Therapeutic Hypothermia

ANADIOTIS THANOS
KONSTANTOPOULEIO HOSPITAL
Therapeutic Hypothermia

CONFLICTS  NONE
Therapeutic Hypothermia

- CARDIAC ARREST AND HYPOTHERMIA
- CARDIAC INFARCTION AND HYPOTHERMIA
Therapeutic Hypothermia

Hypothermia protects the heart during:
- Cardiac surgery
- Heart transplantations

- Class I (strong) recommendations for:
  - TTM to treat comatose post-cardiac arrest patients suffering OOH VF/pulseless VT (LOE B-Randomized)
  - TTM to treat comatose post-cardiac arrest patients suffering non-VF/pulseless VT (‘non-shockable’) rhythms and IHCA (stronger recommendation than the 2010 guidelines) (LOE C-Expert Opinion)
  - Selection and maintenance of a constant temperature within the range 32oC and 36oC (LOE B-Randomized)

- Class IIa (moderate) recommendation for TTM to be maintained for at least 24 hours after reaching target temperature (LOE C-Expert Opinion)

- Class IIb (weak) recommendation that it may be reasonable to actively prevent fever in comatose patients (LOE C-Limited Data)

- Class III (moderate – no benefit) recommendation against routine pre-hospital cooling of patients after ROSC with the rapid infusion of cold intravenous fluids. (LOE A)
Survival from Out of Hospital Cardiac Arrest (OHCA)

Survival (%)

USA Australia Europe Asia

Berdowsky et al. Resuscitation 2010
Causes of ICU death

- Olasveegen n=129
- Laver n=126

Brain
Cardiac
MOF
Therapeutic Hypothermia
Therapeutic hypothermia - mechanism of action

- Astroglial cells & macrophages
- Increased calcium influx
- Apoptosis
- Ischemia-reperfusion injury
Therapeutic Hypothermia
Therapeutic Hypothermia

Therapeutic hypothermia—patients comatose after VF OHCA

- 7 centers-5 European countries
- N=273 (TH N=136)
- Age: 18-75
- Randomized
- External cooling
- 32-34°C, 24 h,
- Passive rewarming


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 outcome</td>
<td>54/137 (39%)</td>
<td>75/136 (55%)</td>
<td>1.49 (1.08-1.91)</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 test.
‡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.
The end of cooling?
N=939 pts (36 ICUs Europe/Australia)
OHCA, presumed cardiac cause
All rhythms included

33°C
N=473

36°C
N=466

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

Probability of Survival

Days since Randomization

No. at Risk
33°C group 473 230 151 64 15
36°C group 466 235 144 68 12

P=0.51
Therapeutic Hypothermia

Nielsen et al: ~36.0°C

Bernard et al: ~37.3°C

HACA study: ~37.6°C
A BEFORE AND AFTER STUDY

After the change from a TTM target of 33°C to 36°C, we report low compliance with target temperature, higher rates of fever, and a trend towards clinical worsening in patient outcomes. Hospitals adopting a 36°C target temperature need to be aware that this target may not be easy to achieve, and requires adequate sedation and muscle-relaxant to avoid fever.
Therapeutic Hypothermia

**RINSE TRIAL**

In adults with out-of-hospital cardiac arrest, induction of mild therapeutic hypothermia using a rapid infusion of large-volume, intravenous cold saline during CPR may decrease the rate of return of a spontaneous circulation in patients with an initial shockable rhythm and produced no trend toward improved outcomes at hospital discharge.

**HYPERION TRIAL**

The HYPERION trial is a multicenter, randomized, controlled, assessor-blinded, superiority trial that may provide an answer to an issue of everyday relevance, namely, whether TTM is beneficial in comatose patients resuscitated after nonshockable cardiac arrest. Furthermore, it will provide new data on the tolerance and adverse events (especially infectious complications) of TTM at 32.5-33.5°C.
Get-With-The-Guidelines-Resuscitation-Registry

117005 Patients from 674 hospitals with ROSC after index ICHCA between March 1, 2002, and December 31, 2014.

90822 Excluded
31565 Aged ≥65 y (owing to nonlinkage with Medicare data)
15012 Sites without hypothermia
17117 ICHCA occurred before first hypothermia case at patient’s hospital
26429 Not on mechanical ventilation at time of or after resuscitation from ICHCA
69 Missing data on survival
28 Missing data on comorbidities
602 Initial cardiac arrest was out of hospital

26183 Patients from 355 hospitals (1568 treated with hypothermia)

1524 Hypothermia-treated patients matched by propensity score to 3714 non-hypothermia-treated patients

Table 2. In-Hospital Outcomes and Model Results

Table 3. One-Year Outcomes and Model Results

*Results reported for mean cumulative survival during the first year whether patients were alive at 1 year. One-year survival quantifies the number of patients surviving the first year of follow-up.

**Risk difference is calculated as the absolute survival rate with hypothermia treatment minus the rate with no hypothermia treatment.

For comparison of outcomes within a hospital group.

interaction between hypothermia and initial cardiac arrest and aneurysm for the patients of one hospital group.

Interaction between hypothermia and initial cardiac arrest and aneurysm for the patients of one hospital group.

For comparison of outcomes within a hospital group.

Interaction between hypothermia and initial cardiac arrest and aneurysm for the patients of one hospital group.

For comparison of outcomes within a hospital group.

Interaction between hypothermia and initial cardiac arrest and aneurysm for the patients of one hospital group.

For comparison of outcomes within a hospital group.

Interaction between hypothermia and initial cardiac arrest and aneurysm for the patients of one hospital group.
Therapeutic Hypothermia - Prehospital Crit Care. 2018 The efficacy and safety of pre-hospital cooling after out-of-hospital cardiac arrest: a systematic review and meta-analysis, Danielle Buell, Damon C. Scales
How to start cooling?
• Simple ice packs and/or wet towels are inexpensive
  • more time consuming for nursing staff
  • greater temperature fluctuations
  • not enable controlled rewarming
• Ice cold fluids alone cannot be used to maintain hypothermia
  • the addition of simple ice packs may control the temperature adequately
• Cooling blankets or pads
• Water or air circulating blankets
• Water circulating gel-coated pads
• Transnasal evaporative cooling
  • enables cooling before ROSC
• Intravascular heat exchanger
• Extracorporeal circulation (e.g., cardiopulmonary bypass, ECMO).
How to maintain temperature?
Therapeutic Hypothermia

• a cooling method with effective temperature monitoring is preferred
• avoid temperature fluctuations.
• external or internal cooling devices that include continuous temperature feedback
• The temperature is typically monitored from a thermistor placed in the bladder and/or oesophagus.
• there are no data indicating that any specific cooling technique increases survival when compared with any other cooling technique
• internal devices enable more precise temperature control compared with external techniques.
Complications

- Shivering
- Systemic vascular resistance
- Arrhythmias (usually bradycardia)
  - may be beneficial (similar to the effect achieved by beta-blockers)
  - reduces diastolic dysfunction
- Diuresis and electrolyte abnormalities such as hypophosphataemia, hypokalaemia, hypo-magnesaemia and hypocalcaemia
- Insulin sensitivity and insulin secretion, and causes hyperglycaemia
- Serum amylase
- Impairs coagulation, may increase bleeding
- Hypothermia can impair the immune system and increase infection rates (pneumonia)
  - no impact on outcome
  - early use of antibiotics was associated with improved survival
Therapeutic Hypothermia

The clearance of sedative drugs and neuromuscular blockers is reduced by up to 30% at a core temperature of 34°C
Contraindications

• Generally recognised contraindications to TTM at 33 °C
  
  • severe systemic infection
  
  • pre-existing medical coagulopathy (fibrinolytic therapy is not a contraindication to mild induced hypothermia)
Therapeutic Hypothermia
CARDIOPROTECTION

Mild hypothermia (32–35°C) has consistently been shown to be cardioprotective in preclinical studies. Mechanisms of hypothermia protection during ischemia are:
• – Reduction in metabolism and preservation of ATP;
• – Stabilization of mitochondrial membrane;
• – Inhibition of generation of reactive oxygen species.
Mechanisms of hypothermia protection during reperfusion are:
• – Decrease in microvascular injury;
• – Induction of heat shock proteins;
• – Activation of Akt and nitric oxide production;
• – Activation of protective kinases ERK;
• – Inhibition of apoptosis;
• – Inhibition of inflammation and platelet aggregation.

Partial List of pharmacologic studies to reduce Reperfusion Injury that failed!

<table>
<thead>
<tr>
<th>Trial</th>
<th>Agent</th>
<th>Proposed mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAMI 9</td>
<td>Fluclo</td>
<td>Inhibits neutrophils, enhances O2 delivery</td>
</tr>
<tr>
<td>ISIS-4, MAGIC</td>
<td>Fluclo</td>
<td>Membrane stabilization</td>
</tr>
<tr>
<td>CORE</td>
<td>Fluclo</td>
<td>Enhances O2 delivery</td>
</tr>
<tr>
<td>EMIR-PR</td>
<td>Fluclo</td>
<td>Less Htr, free radicals, neutrophils</td>
</tr>
<tr>
<td>Fisherty</td>
<td>Fluclo</td>
<td>Free radical scavenger</td>
</tr>
<tr>
<td>CALYPSO</td>
<td>Fluclo</td>
<td>Inhibits p-selecte, neutrophils</td>
</tr>
<tr>
<td>AMISTAD I, II</td>
<td>Fluclo</td>
<td>Inhibits neut., vasodilates, metab.</td>
</tr>
<tr>
<td>Halt, Limit</td>
<td>Fluclo</td>
<td>Inhibits neutrophils</td>
</tr>
<tr>
<td>ESCAMI</td>
<td>Fluclo</td>
<td>Na+/H+ exchange inhibitor</td>
</tr>
<tr>
<td>APEX-AMI</td>
<td>Fluclo</td>
<td>C5b-9 complement inhibition</td>
</tr>
<tr>
<td>TRIUMPH</td>
<td>Fluclo</td>
<td>Nitric oxide donor</td>
</tr>
<tr>
<td>REVIVAL, HEBE-3</td>
<td>Fluclo</td>
<td>Enhances O2 delivery</td>
</tr>
<tr>
<td>REVEAL</td>
<td>Fluclo</td>
<td></td>
</tr>
<tr>
<td>NAMI</td>
<td>Fluclo</td>
<td></td>
</tr>
<tr>
<td>CIRCUS, CYCLE</td>
<td>Fluclo</td>
<td></td>
</tr>
<tr>
<td>MITOCARE</td>
<td>TRO40303</td>
<td>NO-like (vasodilates, antplatelet, etc.)</td>
</tr>
<tr>
<td>PROTECTION ANI</td>
<td>Fluclo</td>
<td>Inhibits mitochondrial permeability transition</td>
</tr>
<tr>
<td>GIPS III</td>
<td>Fluclo</td>
<td>Pero opening</td>
</tr>
<tr>
<td>EMBRACE-STEMI</td>
<td>Fluclo</td>
<td>Inhibits mitochondrial d-protein kinase C</td>
</tr>
<tr>
<td></td>
<td>Fluclo</td>
<td>AMP-activated protein kinase, mitochondrial kin</td>
</tr>
<tr>
<td></td>
<td>Fluclo</td>
<td>Binds cardiolipin, improves mitochondrial fns</td>
</tr>
</tbody>
</table>

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70 ΧΡΟΝΙΑ ΚΑΡΔΙΟΛΟΓΙΑΣ (ΕΚΕ)
70 YEARS OF CARDIOLOGY (HSC)

ΠΑΝΕΛΛΗΝΙΟ ΚΑΡΔΙΟΛΟΓΙΚΟ ΣΥΝΕΔΡΙΟ
PANHELLENIC CONGRESS OF CARDIOLOGY
Reperfusion injury

- Myocardial infarction (% AAR) without reperfusion
- Myocardial infarction (% AAR) with reperfusion
- Myocardial infarction (% AAR) with reperfusion and cardioprotection

Frohlich et al. Eur Heart J, 2013; 34, 1714-1724
Therapeutic Hypothermia - Animal studies

Hale, Dave & Klener 1997 (Maxx Res Cardiol 97, 351)
Open chest rabbit. Ligation of LAD. Topical cooling on the myocardium.
Temp lowered locally by 5 C within 5 min.
To examine if hypothermia insteructed post onset of ischemia is effective.

- Early hypothermia
- Late hypothermia

Infarct size (% of area at risk):
- Early local hypothermia 23%
- Late local hypothermia 43%
- Nonhypothermia 44%

Conclusion:
Hypothermia after onset of ischemia can protect the heart.

80% relative reduction in infarct size (P < 0.001)
Based on this study on 22 animals two major clinical trials were conducted.
Therapeutic Hypothermia - Studies

Table 1  
Baseline characteristics of studies investigating the efficacy of TH

<table>
<thead>
<tr>
<th>Study name</th>
<th>DIAMOND (n)</th>
<th>COOL-MAG (n)</th>
<th>ICE-I (n)</th>
<th>RAPID-MRI (n)</th>
<th>CHILL-MRI (n)</th>
<th>VELOCITY (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>42</td>
<td>352</td>
<td>228</td>
<td>20</td>
<td>129</td>
<td>54</td>
</tr>
<tr>
<td>Age (years), (mean vs. TH)</td>
<td>58 ± 52</td>
<td>59 ± 60</td>
<td>57 ± 57</td>
<td>58 ± 57</td>
<td>58 ± 57</td>
<td>57 ± 57</td>
</tr>
<tr>
<td>Male (%) (control vs. TH)</td>
<td>76 vs 90</td>
<td>74 ± 36</td>
<td>80 ± 75</td>
<td>78 ± 78</td>
<td>80 ± 79</td>
<td>81 vs 94</td>
</tr>
<tr>
<td>IVR (control vs. TH)</td>
<td>57 vs 35</td>
<td>56 ± 43</td>
<td>66 vs 24</td>
<td>63 ± 35</td>
<td>64 vs 34</td>
<td>65 vs 35</td>
</tr>
<tr>
<td>ICS (control vs. TH)</td>
<td>54 vs 43</td>
<td>54 ± 38</td>
<td>59 ± 34</td>
<td>58 ± 33</td>
<td>58 ± 34</td>
<td>57 vs 34</td>
</tr>
<tr>
<td>Current smoker (%) (control vs. TH)</td>
<td>50 vs 54</td>
<td>48 ± 44</td>
<td>52 ± 46</td>
<td>51 ± 46</td>
<td>52 ± 46</td>
<td>51 ± 46</td>
</tr>
<tr>
<td>Prior MI (%) (control vs. TH)</td>
<td>5 vs 14</td>
<td>12 ± 10</td>
<td>12 ± 10</td>
<td>12 ± 10</td>
<td>12 ± 10</td>
<td>12 ± 10</td>
</tr>
<tr>
<td>Follow-up time (days)</td>
<td>120</td>
<td>30</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Primary end point</td>
<td>MACE at 30 days</td>
<td>MACE at 30 days</td>
<td>MACE at 30 days</td>
<td>MACE at 30 days</td>
<td>MACE at 30 days</td>
<td>MACE at 30 days</td>
</tr>
<tr>
<td>Secondary end point</td>
<td>15 ± 30 days</td>
<td>15 ± 30 days</td>
<td>15 ± 30 days</td>
<td>15 ± 30 days</td>
<td>15 ± 30 days</td>
<td>15 ± 30 days</td>
</tr>
<tr>
<td>Specific end point (control vs. TH)</td>
<td>Events, non-fatal reinfections, TVE</td>
<td>Events, non-fatal reinfections, TVE</td>
<td>Events, non-fatal reinfections, TVE</td>
<td>Events, non-fatal reinfections, TVE</td>
<td>Events, non-fatal reinfections, TVE</td>
<td>Events, non-fatal reinfections, TVE</td>
</tr>
</tbody>
</table>

Table 2  
Design of studies investigating the efficacy of TH

<table>
<thead>
<tr>
<th>Study name</th>
<th>DIAMOND (n)</th>
<th>COOL-MAG (n)</th>
<th>ICE-I (n)</th>
<th>RAPID-MRI (n)</th>
<th>CHILL-MRI (n)</th>
<th>VELOCITY (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time criteria for inclusion</td>
<td>Within 6 h of onset of symptoms</td>
<td>Within 6 h of onset of symptoms</td>
<td>Within 6 h of onset of symptoms</td>
<td>Within 6 h of onset of symptoms</td>
<td>Within 6 h of onset of symptoms</td>
<td>Within 6 h of onset of symptoms</td>
</tr>
<tr>
<td>Cooling method</td>
<td>Endovascular IVC catheter</td>
<td>Endovascular IVC catheter</td>
<td>Endovascular IVC catheter</td>
<td>Endovascular IVC catheter</td>
<td>Endovascular IVC catheter</td>
<td>Endovascular IVC catheter</td>
</tr>
<tr>
<td>Target temperature (°C)</td>
<td>37°C</td>
<td>37°C</td>
<td>37°C</td>
<td>37°C</td>
<td>37°C</td>
<td>37°C</td>
</tr>
<tr>
<td>Protocol cooling time (h)</td>
<td>3 h</td>
<td>3 h</td>
<td>3 h</td>
<td>3 h</td>
<td>3 h</td>
<td>3 h</td>
</tr>
<tr>
<td>Average duration of cooling (h)</td>
<td>3 h</td>
<td>3 h</td>
<td>3 h</td>
<td>3 h</td>
<td>3 h</td>
<td>3 h</td>
</tr>
<tr>
<td>Time until target cooling achieved (min)</td>
<td>45</td>
<td>45</td>
<td>45</td>
<td>45</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>Target temperature not reached</td>
<td>37°C</td>
<td>37°C</td>
<td>37°C</td>
<td>37°C</td>
<td>37°C</td>
<td>37°C</td>
</tr>
<tr>
<td>Acknowledged target temperature (%)</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Reperfusion therapy</td>
<td>Primary PCI</td>
<td>Primary PCI</td>
<td>Primary PCI</td>
<td>Primary PCI</td>
<td>Primary PCI</td>
<td>Primary PCI</td>
</tr>
<tr>
<td>Door-to-balloon time (control vs. TH)</td>
<td>14 vs 16</td>
<td>14 vs 16</td>
<td>14 vs 16</td>
<td>14 vs 16</td>
<td>14 vs 16</td>
<td>14 vs 16</td>
</tr>
<tr>
<td>TIMI flow 3 and protease inhibitors (%) (control vs. TH)</td>
<td>90 vs 90</td>
<td>90 vs 90</td>
<td>90 vs 90</td>
<td>90 vs 90</td>
<td>90 vs 90</td>
<td>90 vs 90</td>
</tr>
<tr>
<td>Patients on glycoprotein IIb/IIIa inhibitors (%) (control vs. TH)</td>
<td>85 vs 71</td>
<td>85 vs 71</td>
<td>85 vs 71</td>
<td>85 vs 71</td>
<td>85 vs 71</td>
<td>85 vs 71</td>
</tr>
<tr>
<td>ISIS (%) (control vs. TH)</td>
<td>74 vs 71</td>
<td>74 vs 71</td>
<td>74 vs 71</td>
<td>74 vs 71</td>
<td>74 vs 71</td>
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</tr>
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</table>

70 ΧΡΟΝΙΑ ΚΑΡΔΙΟΛΟΓΙΑΣ (EKE) 70 YEARS OF CARDIOLOGY (HSC) ΠΑΝΕΛΛΗΝΙΟ ΚΑΡΔΙΟΛΟΓΙΚΟ ΣΥΝΕΔΡΙΟ ΠΑΝΗΠΙΟΡΡα ΚΟΝΓΡΕΣΟΣ ΚΑΡΔΙΟΛΟΓΙΑΣ
SAFETY

Ventricular Tachycardia / Ventricular Fibrillation

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Events/Total</th>
<th>Odds ratio (95% CI)</th>
<th>Hypothermia: Control</th>
<th>Relative weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown</td>
<td>0.64 (0.50, 0.85)</td>
<td>3/5</td>
<td>0.71 (0.57, 0.87)</td>
<td>0.71 (0.55, 0.90)</td>
<td>15.16</td>
</tr>
<tr>
<td>COOL 76</td>
<td>0.65 (0.20, 2.14)</td>
<td>2/3</td>
<td>0.69 (0.20, 2.26)</td>
<td>0.69 (0.20, 2.26)</td>
<td>20.40</td>
</tr>
<tr>
<td>Ellin 813</td>
<td>0.64 (0.20, 2.14)</td>
<td>2/3</td>
<td>0.69 (0.20, 2.26)</td>
<td>0.69 (0.20, 2.26)</td>
<td>20.40</td>
</tr>
<tr>
<td>IFRD 257</td>
<td>0.64 (0.20, 2.14)</td>
<td>2/3</td>
<td>0.69 (0.20, 2.26)</td>
<td>0.69 (0.20, 2.26)</td>
<td>20.40</td>
</tr>
<tr>
<td>VELOCITY 5</td>
<td>0.64 (0.20, 2.14)</td>
<td>2/3</td>
<td>0.69 (0.20, 2.26)</td>
<td>0.69 (0.20, 2.26)</td>
<td>20.40</td>
</tr>
</tbody>
</table>

In heterogeneity: Tau² = 0.21, CH² = 21.16 (P = 0.02), F = 20.12 (P = 0.05)
Safar Hypothermia: Farrar Control

Meta-Analysis Brady-Arrhythmias

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Events/Total</th>
<th>Odds ratio (95% CI)</th>
<th>Hypothermia: Control</th>
<th>Relative weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown</td>
<td>1.19 (0.64, 2.21)</td>
<td>1/3</td>
<td>0.52 (0.21, 1.29)</td>
<td>0.52 (0.21, 1.29)</td>
<td>5.08</td>
</tr>
<tr>
<td>COOL 76</td>
<td>1.19 (0.64, 2.21)</td>
<td>1/3</td>
<td>0.52 (0.21, 1.29)</td>
<td>0.52 (0.21, 1.29)</td>
<td>5.08</td>
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<td>1.19 (0.64, 2.21)</td>
<td>1/3</td>
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<td>1/3</td>
<td>0.52 (0.21, 1.29)</td>
<td>0.52 (0.21, 1.29)</td>
<td>5.08</td>
</tr>
</tbody>
</table>

In heterogeneity: Tau² = 0.01, CH² = 1.49 (P = 0.2), F = 2.71 (P = 0.1)
Safar Hypothermia: Farrar Control

Meta-Analysis All-Bleeding

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Events/Total</th>
<th>Odds ratio (95% CI)</th>
<th>Hypothermia: Control</th>
<th>Relative weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown</td>
<td>1.22 (0.64, 2.32)</td>
<td>2/2</td>
<td>1.22 (0.64, 2.32)</td>
<td>1.22 (0.64, 2.32)</td>
<td>2.10</td>
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<td>COOL 76</td>
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<tr>
<td>Ellin 813</td>
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<td>IFRD 257</td>
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<td>VELOCITY 5</td>
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<td>1.22 (0.64, 2.32)</td>
<td>1.22 (0.64, 2.32)</td>
<td>2.10</td>
</tr>
</tbody>
</table>

In heterogeneity: Tau² = 0.01, CH² = 2.71 (P = 0.1), F = 2.10 (P = 0.1)
Safar Hypothermia: Farrar Control

Meta-Analysis
Should we cool everyone?
Hypothermia protocol for rapid cooling

**Speed of cooling**

Endovascular alone: ~ 20-25 min to reach < 35°C

Combination hypotermia: ~ 5 min to reach < 35°C (Cold saline and endovascular cooling)
Hypothermia protocol for rapid cooling

Combination hypothermia: Cold saline (4°C), 1000 ml iv infusion in 5 min as a “kick start” for quick initiation of hypothermia together with an endovascular cooling catheter.

1000 ml cold saline (4°C)  
Quick initiation of hypothermia

Celsius Celsius Control System™  
Endovascular cooling catheter (14 F)  
Initiation and maintaining hypothermia
What is the best temperature? Subgroup analysis of the selected studies suggests that the target temperature should be above $32^\circ C$ and $\leq 35^\circ C$ to avoid potential adverse reactions of the intervention.
Hypothermia **before** ischemia:
- Cold-seeking behavior during hypoxia is used to enhance survival in many species;
- There is a linear relationship between core body temperature and infarct size in experimental animals from various species.

Hypothermia **during** ischemia before reperfusion:
- Numerous studies have shown a reduction in infarct size when mild hypothermia is instituted after coronary occlusion before reperfusion;
- Hypothermia initiated **after** reperfusion does **not** reduce infarct size;
- Microvascular injury (no-reflow) is reduced by mild hypothermia, distinct from a reduction in myocyte necrosis.

Mild Hypothermia in Cardiogenic Shock Complicating Myocardial Infarction

SHOCK-COOL trial failed to show that targeted temperature management improved cardiac power index among patients with cardiogenic shock complicating AMI.

The ideal STEMI patient for hypothermia treatment:

- Early presenter (4-6h)
- Large area at risk (anterior STEMI)
- Fast cooling
- Low T prior to reperfusion

Erlinge et al. Ther Hypothermia Temp Manag. 2015;5:77-84.
### FUTURE

#### Definite Stent Thrombosis in Comatose Out of Hospital Cardiac Arrest Survivors (ST OHCA)

<table>
<thead>
<tr>
<th>Study Title</th>
<th>Status</th>
<th>Description</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNICORN STUDY</td>
<td>Recruiting</td>
<td>Mild Therapeutic Hypothermia for Patients With Acute Coronary Syndrome and Cardiac Arrest Treated With PCI</td>
<td>Cardiac Arrest • Acute Coronary Syndrome • Procedure: Mild Therapeutic Hypothermia (MHT) • Cardiology Department, Dr. A. Jurasz University Hospital Bydgoszcz, Kujawsko-pomorskie, Poland</td>
</tr>
</tbody>
</table>

#### EUROpean Study of Intracoronary Cooling in ST-Elevation Myocardial Infarction (EURO-ICE)

<table>
<thead>
<tr>
<th>Study Title</th>
<th>Status</th>
<th>Description</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>COOL-MI EU PIVOTAL STUDY</td>
<td>Enrolling by invitation</td>
<td>COOL-AMI EU Pivotal Trial</td>
<td>Acute Myocardial Infarction • Device: Intravascular permissive hypothermia as an adjunct to PCI • University Medical Centre Ljubljana Ljubljana, Slovenia</td>
</tr>
</tbody>
</table>
FUTURE
Therapeutic Hypothermia
THANK YOU
THROMBOSIS

Whether the theoretical risk of stent thrombosis with therapeutic hypothermia translates into clinically significant events remains controversial. The current literature on stent thrombosis in AMI patients undergoing therapeutic hypothermia is limited by few studies with small sample sizes showing no consistent relationship between therapeutic hypothermia and stent thrombosis. Most of these studies lack robust comparison groups. In 2007, Knafelj et al. in a study of 72 patients with AMI and cardiac arrest undergoing PCI showed 1 stent thrombosis event (3.1%) in the therapeutic hypothermia group (n = 32) and no stent thrombosis events (0%) in the group not receiving therapeutic hypothermia (n = 40). In 2011, Ibrahim et al. reported a 14.8% incidence of stent thrombosis in 27 cardiac arrest patients undergoing therapeutic hypothermia and PCI, compared with no stent thrombosis events in 30 cardiac arrest patients undergoing PCI without therapeutic hypothermia. In 2013, Penela et al. observed 5 stent thrombosis events in 11 cardiac arrest patients treated with therapeutic hypothermia; however, there was no comparison group. Kozinski et al. showed no stent thrombosis events in 37 OHCA patients with AMI undergoing therapeutic hypothermia and PCI. Similarly, Casella et al. showed no stent thrombosis events in 45 cardiac arrest patients undergoing PCI and therapeutic hypothermia treatment. In 2014, Rosillo et al. reported a 2.7% stent thrombosis incidence in 77 patients undergoing therapeutic hypothermia and primary PCI, which was not significantly different from the incidence in non-cardiac arrest AMI patients undergoing primary PCI. Both studies lacked a comparison group. In 2015, a report from the International Cardiac Arrest Registry showed 2 definite early stent thrombosis events (1.4%) in 141 cardiac arrest patients undergoing PCI and therapeutic hypothermia. In 2015, Erlinge et al., in a combined analyses of 2 prospective randomized controlled trials of therapeutic hypothermia in AMI with a total of 140 patients (70 in each group), reported only 1 patient in the therapeutic hypothermia group to have a reinfarction without specifically mentioning stent thrombosis. Finally, a meta-analysis by Villalba et al. including data from 6 randomized controlled trials with a total of 819 patients showed no difference in all-cause mortality, major adverse cardiovascular events, or recurrent infarction in AMI patients receiving therapeutic hypothermia compared with those not receiving therapeutic hypothermia.
- a reduction in the overall metabolic rate by 5-7% per 1°C decrease of body temperature
- a reduction of the myocardial metabolic rate influencing reperfusion injury positively and
- an increased contractility of cardiac myocytes without increase of oxygen consumption.