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Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation

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ABSTRACT

Background

Good neurologic outcome after cardiac arrest is hard to achieve. Interventions during the resuscitation phase and treatment within the first hours after the event are critical. Experimental evidence suggests that therapeutic hypothermia is beneficial, and a number of clinical studies on this subject have been published. This review was originally published in 2009.

Objectives

We performed a systematic review and meta-analysis to assess the effectiveness of therapeutic hypothermia in patients after cardiac arrest. Neurologic outcome, survival and adverse events were our main outcomes. We aimed to perform individual patient data analysis, if data were available, and to form subgroups according to the cardiac arrest situation.

Search methods

We searched the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2001, Issue 7); MEDLINE (1971 to July 2011); EMBASE (1987 to July 2011); CINAHL (1988 to July 2011); PASCAL (2000 to July 2011); and BIOSIS (1989 to July 2011). The original search was performed in January 2007.

Selection criteria

We included all randomized controlled trials assessing the effectiveness of therapeutic hypothermia in patients after cardiac arrest, without language restrictions. Studies were restricted to adult populations cooled with any cooling method, applied within six hours of cardiac arrest.

Data collection and analysis

Validity measures, the intervention, outcomes and additional baseline variables were entered into a database. Meta-analysis was only done for a subset of comparable studies with negligible heterogeneity. For these studies, individual patient data were available.
Main results

We included four trials and one abstract reporting on 481 patients in the systematic review. The updated search resulted in no new studies to include. Quality of the included studies was good in three out of five studies. For the three comparable studies on conventional cooling methods all authors provided individual patient data. With conventional cooling methods, patients in the hypothermia group were more likely to reach a best cerebral performance categories (CPC) score of one or two (five point scale: 1 = good cerebral performance, to 5 = brain death) during the hospital stay (individual patient data; RR 1.55; 95% CI 1.22 to 1.96) and were more likely to survive to hospital discharge (individual patient data; RR 1.35; 95% CI 1.10 to 1.65) compared to standard post-resuscitation care. Across all studies, there was no significant difference in reported adverse events between hypothermia and control.

Authors’ conclusions

Conventional cooling methods to induce mild therapeutic hypothermia seem to improve survival and neurologic outcome after cardiac arrest. Our review supports the current best medical practice as recommended by the International Resuscitation Guidelines.

Plain Language Summary

Cooling the body after cardiac arrest

Sudden cardiac death means that the heart and subsequently the circulation stops. Patients with a structural heart disease like coronary heart disease have a higher risk for sudden cardiac death. Around 30% to 50% of all patients with coronary heart disease suffer sudden cardiac death at some stage of their illness. In cardiac arrest the brain lacks blood and oxygen and the patient loses consciousness. After a few minutes of lack of oxygen brain cells begin to be irreversibly damaged. Although potentially lethal, if a patient in cardiac arrest is found and resuscitated early, they may be saved and brain damage prevented. To date about one tenth to a third of successfully resuscitated patients leave hospital to live an independent life again.

One form of therapy that may help to improve these neurologic deficits is called ‘therapeutic hypothermia’ or ‘resuscitativve hypothermia’. It is a form of therapy where patients that have been resuscitated after cardiac arrest and are still unconscious after resuscitation are cooled to 33 °C for several hours. Clinical trials have shown that with therapeutic hypothermia the neurologic damage caused by the cardiac arrest may be attenuated. Pathophysiologic studies discovered that therapeutic hypothermia works in many different ways. One way is that it lowers cell metabolism and prevents the production of harmful substances that form during resuscitation and continuously damage the brain cells. Hypothermia may be initiated by different methods like cold drips, cooling pads or cooling catheters.

We have summarized three randomized trials with conventional cooling methods on a total of 383 patients that evaluated the effects of therapeutic hypothermia in patients resuscitated after cardiac arrest in comparison to resuscitated patients treated without therapeutic hypothermia. With conventional cooling methods like cooling blankets or cooling helmets, patients were 55% more likely to leave the hospital without major brain damage. When the results of two additional studies (one study only published as an abstract and another comparing cooling through haemofiltration) were added, this effect remained unchanged. No cooling specific adverse events were reported. One of the limitations of our review is that the majority of patients had a specific form of cardiac arrest, with ventricular fibrillation and ventricular tachycardia as the underlying cardiac rhythm. In summary, there is current evidence supporting the use of conventional cooling to induce mild hypothermia in cardiac arrest survivors within the first hours of resuscitation.
### SUMMARY OF FINDINGS FOR THE MAIN COMPARISON

**Neurological Outcome and Survival: conventional cooling compared to no cooling for neuroprotection and survival in adults after cardiopulmonary resuscitation**

**Patient or population:** Comatose patients after cardiopulmonary resuscitation

**Settings:**
- Intervention: conventional cooling
- Comparison: no cooling

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Assumed risk</th>
<th>Corresponding risk</th>
<th>Relative effect (95% CI)</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
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<td>conventional cooling</td>
<td><strong>Study population</strong></td>
<td><strong>RR 1.55</strong></td>
<td>383</td>
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<tr>
<td><strong>CPC</strong></td>
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<td>27 per 100</td>
<td>42 per 100 (33 to 53)</td>
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<td><strong>Survival</strong></td>
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<td><strong>RR 1.35</strong></td>
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<td>42 per 100</td>
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</tbody>
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The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

| **GRADE Working Group grades of evidence** |  |
| **High quality:** Further research is very unlikely to change our confidence in the estimate of effect |  |
| **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. |  |
| **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. |  |
| **Very low quality:** We are very uncertain about the estimate. |  |

---

1. Cerebral Performance Category (I-V)
2. One quasi-randomised trial but not contributing the majority of data
3. Total number of events <300
BACKGROUND

Description of the condition

The incidence of out-of-hospital sudden cardiac arrest in industrial countries varies greatly over different study groups. It is reported to range between 0.05% and 0.19% per year (Chugh 2004; Rea 2004). Of all patients where resuscitation was attempted, 14% to 40% achieved return of spontaneous circulation and were admitted to hospital (Finn 2001; Fischer 1997; Giraud 1996; Herlitz 2001; Jennings 2001; Leung 2001; Sun 2003a). Of those patients admitted to hospital, only between 7% and 30% were discharged from hospital with good neurologic outcome (Absalom 1999; Böttiger 1999; Fischer 1997; Herlitz 1999; Jennings 2001; Westfal 1996; Weston 1997). Many new concepts in post-resuscitation care have been developed in the past few years that aim at improving neurological outcome and survival of patients after cardiac arrest. These comprise optimising haemodynamics and ventilation, electrolytes, seizure control, temperature and glucose control and are summarized in the main resuscitation guidelines (Deakin 2010; Peberdy 2010).

Description of the intervention

Therapeutic hypothermia is still a relatively new concept for the preservation of cerebral function in patients who are resuscitated after cardiac arrest. After patients have been stabilized their body temperature is lowered to 32 °C to 34 °C for a duration of 24 hours.

How the intervention might work

It is believed that therapeutic hypothermia works in multiple ways. Cerebral reperfusion after successful resuscitation, although essential and effective in restoring energy stores, can also trigger harmful chemical cascades. The generation of free radicals and other mediators, which leads to multifocal damage of the brain, was first described by Negovsky as “postresuscitation syndrome” (Negovsky 1988). In contrast to accidental hypothermia, therapeutic mild hypothermia (32 °C to 34 °C) is administered in a controlled way. Intra-ischaemic hypothermia for brain protection has been used for several years with certain surgical procedures and circulatory arrest states. Clinical and experimental results show a protective effect of hypothermia during and also after ischaemic situations (Rosomoff 1954). Therapeutic hypothermia can inhibit the biosynthesis, release and uptake of several catecholamines and neurotransmitters (Okuda 1986; Sun 2010; Szelenyi 2012), especially glutamate and dopamine, which could lead to tissue damage (D’Cruz 2002; Hachimi-Idrissi 2004). Other beneficial effects of hypothermia include the preservation of the blood brain barrier (Baumann 2009; Karibe 1994); the protection of adenosine triphosphate (ATP) stores (McCullough 1999; Mizuhara 1996), which are necessary for energy provision; the restitution of post-ischaemic cerebral microcirculation (Takasu 1996); and possibly also decreased intracranial pressure (Lee 2010; Schreckinger 2009). Subsequently, hypothermia seems to act in a multifactorial way by influencing several damaging pathways simultaneously (Holzer 2010) to reduce the amount of cell death in the brain.

Why it is important to do this review

Two randomized controlled trials (RCTs) showed that induced hypothermia has a neuroprotective effect in patients who are primarily resuscitated from cardiac arrest (Bernard 2002; HACA 2002). A meta-analysis pooled the data of these two RCTs plus the data of one additional feasibility study and showed a clear benefit in terms of neurologic outcome and survival with hypothermia treatment for patients successfully resuscitated after cardiac arrest (Holzer 2005). Although recommended in the guidelines of the International Liaison Committee on Resuscitation (ILCOR) (Nolan 2003) and the recent resuscitation guidelines (Deakin 2010; Peberdy 2010), therapeutic hypothermia still is a relatively new concept. At the moment many different cooling methods exist. Conventional cooling comprises extracorporeal methods with cooling pads, ice packs, water immersion or intravascular cooling with cooling catheters or simply cold fluids. Cooling can also be combined with haemofiltration or any extracorporeal cardiopulmonary support. Studies with different treatment modalities are emerging and therefore systematic and regular updates of the literature are important to monitor new and effective developments. We present an update of a Cochrane review (Arrich 2009) with a view to assembling the data from the published randomized controlled trials.

OBJECTIVES

We aimed to perform a systematic review and meta-analysis to assess the effectiveness of therapeutic hypothermia in patients after cardiac arrest. Neurologic outcome, survival and adverse events were our main outcomes. We aimed to perform individual patient data analysis if data were available. We intended to form subgroups according to the cardiac arrest situation.

METHODS

Criteria for considering studies for this review

Types of studies
We included randomized and 'quasi-randomized' controlled trials. Quasi-randomized refers to allocation procedures such as alternating days, odd and even days, and the like.

Types of participants
We included studies in adult patients who suffered from cardiac arrest (regardless of if in-hospital or out-of-hospital cardiac arrest) and were successfully resuscitated.
We excluded studies on children and adolescents (aged less than 18 years) as the presumed cause of cardiac arrest is different to the causes in adults.
Although patients with a prior neurologic history may not greatly benefit from the intervention, we did not exclude them for the following reasons:
1. the number of such patients is most likely negligible; and
2. in a real life situation information on neurological performance before the arrest is often not available when starting post-resuscitation therapy.

Types of interventions
The intervention of interest was therapeutic hypothermia, regardless of how body temperature was reduced, applied within six hours of arrival at hospital. We defined therapeutic as any body target temperature below 35 °C. We defined the control intervention as treatment according to the standard treatment after cardiac arrest at the time of the trial.

Types of outcome measures

Primary outcomes
The primary outcome measure was neurological recovery. Ideally, we expected the outcome to be reported as best neurologic outcome during hospital stay and in cerebral performance categories (CPC) (Stiell 2009). The CPC categories are defined as follows.
1. Good cerebral performance: conscious, alert, capable of normal life. Normal cerebral function. May have minor psychological or neurological deficits, which do not significantly compromise cerebral or physical function.
2. Moderate cerebral disability: conscious, alert, sufficient cerebral function for activities of daily life (e.g. dress, travel by public transportation, food preparation). May have hemiplegia, seizures, ataxia, dysarthria, dysphasia, or permanent memory or mental changes.
3. Severe cerebral disability: conscious, has at least limited cognition. Dependant on others for daily life support (i.e., institutionalised or at home with exceptional family effort) because of impaired brain function. Includes wide range of cerebral abnormalities, from ambulatory patients who have severe memory disturbance or dementia precluding independent existence to paralysed patients who can only communicate with their eyes (e.g. the locked-in syndrome).
4. Coma or vegetative state: not conscious, unaware of surroundings, no cognition. No verbal or psychological interaction with environment. May appear awake because of spontaneous eye opening or sleep-wake cycle. Includes all degrees of unresponsiveness, which are neither CPC three (conscious) nor CPC five (coma, which satisfies brain death criteria).
5. Certified brain death.
If authors grouped this outcome into one or two (good recovery) and three to five (unfavourable recovery) we adapted it for our meta-analysis. If not reported in CPC categories, we accepted when authors reported 'good' neurologic outcome and we assumed it to be comparable with a CPC score of one or two.

Secondary outcomes
Survival to hospital discharge, survival at six months and long-term, quality of life at six months and long-term, dependency, and cost-effectiveness. We defined long-term as a minimum of one year.

Adverse events
We aimed at reporting adverse events as given by the authors.

Search methods for identification of studies

Electronic searches
We searched the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2011, Issue 7); MEDLINE (1971 to July 2011); EMBASE (1987 to July 2011); CINAHL (1988 to July 2011); PASCAL (2000 to July 2011); and BIOSIS (1989 to July 2011). The original search was performed in January 2007 (Arrich 2009).
We performed the searches by entering search terms as multiple postings (.mp, term appears in the title, abstract or MeSH) and some as medical subject headings (MeSH) for MEDLINE and exploded terms for EMBASE and CINAHL (search terms for CENTRAL, Appendix 1; MEDLINE, Appendix 2; EMBASE, Appendix 3; CINAHL, Appendix 4; BIOSIS and PASCAL, Appendix 5).
A search strategy for identifying RCTs was used with MEDLINE (Dickersin 1994) and EMBASE (Lefebvre 1996). We did not apply any language restrictions.

Searching other resources
In an attempt to identify further studies we asked experts in the field whether they were aware of any ongoing, unpublished or published trials on this subject.
Data collection and analysis

Selection of studies
We imported all retrieved results into EndNote (version 7.0, Thomson Corporation) and eliminated duplicates. Two authors (JA, MH or CH; HH as arbiter in case of discrepancies) independently scanned each reference for inclusion in the review.

Data extraction and management
We independently extracted data using a data extraction form (see Appendix 6). As we intended to use the original individual patient data of the identified trials we contacted the respective corresponding authors and asked for collaboration. Two review authors independently entered all relevant data into the Cochrane Collaboration's software program Review Manager (RevMan 5.1). We compared the two versions and resolved disagreements by discussion.

The following variables were entered into RevMan 5.1:
1. allocated intervention;
2. event (best neurological recovery during hospital stay, survival to hospital discharge);
3. additional baseline variables: cause of cardiac arrest (presumed cardiac versus non-cardiac); location of arrest (in-hospital versus out-of-hospital); witnessed versus non-witnessed arrest; primary electrocardiogram (ECG) rhythm (ventricular fibrillation versus other).

Assessment of risk of bias in included studies
To assess the internal validity of the identified trials, we assessed allocation sequence generation, allocation concealment, blinding of outcome assessment, exclusion of randomized patients from the analysis, comparability of groups, and loss to follow up.

Measures of treatment effect
We calculated risk ratios (RR) and their 95% confidence intervals.

Unit of analysis issues
Cluster randomized trials were not included in the analysis; in the case of multiple treatment groups we planned to combine the groups to create a single pair-wise comparison; cross-over trials, by nature of the outcome, did not appear.

Dealing with missing data
All analyses were according to the intention-to-treat principle. If data were missing we attempted to receive information by contacting the study authors. An assessment of loss to follow up was included in our quality assessment and reported in the table 'Characteristics of included studies'. If a considerable amount of data was missing we would investigate the possible mechanism of the missing data (randomly or not). We planned to assess the influence of this possible selection bias on our estimates in a sensitivity analysis.

Assessment of heterogeneity
We assessed data for clinical and statistical heterogeneity. We only performed quantitative synthesis of the data if clinical heterogeneity was negligible. Clinical heterogeneity may be caused by differences in study populations, interventions or definitions of the endpoint (Thompson 2001). In the case of severe heterogeneity it may not be suitable to pool the data because the trials measure a different effect altogether.

Assessment of reporting biases
We assessed the presence of possible publication bias and heterogeneity using funnel plots (plotting the effect against precision) (Egger 1997).

Data synthesis

Analysis at the individual level
Quantitative analysis of individual patient data was intended when studies had negligible heterogeneity and individual patient data were available at least for a clinically comparable subset. In the case that individual patient data were unavailable for at least one study, we planned to do an analysis at the study level. This applies in particular to further updates. We performed quantitative analysis of individual patient data using standard statistical procedures provided in RevMan 5.1. The principal measure of effect was the relative risk of achieving good neurological recovery defined as a best CPC category of one or two or the definition which was given by the author for 'good neurologic outcome'.

Analysis at the study level
Here also the principal measure of effect was the relative risk of achieving good neurological recovery at hospital discharge in patients allocated to hypothermia when compared to those not receiving hypothermia. In the case of negligible statistical heterogeneity we used fixed-effect models to calculate summary effects, otherwise we used random-effects models. Statistical heterogeneity was assessed using the $I^2$ statistic (Higgins 2003). Statistical heterogeneity was considered relevant with $I^2 > 50%$.

Subgroup analysis and investigation of heterogeneity
For the primary endpoint we formed subgroups using the individual patient data and according to the following variables:
• cause of cardiac arrest (presumed cardiac versus non-cardiac);
• location of arrest (in-hospital versus out-of-hospital);
• witnessed versus non-witnessed arrest;
• primary ECG rhythm (ventricular fibrillation versus other).

**Sensitivity analysis**

We performed sensitivity analyses for the impact of study quality issues, as measured by allocation concealment, on the overall effect estimate and the effect size of all identified trials when neglecting heterogeneity and publication status.

**R E S U L T S**

**Description of studies**

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

**Results of the search**

Our original systematic search of databases (inception to 2007) (Arrich 2009) and our updated search (searching from 2007 to July 2011) of the medical literature resulted in 1851 hits (duplicates excluded). From these, we excluded 1819 according to our eligibility criteria (randomized studies on adult cardiac arrest patients treated with therapeutic hypothermia) by judging the abstract or the title. Thirty-two papers remained for closer inspection. From those we excluded 11 non-original papers (comments, editorials, reviews, correspondences), 10 non-randomized papers, and six papers where the intervention or control groups did not meet the inclusion criteria. In addition, we identified one ongoing study (see Characteristics of excluded studies and Figure 1).
Looking through the references of a recently published systematic review on therapeutic hypothermia (Cheung 2006) we found one additional reference, published only as an abstract (Mori 2000). Hence five randomized and quasi-randomized controlled trials with a total of 481 patients remained for analysis (Bernard 2002; HACA 2002; Hachimi-Idrissi 2001; Laurent 2005; Mori 2000), see Characteristics of included studies.

One previously unclassified study (Tiainen 2007) and two additional studies (Tiainen 2003; Tiainen 2005) were found to be reports of the HACA 2002 study. The updated search resulted in no new studies for inclusion.

### Included studies

See table Characteristics of included studies.

### Excluded studies

**Clinical heterogeneity**

We identified clinical heterogeneity due to cooling methods. In contrast to the other studies, Laurent 2005 used haemofiltration as the mode of cooling, which is substantially different to the standard cooling methods used in the other RCTs. As the cooling method of Mori 2000 was unclear, we presented this study separately and did not pool the effect with those of the remaining studies. For the three comparable studies on conventional cooling methods all three authors provided individual patient data (Bernard 2002; HACA 2002; Hachimi-Idrissi 2001). We tried to contact Kazuhisa Mori (Mori 2000) for more information on his study but were unsuccessful.
See table Characteristics of excluded studies.

**Risk of bias in included studies**

We assessed each included trial by the following criteria: mode of randomization, allocation concealment, level of blinding, loss to follow up, comparability of groups and use of measures to account for differences between groups (see Characteristics of included studies; Figure 2; Figure 3). Quality of the included studies was good in three out of five studies.

**Figure 2. Risk of bias graph: review authors’ judgements about each risk of bias item presented as percentages across all included studies.**

![Risk of bias graph](image)
Figure 3. Risk of bias summary: review authors’ judgements about each risk of bias item for each included study.
Allocation
Three trials (HACA 2002; Hachimi-Idrissi 2001; Laurent 2005) reported adequate randomization methods and the use of opaque envelopes to conceal treatment allocation.

Blinding
Three trials reported blinded outcome assessment (Bernard 2002; HACA 2002; Hachimi-Idrissi 2001).

Incomplete outcome data
One study lost information for two patients for the primary end-point (HACA 2002). All other studies had a complete follow up.

Selective reporting
There was no indication of selective outcome reporting.

Other potential sources of bias
In two studies the treatment and control groups did not differ significantly in reported baseline characteristics (Hachimi-Idrissi 2001; Laurent 2005) while one of these had rather small groups (Hachimi-Idrissi 2001). In HACA 2002 there were some baseline differences between groups. Patients in the normothermia group were more likely to have a history of diabetes mellitus or coronary heart disease and to have received basic life support from a bystander than were those in the hypothermia group. The authors adjusted for all baseline variables and the risk ratio increased slightly, from 1.40 (95% confidence interval (CI) 1.08 to 1.81) to 1.47 (95% CI 1.09 to 1.82). Bernard 2002 reported differences in sex and rate of bystander cardiopulmonary resuscitation between groups but did not further adjust for this possible bias. Mori 2000 did not provide information on the baseline characteristics of the patient groups.

Effects of interventions
See: Summary of findings for the main comparison Neurological outcome and survival: conventional cooling compared to no cooling for neuroprotection and survival in adults after cardiopulmonary resuscitation

Primary outcome

Good neurologic outcome

With only three studies reporting on conventional cooling methods (involving 195 cases and 188 controls), the pooled result showed a better neurologic outcome for the hypothermia group (individual patient data; RR 1.55; 95% CI 1.22 to 1.96; I^2 = 32%; see Analysis 1.1.1).

As there was only one study for patients undergoing haemofiltration after cardiac arrest (Laurent 2005) it was not possible to employ meta-analysis. Using the data in the study, however, and carrying out a Chi^2 test we found no statistical difference (Pearson Chi^2 statistic = 0.16, P = 0.69; RR 0.71; 95% CI 0.32 to 1.54; see Analysis 1.1.2).

The one study reporting on an unknown cooling method (Mori 2000) showed better survival for the hypothermia group (Pearson Chi^2 = 7.78, P = 0.005; RR 4.50; 95% CI 1.17 to 17.30; see Analysis 1.1.3).

Secondary outcomes

Survival to hospital discharge
With only three studies reporting on conventional cooling methods (involving 195 cases and 188 controls) the pooled result showed better survival for the hypothermia group (individual patient data; RR 1.35; 95% CI 1.10 to 1.65; I^2 = 0%; see Analysis 2.1.1).

As there was only one study for patients undergoing haemofiltration after cardiac arrest (Laurent 2005) the Chi^2 test found that there was no statistical difference (Pearson Chi^2 = 0.77, P = 0.38; RR 0.71; 95% CI 0.32 to 1.54; see Analysis 2.1.2).

Survival at six months and long-term
We found no data on this outcome.

Quality of life at six months and long-term dependency
We found no data on this outcome.

Cost-effectiveness
We found no data on this outcome.

Subgroup analyses
According to the number of patients and information provided by the authors we formed subgroups of the meta-analysis by the following variables: cause of cardiac arrest (presumed cardiac versus...
non-cardiac); location of arrest (in-hospital versus out-of-hospital); witnessed versus non-witnessed arrest; primary ECG rhythm (ventricular fibrillation (VF) or ventricular tachycardia (VT) versus other). The endpoint was ‘best ever reached CPC during hospital stay’ (see Additional Table 1).

- The effect size for patients with a cardiac cause (three studies) and VF or VT was nearly the same (two studies).
- Groups of patients with non-VF or VT rhythm as the first cardiac rhythm (n = 52), patients with a non-cardiac cause (n = 11), and in-hospital arrests (n = 17) were small and did not show a statistically significant effect (non-VF or VT: RR 2.17; 95% CI 0.68 to 6.93; $I^2 = 50$%; two studies) (non-cardiac cause: RR 3.80; 95% CI 0.55 to 26.29; $I^2 = 0$%; two studies) (in-hospital: RR 1.67; 95% CI 0.47 to 5.73).
- Also a small number of patients had non-witnessed arrest (n = 22). Among these patients the effect size was substantially bigger than the summary effect for the whole study population (RR 5.31; 95% CI 1.40 to 20.21; $I^2 = 0$%; three studies).
- For patients with witnessed cardiac arrest the effect size was slightly smaller than the effect size for the whole study population (RR 1.43; 95% CI 1.13 to 1.81; $I^2 = 0$%; three studies).

**Long-term outcome, cost-effectiveness and quality of life**

None of the retrieved studies provided data on long-term survival and dependency, quality of life or cost-effectiveness.

**Adverse events**

We included all trials that reported on adverse events in the analysis, regardless of heterogeneity. The following adverse events were reported in the four studies: bleeding of any severity, need for platelet transfusions, pneumonia, sepsis, pancreatitis, renal failure or oliguria, haemodialysis, pulmonary oedema, seizures, lethal or long-lasting arrhythmias, cardiac complications, hypocalcaemia and hypophosphataemia. There were no significant differences between the groups (see Additional Table 2).

**Sensitivity analysis**

Does allocation concealment influence the effect? For studies using conventional cooling methods, cooling had a favourable effect on good neurological outcome in studies with adequate allocation concealment. This effect, however, was significant in a fixed-effect model (RR 1.50; 95% CI 1.16 to 1.93) (see Additional Table 3) but not significant in a random-effects model (RR 1.97; 95% CI 0.71 to 5.45). This result comes from two studies which showed both a significant and positive effect but there was statistical heterogeneity ($I^2 = 59$%) and the total sample size comprised only 306 patients. As we were concerned that the model choice might influence our results, we also examined whether the model choice might cause changes in our main effect as a post hoc sensitivity analysis. The effect for conventional cooling as presented in Analysis 1.1.1 did not change by model choice (fixed-effect RR 1.55; 95% CI 1.22 to 1.96) (random-effects RR 1.64; 95% CI 1.10 to 2.45; data not shown). This indicates that the effect is robust according to model choice.

Does allowing for clinical heterogeneity and publication status affect the results? When we ignored clinical heterogeneity and publication status the pooled effect of all studies did not change substantially, whether fixed-effect models (RR 1.55; 95% CI 1.24 to 1.94; Table 3), or random-effects models (RR 1.68; 95% CI 1.00 to 2.68; data not shown) were used. There was some indication of a subgroup difference (test for subgroup difference Chi$^2 = 6.20$ (df = 2), $P = 0.05$).

**Publication bias**

At the moment there are too few studies to draw inferences from funnel plots, we have therefore not presented them in the current version of this review.

**DISCUSSION**

**Summary of main results**

Our review shows that therapeutic hypothermia with conventional cooling methods improves neurologic outcome and survival of patients successfully resuscitated after cardiac arrest. Currently available evidence suggests that patients with out-of-hospital cardiac arrest, a presumed cardiac cause of cardiac arrest, and for patients with a VF or VT rhythm as the first recorded cardiac rhythm benefit from therapeutic hypothermia. For patients with in-hospital cardiac arrest, asystole and non-cardiac causes of arrest the group sizes are too small to make firm inferences. There were no statistically significant differences in any of the reported adverse events between hypothermia and non-hypothermia patients.

**Overall completeness and applicability of evidence**

After our literature search we were able to include the data of all eligible studies we retrieved. It was not possible to obtain individual patient data for Laurent 2005 or Mori 2000, but even if they had been available we would not have included either study in the meta-analysis. In the case of Laurent 2005 the two treatment modalities (mild therapeutic hypothermia with or without haemodialysis) are clinically too heterogeneous to be combined with the other studies. As mentioned in the background section,
one of the theories of the beneficial effects of cooling deals with attenuation of the effect of free radicals and other mediators. Haemofiltration may act in a similar way, by reducing the number of free radicals. It may add to or even supersede the effect of therapeutic hypothermia. In the case of Mori 2000 we do not know anything about the treatment.

The major limitation of this review is the small number of randomized controlled trials and hence small numbers of included patients. Therefore, the precision of our effects is generally low and, particularly in subgroup and sensitivity analyses, this is a matter for concern. The confidence intervals of the intervention come near the null difference and looking in our sensitivity analysis at studies with adequate allocation concealment resulted in an effect which was not robust to model choice. On the other hand, only two studies have been included in the sensitivity analysis, which is probably too small a number to make firm conclusions. Nonetheless, given these limitations the effect of conventional cooling methods consistently points towards a favourable neurological outcome. Another consequence of the small number of available studies is the many single study comparisons.

One might argue that therapeutic hypothermia is only available to countries with sufficient financial resources. But there are many cooling methods, ranging from expensive device controlled methods to very cheap cold fluids and ice packs which are available in all facilities where post-resuscitation care is performed. Proof of superiority of any cooling method above others is still lacking, and there are currently no formal cost-benefit analyses.

After the publication of the two RCTs on therapeutic hypothermia (Bernard 2002; HACA 2002), guidelines were published by the International Liaison Committee on Resuscitation (ILCOR) on the application of therapeutic hypothermia after cardiac arrest (Nolan 2003). Despite a small number of included trials and patients the results of our review support those recommendations.

**Quality of the evidence**

We found five studies on the application of mild hypothermia, with a total of 481 patients (Bernard 2002; HACA 2002; Hachimi-Idrissi 2001; Laurent 2005; Mori 2000). All studies were academia initiated. Quality of the studies was generally good. Except for the abstract (Mori 2000), all studies reported on almost all essential quality criteria and loss to follow up was within an acceptable range. One study could have done better on the randomization process and the adjustment for inequalities in baseline characteristics between the treatment and the control groups (Bernard 2002).

All studies planned to include consecutive patients (no information available on Mori 2000). In HACA 2002 10% and in Bernard 2002 8% of all eligible patients were not randomized because of logistic problems or because the next of kin did not give consent. In Laurent 2005 and Hachimi-Idrissi 2001 inclusion of all eligible patients was reported. We do not have any information on the patients that were not randomized.

In HACA 2002 hypothermia was discontinued in 14 patients because of death, arrhythmia, haemodynamic instability, technical problems with the cooling device, one liver rupture, one randomized patient that had already been included in the study before, and one error in the duration of cooling. These patients were included in the intention-to-treat analysis of primary and secondary outcomes. One patient in each group was lost to follow up for the primary outcome. All other studies had a complete follow up.

The control groups differed with regard to fever control. Mean body temperature 12 hours after start of cooling in the ‘normothermia group’ was around 37.6 °C in HACA 2002 and 37.4 °C in Bernard 2002. Hachimi-Idrissi 2001 did not report on the body temperature of the control group. It is known that for each degree rise in temperature over 37 °C the risk of an unfavourable neurologic outcome increases, with an odds ratio of 2.26 (Zeiner 2001). If this is true even for smaller temperature differences, the beneficial effect of therapeutic hypothermia might at least partly be due to an antipyretic rather than a hypothermic effect. It is questionable whether a strict temperature control would have the same effect as mild hypothermia, as shown in a study of fever control in patients in a neurologic intensive care unit, where no difference in outcome was found with fever control (Diringer 2001).

**Potential biases in the review process**

For the primary data analysis, individual patient analysis gave the same results as the study-based results. We still made the effort to obtain individual patient data as it was useful for investigating the subgroups.

All studies with individual patient data reported on the same outcome and all outcome assessors were blind to the treatment (Bernard 2002; HACA 2002; Hachimi-Idrissi 2001; Laurent 2005). The cerebral performance category (CPC) is easy to measure and gives a crude approximation of the patient’s ability to perform tasks of daily life. One of its limitations is the lack of accuracy when it comes to estimating cognitive functions and personal and social impacts of cardiac arrest.

For the subgroup of patients with non-witnessed arrests we observed an effect size substantially bigger than the pooled summary effect (RR 5.31; 95% CI 1.40 to 20.21) (Table 1). However, the group of non-witnessed arrests was small (22 patients only) and yielded large confidence intervals. Although it seems that patients benefit from the treatment, the result should be interpreted with caution.

One of the problems with merging the data for this review was the difference in the inclusion criteria. Generally, among all patients that are resuscitated and brought to hospital between 18% and 42% have non-witnessed arrests, only 30% to 58% have a confirmed VF rhythm as first rhythm (Haukoos 2004; Herlitz 2003a; Kim 2001) and 40% of all resuscitations happen in hospital. In
this review the two bigger studies included only patients with a cardiac cause of cardiac arrest, and with VF or VT rhythm as the first cardiac rhythm (Bernard 2002; HACA 2002). Most of these patients had an out-of-hospital cardiac arrest. From the pathogenesis of global cerebral ischaemia and the theories as to why therapeutic hypothermia is effective, there is no reason why therapeutic hypothermia should not be as effective in patients with asystole as the first cardiac rhythm or non-cardiac causes for cardiac arrest. In a meta-analysis (Holzer 2005) the effect of therapeutic hypothermia was only slightly changed by baseline variables. A retrospective cohort study showed that the effect of therapeutic hypothermia was independent of various confounders including cardiac arrest conditions (Arrich 2006).

Agreements and disagreements with other studies or reviews

We are aware of three other meta-analyses with similar objectives. The meta-analysis by Holzer et al is very similar to our review method-wise and was in many ways a predecessor to our current Cochrane review. We were able to include two additional studies (Laurent 2005; Mori 2000) but the main result is comparable. Another meta-analysis was published recently (Nielsen 2011). The authors judged the overall quality of the included studies at a lower level than we did in our review. From the available five studies they combined four and five based on a different judgement on clinical heterogeneity, and they provided a trial sequential analysis. The main findings were comparable between the two reviews, whereas their interpretation was much more conservative than ours. Their main conclusion was proposing a new large scale clinical trial.

AUTHORS’ CONCLUSIONS

Implications for practice

Conventional cooling methods to induce mild therapeutic hypothermia seem to improve survival and neurologic outcome after cardiac arrest. Our review supports the current best medical practice as recommended by the International Resuscitation Guidelines.

Implications for research

Future research should be done with standardized temperature monitoring (either oesophagus or bladder temperature measurements) in order to be able to compare between groups and between studies at a later stage. Effective measures need to be advanced to cool the patient to the target temperature within a short time period, which should decrease heterogeneity within the study population. For studies with a focus on out-of-hospital cooling, practical methods need to be evaluated. To further investigate the effect of cooling on subgroups, like patients with non-VF or VT as primary cardiac rhythm, or patients with in-hospital cardiac arrest, methodologically sound studies are needed. There is a knowledge gap concerning an optimal cooling protocol. For this purpose, inclusion criteria should be widened and comparisons of earlier cooling (pre-hospital) versus late cooling (in-hospital), different levels of hypothermia (for example 32 °C versus 34 °C) and different durations of cooling (for example 12 hours versus 24 hours versus 48 hours) should be included. Reporting on safety should not only comprise the known but also any unexpected adverse events. It would be useful to include cost-benefit analyses in future studies.

ACKNOWLEDGEMENTS

We would like to thank Dr Mathew Zacharias (content editor), Dr Marialena Trivella (statistical editor) and Dr Malcolm G Booth, Dr George Djaiani and Shafi Mussa (peer reviewers) for their help and editorial advice during the preparation of the published review (Arrich 2009).

We would also like to thank Dr Mathew Zacharias, Dr Marialena Trivella, Dr Malcolm Booth, Dr Karen Rees, Prof Ian Jacobs and Jane Cracknell for their help and editorial advice during the preparation of the protocol for the systematic review.

REFERENCES

References to studies included in this review

Bernard 2002 [published data only]*


HACA 2002 [published data only]*


Taina M, Poultainen E, Kovala T, Takkunen O, Happonen O, Roine RO. Cognitive and neurophysiological


Hachimi-Idrissi 2001 [published and unpublished data]

Laurent 2005 [published data only]

Mori 2000 [published data only]

References to studies excluded from this review

Ballew 2002 [published data only]
Ballew KA. Mild hypothermia improved neurologic outcome and reduced mortality after cardiac arrest because of ventricular arrhythmia. ACP Journal Club 2002;137(2):46. [MEDLINE: 12207424]

Batista 2010 [published data only]

Bernard 1997 [published data only]

Bernard 2004 [published data only]

Bernard 2010 [published data only]

Callaway 1997 [published data only]

Callaway 2002 [published data only]

Castrejon 2009 [published data only]

Castrén 2010 [published data only]

Chanin 2002 [published data only]

Ebell 2002 [published data only]

Gwinnutt 2003 [published data only]

Heard 2007 [published data only]

Huang 2008 [published data only]

Kamarainen 2009 [published data only]

Kim 2007 [published data only]
4 degrees C normal saline. [PUBMED: 20825779]

Kitamura 1989 [published data only]

Mayer 2002 [published data only]

Nagao 2008 [published data only]

Nielsen 2010a [published data only]

Nielsen 2011a [published data only]

Smith 2002 [published data only]
Smith T1, Bleck TP. Hypothermia and neurologic outcome in patients following cardiac arrest: Should we be hot to cool off our patients?. *Critical Care* 2002;6(5):377–80. [MEDLINE: 12398769]

Takeda 2009 [published data only]

Ungerleider 1998 [published data only]

Yanagawa 1998 [published data only]

Zeiner 2000 [published data only]

References to ongoing studies

Nielsen 2010 [published data only]

Additional references

Absalom 1999

Arrich 2006

Baumann 2009

Böttiger 1999
Hachimi-Idrissi 2004

Haukoos 2004

Herlitz 1999

Herlitz 2003a

Herlitz 2003b

Higgins 2003

Holzer 2005

Holzer 2010

Jennings 2001

Karibe 1994
Karibe H, Zarow GJ, Graham SH, Weinstein PR. Mild intraschismic hypothermia reduces postschismic hyperperfusion, delayed postschismic hypoperfusion, blood-brain barrier disruption, brain edema, and neuronal damage volume after temporary focal cerebral ischemia in...

**Kim 2001**

**Kuisma 1996**

**Lee 2010**

**Lefebvre 1996**

**Leung 2001**

**McCullough 1999**

**Mizuhara 1996**

**Negovsky 1988**

**Nielsen 2011**

**Nolan 2003**

Okuda 1986

Peberdy 2010

Rea 2004

RevMan 5.1

Rewers 2000

Rosomoff 1954

Schreckinger 2009
Schreckinger M, Marion DW. Contemporary management of traumatic intracranial hypertension: is there a role for therapeutic hypothermia?. *Neurocritical Care* 2009;11(3):427–36. [PUBMED: 19644773]

Stiell 2009

Sun 2010

Szelenyi 2012
Takasu 1996

Thompson 2001

Tiainen 2003

Tiainen 2005

Tiainen 2007

Westfal 1996

Winston 1997

Zeiner 2001

References to other published versions of this review

Arrich 2009

* Indicates the major publication for the study
### CHARACTERISTICS OF STUDIES

**Characteristics of included studies**  [ordered by study ID]

**Bernard 2002**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomization: pre-hospital</th>
</tr>
</thead>
</table>
| Participants | Total number of patients 77, mean age of 66 years, 33% female  
Out-of-hospital cardiac arrest of cardiac cause, ventricular fibrillation as first cardiac rhythm, comatose after resuscitation  
Participating sites: Australian university and community hospitals  
Multicentre: yes  
Language: English  
Allocation concealment: not applicable (odd and even days)  
Outcome assessor blind: yes  
Intention-to-treat: yes  
Groups comparable: more females and more bystander CPR in hypothermia group  
Follow up > 80% of randomized patients: yes |
| Interventions | Therapeutic hypothermia versus standard pre-hospital treatment protocols and intensive care treatment  
Means of cooling: packs placed around the head, neck, torso, and limbs  
Cooling rate: time from ROSC to target temperature: two hours  
Target temperature: 33°C  
Duration of cooling: 12 hours after target temperature was reached  
Rewarming: passive after 12 hours, active after 18 hours |
| Outcomes | Survival with good neurologic function to be sent home or to a rehabilitation facility at discharge  
In-hospital death  
Haemodynamic, biochemical, and haematologic effects of hypothermia  
For IPD analysis best ever reached CPC during hospital stay and CPC discharge were provided |
| Notes | Randomization: odd and even days |

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
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<th>Support for judgement</th>
</tr>
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### Bernard 2002

(Continued)

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<td>Other bias</td>
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</table>

### HACA 2002

**Methods**
- Randomization: in hospital

**Participants**
- Total number of patients 275, mean age 59 years, 24% female
- In and out-of-hospital bystander-witnessed cardiac arrest of presumed cardiac cause, ventricular fibrillation or non-perfusing ventricular tachycardia as first cardiac rhythm, comatose after resuscitation
- Participating sites: European university and community hospitals
- Multicenter: yes
- Language: English
- Allocation concealment: opaque envelopes
- Outcome assessor blind: yes
- Intention-to-treat: yes
- Groups comparable: significantly more diabetes and coronary heart disease and bystander CPR in control group
- Follow up > 80% of randomized patients: yes

**Interventions**
- Therapeutic hypothermia versus standard intensive care treatment
- Means of cooling: cooling blanket that covered the whole body and released cooled air
- Cooling rate: time from ROSC to target temperature: median of 8 hours
- Target temperature: 32 to 34°C
- Duration of cooling: median of 24 hours
- Rewarming: passive over eight hours

**Outcomes**
- Best CPC of 1, 2 versus CPC of 3, 4, 5 during six months
- Mortality at six months, rate of complication during first seven days after cardiac arrest (bleeding of any severity, Pneumonia, sepsis, pancreatitis, renal failure, pulmonary edema, seizures, arrhythmias, and pressure sores)
- For IPD analysis best ever reached CPC during hospital stay and CPC discharge were provided

**Notes**
- Randomization: computer generated random sequence
- Centre-specific subsets of this study are also published as Tiainen 2003 (n=70), Tiainen 2005 (n=60), and Tiainen 2007 (n=70) with more detailed investigations of neuropsychological and laboratory outcomes

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
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<th>Support for judgement</th>
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### Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation (Review)

#### Risk of bias

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### Hachimi-Idrissi 2001

#### Methods

- Randomization: in hospital

#### Participants

- Total number of patients 33, mean age 72 years, 39% female
- Out-of-hospital cardiac arrest of cardiac cause, asystole as first cardiac rhythm, comatose after resuscitation
- Participating site: Belgian university hospital.
- Multicenter: no
- Language: English
- Outcome assessor blind: yes
- Intention-to-treat: yes
- Groups comparable: yes, although groups were small, no significant difference
- Follow up > 80% of randomized patients: yes

#### Interventions

- Therapeutic hypothermia versus standard post-resuscitation care protocol
- Means of cooling: helmet device placed around the head and neck and containing a solution of aqueous glycerol
- Cooling rate: starting point until target temperature not clearly stated
- Target temperature: 34°C
- Duration of cooling: start of cooling to start of rewarming, mean three hours
- Rewarming: passive over eight hours

#### Outcomes

- Haemodynamic data, arterial pH, electrolytes, haematological data
- Complications such as pneumonia, sepsis, cardiac arrhythmia, coagulopathy
- Survival to hospital discharge and overall performance categories (OPC)
- For IPD analysis best ever reached CPC during hospital stay and CPC discharge were provided

#### Notes

- Randomization: random number tables
- IPD included 33 patients, the article only reported on 30 as the follow up was not completed at the time of submission
### Hachimi-Idrissi 2001 (Continued)

<table>
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<th>Support for judgement</th>
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### Laurent 2005

#### Methods

Randomization: pre-hospital

#### Participants

- Total number of patients 42, mean age 52 years in the HF group, 56 years in the HF+HT group, 19% female
- Out-of-hospital cardiac arrest of presumed cardiac cause, ventricular fibrillation or asystole as first cardiac rhythm, comatose after resuscitation
- Participating sites: French university and community hospital
- Multicentre: yes
- Language: English
- Allocation concealment: opaque envelopes
- Outcome assessor blind: not stated
- Intention-to-treat: yes
- Groups comparable: yes
- Follow up > 80% of randomized patients: yes

#### Interventions

- High-flow haemofiltration versus high-flow haemofiltration plus therapeutic hypothermia versus standard supportive care
- Means of cooling: direct external cooling of the blood
- Cooling rate: four hours after ICU admission the median temperature was 31.7°C
- Target temperature: 32 to 33°C
- Duration of cooling: 24 hours
- Rewarming: passive

#### Outcomes

- Survival at six months
- Rate of death by intractable shock in patients who had a favourable Glasgow coma scale (M5 or M6) or required sedation
- Survival at CPC 1, 2 versus all else at six months
### Laurent 2005 (Continued)

| Notes | Randomization pre-hospital to save time for haemofiltration  
We did not pool data from this study with data from the three other studies, since the treatment schemes with haemofiltration are not comparable to non-haemofiltration treatment (clinical heterogeneity) |
|---|---|

### Risk of bias

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</table>

### Mori 2000

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<tr>
<th>Methods</th>
<th>Randomization: unknown</th>
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</table>
| Participants | Total number of patients 54, mean age unknown, gender distribution unknown  
Out-of-hospital cardiac arrest of unknown cause with a Glasgow Coma Scale of less than eight  
Participating site: Japanese university hospital  
Multicentre: unknown  
Language of abstract: English  
Allocation concealment: unknown  
Outcome assessor blind: not stated  
Intention-to-treat: unknown  
Groups comparable: unknown  
Follow up > 80% of randomized patients: yes |
| Interventions | “Brain-hypothermic treatment” versus “brain normothermic treatment”  
Means of cooling: unknown  
Cooling rate: unknown  
Target temperature: 32 to 34°C  
Duration of cooling: three days  
Rewarming: unknown |
| Outcomes | Glasgow outcome scale at one month (5 point scale). The categories “moderate, mild, or no disabilities” were defined as “good neurologic outcome” |
Notes
Only abstract published
Study was not included in the pooled analysis as we did not have any information on the cooling method, whether cooling was applied locally or systemically, and whether cooling was successful
Attempts to contact the authors were unsuccessful.

Risk of bias

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CPR=cardiopulmonary resuscitation
ROSC=restoration of spontaneous circulation
CPC=cerebral performance categories
HF=haemofiltration
ICU=intensive care unit
M5=localizes painful stimuli
M6=obeys commands

Characteristics of excluded studies  [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
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<tbody>
<tr>
<td>Ballew 2002</td>
<td>Comment</td>
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<tr>
<td>Batista 2010</td>
<td>Non-randomized</td>
</tr>
<tr>
<td>Bernard 1997</td>
<td>Non-randomized, controlled study, historical controls</td>
</tr>
<tr>
<td>Bernard 2004</td>
<td>Review</td>
</tr>
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<td>Study Type</td>
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<tr>
<td>Bernard 2010</td>
<td>Intervention or control groups did not meet the inclusion criteria</td>
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<tr>
<td>Callaway 1997</td>
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<tr>
<td>Kitamura 1989</td>
<td>Non-randomized</td>
</tr>
<tr>
<td>Mayer 2002</td>
<td>Summary and comment of HACA 2002</td>
</tr>
<tr>
<td>Nagao 2008</td>
<td>Non-randomized</td>
</tr>
<tr>
<td>Nielsen 2010a</td>
<td>Ongoing study</td>
</tr>
<tr>
<td>Nielsen 2011a</td>
<td>Correspondance</td>
</tr>
<tr>
<td>Smith 2002</td>
<td>Review</td>
</tr>
<tr>
<td>Takeda 2009</td>
<td>Intervention or control groups did not meet the inclusion criteria</td>
</tr>
<tr>
<td>Ungerleider 1998</td>
<td>Review</td>
</tr>
<tr>
<td>Ungerleider 2004</td>
<td>Comment</td>
</tr>
<tr>
<td>Yanagawa 1998</td>
<td>Non-randomized controlled study, historical controls</td>
</tr>
<tr>
<td>Zeiner 2000</td>
<td>Non-randomized controlled study, historical controls</td>
</tr>
</tbody>
</table>
### Characteristics of ongoing studies [ordered by study ID]

**Nielsen 2010**

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>Target temperature management after out-of-hospital cardiac arrest, an international, multicentre, randomized, parallel groups, assessor blinded clinical trial—rationale and design of the ttm-trial</th>
</tr>
</thead>
</table>
| Methods             | European multicentre trial  
|                     | Randomization: in-hospital                                                                                                               |
| Participants        | Patients over 17 years of age resuscitated from out-of-hospital cardiac arrest of presumed cardiac cause, unconscious (Glasgow Coma Score < 8) (patients not able to obey verbal commands) after resuscitation |
| Interventions       | Therapeutic hypothermia at 33°C versus normothermia at 36°C.  
|                     | Means of cooling: 30 ml/kg of crystalloid infusion (4°C or room temperature according to treatment arm) initially. Further temperature control will be at the discretion of the trial sites  
|                     | Cooling rate: not specified  
|                     | Target temperature: 33°C  
|                     | Target temperature of control: 36°C  
|                     | Duration of cooling: 24 hours  
|                     | Rewarming: not specified                                                                                                                 |
| Outcomes            | Primary Outcome Measures: All-cause mortality [Time Frame: Maximum follow-up with a minimum of 180 days] [Designated as safety issue: No]  
|                     | Secondary Outcome Measures: Composite outcome of all-cause mortality and poor neurological function (CPC 3 and 4) [Time Frame: 180 days]  
|                     | Bleeding [Time Frame: During day 1-7 of intensive care treatment]  
|                     | Neurological status and quality of life (Cerebral Performance Category, Modified Rankin Scale, Mini-mental test, IQCODE, SF-36) [Time Frame: 180 days]  
|                     | Pneumonia [Time Frame: During day 1-7 of intensive care treatment]  
|                     | Electrolyte disorders [Time Frame: During day 1-7 of intensive care treatment]  
|                     | Hyperglycaemia > 10 mmol/l [Time Frame: During day 1-7 of intensive care treatment]  
|                     | Hypoglycaemia < 3mmol/l [Time Frame: During day 1-7 of intensive care treatment]  
|                     | Cardiac arrhythmia [Time Frame: During day 1-7 of intensive care treatment]  
|                     | The need for renal replacement therapy [Time Frame: During day 1-7 of intensive care treatment] |
| Starting date       | November 2010                                                                                                                                                                                   |
| Contact information | Niklas Nielsen, Helsingborgs Hospital, info@ttm-trial.org                                                                                                                                          |
| Notes               | NCT01020916                                                                                                                                                                                     |
### Comparison 1. Neurological outcome: cooling versus no cooling

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Good neurological outcome</td>
<td>5</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>1.1 Conventional cooling without extracorporeal methods (IPD, best ever reached CPC of 1 or 2 during hospital stay)</td>
<td>3</td>
<td>383</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.55 [1.22, 1.96]</td>
</tr>
<tr>
<td>1.2 Cooling with haemofiltration (no IPD, CPC of 1 or 2 at six months)</td>
<td>1</td>
<td>42</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.71 [0.32, 1.54]</td>
</tr>
<tr>
<td>1.3 Unknown method (no IPD, Glasgow Outcome scale of 1-3 at one month)</td>
<td>1</td>
<td>54</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>4.5 [1.17, 17.30]</td>
</tr>
</tbody>
</table>

### Comparison 2. Survival: cooling versus no cooling

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Survival</td>
<td>4</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>1.1 Conventional cooling without extracorporeal methods (IPD, survival to discharge)</td>
<td>3</td>
<td>383</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.35 [1.10, 1.65]</td>
</tr>
<tr>
<td>1.2 Cooling with haemofiltration (no IPD, six-months survival))</td>
<td>1</td>
<td>42</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.71 [0.32, 1.54]</td>
</tr>
</tbody>
</table>
### Analysis 1.1. Comparison 1 Neurological outcome: cooling versus no cooling, Outcome 1 Good neurological outcome.

#### Review: Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation

#### Comparison: 1 Neurological outcome: cooling versus no cooling

#### Outcome: 1 Good neurological outcome

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Conventional cooling without extracorporal methods (IPD, best ever reached CPC of 1 or 2 during hospital stay)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bernard 2002</td>
<td>21/43</td>
<td>9/34</td>
<td>1.84 [0.97, 3.49]</td>
<td>15.3 %</td>
</tr>
<tr>
<td>HACA 2002</td>
<td>75/136</td>
<td>54/137</td>
<td>1.40 [1.08, 1.81]</td>
<td>81.8 %</td>
</tr>
<tr>
<td>Hachimi-Idrissi 2001</td>
<td>8/16</td>
<td>2/17</td>
<td>4.25 [1.06, 1.70]</td>
<td>2.9 %</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>195</strong></td>
<td><strong>188</strong></td>
<td></td>
<td><strong>1.55 [1.22, 1.96]</strong></td>
</tr>
<tr>
<td>Total events: 104 (Experimental), 65 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 2.92, df = 2 (P = 0.23); I² = 32%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.64 (P = 0.00027)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Cooling with haemofiltration (no IPD, CPC of 1 or 2 at six months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laurent 2005</td>
<td>7/22</td>
<td>9/20</td>
<td>0.71 [0.32, 1.54]</td>
<td>100.0 %</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>22</strong></td>
<td><strong>20</strong></td>
<td></td>
<td><strong>0.71 [0.32, 1.54]</strong></td>
</tr>
<tr>
<td>Total events: 7 (Experimental), 9 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.87 (P = 0.38)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Unknown method (no IPD, Glasgow Outcome scale of 1-3 at one month)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mori 2000</td>
<td>18/36</td>
<td>2/18</td>
<td>4.50 [1.17, 17.30]</td>
<td>100.0 %</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>36</strong></td>
<td><strong>18</strong></td>
<td></td>
<td><strong>4.50 [1.17, 17.30]</strong></td>
</tr>
<tr>
<td>Total events: 18 (Experimental), 2 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.19 (P = 0.029)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi² = 6.20, df = 2 (P = 0.05); I² = 68%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0.2 0.5 1 2 5

Favours no cooling

Favours cooling

---

Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation (Review)

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Analysis 2.1. Comparison 2 Survival: cooling versus no cooling, Outcome 1 Survival.

Review: Use of hypothermia for neuroprotection in adults after cardiopulmonary resuscitation

Comparison: 2 Survival: cooling versus no cooling

Outcome: 1 Survival

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>1 Conventional cooling without extracorporeal methods (IPD, survival to discharge)</td>
<td>21/43</td>
<td>11/34</td>
<td>15.4%</td>
<td>1.51 [0.85, 2.68]</td>
<td></td>
</tr>
<tr>
<td>Bernard 2002</td>
<td>21/43</td>
<td>11/34</td>
<td>15.4%</td>
<td>1.51 [0.85, 2.68]</td>
<td></td>
</tr>
<tr>
<td>HACA 2002</td>
<td>85/136</td>
<td>67/137</td>
<td>83.4%</td>
<td>1.28 [1.03, 1.58]</td>
<td></td>
</tr>
<tr>
<td>Hachimi-Idrissi 2001</td>
<td>4/16</td>
<td>1/17</td>
<td>1.2%</td>
<td>4.25 [0.53, 34.10]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>195</td>
<td>188</td>
<td>100.0%</td>
<td>1.35 [1.10, 1.65]</td>
<td></td>
</tr>
<tr>
<td>Total events: 110 (Experimental), 79 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 1.56, df = 2 (P = 0.46); I² = 0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.90 (P = 0.0038)</td>
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<td></td>
</tr>
</tbody>
</table>

2 Cooling with haemofiltration (no IPD, six-months survival)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Laurent 2005</td>
<td>7/22</td>
<td>9/20</td>
<td>100.0%</td>
<td>0.71 [0.32, 1.54]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>22</td>
<td>20</td>
<td>100.0%</td>
<td>0.71 [0.32, 1.54]</td>
<td></td>
</tr>
<tr>
<td>Total events: 7 (Experimental), 9 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.87 (P = 0.38)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADDITIONAL TABLES

Table 1. Subgroup analyses

<table>
<thead>
<tr>
<th>Outcome or Subgroup</th>
<th>Studies</th>
<th>Participants</th>
<th>Risk Ratio (M-H, Fixed, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good neurological outcome by cardiac cause versus non-cardiac cause</td>
<td>3</td>
<td>383</td>
<td>1.54 [1.22, 1.95]</td>
</tr>
<tr>
<td>Cardiac cause</td>
<td>3</td>
<td>372</td>
<td>1.51 [1.19, 1.91]</td>
</tr>
<tr>
<td>Non-cardiac cause</td>
<td>2</td>
<td>11</td>
<td>3.80 [0.55, 26.29]</td>
</tr>
<tr>
<td>Good neurological outcome by location of cardiac arrest</td>
<td>3</td>
<td>382</td>
<td>1.56 [1.23, 1.98]</td>
</tr>
</tbody>
</table>
Table 1. Subgroup analyses  

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Studies</th>
<th>Participants</th>
<th>Risk Ratio (M-H, Fixed, 95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital</td>
<td>1</td>
<td>17</td>
<td>1.64 [0.47, 5.73]</td>
</tr>
<tr>
<td>Out-of-hospital</td>
<td>3</td>
<td>365</td>
<td>1.56 [1.23, 1.99]</td>
</tr>
<tr>
<td>Good neurological outcome by witnessed cardiac arrest</td>
<td>3</td>
<td>382</td>
<td>1.49 [1.18, 1.88]</td>
</tr>
<tr>
<td>Witnessed cardiac arrest</td>
<td>3</td>
<td>360</td>
<td>1.43 [1.13, 1.81]</td>
</tr>
<tr>
<td>Non-witnessed cardiac arrest</td>
<td>3</td>
<td>22</td>
<td>5.31 [1.40, 20.21]</td>
</tr>
<tr>
<td>Good neurological outcome by primary ECG rhythm</td>
<td>3</td>
<td>382</td>
<td>1.51 [1.19, 1.91]</td>
</tr>
<tr>
<td>VF/VT rhythm</td>
<td>2</td>
<td>330</td>
<td>1.47 [1.15, 1.88]</td>
</tr>
<tr>
<td>Non-VF/VT rhythm</td>
<td>2</td>
<td>52</td>
<td>2.17 [0.68, 6.93]</td>
</tr>
</tbody>
</table>

Table 2. Adverse events

<table>
<thead>
<tr>
<th>Outcome or Subgroup</th>
<th>Studies</th>
<th>Participants</th>
<th>Risk Ratio (M-H, Fixed, 95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding of any severity</td>
<td>1</td>
<td>273</td>
<td>1.38 [0.88, 2.16]</td>
</tr>
<tr>
<td>Need for platelet transfusion</td>
<td>1</td>
<td>273</td>
<td>5.11 [0.25, 105.47]</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1</td>
<td>273</td>
<td>1.27 [0.90, 1.78]</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1</td>
<td>273</td>
<td>1.93 [0.89, 1.78]</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>1</td>
<td>273</td>
<td>0.51 [0.05, 5.57]</td>
</tr>
<tr>
<td>Renal failure or oliguria</td>
<td>2</td>
<td>303</td>
<td>0.88 [0.48, 1.61]</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>2</td>
<td>350</td>
<td>1.11 [0.41, 3.01]</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>1</td>
<td>273</td>
<td>1.76 [0.61, 5.12]</td>
</tr>
<tr>
<td>Seizures</td>
<td>1</td>
<td>273</td>
<td>0.89 [0.39, 2.02]</td>
</tr>
<tr>
<td>Lethal or long lasting arrhythmia</td>
<td>2</td>
<td>315</td>
<td>1.21 [0.88, 1.67]</td>
</tr>
<tr>
<td>Pressure sores</td>
<td>1</td>
<td>273</td>
<td>Not estimable</td>
</tr>
</tbody>
</table>
Table 2. Adverse events  (Continued)

<table>
<thead>
<tr>
<th>Event</th>
<th>Studies</th>
<th>Participants</th>
<th>Risk Ratio (M-H, Fixed, 95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant haemorrhagic complications</td>
<td>1</td>
<td>77</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Cardiac complications</td>
<td>1</td>
<td>77</td>
<td>0.16 [0.01, 3.21]</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>1</td>
<td>42</td>
<td>0.91 [0.31, 2.68]</td>
</tr>
<tr>
<td>Hypophosphataemia</td>
<td>1</td>
<td>42</td>
<td>1.12 [0.65, 2.25]</td>
</tr>
</tbody>
</table>

Table 3. Sensitivity analysis

<table>
<thead>
<tr>
<th>Outcome or Subgroup</th>
<th>Studies</th>
<th>Participants</th>
<th>Risk Ratio (M-H, Fixed, 95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good neurological outcome all studies</td>
<td>5</td>
<td>479</td>
<td>1.55 [1.24, 1.94]</td>
</tr>
<tr>
<td>Studies with conventional cooling and adequate allocation concealment</td>
<td>2</td>
<td>306</td>
<td>1.50 [1.16, 1.93]</td>
</tr>
<tr>
<td>Studies with conventional cooling and inadequate or unknown allocation concealment</td>
<td>1</td>
<td>77</td>
<td>1.84 [0.97, 3.49]</td>
</tr>
<tr>
<td>Studies with other cooling methods and adequate allocation concealment</td>
<td>1</td>
<td>42</td>
<td>0.71 [0.32, 1.54]</td>
</tr>
<tr>
<td>Studies with other cooling method and inadequate or unknown allocation concealment</td>
<td>1</td>
<td>54</td>
<td>4.50 [1.17, 17.30]</td>
</tr>
</tbody>
</table>
**APPENDICES**

**Appendix 1. Search strategy: CENTRAL, The Cochrane Library**

#1 MeSH descriptor Resuscitation explode all trees  
#2 MeSH descriptor Cardiopulmonary Resuscitation explode all trees  
#3 MeSH descriptor Resuscitation Orders explode all trees  
#4 MeSH descriptor Heart Arrest explode all trees  
#5 MeSH descriptor Heart Massage explode all trees  
#6 ((cardio?pulmonary or order*) near2 resuscitation):ti,ab  
#7 reanimation:ti,ab  
#8 ((circulatory or circulation or cardiac) near arrest):ti,ab or heart standstill:ti,ab  
#9 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)  
#10 MeSH descriptor Cryotherapy explode all trees  
#11 MeSH descriptor Hypothermia explode all trees  
#12 MeSH descriptor Hypothermia, Induced explode all trees  
#13 ((resuscitative or therapeutic or artificial or induced or extracorporeal) near hypothermia)  
#14 artificial hibernation or body cooling or refrigeration anesthesia or body temperature:ti,ab or refrigeration:ti,ab  
#15 (#10 OR #11 OR #12 OR #13 OR #14)  
#16 (#9 AND #15)

**Appendix 2. Search strategy: MEDLINE (Ovid SP)**

1. Resuscitation/ or Cardiopulmonary Resuscitation/ or Resuscitation Orders/ or Heart Arrest/ or Heart Massage/ or advanced cardiac life support.mp. or ((cardio?pulmonary or order*) adj2 resuscitation).ti,ab. or reanimation.ti,ab. or ((circulatory or circulation or cardiac) adj3 arrest).ti,ab or heart standstill.ti,ab.  
2. Cryotherapy/ or Hypothermia/ or Circulatory Arrest, Deep Hypothermia Induced/ or Hypothermia, Induced/ or ((resuscitative or therapeutic or artificial or induced or extracorporeal) adj3 hypothermia).mp. or artificial hibernation.mp. or body cooling.mp. or chilling.mp. or refrigeration anesthesia.mp. or body temperature.ti,ab. or refrigeration.ti,ab.  
3. 1 and 2  
4. ((randomised controlled trial or controlled clinical trial).pt. or randomised.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh.  
5. 3 and 4

**Appendix 3. Search strategy: EMBASE (Ovid SP)**

1. resuscitation/ or heart arrest/ or heart massage/ or advanced cardiac life support.mp. or ((cardio?pulmonary or order*) adj2 resuscitation).ti,ab. or reanimation.ti,ab. or ((circulatory or circulation or cardiac) adj3 arrest).ti,ab or heart standstill.ti,ab.  
2. cryotherapy/ or hypothermia/ or ((resuscitative or therapeutic or artificial or induced or extracorporeal) adj3 hypothermia).mp. or artificial hibernation.mp. or body cooling.mp. or chilling.mp. or refrigeration anesthesia.mp. or body temperature.ti,ab. or refrigeration.ti,ab.  
3. 1 and 2  
4. (placebo.sh. or controlled study.ab. or random*.ti,ab. or trial*.ti,ab. or ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*))).ti,ab.) not (animals not (humans and animals)).sh.  
5. 3 and 4
Appendix 4. Search strategy: CINAHL (EBSCO host)
S1 ((MH “Resuscitation”) OR (MH “Resuscitation Orders”) OR (MH “Resuscitation, Cardiopulmonary”) OR (MH “Heart Arrest”) OR (MH “Heart Massage”)) OR AB ((cardio?pulmonary or order*) and resuscitation) OR AB reanimation OR (circulatory or circulation or cardiac) and arrest OR heart standstill
S2 ((MH “Cryotherapy”) OR (MH “Hypothermia”) OR (MH “Hypothermia, Induced”) OR ((resuscitative or therapeutic or artificial or induced or extracorporeal) and hypothermia) OR artificial hibernation OR body cooling OR refrigeration anesthesia
S3 ((MH “randomised Controlled Trials”) OR (MH “Random Assignment”) OR (MH “Prospective Studies”) OR (MH “Multicenter Studies”) OR (MH “Clinical Trials”) OR (MH “Clinical Trial Registry”) OR (MH “Double-Blind Studies”) OR (MH “Single-Blind Studies”) OR (MH “Triple-Blind Studies”) OR (MH “Placebos”) OR (random* or controlled clinical trial or placebo))
S4 S1 and S2 and S3

Appendix 5. Search Strategy: BIOSIS (Ovid SP) and PASCAL
1. advanced cardiac life support.mp. OR ((cardio?pulmonary or order*) adj2 resuscitation).ti,ab. OR reanimation.ti,ab. OR ((circulatory or circulation or cardiac) adj3 arrest).ti,ab. OR heart standstill.ti,ab.
2. (((resuscitative or therapeutic or artificial or induced or extracorporeal) adj3 hypothermia) OR artificial hibernation OR body cooling OR chilling OR refrigeration anesthesia).mp. OR body temperature.ti,ab. OR refrigeration.ti,ab.
3. 1 and 2
### Appendix 6. Data extraction sheet

<table>
<thead>
<tr>
<th>Hypothermia for neuroprotection after cardiopulmonary resuscitation</th>
<th>Allocation concealment</th>
<th>Outcome assessor blind</th>
<th>Outcome assessor blind</th>
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</thead>
<tbody>
<tr>
<td>Reviewer:</td>
<td>A. adequate</td>
<td>• yes</td>
<td>• yes</td>
</tr>
<tr>
<td>Date:</td>
<td>B. unclear</td>
<td>• no</td>
<td>• no</td>
</tr>
<tr>
<td>Decision:</td>
<td>C. inadequate</td>
<td>• if unclear, please explain</td>
<td>• if unclear, please explain</td>
</tr>
</tbody>
</table>

**Inclusion**

- Reasons for exclusion:
- Study characteristics
- Publication type:
- Language:
- Setting
- Multicenter:
  - yes
  - no
- Participating sites:
  - university hospital
  - community hospital
  - other, please specify
- Participants, inclusion/exclusion criteria
- Total number of patients:
- Mean age:
- Percent female:
- Cardiac arrest:
  - out-of-hospital
  - in-hospital
- Cause of cardiac arrest:
  - cardiac
  - non cardiac
- Primary cardiac rhythm:
  - ventricular fibrillation
  - ventricular tachycardia
  - asystole
  - pulseless electrical activity
- Quality

<table>
<thead>
<tr>
<th>Intention-to-treat:</th>
<th>Groups comparable:</th>
<th>Follow-up &gt; 80% of randomized patients:</th>
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</thead>
<tbody>
<tr>
<td>• yes</td>
<td>• yes</td>
<td>• yes</td>
</tr>
<tr>
<td>• no</td>
<td>• if not, please specify</td>
<td>• if not, please specify</td>
</tr>
<tr>
<td>• if unclear, please explain</td>
<td></td>
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**Intervention**

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<th>Type of intervention:</th>
<th>Controls:</th>
<th>Time from restoration of spontaneous circulation to target temperature:</th>
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(Continued)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Types of outcome measures:</th>
<th>Duration of cooling:</th>
<th>Rewarming:</th>
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</table>

Notes

Results primary:

**Type of outcome:**

<table>
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<th>Cooling</th>
<th>No cooling</th>
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<tr>
<td>Events (n)</td>
<td>Total (N)</td>
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Results secondary:

**Type of outcome:**

<table>
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<tbody>
<tr>
<td>Events (n)</td>
<td>Total (N)</td>
</tr>
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WHAT'S NEW

Last assessed as up-to-date: 25 July 2011.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>31 July 2012</td>
<td>New search has been performed</td>
<td>This review is an update of the previous Cochrane systematic review (Arrich 2009) that included four trials and one abstract reporting on 481 patients. In the previous version (Arrich 2009) we searched the databases until January 2009. In this updated version we reran the searches to July 2011. We updated the methods, allocated all chapters, updated references, added a risk of bias table and summary of findings table. A typing error (survival instead of neurologic outcome) in the results section was spotted by a reader and corrected accordingly.</td>
</tr>
<tr>
<td>31 July 2012</td>
<td>New citation required but conclusions have not changed</td>
<td>Christof Havel was added as an author.</td>
</tr>
</tbody>
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HISTORY

Review first published: Issue 4, 2009

<table>
<thead>
<tr>
<th>Date</th>
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<tr>
<td>28 June 2010</td>
<td>Amended</td>
<td>Contact details updated</td>
</tr>
<tr>
<td>29 October 2009</td>
<td>Amended</td>
<td>Typo corrected in co-author’s address (Müllner)</td>
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</tbody>
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CONTRIBUTIONS OF AUTHORS

Conceiving the review and update: Harald Herkner (HH), Michael Holzer (MH), Marcus Müllner (MM), and Christof Havel (CH)

Co-ordinating the review: HH, MM

Undertaking manual searches: MH, Jasmin Arrich (JA)

Screening search results: MH, JA, CH

Organizing retrieval of papers: JA

Screening retrieved papers against inclusion criteria: MH, JA, MM, CH

Appraising quality of papers: MH, HH, JA, MM, CH

Abstracting data from papers: MH, JA, CH
Writing to authors of papers for additional information: MH
Providing additional data about papers: MH
Obtaining and screening data on unpublished studies: MH, JA
Data management for the review: HH, JA, MM
Entering data into Review Manager (RevMan 5.1): MH, JA
RevMan statistical data: HH, MM, JA
Other statistical analyses not using RevMan: HH, MM
Double entry of data: MH, JA
Interpretation of data: MH, HH, JA, MM, CH
Statistical inferences: HH, MM, JA
Writing the review: JA, MM, HH
Securing funding for the review: not applicable
Performing previous work that was the foundation of the present study: MM, MH, CH
Guarantor for the review (one author): JA
Person responsible for reading and checking review before submission: HH

DECLARATIONS OF INTEREST

The Medical University of Vienna received an unrestricted scientific grant from Alsius Corporation for an independent scientific project, which was used for financing the post of Jasmin Arrich.

Michael Holzer received travel grants for scientific conferences from Alsius Corporation and Kinetic Concepts, Inc (KCI) and honoraria for lectures from Medivance and KCI. He is a member of the scientific advisory board of KCI.

Marcus Müllner, Michael Holzer and Christof Havel were involved in the design, conduct and publication of the HACA 2002 trial. Harald Herkner has no conflicts of interest.

SOURCES OF SUPPORT

Internal sources
• Medical University of Vienna, Austria.
External sources
• No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In our protocol we aimed to include additional endpoints like the six month and final CPC score, long-term mortality, quality of life at six months, long-term dependency, and cost-effectiveness. The retrieved studies did not provide any information on long-term mortality and dependency, quality of life, or cost-effectiveness.

All studies that were included in the individual patient analysis provided data on both best and final neurologic outcome (Bernard 2002; HACA 2002; Hachimi-Idrissi 2001). In our opinion the 'best neurological score during hospital stay' is superior to the final score as the final score may be influenced by other factors like worsening of body functions or re-arrests.

Bernard 2002 and Hachimi-Idrissi 2001 gave information on survival to hospital discharge, HACA 2002 additionally on six-month survival, Laurent 2005 only gave information on the six-month survival. As the study by Laurent was not included in the individual patients analysis we chose survival to hospital discharge as a secondary endpoint for the individual patient analysis.

The documentation of adverse effects was overlooked in the original protocol. As they form a vital part of every review we included them in the data extraction sheet before we performed the literature search.

In accordance with our reviewers, to better explain the reasons for dual analysis and the way it was carried out, we have changed the wording of the objectives from:

“The aim of this study is to present a systematic review of the literature and, if applicable, a meta-analysis, concerning the neuroprotective effect of induced hypothermia in primary cardiac arrest survivors. We plan to use data at the aggregate (study) level and the individual (patient) level.”

to:

“We aimed to perform a systematic review and meta-analysis to assess the effectiveness of therapeutic hypothermia in patients after cardiac arrest. Neurologic outcome, survival and adverse events were our main outcomes. We aimed to perform individual patient data analysis if data were available. We intended to form subgroups according to the cardiac arrest situation.”

The title has been changed from “Hypothermia for neuroprotection after cardiopulmonary resuscitation” to “Hypothermia for neuro-protection in adults after cardiopulmonary resuscitation”.

INDEX TERMS

Medical Subject Headings (MeSH)
Brain Diseases [*prevention & control]; Cardiopulmonary Resuscitation [*adverse effects]; Heart Arrest [*complications; therapy]; Hypothermia, Induced [*methods]; Randomized Controlled Trials as Topic; Recovery of Function

MeSH check words
Adult; Humans