

**VETERANS HEALTH ADMINISTRATION  
OFFICE OF PATIENT CARE SERVICES  
TECHNOLOGY ASSESSMENT PROGRAM**

**BRIEF OVERVIEW:**

**Hypothermia after Cardiac Arrest**

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March, 2008

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# TECHNOLOGY ASSESSMENT PROGRAM

*An Effective Resource for Evidence-based Managers*

VA's Technology Assessment Program (TAP) is a national program within the Office of Patient Care Services dedicated to advancing evidence-based decision making in VA. TAP responds to the information needs of senior VA policy makers by carrying out systematic reviews of the medical literature on health care technologies to determine "what works" in health care. "Technologies" may be devices, drugs, procedures, and organizational and supportive systems used in health care. TAP reports can be used to support better resource management.

TAP has two categories of products directed toward filling urgent information needs of its VA clients. TAP assigns a category to each new request based largely on the availability of studies from results of initial searches of peer-reviewed literature databases:

- The **Short report** is a self-contained, rapidly-produced qualitative systematic review between 5 and 20 pages in length. It provides sufficient background information and clinical context to its subject to be accessible to a wide audience, including non-clinician managers.
- The **Brief overview** originated as an internal memo to VA clients with both well-defined and urgent information needs. It usually comprises 2 to 10 pages and assumes sufficient existing knowledge regarding clinical context and technology issues by its readers to omit these components. It often requires some additional reading of documents (provided with the overview for the client) to obtain a full and comprehensive picture of the state of knowledge on the topic.

All TAP products are reviewed internally by TAP's physician advisor and key experts in VA. Additional comments and information on this report can be sent to:

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**A SUMMARY FOR HTA REPORTS**  
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VATAP is a member of the International Network of Agencies for Health Technology Assessment (INAHTA) [www.inahta.org]. INAHTA developed this checklist<sup>®</sup> as a quality assurance guide to foster consistency and transparency in the health technology assessment (HTA) process. VATAP added this checklist<sup>®</sup> to its reports in 2002.

This summary form is intended as an aid for those who want to record the extent to which an HTA report meets the 17 questions presented in the checklist. It is NOT intended as a scorecard to rate the standard of HTA reports – reports may be valid and useful without meeting all of the criteria that have been listed.

<b>Brief Overview: Hypothermia after cardiac arrest March 2008</b>			
<b>Item</b>	<b>Yes</b>	<b>Partly</b>	<b>No</b>
<b>Preliminary</b>			
1. Appropriate contact details for further information?	√		
2. Authors identified?	√		
3. Statement regarding conflict of interest?			√
4. Statement on whether report externally reviewed?			√
5. Short summary in non-technical language?			√
<b>Why?</b>			
6. Reference to the question that is addressed and context of the assessment?	√		
7. Scope of the assessment specified?	√		
8. Description of the health technology?	√		
<b>How?</b>			
9. Details on sources of information?	√		
10. Information on selection of material for assessment?	√		
11. Information on basis for interpretation of selected data?	√		
<b>What?</b>			
12. Results of assessment clearly presented?	√		
13. Interpretation of assessment results included?	√		
<b>What Then?</b>			
14. Findings of the assessment discussed?	√		
15. Medico-legal implications considered?			√
16. Conclusions from assessment clearly stated?	√		
17. Suggestions for further actions?	√		

**BRIEF OVERVIEW:**

**HYPOTHERMIA AFTER CARDIAC ARREST**

**ABBREVIATIONS IN THIS REVIEW**

**AAA**, abdominal aortic aneurysm

**AMI**, acute myocardial infarction

**BP**, blood pressure

**CABG**, coronary artery bypass graft

**CI**, 95% confidence interval

**CVA**, cerebrovascular accident

**ED**, emergency department

**ERC**, European Resuscitation Council

**GP**, general practitioner

**GCS**, Glasgow Coma Score

**HACA-R**, Hypothermia After cardiac Arrest Registry

**HF**, hemofiltration

**JCAHO**, Joint Commission on Accreditation of Healthcare Organizations

**ILCOR**, International Liaison Committee on Resuscitation

**LR**, likelihood ratio

**MI**, myocardial infarction

**NNT**, number needed to treat

**NS**, not significant

**OHCA**, out of hospital cardiac arrest

**OR**, odds ratio

**Q-EEG**, quantitative electroencephalography

**RCT**, randomized controlled trial

**ROSC**, return of spontaneous circulation

**RR**, relative risk

**RRS**, rapid response systems

**TAAG**, Technology Assessment Advisory Group (VHA Office of Patient Care Services)

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**BRIEF OVERVIEW:****HYPOTHERMIA AFTER CARDIAC ARREST****INTRODUCTION**

*“Sudden death from cardiac arrest is a major public health problem. The Centers for Disease Control and Prevention, Atlanta, GA, has estimated that approximately 400,000 individuals in the United States experience a sudden cardiac arrest each year. Aung (2005).*

*“Important factors for determining outcome after out-of-hospital cardiac (OHCA) arrest are primary and secondary brain damage. Neurological complications account for two thirds of deaths after initial resuscitation of OHCA patients. Recently, the use of mild hypothermia to lower body metabolism and decrease mechanisms of secondary brain damage has been advocated as standard of care.” Bergman (2008).*

*“The first report of the clinical use of hypothermia for the treatment of severe traumatic brain injury in adults was by Fay in 1945. In 1950, the experimental studies of Bigelow et al. created the basis for the use of hypothermia for cerebral protection. By the end of the 1950s, there were other reports about the beneficial use of hypothermia in traumatic brain injury in adults and children.” Arrica (2007).*

*“Post-resuscitation care of comatose survivors of cardiac arrest using induced hypothermia (IH) is recommended by the American Heart Association (AHA) and the International Liaison Committee on Resuscitation (ILCOR) to improve neurological outcomes but it has been performed primarily later in the course of care. Recently, it has been shown that pre-hospital cooling is feasible, safe, and effective in lowering patient temperature.” Suffoletto (2008).*

*“Mortality is high and depends on the initially observed cardiac rhythm. Mortality in patients with asystole has been reported to be as high as 85%, but some studies suggest a better prognosis for ventricular fibrillation, with 25-30% recovery. Furthermore, neurological recovery without sequelae is uncommon, and in one study, severe neurological damage has been observed in approximately 64% of patients who finally recover....*

*“After initial resuscitation, a number of mechanisms are directly responsible for cerebral damage, multi-organ failure, and finally death... For a long time, experimental studies have suggested that hypothermia could affect many of these mechanisms and protect the brain by reducing cerebral metabolism and oxygen consumption. This has led to the concept of neuroprotection.” Belliard (2007).*

*“The incidence of out-of-hospital cardiac arrest in industrialized countries ranges from 0.04 to 0.13% of the total population per year. Of those patients admitted to the hospital, only 11-44% will be discharged with a good neurologic outcome.*

*“For successful resuscitation with favorable neurologic recovery, it is important not only to stop the ischemia process caused by cardiac arrest as fast as possible but also to overcome the following post-resuscitation syndrome...*

*“Clinical and experimental results show a multi-factorial neuro-protective effect of hypothermia during and after ischemic situations by simultaneously influencing several damaging pathways...” Holzer (2005).*

*“Hypothermia is well known to provide neuroprotection following various brain insults in experimental animals. Two recently completed clinical trials of whole body hypothermia in out-of-hospital cardiac arrest patients demonstrated significantly improved survival rates and neurologic outcomes. These results provide new excitement and*

*encouragement for clinical application of hypothermia in cerebrovascular disease. However, the intensive care challenges and adverse events (e.g. prolonged times to target temperatures, shivering and sedation, pneumonia) during the management of hypothermia, dampen enthusiasm for widespread application especially in elderly stroke patients...new technology, the ChillerPad™ and ChillerStrip™ Systems developed by Seacoast Technologies, Inc. (Portsmouth NH, USA). The latter device has received FDA approval...”*Wagner (2005).

*“Despite compelling data supporting its use, hypothermia has yet to be broadly incorporated into physician practice...Among reasons for non-use...were not enough data ...lack of incorporation of hypothermia into advanced cardiovascular support (ACLS) protocols, ...and cooling methods were technically too difficult or too slow.”* Abella (2005).

*“Sudden cardiac arrest is not uncommon as a complication of coronary heart disease (ischemic heart disease)...Most cases of cardiac arrest occur out of hospital...Treatment outcomes in this group have not improved substantially in the past 20 years. Only 4% of those affected are discharged alive from the hospital following resuscitation and treatment. The outcome of treatment depends partly on the time that has elapsed between cardiac arrest and the reestablishment of stable circulation. Most patients who are resuscitated from cardiac arrest are unconscious and require care at an intensive care unit. Lowering the body temperature (induced hypothermia) after resuscitation from cardiac arrest is a treatment method intended to limit the damage, mainly to the brain, that occurs when blood circulation ceases. Body temperature is lowered to 32-34 degrees, which usually requires sedation of the patient, administration of muscle relaxants, and the subsequent use of ventilator treatment...”*

*“The potential target group for therapeutic hypothermia includes people who are unconscious after resuscitation from cardiac arrest and whose condition would suggest a risk for tissue damage due to oxygen deficiency. Most patients would be patients with coronary heart disease. Criteria have not been established for selecting patients for therapeutic hypothermia, so the size of the potential target group for this treatment method cannot be estimated...”* SBU (2006).

*“Most survivors of cardiac arrest are comatose after resuscitation, and meaningful neurological recovery occurs in a small proportion of cases. Treatment can be lengthy, expensive, and often difficult for families and caregivers. Physical examination is potentially useful in this difficult scenario, and the information obtained may help physicians and families make accurate decisions about treatment and/or withdrawal of care.”* Booth (2004).

*“Preliminary clinical studies have shown that patients treated with mild hypothermia after cardiac arrest have an improved neurologic outcome, without important side effects as compared with the outcome in historical controls.”* Hypothermia After Cardiac Arrest Study Group (2002).

## **BACKGROUND**

VHA's TAAG asked TAP for a review of the literature as support for use of hypothermia after cardiac arrest. TAAG did not define a method or device for inducing hypothermia, neither did it specify the point in the process of care where hypothermia would be used, the target temperature, nor the length of time for which hypothermia would be sustained. Therefore, TAP searched for available systematic reviews and technology assessments as a means of quickly gauging the overall status of research on hypothermia in this context.

## METHODS

### **Analytic framework: epidemiologic study cycle**

The progression of epidemiologic studies, or the epidemiologic study cycle, confirming the existence and strength of an observed association between exposure and disease (or intervention and outcome) is both well-documented and the foundation for the systematic review framework outlined below (Ibrahim, 1985; Mausner and Kramer, 1985; Lilienfeld and Stolley, 1994; Muir Gray, 1997): it begins with observational, hypothesis-generating studies such as single case or case series reports, then on to cross-sectional (also known as survey, correlational, or ecological) studies, which ascertain exposure and disease at the same point in time, then progresses through analytic, hypothesis-testing studies (case-control or cohort, from which relative risk or estimates can be calculated), and culminates in the randomized controlled trial confirming causality.

### **Analytic framework: systematic reviews**

Cook (1997) and Mulrow (1997) define systematic reviews: “*Systematic reviews are scientific investigations in themselves, with pre-planned methods and an assembly of original studies as their “subjects”. They synthesize the results of multiple primary investigations by using strategies that limit bias and random error...*”

The same authors further specify characteristics of systematic reviews and contrast them with traditional narrative reviews: the latter synthesize articles without reporting methods of selection or quality assessment criteria and thus do not qualify as reproducible science.

The same authors further specify characteristics of systematic reviews and contrast them with traditional narrative reviews: the latter synthesize articles without reporting methods of selection or quality assessment criteria and thus do not qualify as reproducible science.

Systematic reviews:

- Ask a focused clinical question;
- Conduct a comprehensive search for relevant studies using an explicit search strategy;
- Uniformly apply criteria for inclusion and exclusion of studies;
- Rigorously and critically appraise included studies;
- Provide detailed analyses of the strengths and limitations of included studies.

Systematic reviews can be quantitative (i.e., meta-analytic, applying statistical methods to summarize study results) or qualitative; in either case the inferences or conclusions of the review must follow logically from the evidence presented. The rigor of this approach is illustrated by the place of systematic reviews in evidence grading schemes (Cook, 1995; Guyatt 1995), where they receive the highest level designation.

### **Analytic framework: registries in technology assessment**

Large health care databases, data set, or registries, while not necessarily intended for research use, can make useful contributions to technology assessment (Antczak-Bouckoms, 1991) and have numerous advantages over other information sources: non-intrusive data collection, large population coverage and sample size, low cost, easy long-term follow-up, and no reliance on individual recall (Blais, 1991).

### **Search strategy**

TAP searched Medline via PubMed and Dialog, Embase, and Cochrane databases from 1990 to March 2008. Search terms were: hypothermia, cardiac arrest, and resuscitation; all searches were restricted to adult human patients and English language publications. TAP also included

search terms to identify existing systematic reviews, meta-analyses, economic analyses, and technology assessments i.e., syntheses of the literature that would enhance TAP's ability to meet the information needs of OPCS quickly. Hand searching reference lists of articles initially retrieved, allowed TAP to identify and retrieve additional full-text publications.

Finally, the databases of the International Network of Agencies for Health Technology Assessment (INAHTA; [www.inahta.org](http://www.inahta.org)) were searched, and an electronic query addressed to TAP's colleague INAHTA members requested information on completed or in-progress reviews and technology assessments. One reviewer (KF) read and abstracted all retrievals.

### **Included**

Systematic reviews, along with technology assessments, cost-effectiveness or-utility analyses, or other studies clearly based on systematic reviews were included, as were subsequently (post-2006) published papers representing credible research (i.e., RCTs or registry analyses) and reporting survival, neurologic outcomes, or adverse events for hypothermia after cardiac arrest.

### **Excluded**

- non-English language articles;
- studies in pediatric populations;
- animal studies;
- single case reports;
- case series;
- narrative reviews and other articles lacking primary clinical data.
- primary studies included in available systematic reviews or assessments, which TAP generally considers redundant. However, in this case, two pivotal 2002 RCTs (Hypothermia After Cardiac Arrest Study Group; and Bernard) cited in reviews, assessments, and by the FDA are abstracted in Table 1 to make their results directly available to VHA decision makers. The print version (Holzer, 2005) of an in-progress Cochrane review (Mullner, 2003) is also abstracted in Table 1, although it is cited in Table 1 systematic reviews.

## **RESULTS**

Appendix Table 1 abstracts available systematic reviews and technology assessments; Table 2 abstracts new primary studies not available to Table 1 reviewers. Table 3 lists in- progress clinical studies, which provide a list of hypothermia issues in continuing need of resolution as discussed below.

## **CONCLUSIONS AND DISCUSSION**

The RTC and meta-analytic evidence supporting hypothermia for comatose survivors of resuscitation from ventricular fibrillation cardiac arrest is characterized by some writers as "compelling". Others (SBU, 2006; CEDIT, 2004; ANZHSN, 2005; all in Table 1) are more circumspect, citing heterogeneity among trials, relatively small numbers, technical or organizational impediments to wide implementation, and the need for continuing research.

TAP retrieved no recent rigorous evidence to materially change SBU's conclusions in 2006:

*"The scientific evidence is insufficient to show that treatment with induced hypothermia after resuscitation from cardiac arrest improves survival or lowers the risk for permanent functional impairment. Although the scientific evidence is too weak to support reliable*

*conclusions, the method appears to be promising and potentially may be of clinical importance. However, it is essential to continue testing this method in Sweden under scientifically acceptable conditions so that its benefits, risks, and cost effectiveness can be assessed. Until adequate scientific evidence is available, therapeutic hypothermia should be used only within the framework of well-designed, prospective, and controlled trials.”*

## **IMPLICATIONS FOR RESEARCH**

These conclusions can be transferred to the US in 2008, and Appendix Table 3 lists aspects of hypothermia still under active research:

- Applicability to in-hospital cardiac arrest or pre-hospital (field) use.
- Alternate methods or devices for inducing hypothermia.
- Longer-term effectiveness and cost-effectiveness.

Discussions within TAAG, for which this review was done, raised questions regarding the review conclusions versus those of AHA and ILCOR: As noted above, not everyone interprets the same evidence in the same way. Specifically, AHA is a clinical professional association, most of whose physician-members are not expert in the critique of research design and who might tend to be satisfied by the simple presence of RCTs or meta-analyses in the literature but who don't always analyze closely for research design details. AHA relied on consensus in formulating its recommendations for management of cardiac arrest/adult life support. Its supporting literature review may be characterized as quasi-systematic in that it used ranking of evidence but not critical analysis of individual studies; i.e. adhered to the letter but missed some of the spirit of a true systematic review and thus was prone to bias.

The HTA agencies (including SBU, from which TAP borrowed conclusions above), in contrast, do critique details. As I also noted above, the numbers of patients enrolled in individual trials (and aggregated for meta-analyses) remain small relative to other established therapies. For example, rTPA was tested in close to 3000 patients shortly after FDA approval for acute stroke (Hacke, 2003) vs. <1000 for CoolGard. Larger Ns allow for sub-group analyses, detection of uncommon adverse events, and refinement of patient selection; these advantages are not yet possible for hypothermia in cardiac arrest.

Other unresolved research issues are listed above: they include organizational and technical impediments to broad diffusion, familiar from similar issues for TPA in stroke and critical to national-level implementation (eg. TAP overview of acute stroke management, 2004). To borrow from the acute stroke overview: we know that TPA “works” for well-defined acute stroke patients, but it continues to be under-used due to organizational and institutional barriers, making the HTA agencies assessing on behalf of national healthcare systems and in positions to contribute to research agendas more cautious than AHA. Hypothermia probably “works” for ventricular fibrillation cardiac arrest, but issues still unresolved by definitive research give pause before national-level implementation.

## APPENDIX

**Table 1. Systematic reviews, technology assessments, and policy recommendations: hypothermia after cardiac arrest**

Reference	Purpose/details	Results/Comments
<b>Important RCTs and systematic reviews cited in reviews below and by FDA</b>		
Holzer (2005);  Cochrane review (as Mullner, 2003)	Systematic review with individual patient data meta-analysis; <ul style="list-style-type: none"> <li>• Randomized and quasi-randomized trials;</li> <li>• Adults successfully resuscitated;</li> <li>• Hypothermia (any target temperature &lt; 35 degrees C) applied within 6 hrs of arrival at ED and neurologic outcome compared;</li> <li>• Multiple databases, 1990-2002</li> <li>• Excluded: studies without control groups or with historical controls;</li> <li>• Authors of identified trials supplied individual patient data</li> </ul>	3 RCTs; <ul style="list-style-type: none"> <li>• More patients in hypothermia group were discharged with favorable neurologic recovery (RR, 1.68; CI, 1.29-2.97);</li> <li>• CI for NNT to allow one additional favorable outcome, 4-13;</li> <li>• One study followed patients to 6 months or death: being alive at 6 months with favorable neurologic recovery was more likely in hypothermia group (RR, 1.44; CI, 1.11-1.76).</li> </ul> <p><b>Conclusions:</b> <i>"Mild therapeutic hypothermia improves short-term neurologic recovery and survival in patients resuscitated from cardiac arrest of presumed cardiac origin. Its long-term effectiveness and feasibility at an organizational level need further research."</i></p>
Hypothermia after cardiac arrest study group (2002)	Does mild systemic hypothermia increase the rate of neurologic recovery after resuscitation from cardiac arrest due to ventricular fibrillation?	Multi-center RCT (Europe and Australia) with blinded assessment of outcome: <ul style="list-style-type: none"> <li>• Patients resuscitated after cardiac arrest due to ventricular fibrillation randomly assigned to</li> <li>• Therapeutic hypothermia by external cooling device (target temperature in the bladder, 32-34°C: (n = 136 )); or to standard treatment with normothermia (n = 137);</li> <li>• 55% of hypothermia group had favorable neurologic recovery Vs. 39% of normothermia group (RR, 1.4; CI, 1.08-1.81);</li> <li>• Mortality at 6 months: 41% in hypothermia group Vs 55% in normothermia group (RR, 0.75; CI, 0.58-0.95);</li> <li>• Complication rate did not differ significantly between the groups.</li> </ul> <p><b>Conclusions:</b> <i>"In patients who have been successfully resuscitated after cardiac arrest due to ventricular fibrillation, therapeutic mild hypothermia increased the rate of favorable neurologic outcome and reduced mortality"</i></p>
Bernard (2002)	Effects of hypothermia versus normothermia in patients who remained unconscious after resuscitation from out-of-hospital cardiac arrest	RCT conducted in Melbourne Australia, 1996-1999: <ul style="list-style-type: none"> <li>• Patient selection: ventricular fibrillation on ambulance arrival; successful ROSC followed by persistent coma; transfer to one of four participating EDs;</li> <li>• Exclusions: age &lt; 18 for males; age &lt; 50 for females; cardiogenic shock (systolic BP&lt;90mm Hg despite epinephrine); possible cause of coma other than cardiac arrest (drug overdose, head trauma, CVA); intensive care bed not available at a participating institution.</li> <li>• Patients randomized according to odd- or even-numbered day of month;</li> <li>• Patients assigned to hypothermia: begun by paramedics in the field by removing clothing plus cold packs to head and torso;</li> <li>• Following ED arrival: patients received routine assessment and treatment, including mechanical ventilation and correction of cardiovascular instability;</li> <li>• Patients ready for discharge were evaluated by specialist in rehab medicine blinded to treatment group.</li> </ul>

Reference	Purpose/details	Results/Comments
		<p><b>Results:</b> 84 patients eligible for enrollment over 33 months; data on 7 patients excluded from analyses (transferred to nonparticipating ICU or refused consent);</p> <ul style="list-style-type: none"> <li>• 77 patients randomized (43 hypothermia, 34 normothermia);</li> <li>• 21 of 43 hypothermia patients (49%) survived with good outcome (discharged home or to rehab facility); Vs 9 of 34 normothermia patients (26%; P = 0.046);</li> <li>• After adjustment for baseline differences in age and time from collapse to ROSC: OR for good outcome with hypothermia Vs normothermia, 5.25 (CI, 1.47-18.76; P = 0.011);</li> <li>• Hypothermia was associated with a lower cardiac index, higher systemic vascular resistance, and hyperglycemia;</li> <li>• There was no difference in the frequency of adverse events.</li> </ul> <p><b>Conclusions:</b> <i>“Our preliminary observations suggest that treatment with hypothermia appears to improve outcomes in patients with coma after resuscitation from out-of-hospital cardiac arrest”</i></p>
<p><b>Systematic reviews and assessments of hypothermia for cardiac arrest</b></p>		
<p>Cheung (2006)</p>	<p>Systematic review:</p> <ul style="list-style-type: none"> <li>• Multiple databases, 1966-2005</li> <li>• RCTs: adult patients with primary cardiac arrest who remained comatose after ROSC; randomized to mild induced hypothermia (32-34 degrees C) or normothermia within 24 hrs of presentation and reporting discharge neurologic outcome, mortality, or significant treatment-related adverse effects; no language or publication restrictions</li> </ul>	<p>4 studies involving 436 patients (232 hypothermic) pooled:</p> <ul style="list-style-type: none"> <li>• Mild hypothermia decreased in-hospital mortality (RR, 0.75; CI, 0.62-0.92) and reduced poor neurologic outcome (RR, 0.74; CI, 0.62-0.84; NNT, 7 to save one life, 5 to improve neurologic outcome);</li> <li>• No evidence of treatment-limiting side effects.</li> </ul> <p><b>Conclusions:</b> <i>“Therapeutically induced mild hypothermia decreases in-hospital mortality and improves neurologic outcome in comatose cardiac arrest survivors. The possibility of treatment-limiting side effects cannot be excluded.”</i></p>
<p>SBU (2006)</p>	<ul style="list-style-type: none"> <li>• Early assessment of new health technology: Does treatment that lowers body temperature by 3-5 degrees after resuscitation from cardiac arrest increase the chance for survival or decrease the risk for permanent functional impairment?</li> <li>• Included: RCTs reporting survival and neurological function</li> </ul>	<p><b>2 RCTs:</b></p> <ul style="list-style-type: none"> <li>• One high quality RCT found an association between hypothermia and improved outcome;</li> <li>• The other low quality RCT: intervention group patients could be discharged to a lower level of care than controls.</li> </ul> <p><b>Ethical concerns:</b></p> <ul style="list-style-type: none"> <li>• The method has not been adequately assessed;</li> <li>• It is unknown if benefits from resources devoted to this therapy can be appropriately weighted against alternate uses of the resources.</li> </ul> <p><b>Economic concerns:</b></p> <ul style="list-style-type: none"> <li>• During hypothermia the patient is placed on a ventilator and requires 1-2 extra days of intensive care;</li> <li>• Cost-effectiveness cannot be calculated since treatment effects are uncertain.</li> </ul> <p><b>Conclusions:</b> <i>“The scientific evidence is insufficient to show that treatment with induced hypothermia after resuscitation from cardiac arrest improves survival or lowers the risk for permanent functional impairment. Although the scientific evidence is too</i></p>

Reference	Purpose/details	Results/Comments
		<p><i>weak to support reliable conclusions, the method appears to be promising and potentially may be of clinical importance. However, it is essential to continue testing this method in Sweden under scientifically acceptable conditions so that its benefits, risks, and cost effectiveness can be assessed. Until adequate scientific evidence is available, therapeutic hypothermia should be used only within the framework of well-0designed, prospective, and controlled trials."</i></p>
ANZHSN (2005)	Horizon scanning prioritizing summary: methods not fully reported	<ul style="list-style-type: none"> <li>• Received Therapeutic Goods Administration approval in 2005, but not yet available for purchase in Australia.</li> <li>• Studies (levels I-IV evidence) have demonstrated that moderate hypothermia appears to improve neurological outcomes in cardiac patients.</li> <li>• Mild hypothermia (level I evidence) induced by external cooling demonstrates favorable short term neurologic recovery and survival in comatose patients resuscitated from cardiac arrest.</li> <li>• ILOCr recognized value of hypothermia in the immediate treatment of comatose survivors of ventricular fibrillation cardiac arrest and recommended that hypothermia be induced in unconscious adults with spontaneous circulation who have experienced an out of hospital cardiac arrest: 32-34° C when initial rhythm is ventricular fibrillation.</li> </ul> <p><b>2 feasibility and safety studies:</b></p> <ul style="list-style-type: none"> <li>• 39 patients total;</li> <li>• 4 patients died; 2 cases of sepsis; 2 patients in persistent vegetative state; 18 patients with good neurologic recovery.</li> </ul> <p><b>Conclusions:</b> <i>"There is currently insufficient evidence to assess the effectiveness of hypothermia induction with CoolGard™. However, there is recognition of the benefits of hypothermia for improving neurological outcomes."</i></p> <p><b>Recommendation:</b> <i>"In the absence of randomized studies assessing its safety and effectiveness and comparing it to external surface cooling, it is recommended that this technology be monitored."</i></p>
CEDIT (2004)	Rapid assessment procedure (preliminary investigation of effectiveness): CoolGard™ internal cooling device for acute myocardial infarction	<ul style="list-style-type: none"> <li>• CoolGard 3000™ is the only device available in France: 7-8 units had been purchased or made available but were not used extensively.</li> <li>• Purpose: to induce hypothermia concurrently with coronary reperfusion;</li> <li>• From the little data available in the literature, the best use appears to be anterior wall infarction;</li> <li>• Central unit approx 30,000 Euros; single use consumable supplies, 890 Euros/patient.</li> </ul> <p><b>Conclusions:</b> <i>"CEDIT cannot, based on the data already published, recommend the use of the CoolGard 3000™ internal cooling system to induce hypothermia for the early treatment of myocardial infarction. It should be noted that this opinion does not concern the already recognized indication, i.e., cardiac arrest subsequent to ventricular fibrillation, for which a national assessment comparing internal cooling to external cooling is planned."</i></p>
<b>Other systematic reviews for cardiac arrest</b>		
Winters (2007)	Impact of RRS (specialized teams of caregivers who identify and treat patients with early signs of clinical deterioration on general medical wards) on hospital mortality and cardiac arrest rates: <ul style="list-style-type: none"> <li>• Multiple databases, 1990-2005;</li> </ul>	<p>8 relevant studies met inclusion criteria: 5 used historical controls; one, concurrent controls; and two used cluster-randomized designs:</p> <ul style="list-style-type: none"> <li>• Pooled (two randomized studies RR for hospital mortality, RRS Vs controls, 0.76(CI, 0.39-1.48); five observational studies, 0.87(CI, 0.73-1.04);</li> <li>• RR for cardiac arrest, 0.94 (CI, 0.79-1.13) in single randomized study; and 0.70 (CI, 0.56-0.92) in four observational studies.</li> </ul>

Reference	Purpose/details	Results/Comments
	<ul style="list-style-type: none"> <li>English-language observational and randomized trials of RRS in adults;</li> </ul>	<p><b>Conclusions:</b> <i>"We found weak evidence that rapid response systems are associated with a reduction in hospital mortality and cardiac arrest rates, but limitations in the quality of the original studies, the wide confidence intervals, and the presence of heterogeneity limited our ability to conclude that rapid response systems are effective interventions. Large randomized controlled trials are needed to clarify the efficacy of rapid response systems."</i></p>
Aung (2005)	<p>To determine the effectiveness of vasopressin in treating cardiac arrest:</p> <ul style="list-style-type: none"> <li>RCTs with human subjects and reporting morbidity /mortality outcomes, 1966-2004.</li> </ul>	<p>5 RCTs, 4 in English, 1 in Chinese, enrolling 1519 patients:</p> <ul style="list-style-type: none"> <li>3 trials OHCA, 2 in-hospital;</li> <li>3 high quality, two low;</li> <li>No statistically significant differences between vasopressin and epinephrine groups in failure of return of spontaneous circulation (RR, 0.81; CI, 0.85-1.12); death before hospital admission (RR, 0.72; CI, 0.38-1.39); death within 24 hrs (RR, 0.74; CI, 0.38-1.43); death before discharge (RR, 0.96; CI, 0.94-1.07); or combination of number of deaths and neurologically impaired survivors (RR, 1.00; CI, 0.94-1.07).</li> <li>Subgroup analysis base on initial rhythm showed NS difference between vasopressin and epinephrine in any of 3 subgroups: ventricular fibrillation or ventricular tachycardia (RR, 0.97; CI, 0.79-1.19); pulseless electrical activity (RR, 1.02; CI, 0.95-1.10); or asystole (RR, 0.97; CI, 0.94-1.00)</li> </ul> <p><b>Conclusions:</b> <i>"There is no clear advantage of vasopressin over epinephrine in the treatment of cardiac arrest. Guidelines for Advanced Cardiac Life Support should not recommend vasopressin in resuscitation protocols until more solid human data on its superiority are available."</i></p>
Booth (2004)	<p>Role of clinical examination in predicting poor outcome in post-cardiac arrest coma:</p> <ul style="list-style-type: none"> <li>Multiple databases, 1966-2003;</li> <li>English-language studies assessing precision and accuracy of clinical exam for post-cardiac arrest coma in adults</li> </ul>	<p>11 studies involving 1914 patients:</p> <ul style="list-style-type: none"> <li>5 clinical signs strongly predict death or poor neurological outcome: absent corneal reflexes sat 24 hrs (LR, 12.9; CI, 20.-68.7; absent papillary response at 24 hrs (LR, 10.2; CI, 1.8-48.6); absent withdrawal response to pain at 24 hrs (LR, 4.7; CI, 2.2-9.8); no motor response at 24 hrs (LR, 4.9; CI, 1.6-13.0); and no motor response at 72 hrs (LR, 9.2; CI, 2.1-49.4);</li> <li>Random effects estimate of pretest probability of poor outcome was 77% (CI, 72%-80%);</li> <li>Highest LR increases pretest probability of 77% to posttest probability of 97% (CI, 87%-100%);</li> <li>No clinical finding had LRs that strongly predicted good neurological outcome.</li> </ul> <p><b>Conclusions:</b> <i>"Simple physical examination maneuvers strongly predict death or poor outcome in comatose survivors of cardiac arrest. The most useful signs occur at 24 hours after cardiac arrest, and earlier prognosis should not be made by clinical examination alone. These data provide prognostic information, rather than treatment recommendations, which must be made on an individual basis incorporating many other variables."</i></p>
<b>Policy recommendations</b>		
Nolan (2003)	Narrative review/advisory statement; methods incompletely reported	<p>ILCOR recommendations:</p> <p><i>"On the basis of published evidence to date...:</i></p> <ul style="list-style-type: none"> <li><i>"Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32°C for 12 to 24 hours when the initial rhythm was ventricular fibrillation (VF).</i></li> <li><i>"Such cooling may be beneficial for other rhythms or in-hospital cardiac arrest."</i></li> </ul>

**Table 2. Studies published subsequent to reviews in Table 1**

Reference	Study design	Setting	Results/comments
Uray (2008)	"feasibility trial"	European urban academic hospital and emergency service	<p>15 victims of cardiac arrest: 2006-07:</p> <ul style="list-style-type: none"> <li>• Cooling by external Emscoolpad® initiated at 12(8.5-15) minutes after ROSC; target, 33°C for 24 hrs;</li> <li>• Esophageal temperatures decreased from 36.6 (36.2-37.6)°C to 33°C within 70 (55-106) minutes;</li> <li>• Hospital admission at 45 (34-52) minutes, with esophageal temperatures of 35.4 (34.6-35.9)°C;</li> <li>• Target 33°C achieved 50 (29-82) minutes after admission;</li> <li>• No skin lesions observed.</li> </ul> <p><b>Conclusions:</b> <i>"non-invasive surface cooling with cooling pads was a fast, feasible, and safe method in the out-of-hospital setting for early induction of therapeutic hypothermia after non-traumatic cardiac arrest."</i></p>
Kim (2005; 2007)	Pilot RCT	US academic medical centers	<p>Effect on esophageal temperature of pre-hospital cooling by infusing up to 2L of 4°C normal saline as soon as possible after resuscitation from out-of-hospital cardiac arrest:</p> <ul style="list-style-type: none"> <li>• 125 patients randomized to standard care with or without intravenous cooling;</li> <li>• 64 patients in hypothermia group; mean decrease of 1.24±1°C, with hospital arrival temperature of 34.7°C;</li> <li>• Patients not receiving cooling: mean temperature increase, 0.10±0.94°C (p&lt;0.0001), hospital arrival at 35.7°C;</li> <li>• In-field cooling was not associated with adverse consequences: blood pressure, heart rate, arterial oxygenation; pulmonary edema on initial chest x-ray; or re-arrest;</li> <li>• Secondary end points (awakening, discharge alive from hospital) showed trends toward improvement in ventricular fibrillation patients randomized to cooling.</li> </ul> <p><b>Conclusions:</b> <i>"These pilot data suggest that infusion of up to 2L of 4°C normal saline in the field is feasible safe, and effective in lowering temperature. We propose that the effect of this cooling on neurological outcome after cardiac arrest be studied in larger numbers of patients, especially those whose initial rhythm is ventricular fibrillation."</i></p>
Tiainen (2007)	<ul style="list-style-type: none"> <li>• RCT: Hypothermia (33°C for 24 hrs by external cooling)Vs normothermia;</li> <li>• Patients resuscitated after ventricular fibrillation cardiac arrest;</li> </ul>	Helsinki University Hospital	<p>Patients randomized into HACA trial and surviving at least 3 months: initial results for 70 patients, 36 in hypothermia group, 34 normothermia assessed at 3 months:</p> <ul style="list-style-type: none"> <li>• No differences between groups in demographic, depression, or delays related to resuscitation;</li> <li>• Survival at 3 months: 28 hypothermia (77%); 22 (64.5%); p =0.226;</li> <li>• No differences in cognitive functions: 67% of hypothermia group and 44% of normothermia group were cognitively intact or had only very mild impairment;</li> <li>• Severe cognitive deficits in 25% of hypothermia group and 28% of normothermia group;</li> <li>• All Q-EEG parameters were better in the hypothermia group;</li> <li>• Auditory P300 event-related potentials were significantly higher in hypothermia group;</li> </ul> <p><b>Conclusions:</b> <i>"The use of therapeutic hypothermia was not associated with cognitive decline or neurophysiological deficits after out-of-hospital cardiac arrest. Even though the small sample size limits interpretation of results, we found no evidence that the previously reported increase in survival rate would be translated to clinically significant cognitive deficits."</i></p>

Reference	Study design	Setting	Results/comments
	<ul style="list-style-type: none"> <li>Cognitive functioning and neurophysiological outcome</li> </ul>		
Arrich (2007)	Registry analysis: HACA-R (2003-2005)	ERC: 19 sites within Europe	<p>Data on 650 patients entered in registry, March 2003-June 2005:</p> <ul style="list-style-type: none"> <li>Cardiac arrest with successful ROSC</li> <li>462(79%) received therapeutic hypothermia: 347(59%) cooled with an endovascular device; 114(19%) with other methods(ice packets, cooling blankets, cold fluids);</li> <li>Median cooling rate, 1.1°C.hr;</li> <li>Of all hypothermia patients, 15 (3%) had episode of hemorrhage, 28 (6%) had at least one episode of arrhythmia within 7 days after cooling;</li> <li>There were no fatalities as a result of cooling.</li> </ul> <p><b>Conclusions:</b> <i>"Therapeutic hypothermia is feasible and can be used safely and effectively outside a randomized clinical trial. The rate of adverse events was lower and the cooling rate was faster than in clinical trials published"</i></p>

**Table 3. Ongoing studies of hypothermia for cardiac arrest  
Listed by NIH at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (accessed 3/12/08)**

Purpose	Location	Projected completion (if noted)
Safety and feasibility of endovascular cooling device	Taiwan	
LRS ThermoSuit™ system (IV magnesium sulfate)	Vienna	
LRS ThermoSuit™ system (IV magnesium sulfate)	Canada	
Vigileo (pulse-contour analysis Vs Vigilance (continuous cardiac output devices); observational	Switzerland	
Mortality and neurologic outcomes after in-hospital cardiac arrest; RTC	Germany	
Hypothermia as soon as possible in the field by rapid saline infusion	US	November 2011
Clinical and economic RTC: external Vs internal cooling	France	November 2009

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## TECHNOLOGY ASSESSMENT PROGRAM

### Mission Statement

To enhance the health of veterans and the nation by providing and fostering technology assessment for evidence-based health care

### Values

***Integrity and pride*** in the work that we do

***Quality*** products that are clinically valid and methodologically transparent

***Objectivity*** in evaluating and presenting research evidence

***Commitment*** to continuous quality improvement and to the guiding principles of evidence based practices

***Flexibility*** in responding to changes in VA and the larger healthcare environment

***Innovation*** in designing products and their dissemination to best meet VA's needs

***Accessibility*** of products and services