the possibility that some aspects of care differed between the groups. Therefore, further studies are required to confirm these findings and determine the optimal duration of hypothermia.
Therapeutic Hypothermia for OOH Cardiac Arrest
M-A the five RCTs
[Nielsen et al, International J Cardiol, 2011]

- Their Meta-analysis of the two trials with the least risk of bias (HACA 2002, and Laurent 2005) found
  - NO statistically significant benefits:
    - Reduced mortality NOT statistically significant
      • RR = 0.92 (95% CI 0.56-1.51)
    - Improved neurologic outcome NOT statistically significant
      • RR = 1.24 (95% CI 0.76-2.0)
CONCLUSION

• There is evidence supporting the use of mild therapeutic hypothermia to improve neurological outcome in patients who remain comatose following the return of spontaneous circulation after out-of-hospital cardiac arrest with initial “shockable” rhythms.

• However, much of the evidence is from low-level observational studies.
• But back to our primary topic,

• What about the use of therapeutic hypothermia following resuscitation from **in-hospital** cardiac arrest?
There are reasons to anticipate that therapeutic hypothermia might be less effective for in-hospital CA (IHCA)

- Over 75% are due to non-shockable rhythms (e.g., PEA or asystole)

- Although there are conflicting data, many suggest that TH is less beneficial post non-shockable rhythms (OAH or IH)

**Beneficial**
- Holzer 2006
- Arrich J, 20007
- Nielsen N 2009
- Van der Wal G 2011
- Testori c 2011
- Lundbye JB 2012

**Not beneficial**
- Hachimi-Idrissi S, 2001
- Oddo M 2006
- Kim F 2007
- Rittenberger JC 2008
- Don CW 2011
- Dumas 2011
- Vaahersalo J, 2013
TH for “non-shockable “ rhythms
Examples of Conflicting observational data (no RCTs)

• **Testori etal** (Resuscitation 2011; 1162-7)
  – *Retrospective cohort study*
  – 374 patients with non-shockable rhythms
  – Patients receiving TH had more favorable outcome

• **Dumas, etal** (Circulation 2011; 123: 877-86)
  – *Prospective observational study*
  – 268 patients following PEA/Asystole
  – TH NOT associated with improved neurological outcome
Other reasons to anticipate that therapeutic hypothermia might be less effective for In-hospital CA (IHCA)

- IH-CA often due to hemorrhage, respiratory insufficiency or pulmonary embolism (instead of primary arrhythmias or AMI)

- Victims of In-Hospital CA are often “sicker” and have more co-morbidities

- Diagnosis of cardiac arrest often delayed

- These patients may be more prone to the complications of TH

- Poor outcome following IH-CA less likely to be due to neurologic injury. (See next slide)
**Mode of death after admission to an ICU following cardiac arrest.**


Retrospective observational study of 225 patients single ICU in the United Kingdom, 1998-2003

<table>
<thead>
<tr>
<th></th>
<th>OOH-CA</th>
<th>IH-CA</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>113</td>
<td>92</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>63</td>
<td>72</td>
</tr>
<tr>
<td>Died (percent)</td>
<td>57%</td>
<td>66%</td>
</tr>
<tr>
<td>Cause of death (percent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td>68%</td>
<td>23%</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>23</td>
<td>26</td>
</tr>
<tr>
<td>Multi-organ failure</td>
<td>9</td>
<td>51</td>
</tr>
</tbody>
</table>
Clinical studies of Therapeutic hypothermia post in-hospital cardiac arrest

- **No RCTs**

- **Three observational studies with concurrent or historical controls**
  - Kory P, et al. Beth Israel Medical Center NYC. Neurocritical Care. Published online Jan 7 2012

- **None observed improved outcome with use of therapeutic hypothermia!**
TH for IH-CA
Arrich J, etal, 2007

- **European registry, 19 sites, 2003-2005, first 650 cases**

- **17% in-hospital cardiac arrest**

<table>
<thead>
<tr>
<th></th>
<th>Died in hosp</th>
<th>Poor Neurol outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>No hypothermia</td>
<td>40%</td>
<td>71%</td>
</tr>
<tr>
<td>TH</td>
<td>61%</td>
<td>72%</td>
</tr>
</tbody>
</table>
# TH for IH-CA

**Rittenberger JC, et al, 2008**

- **University of Pittsburgh**
- Retrospective review of all patients with post cardiac arrest (OOH and IH), 2005-2007
- 40 eligible comatose after IH-CA

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Good outcome*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Hypothermia</td>
<td>27</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>TH</td>
<td>13</td>
<td>1 (8%)</td>
</tr>
</tbody>
</table>

*survived with good neurologic outcome
TH for IH-CA
Kory, etal 2012

• Beth Israel Medical Center, NYC

• Retrospective observational study comparing three years before and three years after implementing a TH program (2006), 2003-2009

• Reviewed 118 cases that met criteria for TH as determined by blinded investigators

• 16 cases without hypothermia; 17 cases with TH

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Hospital day</th>
<th>Rhythm</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>VF/PVT</td>
<td>Hosp Surv</td>
</tr>
<tr>
<td>No Hypoth</td>
<td>16</td>
<td>13</td>
<td>2</td>
<td>31%</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>17</td>
<td>12</td>
<td>1</td>
<td>29%</td>
</tr>
</tbody>
</table>
Use of Therapeutic Hypothermia After In-Hospital Cardiac Arrest

Mark E. Mikkelsen, MD, MSCE1,2; Jason D. Christie, MD, MSCE1,2; Benjamin S. Abella, MD, MPhil1,3; Meeta Prasad Kerlin, MD, MSCE1; Barry D. Fuchs, MD1; William D. Schweickert, MD1; Robert A. Berg, MD4; Vincent N. Mosesso, MD5; Frances S. Shofer, PhD3; David F. Gaieski, MD3 for the American Heart Association’s Get With the Guidelines-Resuscitation Investigators

Critical Care Medicine 2013 e-pub ahead of print

Get with the Guidelines- Resuscitation Investigators
538 hospitals, 2003-9,
67,498 patient with ROSC following in-hospital cardiac arrest

Therapeutic hypothermia initiated in only 2.0% (increased from 0.7 to 3.3%)
Factors associated with use included: younger age, occurrence in non-ICU, weekday, teaching hospital and VF/VT at any time during the event (but Not associated with initial rhythm.

Target temperature (32-34° C) not achieved in 44%
18% overcooled

No data provided on outcome in those who did or did-not receive TH!!
Therapeutic hypothermia after in-hospital Cardiac arrest
Mikkelsen ME, et al. CCM 2013
Additional comments and observations

- 210,000 in hospitals cardiac arrests (IHCA) annually in USA
- Rate is increasing
- Less than 25% have VF/VT as the initial rhythm (and this appears to be declining from 31 to 18% (Girotra NEJM 2012; 367: 1912-20)
- IHCA with initial non-shockable rhythm that transitions to VF/VT is common and outcomes are dismal (Meaney, et al. CCM 2010; 38: 101)
- No RCT of TH have been conducted after IHCA
Additional comments and observations, continued

- Data regarding use of TH in non-shockable rhythms is conflicting:
  - 6 studies suggested benefit
  - 6 suggest no benefit.

- **Post hoc analysis** (personal communication from P Pickkers to these authors) of a Dutch National Intensive Care Database (van der Wal et al. CCM 2011; 39: 84-88) found similar mortality reduction when TH was employed for IHCA as for combined OHCA+IHCA and **but the reduction was not statistically significant** (OR 0.84; 95% CI 0.62-1.12, p = 0.24)
In summary

- There are no RCTs evaluating the benefit of TH following out-of-hospital CA due to non-shockable rhythms
- There are no RCTs evaluating the benefit of TH following in-hospital CA
TH following IH-CA

Even if we don’t know for sure that it will help... What’s the harm in trying?

• Potential complications of TH
  Infection, pneumonia, sepsis, hemodynamic instability, arrhythmias, hyperglycemia, coagulopathy, bleeding, electrolyte abnormalities, polyuria, seizures, altered drug metabolism

• Complicates other care (e.g., angiography, interventional cardiology)

• Expensive, labor intensive

• Diverts resources (staff, ICU beds, money)

• False sense of hope for family

• Conversely, failure to use may suggest to the family that the hospital/physicians are not providing optimal care (they have heard about TH in lay press)

• Inhibits the ability to conduct badly needed RCTs.
Furthermore, even if we opt to employ it, *We really don’t know how implement it optimally!* 

- **Time window** of therapeutic effectiveness
- Optimal **method of inducing and maintaining cooling**
- Optimal **temperature**
- Optimal **duration**
- How to **rewarm**
- Where/ how to **measure temperature**
- Proper **sedation and muscle relaxation**
- Need for **EEG monitoring**
- **Seizure detection and management**
- Management of **shivering, hypotension, hypertension**
- **Neurologic assessment**
- How to **assess neurologic prognosis**
- **Criteria for** and **when to withdraw**
• *Intriguingly, it may be that*
  
  *simply preventing hyperthermia*

  *may be as effective*

  *as inducing mild hypothermia following resuscitation from cardiac arrest.*
Finally

* Basing guidelines for medical practice on a single RCT or a few small RCTs or even lower level evidence can be misleading...

- Sweeney 2009
- Bellomo 2009
- Hennekens 2009
- Bertolini 2011
“Once is not enough”
(Regarding the new Xigris™ Trial*)

“Despite many attempts over the last two decades, no drug in this field [sepsis] has reproducibly improved mortality. All agents have failed when tested in a second confirmatory trial. Accordingly, a

This pattern of inconsistent findings between trials serves to remind us of the limits of the single RCT. Namely, while the RCT design minimizes selection bias within a trial, it is still only a single experiment. Moreover, performing one or more RCTs does not guarantee the internal or external validity of the results [50]. In

*Which has now been completed and found no benefit from the use of Xigris.
Review Article

Why we should be wary of single-center trials

Rinaldo Bellomo, MD, FRACP, FJFICM; Stephen J. Warrillow, MBBS, FRACP, FJFICM; Michael C. Reade, MBBS, MPH, DPhil, FANZCA, FJFICM

(Crit Care Med 2009; 37:3114–3119)

Data Synopsis: Many positive single-center trials have been contradicted when tested in other settings and, in one case, the

Conclusions: We recommend that practice guidelines should rarely, if ever, be based on evidence from single-center trials. Physicians should apply the findings of single-center trials only after careful evaluation of their methodology, and in particular after comparing the context of the trial with their own situation.
• “Science needs replication. Approval...needs to be based on more than a single trial”
  (G Bertolini, as quoted by Mullard, 2011)

• Meta-analyses of several small randomized studies can be hypothesis generating but should NOT be the basis of establishing guidelines for clinical care.
  (Hennekens 2009)
• “As a specialty we might be just too quick to jump on the band wagon”

(A Suffredini as quoted by Mullard, 2011)
There are a number of examples of **single center or single RCTs** which have **subsequently been found to be wrong**

- Preoperative beta-blockers
- Recombinant activated protein C (drotrecogin alfa/ Xigris™) for sepsis
- Intensive Insulin Therapy/ Tight glucose control
• One of the most obvious is the **Intensive Insulin Therapy** story...
In 2001

The New England Journal of Medicine

Copyright © 2001 by the Massachusetts Medical Society

VOLUME 345

NOVEMBER 8, 2001

NUMBER 19

PP 1359-67

INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS

GREET VAN DEN BERGHE, M.D., PH.D., PIETER WOUTERS, M.Sc., FRANK WEEKERS, M.D., CHARLES VERWAEST, M.D., FRANS BRUYNINCKX, M.D., MIET SCHETZ, M.D., PH.D., DIRK VLAASSELAERS, M.D., PATRICK FERDINANDE, M.D., PH.D., PETER LAUWERS, M.D., AND ROGER BOUILLON, M.D., PH.D.

Prospective, non-blinded, Randomized Controlled study (RCT)

1548 patients randomized over a one year period (Feb 2000- Jan 2001)
Conclusions  Intensive insulin therapy to maintain blood glucose at or below 110 mg per deciliter reduces morbidity and mortality among critically ill patients in the surgical intensive care unit. (N Engl J Med
### Leuven I (Surgical ICU) Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Conventional</th>
<th>IIT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>783</td>
<td>765</td>
<td></td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In ICU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>8.0</td>
<td>4.6</td>
<td>0.04</td>
</tr>
<tr>
<td>Hospital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>10.9</td>
<td>7.2</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Cause of death</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MOF assoc with sepsis (Pts)</td>
<td>33</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>MOF without sepsis (Pts)</td>
<td>18</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td><strong>Morbidity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged ventilator support</td>
<td>11.9</td>
<td>7.5</td>
<td>0.003</td>
</tr>
<tr>
<td>Dialysis</td>
<td>8.2</td>
<td>4.8</td>
<td>0.007</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>26.7</td>
<td>22.4</td>
<td>0.04</td>
</tr>
<tr>
<td>Septicemia</td>
<td>7.8</td>
<td>4.2</td>
<td>0.003</td>
</tr>
<tr>
<td>Polyneuropathy</td>
<td>51.9</td>
<td>28.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean number of RBCs</td>
<td>2</td>
<td>1</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Figure 1. Kaplan–Meier Curves Showing Cumulative Survival of Patients Who Received Intensive Insulin Treatment or Conventional Treatment in the Intensive Care Unit (ICU).
• As a consequence of this single large RCT...

• Strict glucose control quickly became a standard of care, advocated by national organizations and used as a quality assessment tool for hospitals.

• But...
...in 2009
NICE SUGAR Study

Multicenter RCT involving over 6100 patients

Observed higher mortality, and no improved length of ventilation, ICU or Hospital stay with IIT
These data caused the
American Association of Clinical Endocrinologists

and the

American College of Physicians
to revise their previous guidelines
regarding tight glucose control of
hospitalized and critically ill patients
I recommend this sobering essay for your review.

Essay
Why Most Published Research Findings Are False
John P. A. Ioannidis

The role of hypothermia post-cardiac arrest.
A systematic Review
[Walters JH et al. Resuscitation 2011; 82:508-16]

Conclusions

• The extrapolation of the data from OOH-CA associated with shockable rhythms to other cardiac arrests (e.g., other initial rhythms, in-hospital arrests and cardiac arrests in children)...
  seems reasonable but is supported by only lower level data.

• There is need for randomized controlled trials... in these other groups
In conclusion

- I believe we should NOT use hypothermia for patients following resuscitation from In-Hospital cardiac arrest

- Let us admit what we don’t know and instead of devoting our efforts at implementing an unproven method, we should devote our efforts at conducting needed large well-designed RCTs.

- Let us not repeat our history of the premature adoption of guidelines based on limited data, only to have to revise them subsequently.
I am sorry to raise a note of caution and pessimism at the end of this enlightening conference...

but I hope I have been able to show you the limitations of the data supporting the use of therapeutic hypothermia post cardiac arrest, especially following in-hospital cardiac arrest,

and you now understand the reasons for my skepticism

Thank you for listening.
Thank you for listening.