TITLE: Therapeutic hypothermia following cardiac arrest

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THERAPEUTIC HYPOTHERMIA FOLLOWING CARDIAC ARREST

A Technology Assessment

INTRODUCTION

The California Technology Assessment Forum (CTAF) was asked to assess the evidence for the use of mild therapeutic hypothermia in comatose patients after cardiac arrest. Since 2002, when two randomized trials were published in the New England Journal of Medicine (NEJM), the use of therapeutic hypothermia has steadily increased in emergency rooms and intensive care units around the world. Despite recommendations to use therapeutic hypothermia for post-cardiac arrest management of patients presenting with ventricular fibrillation or ventricular tachycardia from the International Liaison Committee on Resuscitation in 2003 and the American Heart Association in 2005, use of the technology has been inconsistent.

BACKGROUND

Cardiac Arrest

Cardiac arrest, the cessation of effective contraction of the heart confirmed by the absence of a pulse, occurs over 250,000 times annually in the United States. Patients usually become unconscious within seconds and the majority do not report any symptoms prior to the cardiac arrest. Among those treated by emergency medical services, the survival to hospital discharge is only about 8%. Patients with an initial rhythm of ventricular tachycardia have a somewhat better prognosis (21% survive to hospital discharge).

The time to return of spontaneous circulation (ROSC) is the primary predictor of meaningful recovery from cardiac arrest. Considerable public health resources have been directed at teaching the public cardiopulmonary resuscitation (CPR) in order to shorten the time until the return of circulation. The most effective intervention to restore circulation is defibrillation. Thus CPR education stresses early activation of emergency medical services and the use of automatic external defibrillators when available.

Patients who survive cardiac arrest often have significant neurological deficits. The majority are comatose for at least an hour following cardiac arrest and fewer than half have a good neurological recovery. Outcomes from cardiac arrest are primarily assessed using a five-point scale: the Pittsburgh Cerebral
Performance Categories (CPC). In brief, the five categories are defined as follows: 1 – good cerebral performance, capable of normal life with at most minor neurological deficits; 2 – moderate cerebral disability, but conscious, alert and able to perform the activities of daily life although the person may suffer hemiplegia and permanent memory or mental changes; 3 – severe cerebral disability, conscious, but usually institutionalized because of the degree of dependence on others for the activities of daily life; 4 – comatose / vegetative state; and 5 – certified brain death. Most commonly, the scale is dichotomized with categories one and two representing a good outcome and categories three through five representing a poor outcome.

Once circulation has been restored after cardiac arrest, the primary goal of therapy is to maximize the chance for recovery by minimizing damage to the brain and other organ systems. This is primarily done with supportive treatment and careful monitoring in the intensive care unit (ICU).

Therapeutic Hypothermia

Hypothermia is usually divided into three categories: mild (33 to 35°C), moderate (28 to 32°C), and severe (<28°C). Animal studies demonstrated that mild to moderate hypothermia markedly decreases central nervous system damage after cardiac arrest. These studies also reported that neurologic damage is minimized by initiating hypothermia as close to the return of spontaneous circulation as possible.

However hypothermia is not without risk. When temperatures drop below 32°C there is a significant increase in the risk for bradycardia and ventricular arrhythmias that are difficult to treat. Hypothermia is associated with thrombocytopenia, interference with clotting factors and thus an increased risk for bleeding. Additionally, hypothermia suppresses the immune system, raising the risk for systemic infections including sepsis and pneumonia.

The biological mechanisms underlying the beneficial effects of hypothermia are not completely understood. It is hypothesized that hypothermia causes a reduction in cerebral oxygen demand, slowing deleterious enzymatic reactions, decreasing free radical production, and limiting the release of excitatory neurotransmitters. This in turn should help to maintain the integrity of the blood brain barrier, maintain the supply of adenosine triphosphate, and decrease intracranial pressure.

There are many approaches to cooling the patients and maintaining hypothermia. Early studies used of ice packs positioned around the patient’s head and body. Cooling mattresses and blankets, temperature controlled gel packs, cold water immersion, cooling helmets, rapid infusion of cold fluids, direct cooling of the patient's blood via hemofiltration, endovascular cooling devices, and nasopharyngeal evaporative
cooling have all been used in the clinical trials described below. There is no agreement on the optimal rate or method for cooling patients.

The body’s homeostatic mechanisms to maintain body temperature through peripheral vasoconstriction and shivering would blunt the effect of any of these therapeutic approaches, particularly those utilizing surface cooling. Patients who are treated with therapeutic hypothermia are generally paralyzed with neuromuscular blocking drugs to avoid the shivering response and thus patients must be intubated and sedated. Core body temperature also needs to be monitored to insure that the target temperature is reached and that patients are not over-cooled. The gold standard for monitoring core temperature requires a pulmonary artery catheter, but it is rarely used because of the risks involved. More commonly, endotracheal or bladder temperature monitors are used as patients are routinely intubated and have Foley catheters in place. These approaches to core temperature monitoring all have limitations, but are reasonable surrogate measures.

After 12 to 24 hours from the initiation of hypothermia, patients are allowed to slowly warm up over about eight hours. This process is generally passive by selectively reducing the application of whatever cooling method is being used, followed by a reduction in sedation and neuromuscular blockade once the temperature rises above 35° C. Heated blankets and other devices are sometimes used.

TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.

Surface cooling products have received FDA 510(K) marketing clearance for general indication of temperature reduction when clinically indicated. Most recently, the Arctic Sun 5000 Temperature Management System by Medivance received 510(K) clearance in July 2010. No catheter based product has received FDA 510(K) clearance specifically for use after cardiac arrest. Cather-based cooling products that have received FDA marketing clearance for other indications (e.g., during neurosurgery and recovery, during cardiac surgery and recovery, for fever reduction) are being used off-label following cardiac arrest.

TA Criterion 1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.
The Medline database, Embase, Cochrane clinical trials database, Cochrane reviews database and the Database of Abstracts of Reviews of Effects (DARE) were searched using the key words “cardiac arrest,” “cardiopulmonary arrest,” or “resuscitation.” The results were crossed with the results from a search on “hypothermia” or “cooling.” The search was performed for the period from 1945 through January 2011 (see Appendix for details). The bibliographies of systematic reviews and key articles were manually searched for additional references. References were also solicited from the manufacturers and local experts. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full. This review focuses on the essential patient oriented outcomes: survival and good neurologic recovery.

The search identified 1,081 potentially relevant trials. After elimination of duplicate and non-relevant references including animal model studies, 112 articles were reviewed in full. These references included 57 case series, 24 controlled studies, and seven randomized trials. For the controlled studies and randomized trials, studies without a comparison group that did not receive hypothermia were excluded. Three randomized trials that evaluated the use of hypothermia in the pre-hospital setting were included even though many of the patients in the control group received therapeutic hypothermia once they arrived at the hospital. One randomized trial reported only in abstract form, two randomized trials of therapeutic hypothermia during cardiac arrest, and two trials with no usual care arm were excluded.
Figure: Selection of studies for inclusion in review

Level of Evidence: 1 through 5.

TA Criterion 2 is met.

TA Criterion 3: The technology must improve net health outcomes.

The key health outcomes following cardiac arrest are survival and good neurologic function as assessed by the CPC scale described above. The assessment will focus on the results from the published randomized trials, but the case series and non-randomized, controlled literature will be summarized in order to better assess the incidence of adverse effects and the real world effectiveness of therapeutic hypothermia.

Randomized trials comparing hypothermia to control

The data from the randomized trials are described in Tables 1 through 4 below. The first four trials compare therapeutic hypothermia to usual care and the last three investigate the utility of initiating therapeutic
hypothermia by emergency medical services prior to the arrival of the participant at the hospital. Table 1 summarizes the methodological characteristics of the trials that determine the quality of the trials. Table 2 summarizes the participant characteristics, the details of the intervention and control, the inclusion and exclusion criteria, and the length of follow-up for the primary outcomes. Table 3 describes the primary outcomes of the trials and Table 4 describes the reported adverse events.
Table 1: Randomized trials of therapeutic hypothermia - Study quality

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomization</th>
<th>Allocation concealment</th>
<th>Groups comparable</th>
<th>Outcome assessment blinded</th>
<th>Follow-up &gt; 80%</th>
<th>Intention to treat analysis</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In hospital hypothermia</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hachimi-Idrissi 2001</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes 100%</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>HACA 2002</td>
<td>Yes</td>
<td>Yes</td>
<td>No: More diabetes, CHD, bystander CPR in control</td>
<td>Yes</td>
<td>Yes 99% at 6 months</td>
<td>Yes</td>
<td>Largest, highest quality study</td>
</tr>
<tr>
<td>Bernard 2002</td>
<td>No Even / Odd days</td>
<td>No</td>
<td>No: more women and bystander CPR in hypothermia</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Poor</td>
</tr>
<tr>
<td>Laurent 2005</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td><strong>Pre-hospital therapeutic hypothermia</strong></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Kim 2007</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Kamarainen 2009</td>
<td>Yes</td>
<td>Yes</td>
<td>No: 58% versus 22% received CPR</td>
<td>NR</td>
<td>Yes</td>
<td>No: 14% of randomized patients excluded from analysis</td>
<td>Poor</td>
</tr>
<tr>
<td>Bernard 2010</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, 100%</td>
<td>Yes</td>
<td>Good</td>
</tr>
<tr>
<td>Study Location</td>
<td>N</td>
<td>Age% Female</td>
<td>Intervention</td>
<td>Control</td>
<td>Inclusion criteria</td>
<td>Exclusion Criteria</td>
<td>Follow-up</td>
</tr>
<tr>
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<tr>
<td>In hospital hypothermia</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Hachimi-Idrissi 2001 Belgium No</td>
<td>30</td>
<td>75 years 39%</td>
<td>Helmet. 34° C. 3 hours. To TT or maximum 4 hours.</td>
<td>Standard ICU care</td>
<td>OOH Asystole or PEA Comatose Age &gt; 18 Temp &gt; 30° C</td>
<td>Pregnant Coagulopathy Cardiogenic shock</td>
<td>14 days</td>
</tr>
<tr>
<td>HACA 2002 Europe Yes</td>
<td>275</td>
<td>59 years 24%</td>
<td>Cooling blanket / mattress/ air. 32° to 34° C. 8 hours. 24 hours.</td>
<td>Standard ICU care</td>
<td>OOH + IH VF or VT Comatose Witnessed arrest Age 18 to 75</td>
<td>Pregnant Coagulopathy T &lt; 30° C MAP &lt; 60 x 30 minutes Terminal illness</td>
<td>6 months</td>
</tr>
<tr>
<td>Bernard 2002 Australia Yes</td>
<td>77</td>
<td>66 years 33%</td>
<td>Ice packs. 33° C. 2 hours. 12 hours.</td>
<td>Standard ICU care</td>
<td>OOH VFib Comatose Age ≥ 18 for M Age ≥ 50 for F</td>
<td>Cardiogenic shock</td>
<td>Hospital discharge</td>
</tr>
<tr>
<td>Laurent 2005 France Yes</td>
<td>42</td>
<td>54 years 19%</td>
<td>HF w/ blood cooling. 32° to 33° C. 4 hours. 18 hours.</td>
<td>HF to maintain temperature at 37° C</td>
<td>OOH VF or Asystole Comatose Age 18 to 75</td>
<td>Pregnant Terminal illness &gt; 10 min to CPR &gt; 50 min CPR to ROSC</td>
<td>6 months</td>
</tr>
<tr>
<td>Study Location Multicenter?</td>
<td>N</td>
<td>Age</td>
<td>% Female</td>
<td>Intervention Target temp Time to TT Length cooled</td>
<td>Control</td>
<td>Inclusion criteria</td>
<td>Exclusion Criteria</td>
</tr>
<tr>
<td>-----------------------------</td>
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</tr>
<tr>
<td>Pre-hospital therapeutic hypothermia</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim 2007 Seattle, WA Yes</td>
<td>125</td>
<td>66 years</td>
<td>19%</td>
<td>2L 4°C NS. NA. NA. Until Hospital.</td>
<td>Usual care</td>
<td>OOH All rhythms ROSC Age ≥ 18 IV access</td>
<td>T &lt; 34°C Following commands</td>
</tr>
<tr>
<td>Kamarainen 2009 Finland Yes</td>
<td>43</td>
<td>61 years</td>
<td>5%</td>
<td>4°C RL infusion. 33°C.</td>
<td>Usual care</td>
<td>OOH All rhythms ROSC &gt; 9 min Age ≥ 18 IV access</td>
<td>Pregnant Trauma GCS &gt; 5 Cardiogenic shock</td>
</tr>
<tr>
<td>Bernard 2010 Australia Yes</td>
<td>234</td>
<td>63 years</td>
<td>15%</td>
<td>2L 4°C RS. NA. NA. Until Hospital.</td>
<td>Usual care including therapeutic hypothermia in ICU</td>
<td>OOH VFib Comatose ROSC &gt;10 min Age ≥ 15 IV access</td>
<td>Not intubated T &lt; 34°C Pregnant</td>
</tr>
</tbody>
</table>

Target temp, method of cooling, average temperature, time to cool, time to ROSC, age, sex, %VF, length of hypothermia

VF Ventricular fibrillation
VT Ventricular tachycardia
HF Hemofiltration
OOH Out of hospital cardiac arrest
NA Not applicable
NR Not reported
NS Normal saline
RS Ringer’s solution
ROSC Return of spontaneous circulation
CPR Cardiopulmonary resuscitation
ICU Intensive Care Unit
TT Target temperature
IH In hospital
MAP Mean arterial pressure
IV Intravenous
GCS Glasgow coma scale
### Table 3: Randomized trials of therapeutic hypothermia - Study outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Study group, n</th>
<th>Survival, n (%)</th>
<th>Good recovery, n (%)</th>
<th>Other outcomes</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In hospital hypothermia</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hachimi-Idrissi 2001</td>
<td>Hypo 16</td>
<td>3 (19%)</td>
<td>2 (14%)</td>
<td></td>
<td>Outcomes at hospital discharge. High mortality because of initial rhythms.</td>
</tr>
<tr>
<td></td>
<td>Control 14</td>
<td>1 (7%)</td>
<td>0 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HACA 2002</td>
<td>Hypo 137</td>
<td>81 (59%)</td>
<td>75 (55%)</td>
<td></td>
<td>These are outcomes at 6 months.</td>
</tr>
<tr>
<td></td>
<td>Control 138</td>
<td>62 (45%)</td>
<td>54 (39%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bernard 2002</td>
<td>Hypo 43</td>
<td>21 (49%)</td>
<td>21 (49%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control 34</td>
<td>11 (32%)</td>
<td>9 (26%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laurent 2005</td>
<td>Hypo 22</td>
<td>7 (32%)</td>
<td>7 (32%)</td>
<td></td>
<td>Outcomes at 6 months. Survival to hospital discharge was 45% in both groups (10/22 vs. 9/20).</td>
</tr>
<tr>
<td></td>
<td>Control 20</td>
<td>9 (45%)</td>
<td>9 (45%)</td>
<td></td>
<td></td>
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<tr>
<td><strong>Pre-hospital therapeutic hypothermia</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Kim 2007</td>
<td>Hypo 63</td>
<td>21 (32%)</td>
<td>NR</td>
<td>49 (78%)</td>
<td>Trend towards better outcomes in patients with VF (66% versus 45% discharged alive)</td>
</tr>
<tr>
<td></td>
<td>Control 62</td>
<td>18 (29%)</td>
<td></td>
<td>48 (77%)</td>
<td></td>
</tr>
<tr>
<td>Kamarainen 2009</td>
<td>Hypo 19</td>
<td>8 (42%)</td>
<td></td>
<td>8 (42%)</td>
<td>Cooling was faster, but no improvement in outcomes.</td>
</tr>
<tr>
<td></td>
<td>Control 18</td>
<td>8 (44%)</td>
<td></td>
<td>8 (44%)</td>
<td></td>
</tr>
<tr>
<td>Bernard 2010</td>
<td>Hypo 118</td>
<td>56 (47%)</td>
<td></td>
<td>56 (47%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control 116</td>
<td>62 (53%)</td>
<td></td>
<td>61 (53%)</td>
<td></td>
</tr>
</tbody>
</table>
### Table 4: Randomized trials of therapeutic hypothermia - Potential harms from hypothermia

<table>
<thead>
<tr>
<th>Study</th>
<th>Study group, n</th>
<th>Arrhythmia</th>
<th>Pneumonia</th>
<th>Sepsis</th>
<th>Bleeding</th>
<th>Pancreatitis</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In hospital hypothermia</strong></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hachimi-Idrissi 2001</td>
<td>Hypo 16</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Control 14</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>HACA 2002</td>
<td>Hypo 136</td>
<td>49 (36%)</td>
<td>50 (37%)</td>
<td>17 (13%)</td>
<td>35 (26%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Control 137</td>
<td>44 (32%)</td>
<td>40 (29%)</td>
<td>9 (7%)</td>
<td>26 (19%)</td>
<td>2 (1%)</td>
<td></td>
</tr>
<tr>
<td>Bernard 2002</td>
<td>Hypo 43</td>
<td>0 (0%)</td>
<td>NR</td>
<td>NR</td>
<td>0 (0%)</td>
<td>NR</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Control 34</td>
<td>1 (3%)</td>
<td>NR</td>
<td>NR</td>
<td>0 (0%)</td>
<td>NR</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Laurent 2005</td>
<td>Hypo 22</td>
<td>6 (27%)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control 20</td>
<td>2 (10%)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td><strong>Pre-hospital therapeutic hypothermia</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Kim 2007</td>
<td>Hypo 63</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Control 62</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Kamarainen 2009</td>
<td>Hypo 19</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Control 18</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Bernard 2010</td>
<td>Hypo 118</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Control 116</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
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</table>
Hachimi-Idrissi and colleagues published the first randomized trial\(^{106}\) of therapeutic hypothermia. In this single site feasibility study in Brussels, the investigators randomized 30 participants greater than 18 years old who presented with asystole or pulseless electrical activity (PEA) and remained comatose following ROSC. They used a cooling helmet filled with aqueous glycerol to rapidly cool the participant’s brain to a target temperature of 34° C. Once their bladder temperature reached 34° C or cooling had been ongoing for four hours, the participants were allowed to passively rewarm. The trial randomized 16 participants to the hypothermia group and 14 participants to the usual care group. Baseline characteristics were similar in the two groups. The median age of the participants was 75 years and the median time from collapse to ROSC was 33 minutes. On arrival to the emergency room (ER), the median temperature of the participants was 35.7° C. In the hypothermia group, three participants survived at least two weeks, of whom two had a good neurologic recovery. Only one participant in the usual care group survived and that individual had a poor neurologic recovery. The difference in survival (19% versus 7%) was not statistically significant, but the trial was underpowered to detect a difference. The high mortality is consistent with the poor prognosis for cardiac arrest with an initial rhythm of asystole or PEA. No treatment related adverse events were identified.

The Hypothermia After Cardiac Arrest Study (HACA) was published in the NEJM in 1992.\(^1\) This multicenter European trial randomized 275 patients and remains the largest and best quality study published to date. The study enrolled patients ages 18 to 75 years who had a witnessed arrest with a first rhythm of ventricular fibrillation (VF) or ventricular tachycardia (VT) and remained comatose after ROSC. The participants were followed for six months for the primary outcome. Participants in the hypothermia group were cooled with a device using a mattress and blanket to deliver cold air over the entire body. Ice packs were also used to cool 70% of the participants in the hypothermia group. The target temperature in the hypothermia group was 32° to 34° C and the participants were maintained at this temperature for 24 hours from the time cooling was initiated. Participants were then allowed to rewarm passively. Participants had similar baseline characteristics (age 59 years, 24% female, 22 minutes to ROSC) except that the hypothermia group had fewer patients with diabetes (8% versus 19%), coronary heart disease (32% versus 43%), and CPR from a bystander (43% versus 49%). Survival at six months was higher in the hypothermia group (59% versus 45%, \(p = 0.02\), number needed to treat (NNT) to save one life equal to seven). Similarly, the proportion of patients with a good neurological outcome at six months was greater in the hypothermia group (55% versus 39%, \(p = 0.009\)). These differences remained statistically significant after adjustment for baseline variables, including those with important differences between the two groups. The rate of complications did not differ between the two groups (70% versus 73%, \(p=0.70\)), but there was a trend towards more sepsis in the hypothermia group (13% versus 7%, \(p\) NS). It is likely that overall mortality was much lower in this trial than in the prior trial because patients presenting the initial rhythms required for randomization in HACA (VF, VT)
have a much better prognosis than patients presenting with asystole or PEA. The investigators also performed detailed cognitive and neuropsychological testing on 45 of the patients who survived three months.\textsuperscript{109} There were no statistically significant differences between the two groups, although trends favored the hypothermia group. Overall, 67\% of the survivors in the hypothermia group had either mild or no cognitive defects compared with 44\% in the control group (p NS).

A second, smaller Australian study on hypothermia was published by Bernard and colleagues in the same issue of the NEJM.\textsuperscript{2} This study enrolled 84 patients with an out of hospital cardiac arrest with a first rhythm of VF who remained comatose after ROSC. The age cutoff was 18 years for men, but 50 years for women in order to minimize the likelihood of pregnancy. It was not a true randomized trial – on odd numbered days, participants were treated with hypothermia and on the even numbered days they received standard therapy. Participants in the hypothermia group (n = 43) were cooled with ice packs to the head, neck, torso and limbs. Limited cooling was initiated by emergency medical services before arriving at the hospital. The target temperature in the hypothermia group was 33° C and the participants were maintained at this temperature for 12 hours from arrival at the hospital. After 18 hours, the patients were actively warmed over six hours. Participants in the control group (n = 34) were paralyzed and sedated with the same protocol as the hypothermia group, but their target temperature was 37° C. The primary outcome was survival to discharge with discharge home or to a rehabilitation facility considered a good outcome. Discharge to a long term nursing facility and in-hospital death was considered poor outcomes. A blinded specialist in rehabilitation medicine evaluated the patient and made the decision about where patients were discharged. The participants in both groups were similar at baseline (age 66 years, 26 minutes to ROSC) except that the hypothermia group had fewer men (58\% versus 79\%, p = 0.05) and fewer participants who received CPR from a bystander (49\% versus 71\%, p = 0.05). There was a non-significant trend towards higher survival at hospital discharge in the hypothermia group (49\% versus 32\%, p = 0.145). The primary outcome in the study, the proportion of patients with a good neurological outcome at hospital discharge, was greater in the hypothermia group (49\% versus 26\%, p = 0.046). In bivariate analyses, the participant’s age and the time from collapse to ROSC were both significantly associated with the primary outcome. After adjustment for these two variables in multivariate logistic regression, the odds ratio for a good neurologic outcome for hypothermia was 5.25 (95\% CI 1.5 to 18.8, p = 0.011). No multivariate model adjusting for the baseline differences in sex and bystander CPR were reported. There were no important adverse events associated with hypothermia. One patient in the control group developed 3rd degree heart block requiring a transvenous pacemaker and no patients in either arm experienced significant bleeding complications.

The last of the published trials directly evaluating therapeutic hypothermia to treatment without hypothermia was a three-arm multicenter trial in France.\textsuperscript{107} This study enrolled 61 patients between the ages of 18 and
75 with an out of hospital cardiac arrest with a first rhythm of VF or asystole who remained comatose after ROSC. Patients were randomized to high volume hemofiltration with or without hypothermia or to usual care without hemofiltration or hypothermia. For the purposes of this assessment, comparing the hemofiltration plus hypothermia group to the hemofiltration alone group isolates the independent effect of hypothermia. Participants in the hypothermia group (n = 22) were cooled by external cooling of their blood during hemofiltration. The target temperature in the hypothermia group was 32° to 33° C and the participants were maintained at this temperature for 18 hours. After 18 hours, the patients were allowed to warm passively.

Participants in the control hemofiltration only group (n = 34) were paralyzed, sedated, and received hemofiltration with the same protocol as the hypothermia group, but their target temperature was 37° C. The primary outcome of the study was survival at six months and the secondary outcome was survival with a favorable neurologic outcome (CPC score of one or two). Baseline characteristics were similar in the two groups (age 54 years, 19% female), although there was a trend towards a shorter time to ROSC in the hypothermia group (16 minutes versus 25 minutes, p NS). There was a trend towards lower survival at six months in the hypothermia group (32% versus 45%, p NS), although survival at hospital discharge was 45% in both groups. Survival at six months was significantly higher in both of these groups compared to the control group who received usual care without hemofiltration or hypothermia (21% survival, p = 0.018).

Similarly, there was a trend towards fewer participants with a good neurological outcome at six months in the hypothermia group compared with the hemofiltration alone group (32% versus 45%, p NS). There was a trend toward more ventricular tachycardia in the hypothermia group (27% versus 10%), but no other adverse events were reported.

The quality of the randomized trials was somewhat uneven. None of the trials could feasibly blind treating personnel to the treatment intervention, which raises the possibility of differential co-interventions that could impact survival. Given the paucity of known effective interventions following cardiac arrest, this is unlikely to have had a large impact on the outcomes. Follow-up was nearly 100% for the primary outcomes in all of the trials and all used an intention to treat analysis. Three of the four trials used appropriate randomization and allocation concealment, but Bernard and colleagues used a pseudo-randomization scheme (odd and even day assignment), which could have introduced selection bias. Two of the trials were too small to have sufficient statistical power to demonstrate significant results. Finally, in the largest study, the HACA trial, there were baseline differences in the characteristics of the two study groups despite randomization. When the investigators adjusted for these differences in a secondary analysis, the results remained significant in favor of hypothermia, but the imbalances introduce some uncertainty about the quality of the trial.

In addition to the methodological concerns, there was significant heterogeneity in the patient populations
studied and the methods used to cool the study participants. Only one study included participants presenting with an initial rhythm of PEA\textsuperscript{106}, two allowed participants with asystole\textsuperscript{106,107}, and two focused primarily on participants with VF.\textsuperscript{1,2} It is important to note that all of the trials excluded patients younger than 18 years, so the results only apply to adults. Cooling was done with four different approaches: a cooling helmet, ice bags, cool air delivered by a mattress and blanket device, and external cooling of blood during hemofiltration. The target temperature was similar in all four trials (32° to 34° C), but the length of time that participants were cooled varied from three hours to 24 hours. In addition, the time to reach the target temperature varied from two to eight hours. Finally, a non-standard intervention, hemofiltration, was used in both the hypothermia group and the control group in one of the trials. The lack of consistency in the patient populations and approaches to cooling make it difficult to combine the results of these trials. The two largest trials that reported statistically significant benefits excluded patients who presented with PEA and asystole and they cooled patients for 12 to 24 hours.

Meta-analyses of randomized trials

Despite the small number of randomized trials and the heterogeneity of the populations, interventions, and results, there have been a relatively large number of systematic reviews and meta-analyses of therapeutic hypothermia following cardiac arrest.\textsuperscript{115-121} Using individual patient data from the trials, the Cochrane review\textsuperscript{115} found that patients in the hypothermia group were more likely to reach a best cerebral performance categories score of one or two (RR, 1.55; 95% CI 1.22 to 1.96) and were more likely to survive to hospital discharge (RR, 1.35; 95% CI 1.10 to 1.65) compared to standard post-resuscitation care. The review did not find any important differences in the rates of adverse events between the hypothermia and standard care groups. All of the other meta-analyses agreed with the conclusions of the Cochrane review except Nielsen et al\textsuperscript{120}, which agreed that the evidence suggested both an improvement in mortality and neurologic outcomes, but concluded that quality of the evidence was low because the methodological issues discussed above raised important concerns about systematic and random errors. They called for additional large, well-designed randomized trials to address this uncertainty. Several of the reviews highlight the limitations in the evidence for patients presenting with rhythms other than ventricular fibrillation and the need to avoid fever in the control group as fever may be associated with neurologic damage. Ongoing trials will address some of these issues.

Ongoing trials of therapeutic hypothermia

There are a many ongoing trials indexed on ClinicalTrials.gov. The largest is an international trial, the Target Temperature Management After Cardiac Arrest study, which is randomizing 850 participants resuscitated from an out of hospital cardiac arrest to a target temperature of 33° C or a target temperature of 36° C.
Other trials are investigating the utility of hypothermia in pediatric patients, comparing internal versus external cooling devices, and evaluating the impact of inducing hypothermia during prior to the return of spontaneous circulation. These trials should help address many of the questions not yet answered by the published clinical trials.

**Observational studies comparing hypothermia to control**

Because of the uncertainties raised by the methodologic issues in the published randomized trials, it is important to carefully evaluate the results of the observational studies of therapeutic hypothermia. Since the publication of the two studies in 2002 in the NEJM, many organizations began to use therapeutic hypothermia to treat comatose survivors of cardiac arrest. These organizations have published a number of small studies of less than 100 patients that compare the survival and neurologic outcomes in patients treated with therapeutic hypothermia to historical controls. The results consistently favored therapeutic hypothermia and almost all of the studies reported differences in survival and neurological outcome were statistically significant. Since these are non-randomized trials, they are subject to potential selection bias and confounding. In particular, improvements over time in the management of patients in the ICU following cardiac arrest other than therapeutic hypothermia may explain some of the observed improvements in survival. These comparative studies are important to consider in evaluating therapeutic hypothermia because there were relatively few participants in the published randomized trials. Furthermore, these comparative studies reflect the experience in larger community practices, not just centers with particular expertise and interest in hypothermia. They also present data on subgroups underrepresented in the randomized trials such as patients with an in-hospital arrest or patients presenting with PEA or asystole. The largest of the studies are described below.

Arrich and colleagues published data on 585 patients (462 treated with hypothermia, 123 controls) followed in the prospective European Resuscitation Council Hypothermia After Cardiac Arrest Registry. There were many significant differences between the two groups: the hypothermia group was more likely to have suffered an out of hospital arrest (91% versus 53%, p<0.001); was more likely to have a first rhythm of VF or VT (68% versus 37%, p<0.001); and had a longer time from collapse to ROSC (23 minutes versus 17 minutes, p<0.001). Survival was higher in the hypothermia group (57% versus 32%, p<0.001), but this was not adjusted for the baseline differences in the patients nor was any matched analysis or propensity score adjusted analysis presented. Among patients with an in-hospital arrest (n= 43 hypothermia, n=58 control), there was a trend towards lower survival in the hypothermia group (39% versus 60%, p=0.30). However, in the subgroup of patients presenting with PEA or asystole (n= 124 hypothermia, n=73 control), survival was higher in the hypothermia group (35% versus 19%, p=0.023). The majority of the patients in the
hypothermia group were treated with an endovascular device (75%). The remaining 25% were cooled with ice packs, cooling blankets, and cold fluids. In the hypothermia group, 3% had significant bleeding and 6% had an arrhythmia within seven days of cooling. The adverse event rates in the control group were not presented.

Don et al assessed the survival and neurologic outcome in 491 consecutive patients in Seattle, Washington. Therapeutic hypothermia with ice packs, cooling blankets, or cooling pads was initiated in 204 patients. Multivariable logistic regression was used to adjust for baseline differences in the two groups. Survival to hospital discharge was improved with hypothermia in the subgroup of patients who presented with an initial rhythm of VF (OR 1.88, 95% CI 1.03-3.45), but not in patients with other initial rhythms (OR 1.17, 95% CI 0.66-2.05). In the adjusted analyses, patients in the subgroup presenting with VF who were treated with hypothermia had favorable neurologic outcomes (OR 2.62, 95% CI 1.1-6.27). There was no significant benefit in patients whose initial rhythm was PEA or asystole.

The largest comparative analysis was recently published by van der Wal and colleagues using data on patients who were comatose following cardiac arrest in the Dutch National Intensive Care Evaluation database. They compared outcomes in 3770 patients treated with therapeutic hypothermia to outcomes in 1547 historical controls from the same database. They adjusted their analysis for the Simplified Acute Physiology Score II, age, gender, in- versus out-of-hospital arrest, and a propensity score for receiving hypothermia. Characteristics of the two groups were remarkably similar: their average age (63.6 versus 64.3 years), sex (35.9% female in both groups), use of vasopressors (77.1% versus 77.2%), and median Glasgow coma scale (three in both groups) did not differ significantly. Crude survival was 35% in the hypothermia group and 28% in the control group. In the adjusted analysis, use of hypothermia was associated with a 20% lower odds of in-hospital death (OR 0.80, 95% CI 0.65 to 0.98, p = 0.029). No adverse outcomes data were reported, but the ICU length of stay (3.0 days versus 2.6 days) and total hospital stay (6.0 versus 5.0 days) increased significantly (p<0.001 for both comparisons).

Kagawa et al recently published a comparative study (110 patients treated with hypothermia, 290 controls) that looked carefully at the impact of time to ROSC on the relative benefit of therapeutic hypothermia. In their initial analysis, the hypothermia group had a higher rate of favorable neurological outcome (39% vs. 14%, P < 0.001) and higher 30-day survival (48% vs. 16%, P < 0.001). The differences were particularly strong when the time from collapse to ROSC was greater than 15 minutes. For example, the rates of favorable neurological outcome in patients with ROSC between 15 and 20 minutes was 64% vs. 17%, P < 0.01 and for patients with ROSC between 25 and 30 minutes the were 50% vs. 7%, P = 0.02. The investigators used propensity scoring to adjust for baseline differences between the two groups. In that
analysis, the benefits of therapeutic hypothermia on favorable neurological outcome was only significant for patients with time to ROSC greater than 15 minutes (p<0.001). If these findings are replicated within randomized trials of hypothermia, they may be used to better target the use of therapeutic hypothermia.

In summary, the comparative data confirm that therapeutic hypothermia can improve survival after cardiac arrest in the community setting. Most of the studies reported no increase in adverse effects potentially associated with hypothermia such as bleeding, arrhythmias, infections, or poor glycemic control. The benefits appear to be primarily in patients presenting with ventricular fibrillation as their first rhythm. Further study is needed to evaluate whether therapeutic hypothermia is beneficial in patients presenting with asystole or PEA. Similarly, some of the comparative data suggested that the benefit of hypothermia is primarily in patients with out-of-hospital cardiac arrest with a time from collapse to return of spontaneous circulation of greater than 15 minutes. It would be helpful to see subgroup analyses within the completed and ongoing randomized trials to better define which patients benefit most from therapeutic hypothermia.

Case Series

A large number of case series have been published describing individual institutions, regions or countries experience with therapeutic hypothermia. Most case series were small and focused on the feasibility of implementing therapeutic hypothermia or describing new techniques and devices for lowering body temperature. Large case series add real-world data to randomized trials and can help to more precisely define known adverse events, identify rare adverse events, and evaluate long term outcomes.

Nielsen and colleagues reported on 986 patients entered into the prospective Hypothermia Registry representing 34 centers in seven countries. All patients with ROSC following out-of-hospital cardiac arrest who were comatose were entered into the registry. There were no exclusion criteria. Hypothermia was initiated and maintained by a variety of methods including ice packs, cold fluid infusion, air cooling, circulating water blankets, and intravascular devices. The patients’ median age was 63 years and 36% were female. The initial rhythm was VT or VF in 70%, asystole in 22%, and PEA in 7%. The median time to ROSC was 20 minutes. Therapeutic hypothermia was started a median of 90 minutes following the arrest and the target temperature (< 34°C) was reached after a median of 260 minutes. At hospital discharge survival was 56% and 434 (44%) patients had a good neurological outcome. At long-term follow-up (greater than six months) survival was 50% and 447 (46%) patients had a good neurological outcome. Long-term survival was higher in patients initially presenting with VT or VF (61%) than in patients presenting with asystole (25%) or PEA (27%). In multivariate modeling, the factors significantly associated with a poor long-term outcome included older age, longer time to ROSC, lower Glasgow Coma Scale on admission, unwitnessed arrest, and an initial rhythm of asystole (all p < 0.001). Notably, neither the time to initiation of
hypothermia (p=0.48), nor the time to reach the target temperature (p=.91) were associated with a poor outcome.

Arrhythmias were a common adverse event (33%) with 13% of patients experiencing bradycardia, 9% atrial fibrillation, 9% VT, and 7% VF. Infectious complications included pneumonia (46%), sepsis (4%), and other infections (4%). Bleeding requiring transfusions occurred in 4% and only 0.2% of patients had intracerebral bleeding. Because there was not a control group treated, it is impossible to determine whether there is an excess of any of these adverse events. However, the incidence of arrhythmias was comparable to that observed in both the control and hypothermia group in the HACA trial. The observed bleeding may be due in part to hypothermia, but 49% of the patients underwent emergent coronary angiography and 31% of the patients received some form of percutaneous coronary intervention. Thus, at least half of the patients received heparin and at least one third were placed on long-term anti-platelet therapy. The rate of pneumonia was higher than that observed in the HACA trial, but the rate of sepsis was lower.

**Randomized trials evaluating pre-hospital therapeutic hypothermia**

The three most recent randomized trials\(^7^4,^1^0^8,^1^1^0\) summarized in Tables 1 through 4 evaluated the impact of pre-hospital initiation of hypothermia in order to shorten the time from ROSC to hypothermia. Animal model data suggested that this should improve clinical outcomes.\(^1^6^-^2^0\) The quality of the trials was somewhat variable. None of the trials could blind study personnel to the intervention. Only Kim et al.\(^1^0^8\) did not blind the outcome assessment. Kamarainen et al.\(^1^1^0\) was the smallest of the trials, had large differences in baseline characteristics, and failed to analyze the data by intention-to-treat. The most recent trial, by Bernard et al.\(^7^4\) included more patients than the other two combined and was the highest quality of the three. All three of the trials used up to two liters of intravenous fluids chilled to 4° C (normal saline or Ringers solution) to initiate hypothermia. At arrival to the hospital, temperatures in the hypothermia group were approximately 1° C lower than the control group in all three trials even though the majority of patients in the hypothermia groups did not receive the full two liters of cold fluid. None of the trials found a benefit to hypothermia in improving survival to hospital discharge. In Kim et al.\(^1^0^8\) there was a slight trend toward higher survival in the hypothermia group (32% versus 29%), particularly in patients presenting with VF (66% versus 45%). However, survival trends went in the opposite direction in the randomized trials of Kamarainen\(^1^1^0\) (42% versus 44%) and Bernard\(^7^4\) (47% versus 53%). Notably, Bernard et al. only randomized patients presenting with VF.\(^7^4\) Thus the trend identified in the subgroup analyses of Kim et al\(^1^0^8\) was not confirmed in the larger, higher quality trial. It is also interesting that the large observational Hypothermia Registry, there was no association of time to initiation of hypothermia with survival or good neurologic outcome, contradicting the findings in one much smaller case series (n=49) that had suggested a benefit to earlier initiation of
hypothermia. There may be negative consequences from the rapid infusion of chilled fluids intravenously, although none were identified in these three studies. The volume of fluid may increase the risk for heart failure and in animal models, the infusion of cold saline reduces coronary perfusion pressure. Further trials may investigate alternative methods for initiating hypothermia in the pre-hospital setting. Until new randomized trials are published that convincingly demonstrate a survival benefit, pre-hospital initiation of hypothermia should remain investigational.

Summary

Four randomized trials have been published that directly compare therapeutic hypothermia to the same level of ICU care without hypothermia. In 2002, the NEJM published one good quality randomized trial and one pseudo-randomized trial that reported 14% to 17% absolute improvements in survival and 16% to 23% absolute improvements in neurologic outcomes compared to standard ICU care. Thus, for every seven comatose patients treated with therapeutic hypothermia following cardiac arrest, one additional patient would survive with meaningful quality of life. There were non-significant trends towards increased arrhythmias, infection, and bleeding in patients randomized to hypothermia. However, even if some patients were harmed by these adverse events, the net benefit in terms of patient survival and quality of life strongly favored the hypothermia intervention. Both of these trials cooled patients to a target temperature between 32° and 34° C using external cooling methods for a total of 12 to 24 hours. The study population in these two trials was similar: adults at least 18 years old who presented with an initial rhythm of VF or VT.

The other two randomized trials were smaller and one reported trends towards worse outcomes in patients randomized to therapeutic hypothermia. The patient populations in these two trials differed from the two trials that found benefit. Both of the trials included patients who presented with asystole and one of the trials included patients with PEA and excluded patients with VF or VT. The hypothermia interventions were also quite different. The first used a cooling helmet for only three to four hours. The other randomized trial used external cooling of the patient’s blood during hemofiltration and the control group was also treated with hemofiltration, which is not an established therapy for post-cardiac arrest management. These differences in patient populations and in cooling techniques are likely to be responsible for the differences in outcomes. Thus current randomized trials only support using external cooling methods for 12 to 24 hours in comatose survivors of out of hospital cardiac arrest in whom the presenting rhythm is VF or VT.

Because of the relative weakness in the quality of the randomized trial data for therapeutic hypothermia and the small number of patients studied, it was helpful to review the observational literature for evidence that
hypothermia improves outcomes outside the investigational setting. Recent studies that compared outcomes in survivors of cardiac arrest treated with hypothermia to historical or contemporary controls reported improvements in survival of a similar magnitude to the initial randomized trials. They also suggest that the largest benefit from therapeutic hypothermia is in the subgroup of patients presenting with VF or VT who have ROSC more than 15 minutes after the initial cardiac arrest. Some of the larger observational studies reported that therapeutic hypothermia did not improve outcomes in patients suffering cardiac arrest while in the hospital or in patients with asystole or PEA as their presenting rhythm, although the data were not consistent across all observational studies. Thus, the results of observational studies essentially echoes the findings of the randomized trials.

Three additional randomized trials\textsuperscript{74,108,110} failed to demonstrate any improvements in patient outcomes when pre-hospital therapeutic hypothermia was evaluated. The largest case series of therapeutic hypothermia also failed to find an association between the time to induction of hypothermia and clinical outcomes. These results suggest that the currently studied approach to pre-hospital therapy, the infusion of cold normal saline or Ringer’s solution, does not improve outcomes and should not be recommended on a routine basis.

In summary, randomized trial and comparative studies support the use of therapeutic hypothermia with a target temperature of 32° to 34° C for 12 to 24 hours in adult comatose survivors of out of hospital cardiac arrest who present with VF or VT. Further study is needed to extend the indication beyond this patient population. The optimal method for therapeutic hypothermia also remains unclear.

**TA Criterion 3 is met.**

**TA Criterion 4:** The technology must be as beneficial as any established alternatives.

There is no established alternative to therapeutic hypothermia for the care of post-cardiac arrest patients other than standard ICU care. Approaches such as hemofiltration and aggressive maintenance of normothermia remain investigational. The clinical trials discussed above under TA 3 demonstrated improved survival and neurologic outcome in patients treated with therapeutic hypothermia compared to patients treated with standard ICU care. Thus TA criterion 4 is met.

**TA Criterion 4 is met.**
TA Criterion 5: The improvement must be attainable outside of the investigational setting.

Therapeutic hypothermia is not straightforward to administer. Patients are usually paralyzed to prevent shivering and thus the patients often need to be intubated and sedated. In addition, the patient’s core temperature must be carefully monitored to maintain the target temperature without over-cooling the patient, which would increase the likelihood of arrhythmias, infection, bleeding, and electrolyte abnormalities. However, most intensive care units are able to provide this level of care. Most of the randomized trials were multi-institutional. The many published case series and comparative observational studies demonstrate the feasibility of therapeutic hypothermia at care facilities in many countries around the world and demonstrate improvements in survival and neurologic outcome compared with historical controls.

TA Criterion 5 is met.

CONCLUSION

One good quality randomized trial of therapeutic hypothermia and one pseudo-randomized trial published in 2002 reported 14% to 17% absolute improvements in survival and 16% to 23% absolute improvements in neurologic outcomes compared to standard ICU care. Thus, for every seven comatose patients treated with therapeutic hypothermia following cardiac arrest, approximately one additional patient would survive with meaningful quality of life. There were trends towards increased arrhythmias, infection, and bleeding in patients randomized to hypothermia, but these were not large enough to offset the observed improvements in overall survival and neurologic outcome. Both of these trials cooled patients to a target temperature between 32° and 34° C using external cooling methods for 12 to 24 hours. These two trials also limited their study population to adults at least 18 years old who presented with an initial rhythm of VF or VT.

However, the two other published randomized trials had lower survival rates and one reported a trend towards worse outcomes in patients randomized to therapeutic hypothermia. One included only patients presenting with asystole or PEA and used a cooling helmet for three hours. The other randomized trial included patients presenting with either VF or asystole, but compared hypothermia achieved by external cooling of the blood during hemofiltration to hemofiltration alone. The differences in patient populations and in the methods used to cool patients may be responsible for the differences in outcomes.

Subsequent observational studies that compared outcomes in survivors of cardiac arrest treated with
hypothermia to historical or contemporary controls reported improvements in survival of a similar magnitude to the initial randomized trials. They also suggest that the largest benefit from therapeutic hypothermia is in the subgroup of patients presenting with VF or VT who have ROSC more than 15 minutes after the initial cardiac arrest. Some of the larger observational studies reported that therapeutic hypothermia did not improve outcomes in patients suffering cardiac arrest while in the hospital or patients with asystole or PEA as their presenting rhythm, although the data were not consistent across all observational studies.

Finally, three randomized trials\textsuperscript{74,108,110} failed to demonstrate any benefit to pre-hospital therapeutic hypothermia using cold intravenous fluids. The largest case series of therapeutic hypothermia also failed to find an association between the time to induction of hypothermia and clinical outcomes. These results contradict animal studies that demonstrated less nerve cell death in the brain and higher survival in animals treated with rapid induction of hypothermia after ROSC.

In conclusion, there is modest evidence supporting the use of therapeutic hypothermia with a target temperature of 32° to 34° C for 12 to 24 hours in adult comatose survivors of out of hospital cardiac arrest who present with VF or VT. Current evidence supports the use of external methods to cool patients. Randomized trials are needed to evaluate whether therapeutic hypothermia should be extended to other patient populations including children under the age of 18 years, patients suffering cardiac arrest in the hospital, and patients presenting with asystole or PEA. Additional areas of uncertainty include the best methods for inducing and maintaining hypothermia, the optimal target temperature, how long to maintain hypothermia, and whether the risks of hypothermia outweigh the benefits in patients with ROSC in less than 15 minutes. Ongoing randomized trials are addressing many of these questions.

**RECOMMENDATION**

It is recommended that use of therapeutic hypothermia in comatose adults following cardiac arrest with a first rhythm of ventricular fibrillation or ventricular tachycardia meets CTAF Technology Assessment Criteria 1 through 5 for safety, effectiveness and improvement in health outcomes.

**February 16, 2011**

This is the first review of this technology by the California Technology Assessment Forum

*The California Technology Assessment Forum voted to approve the recommendation as presented.*
RECOMMENDATIONS OF OTHERS

American Heart Association

In October, 2002, the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation (ILCOR) recommended that 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 ventricular fibrillation (VF) and that cooling patients might be of benefit to those with other rhythms and in-hospital cardiac arrest.

In 2005, AHA cited two nonrandomized studies that indicate the possible benefit of hypothermia for adults following in-and out-of-hospital cardiac arrest from all other rhythms.

The 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care states that therapeutic hypothermia has been shown to improve outcomes for comatose adult victims of witnessed out-of-hospital cardiac arrest due to ventricular fibrillation.

Blue Cross Blue Shield Association (BCBSA)

The BCBSA Technology Evaluation Center has not conducted an assessment of Therapeutic Hypothermia Used in Cardiac Arrest.

Centers for Medicare and Medicaid Services (CMS)

Neither a National Coverage Determination nor a Local Coverage Determination (CA) was found in a review of the CMS web site

Society of Critical Care Medicine (SCCM)

The SCCM (www.sccm.org) has been invited to attend the meeting and to provide an opinion regarding the use of this technology.

The American Society of Hypothermic Medicine (ASHM)

The ASHM (www.asfhm.com) was invited to attend the meeting and to provide an opinion regarding the use of this technology
ACEP was invited to attend the meeting and to provide an opinion regarding the use of this technology.

ABBREVIATIONS

CTAF  California Technology Assessment Forum
NEJM  New England Journal of Medicine
ROSC  Return of spontaneous circulation
CPR   Cardiopulmonary resuscitation
CPC   Cerebral performance categories
ICU   Intensive care unit
DARE  Database of Abstracts of Reviews of Effects
RCT   Randomized controlled trial
CHD   Coronary heart disease
HACA  Hypothermia after cardiac arrest
NR    Not reported
VF    Ventricular fibrillation
TT    Target temperature
ER    Emergency room
OOH   Out of hospital cardiac arrest
NNT   Number needed to treat
IH    In hospital
T     Temperature
MAP   Mean arterial pressure
NS    Normal saline
HF    Hemofiltration
NA    Not applicable
GCS   Glasgow coma scale
RS    Ringer's solution
IV    Intravenous
PEA   Pulseless Electrical Activity
VT    Ventricular tachycardia
**APPENDIX: Search strategy**

*PubMed:*

<table>
<thead>
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<th>Search</th>
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Access the Embase Info site if you have questions about this message or other features of this service. Please do not reply to this email.

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ID | Search | Hits | Edit | Delete
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   | OR heart massage OR reanimation):ti,ab,kw and (hypothermia):ti,ab,kw |   |      |
REFERENCES


