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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	4
BACKGROUND	6
OBJECTIVES	6
METHODS	6
RESULTS	8
Figure 1.	9
Figure 2.	11
Figure 3.	12
Figure 4.	14
Figure 5.	15
Figure 6.	16
Figure 7.	17
DISCUSSION	17
AUTHORS' CONCLUSIONS	19
ACKNOWLEDGEMENTS	19
REFERENCES	20
CHARACTERISTICS OF STUDIES	24
DATA AND ANALYSES	33
Analysis 1.1. Comparison 1 Neurological outcome: therapeutic hypothermia versus no hypothermia, Outcome 1 All studies with subgroups.	33
Analysis 1.2. Comparison 1 Neurological outcome: therapeutic hypothermia versus no hypothermia, Outcome 2 Conventional cooling.	34
Analysis 2.1. Comparison 2 Survival: therapeutic hypothermia versus no hypothermia, Outcome 1 All studies with subgroups.	35
Analysis 2.2. Comparison 2 Survival: therapeutic hypothermia versus no hypothermia, Outcome 2 Conventional cooling.	36
ADDITIONAL TABLES	36
APPENDICES	38
WHAT'S NEW	43
HISTORY	43
CONTRIBUTIONS OF AUTHORS	44
DECLARATIONS OF INTEREST	44
SOURCES OF SUPPORT	45
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	45
NOTES	45
INDEX TERMS	46

[Intervention Review]

Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation

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ABSTRACT

Background

Good neurological outcome after cardiac arrest is difficult 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 several clinical studies on this topic have been published. This review was originally published in 2009; updated versions were published in 2012 and 2016.

Objectives

We aimed to perform a systematic review and meta-analysis to assess the influence of therapeutic hypothermia after cardiac arrest on neurological outcome, survival and adverse events.

Search methods

We searched the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL; 2014, Issue 10); MEDLINE (1971 to May 2015); EMBASE (1987 to May 2015); the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1988 to May 2015); and BIOSIS (1989 to May 2015). We contacted experts in the field to ask for information on ongoing, unpublished or published trials on this topic. The original search was performed in January 2007.

Selection criteria

We included all randomized controlled trials (RCTs) conducted to assess the effectiveness of therapeutic hypothermia in participants after cardiac arrest, without language restrictions. We restricted studies to adult populations cooled by any cooling method, applied within six hours of cardiac arrest.

Data collection and analysis

We entered validity measures, interventions, outcomes and additional baseline variables into a database. Meta-analysis was performed only for a subset of comparable studies with negligible heterogeneity. We assessed the quality of the evidence by using standard methodological procedures as expected by Cochrane and incorporated the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach.

Main results

We found six RCTs (1412 participants overall) conducted to evaluate the effects of therapeutic hypothermia - five on neurological outcome and survival, one on only neurological outcome. The quality of the included studies was generally moderate, and risk of bias was low in three out of six studies. When we compared conventional cooling methods versus no cooling (four trials; 437 participants), we found

that participants in the conventional cooling group were more likely to reach a favourable neurological outcome (risk ratio (RR) 1.94, 95% confidence interval (CI) 1.18 to 3.21). The quality of the evidence was moderate.

Across all studies that used conventional cooling methods rather than no cooling (three studies; 383 participants), we found a 30% survival benefit (RR 1.32, 95% CI 1.10 to 1.65). The quality of the evidence was moderate.

Across all studies, the incidence of pneumonia (RR 1.15, 95% CI 1.02 to 1.30; two trials; 1205 participants) and hypokalaemia (RR 1.38, 95% CI 1.03 to 1.84; two trials; 975 participants) was slightly increased among participants receiving therapeutic hypothermia, and we observed no significant differences in reported adverse events between hypothermia and control groups. Overall the quality of the evidence was moderate (pneumonia) to low (hypokalaemia).

Authors' conclusions

Evidence of moderate quality suggests that conventional cooling methods provided to induce mild therapeutic hypothermia improve neurological outcome after cardiac arrest, specifically with better outcomes than occur with no temperature management. We obtained available evidence from studies in which the target temperature was 34°C or lower. This is consistent with current best medical practice as recommended by international resuscitation guidelines for hypothermia/targeted temperature management among survivors of cardiac arrest. We found insufficient evidence to show the effects of therapeutic hypothermia on participants with in-hospital cardiac arrest, asystole or non-cardiac causes of arrest.

PLAIN LANGUAGE SUMMARY

Cooling the body after resuscitation following cardiac arrest

Review question

In this review, we asked whether people resuscitated from cardiac arrest benefit when their bodies are cooled to a temperature of 34°C or lower.

Background

Population and outcomes

Around 30% to 50% of all people with coronary heart disease suffer sudden cardiac death at some stage of their illness. Sudden cardiac death means that the heart and subsequently the circulation stop. If these people are not resuscitated, brain cells begin to be irreversibly damaged, and subsequently the person dies. After resuscitation, treatment within the first few hours is critical for avoiding or limiting brain damage. One form of therapy that may help to prevent cell damage consists of cooling the body for several hours after successful resuscitation to 34°C or lower.

Intervention

We compared people who had their bodies cooled to 32°C to 34°C or below after resuscitation with people who were not cooled following successful resuscitation.

Search date

Evidence is current to May 2015.

Study characteristics

We included in our analysis six studies (1412 people overall), four of which (437 people) examined effects of cooling the body by conventional methods after successful resuscitation for cardiac arrest. One study that used haemofiltration (cooling the blood externally - similar to dialysis) as the cooling method and one study in which cooling to 33°C was compared with temperature management at 36°C were treated separately in the review.

Study funding sources

The study that used external cooling was supported by a dialysis-related company. Of the five studies included in the main analysis, two received funding from government or non-profit organizations; three studies did not provide information on funding.

Key results

When we compared people whose bodies were cooled to 32°C to 34°C after resuscitation versus those whose bodies were not cooled at all, we found that 63% of those receiving cooling would suffer no, or only minor, brain damage, while only 33% of those not cooled would suffer no, or only minor, brain damage. Cooling had an important effect on simple survival, with or without brain damage: 57% would survive if their bodies were cooled compared with 42% if their bodies were not cooled at all. No serious side effects occurred, but cooling the body

was associated with increased risk of pneumonia (49% vs 42% of those studied) and increased risk of low concentrations of potassium in the blood (18% vs 13%).

Quality of the evidence

Some studies had quality shortcomings including small numbers of participants and use of inadequate methods to balance participants between intervention and control groups. However, when differences between studies are acknowledged (heterogeneity), it is clear that these shortcomings had no major impact on the main results.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Neurological outcome, survival and adverse events: conventional cooling compared with no cooling and 36°C for neuroprotection and survival in adults after cardiopulmonary resuscitation

Neurological outcome, survival and adverse events: conventional cooling compared with no cooling and 36°C for neuroprotection and survival in adults after cardiopulmonary resuscitation

Patient or population: adults after cardiopulmonary resuscitation

Settings: emergency medicine and intensive care, worldwide

Intervention: conventional cooling 32°C to 34°C

Comparison: no cooling (good neurological outcome and survival); no cooling and 36°C (adverse events)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No cooling	Cooling 32°C to 34°C				
Good neurological outcome	Study population		RR 1.94 (1.18 to 3.21)	437 (4 RCTs)	⊕⊕⊕⊖ MODERATE ^{a,b}	
	325 per 1000	631 per 1000 (384 to 1000)				
Survival	Study population		RR 1.35 (1.10 to 1.65)	383 (3 RCTs)	⊕⊕⊕⊖ MODERATE ^{b,c}	
	420 per 1000	567 per 1000 (462 to 693)				
Adverse events - pneumonia	Study population		RR 1.15 (1.02 to 1.30)	1205 (2 RCTs)	⊕⊕⊕⊖ MODERATE ^d	
	423 per 1000	486 per 1000 (431 to 549)				
Adverse events - hypokalaemia	Study population		RR 1.38 (1.03 to 1.84)	975 (2 RCTs)	⊕⊕⊕⊖ LOW ^{e,f}	
	134 per 1000	185 per 1000 (138 to 247)				

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (with its 95% confidence interval) is based on assumed risk in the comparison group and **relative effect** of the intervention (and its 95% CI)

CI: Confidence interval

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

^aOne quasi-randomized trial ([Bernard 2002](#)) and one abstract ([Mori 2000](#)) but both not contributing to most data (see also [Effects of interventions](#) - '**Sensitivity analysis**')

^bTotal number of events < 300; imprecision therefore was rated as serious, and this resulted in downgrading of the overall quality of the evidence one level from high to moderate

^cOne quasi-randomized trial not contributing to the majority of data (see also [Effects of interventions](#) - '**Sensitivity analysis**')

^dIndirectness was caused mostly by control group treatment ([Nielsen 2013](#)), which resulted in downgrading of the overall quality of the evidence one level from high to moderate

^eIndirectness was rated as very serious because of differences in intervention (haemofiltration, conventional cooling) and control group treatments (no cooling, 36°C), which resulted in downgrading of the overall quality of the evidence two levels from high to low

^f[Laurent 2005](#) had some risk of bias but is not contributing to the majority of data

BACKGROUND

Description of the condition

The incidence of out-of-hospital sudden cardiac arrest in industrial countries varies greatly over different study groups and is reported to range between 0.05% and 0.19% per year (Chugh 2004; McNally 2011; Rea 2004). Among all participants for whom resuscitation was attempted, 14% to 40% achieved return of spontaneous circulation and were admitted to hospital (Finn 2001; Fischer 1997; Giraud 1996; Herlitz 2003b; Kuisma 1996; Leung 2001; Rewers 2000). Of patients admitted to hospital, only between 7% and 30% were discharged from hospital with good neurological outcome (Absalom 1999; Böttiger 1999; Fischer 1997; Herlitz 1999; Jennings 2001; McNally 2011; Weston 1997). To improve neurological outcome and survival of patients after cardiac arrest, providers have applied many methods related to post-resuscitation care. These comprise optimizing haemodynamics and providing ventilation, coronary reperfusion, electrolytes, seizure control, temperature management and glucose control and are summarized in the main resuscitation guidelines (Callaway 2015; Soar 2015).

Description of the intervention

Therapeutic hypothermia (or targeted temperature management/induced hypothermia) is still a relatively new concept for preservation of cerebral function among patients resuscitated from cardiac arrest. After the patient's condition has been stabilized, body temperature is lowered to 32°C to 34°C for a duration of 24 hours. Conventional cooling comprises surface cooling methods requiring cooling pads, ice packs, water immersion or intravascular cooling with cooling catheters or simply cold fluids. Cooling can be combined with haemofiltration or extracorporeal cardiopulmonary support.

How the intervention might work

Therapeutic hypothermia is believed to work in many ways. Cerebral reperfusion after successful resuscitation, although essential and effective in restoring energy stores, can trigger harmful chemical cascades. Generation of free radicals and other mediators, which leads to multi-focal damage to the brain, was first described by Negovsky as "post-resuscitation 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 provided for several years with certain surgical procedures and circulatory arrest states. Clinical and experimental results show protective effects of hypothermia during and 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, thus preventing potential tissue damage (D'Cruz 2002; Hachimi-Idrissi 2004). Other beneficial effects of hypothermia include preservation of the blood-brain barrier (Baumann 2009; Karibe 1994); protection of adenosine triphosphate (ATP) stores (McCullough 1999; Mizuhara 1996) necessary for energy provision; restitution of post-ischaemic cerebral microcirculation (Takasu 1996); and possibly decreased intracranial pressure (Lee 2010; Schreckinger 2009). Subsequently, hypothermia seems to act in a multi-factorial way by influencing

several damaging pathways simultaneously (Holzer 2010) to reduce cell death within the brain.

Why it is important to do this review

The first Cochrane review (Arrich 2009) was conducted to examine the emergence of mild therapeutic hypothermia as part of routine care for survivors of cardiac arrest. Two randomized controlled trials (RCTs) had shown that induced hypothermia has a neuroprotective effect in patients primarily resuscitated from cardiac arrest (Bernard 2002; HACA 2002), and therapeutic hypothermia was recommended in the guidelines of the International Liaison Committee on Resuscitation (ILCOR) (Nolan 2003) and in other resuscitation guidelines of that time (Deakin 2010; Peberdy 2010). It is recommended as "targeted temperature management (induced hypothermia)" in the current resuscitation guidelines (Callaway 2015; Soar 2015). Therapeutic hypothermia remains a relatively new concept. Studies examining different treatment modalities are emerging; therefore systematic and regular updates of the literature are important for monitoring new and effective developments. A recent publication following a large RCT on two different cooling levels described no differences between the two treatment regimens (Nielsen 2013). We present the second update of the original Cochrane review (Arrich 2009; Arrich 2012), which incorporates up-to-date evidence.

OBJECTIVES

We aimed to perform a systematic review and meta-analysis to assess the influence of therapeutic hypothermia after cardiac arrest on neurological outcome, survival and adverse events.

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 participants who suffered from cardiac arrest (regardless of whether in-hospital or out-of-hospital cardiac arrest) and were successfully resuscitated.

We excluded studies of children and adolescents (younger than 18 years), as presumed causes of cardiac arrest are different from causes in adults.

Although participants with a prior neurological history may not greatly benefit from the intervention, we did not exclude them for the following reasons.

- The number of such participants is most likely negligible.
- In a real-life situation, information on neurological performance before cardiac arrest often is not available when post-resuscitation therapy is initiated

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

target body temperature of 34°C or lower. We defined the 'control' intervention as standard treatment (at the time of the trial) provided after cardiac arrest.

Types of outcome measures

Primary outcomes

The primary outcome measure was neurological recovery. We expected the ideal outcome to be reported as best neurological outcome during hospital stay and in cerebral performance categories (CPCs) (Stiell 2009). CPC categories are defined as follows.

- Good cerebral performance: conscious, alert, capable of normal life. Normal cerebral function. May have minor psychological or neurological deficits that do not significantly compromise cerebral or physical function.
- 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.
- Severe cerebral disability: conscious, with at least limited cognition. Dependent on others for daily life support (i.e. institutionalised or at home with exceptional family effort) because of impaired brain function. Includes individuals with wide range of cerebral abnormalities, from ambulatory participants with severe memory disturbance or dementia precluding independent existence to paralysed participants who can communicate only with their eyes (e.g. the locked-in syndrome).
- 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 individuals showing all degrees of unresponsiveness that are neither CPC three (conscious) nor CPC five (coma, which satisfies brain death criteria).
- Certified brain death.

If study authors grouped the primary outcome into one or two (good recovery) and three to five (unfavourable recovery), we adapted it for our meta-analysis. If the primary outcome was not reported in CPC categories, we accepted reports of 'good' neurological outcome, and we assumed that this was comparable with a CPC score of one or two.

Secondary outcomes

- Survival to hospital discharge at six months and long term.
- Quality of life at six months and long term.
- Dependency.
- Cost-effectiveness.

We defined 'long term' as a minimum of one year.

Adverse events

We aimed to report adverse events as described by study authors.

Search methods for identification of studies

Electronic searches

We searched the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL; 2014, Issue 9); MEDLINE (1971 to May 2015); EMBASE (1987 to May 2015); the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1988 to May 2015); and BIOSIS (1989 to May 2015). Original searches were performed in January 2007 (Arrich 2009) and were updated in July 2011 (Arrich 2012).

We performed searches by entering search terms as multiple postings (.mp, term appears in the title, abstract or medical subject heading (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, Appendix 5). We used a search strategy for identifying RCTs with MEDLINE, CINAHL and EMBASE (Higgins 2011), and we applied no language restrictions. We searched three trials registers as well: EudraCT; ClinicalTrials.gov; International Clinical Trials Registry Platform.

Searching other resources

In an attempt to identify additional studies, we asked experts in the field whether they were aware of any ongoing, unpublished or published trials on this topic.

Data collection and analysis

Selection of studies

We imported all retrieved results into EndNote (version X5; Thomson Corporation, Stamford, CT, USA) and eliminated duplicates. Two review 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 (IPD) provided by identified trials, we contacted the respective corresponding authors and asked for collaboration. Two review authors independently entered all relevant data into the Cochrane software program Review Manager (RevMan 5.3). We compared the two versions and resolved disagreements by discussion.

We entered the following variables into RevMan 5.3.

- Study characteristics.
- Data on outcomes.
- Items on risk of bias.
- Within-study subgroup effect estimates as calculated from IPD outside RevMan.

Assessment of risk of bias in included studies

To assess the internal validity of identified trials, we assessed allocation sequence generation, allocation concealment, blinding of outcome assessment, exclusion of randomized participants from the analysis, comparability of groups, loss to follow-up and other potential sources of bias. However, blinding of treating personnel regarding application of therapeutic hypothermia was considered almost impossible.

Measures of treatment effect

We calculated risk ratios (RRs) and their 95% confidence intervals (CIs).

Unit of analysis issues

We did not include cluster-randomized trials in the analysis; in the case of multiple treatment groups, we planned to combine groups to create a single comparison; by nature of the condition and outcomes, we identified no cross-over trials.

Dealing with missing data

All analyses were performed according to the intention-to-treat (ITT) principle. If data were missing, we attempted to obtain the information by contacting study authors. We included assessment of loss to follow-up in our quality assessment and reported this in the table [Characteristics of included studies](#). If a considerable quantity of data was missing, we would investigate the possible mechanism of the missing data (whether random or not). We planned to perform a sensitivity analysis to assess the influence of this possible selection bias on our estimates.

Assessment of heterogeneity

We assessed data for clinical and statistical heterogeneity. We performed quantitative synthesis of data only if clinical heterogeneity was negligible. Clinical heterogeneity may be caused by differences in study populations, interventions and controls, or by variable definitions of the endpoint ([Thompson 2001](#)). Pooling of data may not be suitable in cases of severe heterogeneity.

Assessment of reporting biases

We assessed the presence of possible publication bias and heterogeneity by using funnel plots (plotting effect vs precision) ([Egger 1997](#)) and planned to present this information if we identified more than 10 studies.

Data synthesis

Quantitative analysis of IPD was intended when studies showed negligible heterogeneity and IPD were available at least for a clinically uniform subset. In the case that IPD were not available for at least one study, we planned to perform an analysis at the study level, particularly when we encountered updates. We planned to perform a quantitative synthesis of IPD by using standard statistical procedures provided in [RevMan 5.3](#). The principal summary effect estimate was the risk ratio with a 95% confidence interval.

In the case of negligible heterogeneity, we used a fixed-effect model to calculate summary effects; otherwise we used random-effects models. We assessed statistical heterogeneity by using the I^2 statistic ([Higgins 2003](#)) and considered statistical heterogeneity relevant with I^2 statistic > 50%.

Subgroup analysis and investigation of heterogeneity

For the primary endpoint and for survival, we performed subgroup analyses at the study level.

- Treatment of the control group: no cooling versus temperature management. These ancillary analyses were introduced at the current update following consideration of differences in control group treatment described in a newly included study ([Nielsen](#)

[2013](#)). We used the standard test for subgroup differences to assess differences in effects between study level subgroups.

When data became available, we performed subgroup analyses for the primary outcome using IPD. We used the following variables.

- Cause of cardiac arrest (presumed cardiac vs non-cardiac).
- Location of arrest (in-hospital vs out-of-hospital).
- Witnessed versus non-witnessed arrest.
- Primary electrocardiography (ECG) rhythm (ventricular fibrillation vs other).

We received IPD ([Bernard 2002](#); [HACA 2002](#); [Hachimi-Idrissi 2001](#)) via spreadsheets including participant-specific information on interventions, outcomes and subgroup properties. We calculated subgroup-specific effect estimates across included studies at the individual patient level but performed no tests to examine subgroup differences.

Sensitivity analysis

We performed sensitivity analyses to examine the impact of study quality issues, as measured by allocation concealment, on overall effect estimates and on effect sizes of all identified trials without consideration of heterogeneity and publication status. To investigate whether model choice might influence our results, we compared estimates derived from random-effects models versus those obtained from fixed-effect models.

Summary of findings

We used the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach to interpret findings ([Langendam 2013](#)). The GRADE profiler ([GRADEPRO](#)) allowed us to import data from Review Manager ([RevMan 5.3](#)) to create a 'Summary of findings' table. This table provides outcome-specific information concerning overall quality of evidence gathered from studies included in the comparison, magnitude of effects of the interventions examined and the sum of available data on outcomes considered.

We included the following outcomes in a 'Summary of findings' table.

- Neurological outcome, survival (conventional cooling vs no cooling) and adverse events (vs no cooling and 36°C).

RESULTS

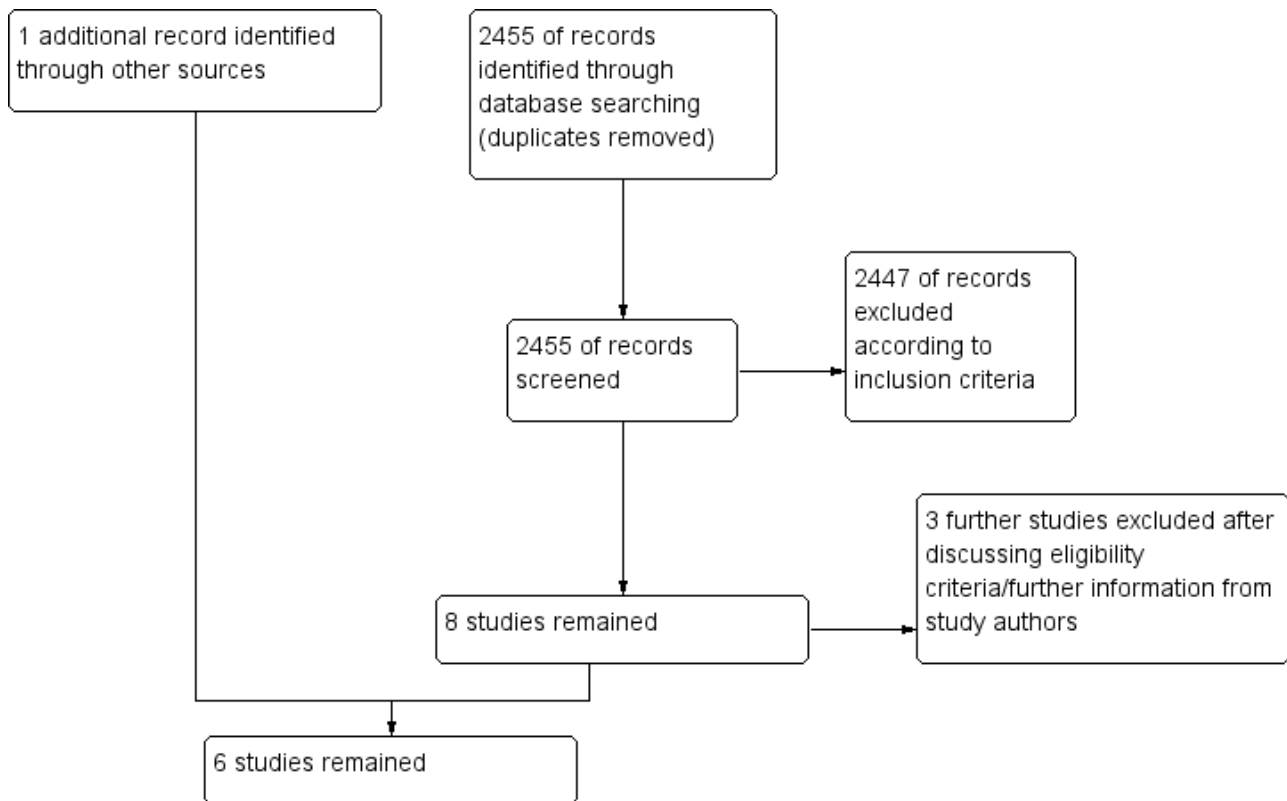
Description of studies

Results of the search

Our original and updated searches (from 2007 to May 2015) resulted in 2425 hits (duplicates excluded). From these, we excluded 2417 according to our eligibility criteria (randomized studies on adult participants with cardiac arrest treated with therapeutic hypothermia) by judging the abstract or the title. Eight papers remained for closer inspection. Of those, we excluded three after further evaluation (see [Characteristics of excluded studies](#); and [Figure 1](#)). Upon looking through the references of a systematic review on therapeutic hypothermia ([Cheung 2006](#)), we found one additional reference, published only as an abstract ([Mori 2000](#)). Hence overall, six randomized and quasi-randomized controlled trials with a total of 1412 participants remained for analysis

(Bernard 2002; HACA 2002; Hachimi-Idrissi 2001; Laurent 2005; Mori 2000; Nielsen 2013) (see Characteristics of included studies).

Figure 1. Study flow diagram.



The decision on inclusion of one study was not unequivocal (Nielsen 2013) because control group participants in the study by Nielsen et al received active temperature management at 36°C, which is clearly different from 'no temperature management'. It is a matter of concern whether temperature control at 36°C can be seen as 'standard therapy', as we outlined in our inclusion criteria for the control group. We decided to include the study in our review while treating it as a separate subgroup for the main analysis. However, in an additional ancillary analysis, we calculated a pooled overall estimate to inform the current controversial discussion.

We found that one previously unclassified study (Tiainen 2007) and two additional studies (Tiainen 2003; Tiainen 2005) were reports of the HACA 2002 study.

Included studies

We included six studies (Bernard 2002; HACA 2002; Hachimi-Idrissi 2001; Laurent 2005; Mori 2000; Nielsen 2013) (see Characteristics of included studies) in this updated review.

The first study (Hachimi-Idrissi 2001) was a feasibility RCT carried out at one 700-bed teaching hospital in Brussels during a six month period. It included 33 consecutive participants with out-of-hospital cardiac arrest and asystole or pulseless electrical activity (PEA) of presumed cardiac origin who achieved return of spontaneous circulation (ROSC). The mean age of participants was 72, and 39% were female. After admission and stabilization, participants were randomly assigned to (1) a helmet device placed around the

head and neck containing a solution of aqueous glycerol, or (2) standard therapy without hypothermia. The target temperature of the intervention group was 34°C, which should be maintained over a period of four hours; this was followed by a passive rewarming phase over eight hours. Outcome parameters were laboratory values and haemodynamics, survival to hospital discharge and overall performance categories (OPCs) and adverse events. No information on funding was provided.

Two studies were published at the same time (Bernard 2002; HACA 2002). The study by Bernard 2002 was a quasi-RCT carried out by the ambulance service of Melbourne and four adjacent emergency departments and intensive care units over a three-year period. It included 77 participants with out-of-hospital cardiac arrest and ventricular fibrillation as first cardiac rhythm who were comatose after they achieved ROSC. The mean age of participants was 66, and 33% were female. Participants were randomly assigned by the ambulance staff to receive (1) therapeutic hypothermia by ice packs placed around the head, neck, torso and limbs, or (2) standard therapy without hypothermia. The target temperature of the intervention group was 33°C, which should be maintained over a period of 24 hours; this was followed by a passive rewarming phase over eight hours. Outcome parameters were survival with good neurological function; in-hospital mortality; haemodynamic, biochemical and haematological effects of hypothermia; and adverse events. No information on funding was provided.

HACA 2002 was an RCT carried out by nine centres in five European countries and four adjacent emergency departments

and intensive care units over a five-year period. It included 275 participants with out-of-hospital bystander-witnessed cardiac arrest of presumed cardiac cause, ventricular fibrillation or non-perfusing ventricular tachycardia as first cardiac rhythm, who were comatose after resuscitation. The mean age of participants was 59, and 24% were female. After admission, participants were randomly assigned to receive (1) therapeutic hypothermia by an external cooling device, or (2) standard therapy without hypothermia. The target temperature of the intervention group was 32°C to 34°C, which should be maintained over a period of 12 hours; this was followed by a passive rewarming phase over 12 hours and, if necessary, active rewarming after 18 hours. Outcome parameters were survival, neurological outcome and adverse events. Funding was provided by grants of the Fourth Research and Technological Development (RTD) Framework Programme 1994 to 1998 of the European Union ([Fourth Framework Programme](#)), the Austrian Ministry of Science and Transport and the Austrian Science Foundation (FWF).

[Laurent 2005](#) was an RCT carried out at two intensive care units in Paris over a two-year period. It included 42 participants with out-of-hospital cardiac arrest of presumed cardiac cause, ventricular fibrillation or asystole as first cardiac rhythm, who were comatose after resuscitation. The mean age of participants was 52 to 56 years, and 19% were female. After admission, participants were randomly assigned to receive (1) high-flow haemofiltration, (2) high-flow haemofiltration plus therapeutic hypothermia or (3) standard therapy without hypothermia. The target temperature of the intervention group was 32°C to 34°C, which should be maintained over a period of 24 hours; this was followed by a passive rewarming phase over 12 hours. Outcome parameters were survival, neurological outcome and adverse events. For this study, haemofiltration circuits, catheters and replacement fluid concentrates were provided by GAMBRO ([GAMBRO](#)).

[Mori 2000](#) was published as an abstract with additional information provided by study authors. It was carried out at a University hospital in Sapporo, Japan, and included 54 participants with out-of-hospital cardiac arrest with a Glasgow Coma Scale (GCS) score less than eight after resuscitation. After admission, participants were randomly assigned to receive (1) therapeutic hypothermia by water-circulating blankets above and below the participant with another ice mounted blanket over the participant, or (2) standard therapy without hypothermia. The target temperature of the intervention group was 32°C to 34°C, which should be maintained over a period of three days. The reported outcome parameter was neurological outcome. Study authors provided no information on funding.

[Nielsen 2013](#), which was published recently, was carried out at 36 intensive care units (ICUs) in Europe and Australia over a three-year

period. It included 950 adults with out-of-hospital cardiac arrest of presumed cardiac cause and sustained return of spontaneous circulation who were comatose after resuscitation (GCS < 8). The mean age of participants was 64 years, and 19% were female. After admission, participants were randomly assigned to receive (1) temperature management at 33°C (method of choice was up to the discretion of treating physicians), or (2) temperature management at 36°C (method of choice was up to the discretion of treating physicians). The target temperature of the intervention group was 32°C to 34°C, which should be maintained over a period of 24 hours; this was followed by a rewarming phase over eight hours. Outcome parameters were survival and neurological and functional outcomes. Funding was provided by the Swedish Heart-Lung Foundation and others.

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 from the standard cooling methods used in the other RCTs; therefore, we did not pool data with those from remaining studies. We now successfully contacted Kazuhisa Mori and Eric Dickson, who provided relevant details of their study ([Mori 2000](#)). On the basis of cooling methods and clinical characteristics, the remaining four studies appeared appropriate for pooling in the main analysis ([Bernard 2002](#); [HACA 2002](#); [Hachimi-Idrissi 2001](#); [Mori 2000](#)).

Excluded studies

We excluded three studies; one was a substudy to the [Nielsen 2013](#) trial that provided no extra information relevant to our review ([CAEP/ACMU 2013](#)), and for two, inclusion criteria for the intervention or control group did not apply ([Lopez-de-Sa 2012](#); [Takeda 2009](#)) (see [Characteristics of excluded studies](#)).

Ongoing studies

We identified no ongoing studies.

Awaiting classification

No studies are awaiting classification.

Risk of bias in included studies

We assessed each included trial by using 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](#); and [Figure 3](#)). Risk of bias in the included studies was generally low, with relevant deficits noted in three out of six studies.

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

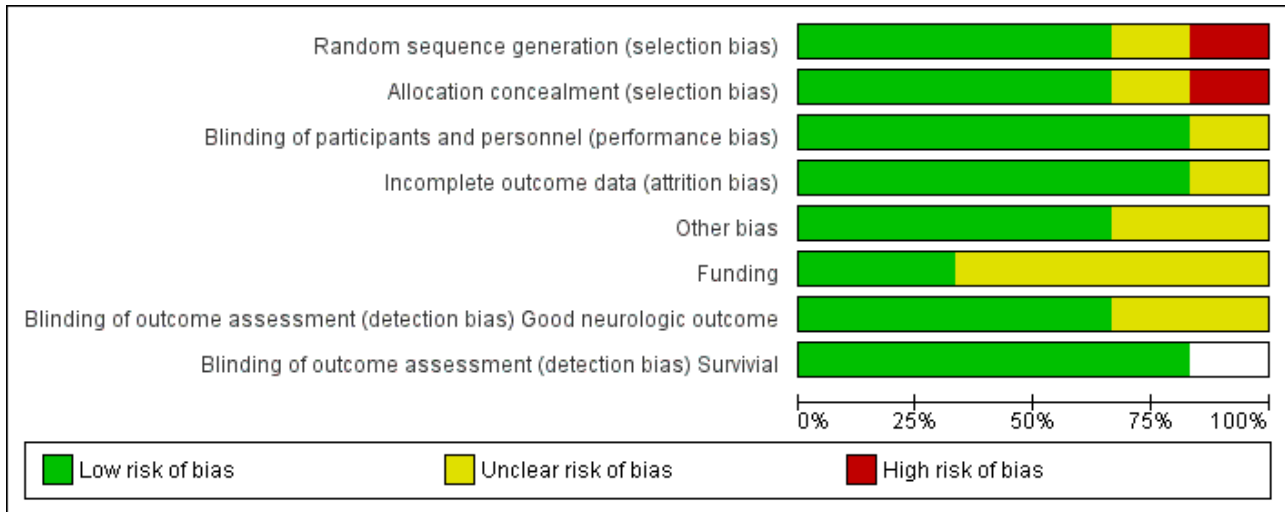


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Incomplete outcome data (attrition bias)	Other bias	Funding	Blinding of outcome assessment (detection bias) Good neurologic outcome	Blinding of outcome assessment (detection bias) Survival
Bernard 2002	⊖	⊖	⊕	⊕	⊕	?	⊕	⊕
HACA 2002	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕
Hachimi-Idrissi 2001	⊕	⊕	⊕	⊕	⊕	?	⊕	⊕
Laurent 2005	⊕	⊕	⊕	⊕	⊕	?	?	⊕
Mori 2000	?	?	?	?	?	?	?	
Nielsen 2013	⊕	⊕	⊕	⊕	?	⊕	⊕	⊕

Figure 3. (Continued)



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 showed deficits in the randomization process and adjustments made for inequalities in baseline characteristics between treatment and control groups (Bernard 2002). Follow-up was generally good in the included studies. In HACA 2002, hypothermia was discontinued in 14 participants because of death, arrhythmia, haemodynamic instability and technical problems with the cooling device; in one case because of liver rupture; in another because a randomly assigned participant had already been included in the study before cooling, and in another case because of an error in the duration of cooling. These participants were included in the intention-to-treat analysis of primary and secondary outcomes.

Allocation

Three trials (HACA 2002; Hachimi-Idrissi 2001; Laurent 2005) reported adequate randomization methods and 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 on two participants for the primary endpoint (HACA 2002). All other studies reported complete follow-up.

Selective reporting

We found no indication of selective outcome reporting.

Other potential sources of bias

In two studies, treatment and control groups did not differ significantly in terms of reported baseline characteristics (Hachimi-Idrissi 2001; Laurent 2005), although Hachimi-Idrissi 2001 included rather small groups.

HACA 2002 described baseline differences between groups. Participants 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. Study authors adjusted for all baseline variables, and the risk ratio increased slightly, from 1.40 (95% 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 adjust for this possible bias.

Mori 2000 provided no information on baseline characteristics of participant groups.

Effects of interventions

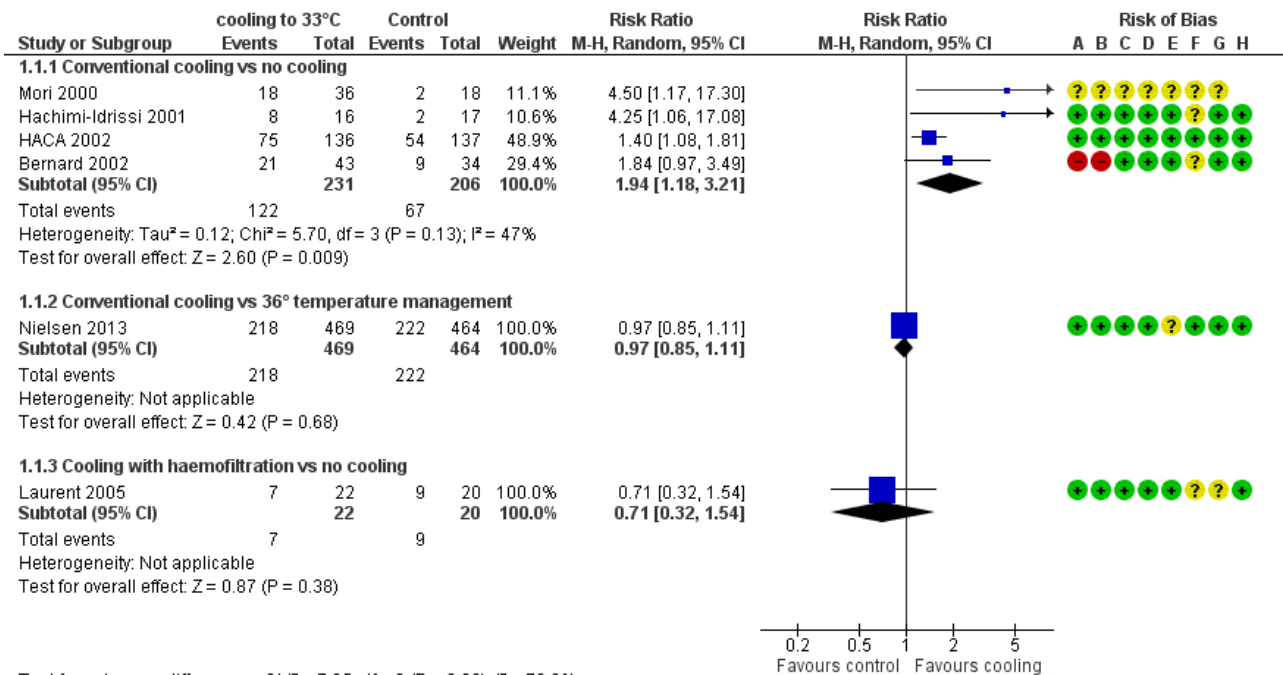
See: [Summary of findings for the main comparison Neurological outcome, survival and adverse events: conventional cooling compared with no cooling and 36°C for neuroprotection and survival in adults after cardiopulmonary resuscitation](#)

Primary outcome

Good neurological outcome

With four studies (Bernard 2002; HACA 2002; Hachimi-Idrissi 2001; Mori 2000) (437 participants) reporting on conventional cooling methods compared with no cooling, the pooled result showed a better neurological outcome for the conventional cooling group (RR 1.94, 95% CI 1.18 to 3.21; I² statistic = 47%; see Figure 4; and Data and analyses). The quality of the evidence was moderate. We downgraded the quality of the evidence as the result of imprecision. One study included 42 participants undergoing haemofiltration after cardiac arrest (Laurent 2005); this introduced considerable clinical heterogeneity and prevented pooling with the studies described above. Cooling using haemofiltration did not result in a difference in good neurological outcome (RR 0.71, 95% CI 0.32 to 1.54; see Figure 4). The quality of the evidence was very low. We downgraded the quality of the evidence as the result of risk of bias, imprecision and indirectness. Another study evaluated the effects of conventional cooling versus targeted temperature management at 36°C (Nielsen 2013). Investigators (Nielsen 2013) noted no effects on neurological outcome if therapeutic hypothermia at 33°C was compared with temperature management at 36°C (RR 0.97, 95% CI 0.85 to 1.11; 933 participants; see Figure 4). The quality of the evidence was moderate. We downgraded the quality of the evidence for this single but large RCT as the result of indirectness.

Figure 4. Forest plot of comparison: 1 Neurological outcome: therapeutic hypothermia versus no hypothermia, outcome: 1.1 All studies with subgroups.



Test for subgroup differences: Chi² = 7.65, df = 2 (P = 0.02), I² = 73.9%

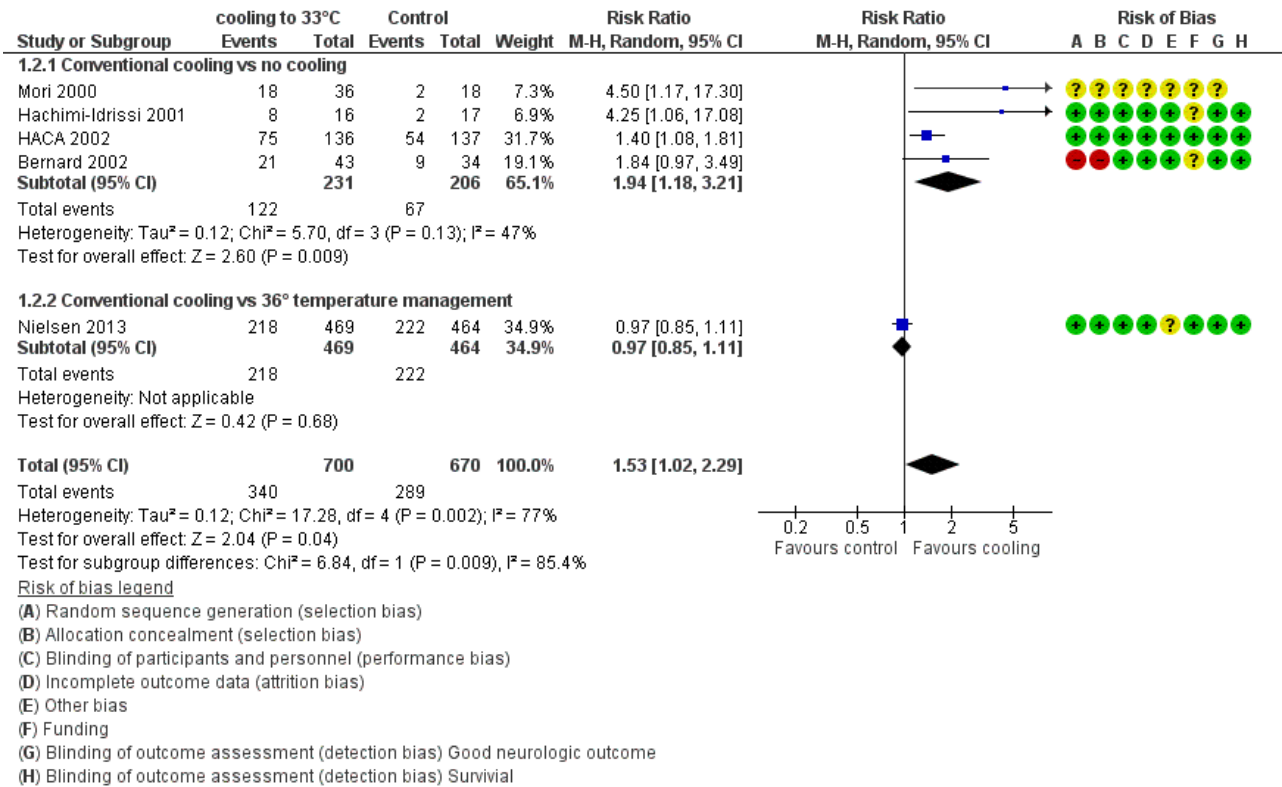
Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Incomplete outcome data (attrition bias)
- (E) Other bias
- (F) Funding
- (G) Blinding of outcome assessment (detection bias) Good neurologic outcome
- (H) Blinding of outcome assessment (detection bias) Survival

When data from all studies that used conventional cooling methods regardless of the control treatment (Bernard 2002; HACA 2002; Hachimi-Idrissi 2001; Mori 2000; Nielsen 2013) were pooled, cooling to 33°C was still superior to no cooling or temperature management at 36°C (RR 1.53, 95% CI 1.02 to 2.29; P value = 0.04; see Figure 5). However, we found considerable heterogeneity when pooling all of these studies (heterogeneity: tau² = 0.12; Chi² = 17.28; df = 4 (P value = 0.002); I² statistic = 77%), possibly because a different control group treatment was given in one study (Nielsen 2013). The

test for subgroup differences according to control group treatment (no cooling vs target temperature at 36°C) was highly positive (Chi² = 6.84; df = 1 (P value = 0.009)). Cautious interpretation of this effect is therefore warranted, but to inform the current discussion, we present the pooled estimate for the primary outcome despite obvious limitations here and restrict the summary of findings to findings with the least ambiguity (Summary of findings for the main comparison).

Figure 5. Forest plot of comparison: 1 Neurological outcome: therapeutic hypothermia versus no hypothermia, outcome: 1.2 Conventional cooling.



Subgroup analyses - IPD level

Influence of cardiac arrest conditions

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

- The risk for participants with a cardiac cause (n = 372; three studies; Bernard 2002; HACA 2002; Hachimi-Idrissi 2001) and VF or VT was 1.51 (95% CI 1.19 to 1.91; n = 330; two studies; Bernard 2002; HACA 2002).
- Groups of participants with non-VF or VT rhythm as the first cardiac rhythm (n = 52; participants with a non-cardiac cause - n = 11, and in-hospital arrests - n = 17) were small and showed no statistically significant effects (non-VF or VT: RR 2.17, 95% CI 0.68 to 6.93; I² statistic = 50%; two studies; HACA 2002; Hachimi-Idrissi 2001) (non-cardiac cause: RR 3.80, 95% CI 0.55 to 26.29; I² statistic = 0%; two studies; HACA 2002; Hachimi-Idrissi 2001) (in-hospital: RR 1.64, 95% CI 0.47 to 5.73).
- A small number of participants had non-witnessed arrest (n = 22). Among these participants, effect size was substantially greater than the summary effect for the whole study population (RR 5.31, 95% CI 1.40 to 20.21; I² statistic = 0%; three studies; Bernard 2002; HACA 2002; Hachimi-Idrissi 2001).

- For participants with witnessed cardiac arrest (n = 360), the risk ratio was 1.43 (95% CI 1.13 to 1.81; I² statistic = 0%; three studies; Bernard 2002; HACA 2002; Hachimi-Idrissi 2001).

Sensitivity analysis

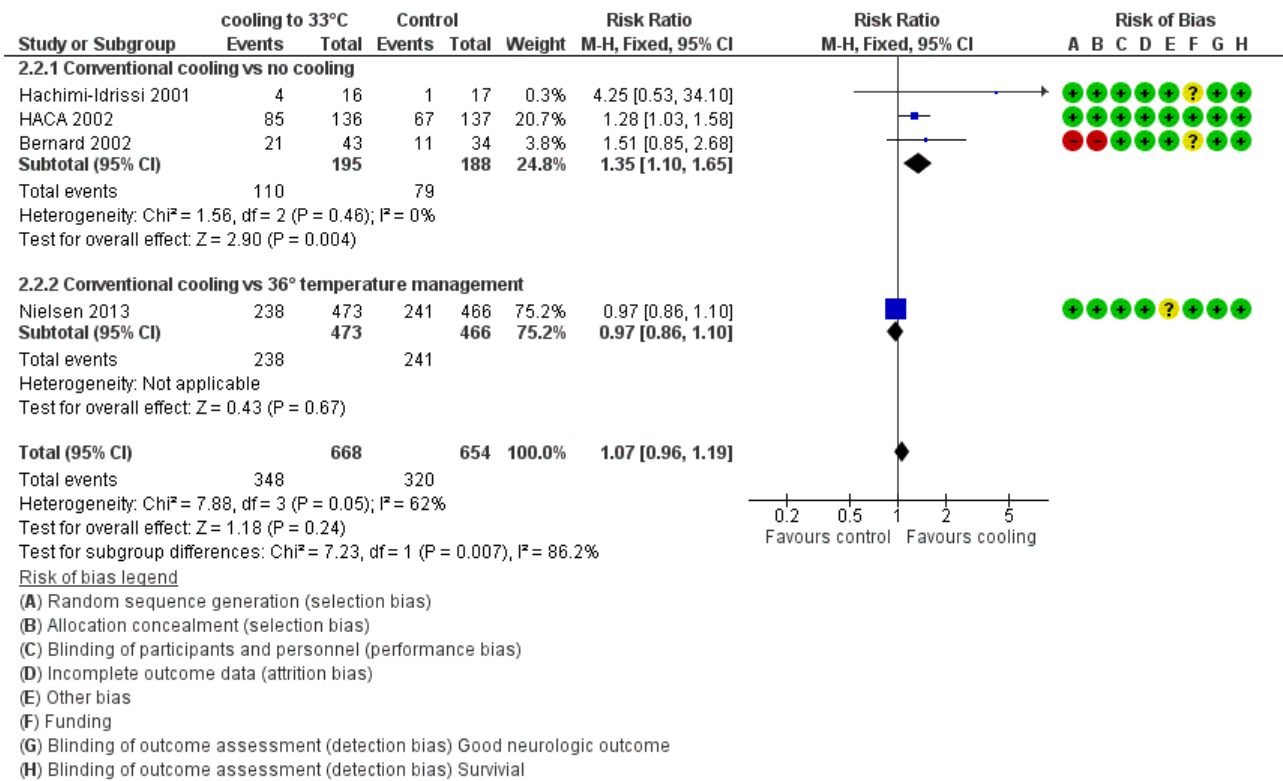
Robustness against risk of bias in individual studies

Two out of four studies (445 participants) reported on adequate allocation concealment (HACA 2002; Hachimi-Idrissi 2001); for one study (Mori 2000; 54 participants), we had no further information, and in another study, allocation concealment was not adequate (Bernard 2002; 77 participants; see Figure 3). Pooling of data for studies in which allocation concealment was adequate or unknown (medium risk) resulted in an effect size that was even augmented (from 1.94 to 2.46; three studies; see Table 2). Pooling of data for studies in which allocation concealment was adequate (low risk) led to an effect size that was virtually unchanged (from 1.94 to 1.97; two studies). Overall effects appeared robust against deficits in allocation concealment.

Influence of model choice

To investigate whether model choice might influence results, we compared estimates from random-effects models with those from fixed-effect models. The effect estimate as presented in Figure 4 did not change much by model choice (fixed-effect RR 1.67, 95% CI 1.32 to 2.11; random-effects RR 1.94, 95% CI 1.18 to 3.21), indicating that the effect is robust against the model choice.

Figure 7. Forest plot of comparison: 3 Survival: therapeutic hypothermia versus no hypothermia, outcome: 3.2 Conventional cooling.



Long term survival

We found no data on this outcome.

Quality of life at six months and long term

We found no data on this outcome.

Dependency

Nielsen 2013 reported on the modified Rankin Scale at six months (RR 1.01, 95% CI 0.89 to 1.14; P value = 0.87). We found no additional data on this outcome.

Cost-effectiveness

We found no data on this outcome.

Adverse events

We included in the analysis all trials that reported on adverse events, regardless of heterogeneity. The following adverse events were reported in five studies (Bernard 2002; HACA 2002; Hachimi-Idrissi 2001; Laurent 2005; Nielsen 2013; 1358 participants): bleeding of any severity and at various locations, need for platelet transfusions, pneumonia, sepsis, pancreatitis, renal failure or oliguria, haemodialysis, pulmonary oedema, seizures, atrial fibrillation/flutter, lethal or long-lasting arrhythmias, cardiac complications and electrolyte and metabolic imbalances (see Table 3).

Two studies with 1205 participants (HACA 2002; Nielsen 2013) reported pneumonia, which was more frequent in the treatment group (RR 1.15, 95% CI 1.02 to 1.30; see Summary of findings for the

main comparison). The quality of the evidence was moderate. We downgraded the quality of the evidence as the result of indirectness (differences in control groups - no temperature management and 36°C). Hypokalaemia was reported in two studies (Laurent 2005; Nielsen 2013) including 975 participants and was more frequent in the intervention group (RR 1.38, 95% C 1.03 to 1.84). The quality of the evidence was low. We downgraded the quality of the evidence as the result of very serious indirectness (differences in intervention - conventional cooling and haemofiltration - and control groups). Otherwise, researchers observed no significant differences between groups.

DISCUSSION

Summary of main results

Evidence from five studies with 1370 participants contributing data to the primary outcomes of this review showed that therapeutic hypothermia with conventional cooling methods improved neurological outcome after cardiac arrest. The impact on survival was less certain, but a strong effect was evident when therapeutic hypothermia was compared with no temperature management.

Overall completeness and applicability of evidence

All studies reported on the same outcomes and, except for Mori 2000, for which we did not receive further information, all outcome assessors were blinded to treatment (Bernard 2002; HACA 2002; Hachimi-Idrissi 2001; Laurent 2005; Nielsen 2013). The cerebral performance category (CPC) is well standardized and easy to

measure, and gives a crude approximation of the person's ability to perform tasks of daily life. One of its limitations is lack of accuracy when it comes to estimating cognitive functions and personal and social impact of cardiac arrest.

After completing our literature search, we were able to include individual patient data (IPD) for only three out of five eligible studies retrieved (Bernard 2002; HACA 2002; Hachimi-Idrissi 2001). Therefore, we had to omit the IPD analysis and could calculate only subgroup analyses using available data. Subsequently, precision in the subsets of participants was humble and maybe was too low to permit firm conclusions about the subgroups.

One of the challenges of this review was heterogeneity at the study level. In the case of Laurent 2005, the two treatment modalities (mild therapeutic hypothermia with and without haemodialysis) were clinically too heterogeneous to be combined with those of other studies. As mentioned in the Background section, one of the theories of the beneficial effects of cooling deals with attenuation of the effects of free radicals and other mediators. Haemofiltration may act in a similar way, by reducing the number of free radicals. This effect is likely to interact with the effect of therapeutic hypothermia.

Control group treatment is another important driver for heterogeneity. Nielsen 2013 differed considerably in terms of control group treatment, as investigators used a target temperature of 36°C in contrast to no temperature management as employed by the other studies. Despite seemingly subtle differences, this can be expressed as two distinct clinical questions: 'Does mild therapeutic hypothermia compared with no mild therapeutic hypothermia at all influence outcome?' versus 'Does temperature management targeted to 33°C compared with 36°C influence outcome?' These questions were often ignored in clinical discussions, however. To meet concerns of heterogeneity and at the same time give a better picture of available data, we decided to perform an ancillary analysis. Without temperature management in the control group, therapeutic hypothermia at 32°C to 34°C improves neurological outcome after cardiac arrest, and this effect persists when the control group receives active temperature management at 36°C. Whether 36°C, cooling to 32°C to 34°C and no cooling are equally effective can be judged only by an indirect comparison. This indirect comparison however should be performed when a sufficient degree of transitivity is present, which is not necessarily the case here (Storm 2014; Stub 2014).

In our sensitivity analysis, the effect was robust against allocation concealment and model choice.

Many cooling methods are available, ranging from expensive device-controlled methods to very cheap cold fluids and ice packs. Proof of superiority of any cooling method above others is still lacking.

After 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). The publication of the Targeted Temperature Management (TTM) trial (Nielsen 2013) has led to ongoing discussion about optimal levels of target temperature. In their most recent statement, ILCOR members have advised that "Pending formal consensus on the optimal temperature, we suggest that

clinicians provide post-resuscitation care based on the current treatment recommendations. We accept that some clinicians may make a local decision to use a target temperature of 36°C pending this further guidance." Similar up-to-date guidelines of the European Resuscitation Council state the following: "Targeted temperature management remains important but there is now an option to target a temperature of 36°C instead of the previously recommended 32 to 34°C" (Soar 2015), and the American Heart Association provides this advice: "We recommend selecting and maintaining a constant target temperature between 32°C and 36°C for those patients in whom temperature control is used (strong recommendation, moderate quality evidence)" (Callaway 2015).

Investigators have observed that pyrexia after the cooling period is associated with increased mortality and unfavourable neurological outcome (Bro-Jeppesen 2013; Leary 2013; Zeiner 2001). Mean body temperature 12 hours after the 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 the body temperature of the control group. Adding results of Nielsen 2013 slightly reduced the effect size, but 33°C in comparison with higher temperatures still showed a significant and relevant beneficial effect for neurological outcome. A dose-response effect over different levels of hypothermia is possible, but studies are still too few to prove this.

Quality of the evidence

Risk of bias was low for most studies and when present did not strongly influence the estimates. Therefore, we considered the results robust against risk of bias from within the studies, and this was confirmed by our sensitivity analysis.

We downgraded the quality of evidence to moderate for main outcomes, mainly as the result of imprecision, as the number of events fell below the limit of the suggested optimal information size (Guyatt 2011).

We graded indirectness as not relevant for the main analysis of our review because it reflects common practice. Furthermore, 90% (in HACA 2002) and 92% (in Bernard 2002) of all eligible participants were randomly assigned. In Laurent 2005 and Hachimi-Idrissi 2001, inclusion of all eligible participants was reported. Generally, participants within the included studies appeared to be treated according to international guidelines. Indirectness, however, was an issue for the analysis of adverse events, for which we pooled all available studies regardless of differences in intervention and control group treatments.

The included studies represent a mixture of efficacy studies and one larger pragmatic study (Nielsen 2013). All studies were academia initiated.

Potential biases in the review process

One of the problems involved with merging the data for this review was the difference in inclusion criteria. Generally, among all participants resuscitated and brought to hospital, between 18% and 42% have non-witnessed arrests, only 30% to 58% have a confirmed ventricular fibrillation (VF) rhythm as first rhythm (Haukoos 2004; Herlitz 2003a; Kim 2001) and 40% are resuscitated in-hospital. In this review, the two larger studies with available IPD included only participants with a cardiac cause of cardiac arrest, and with VF or ventricular tachycardia (VT) rhythm as the

first cardiac rhythm (Bernard 2002; HACA 2002). Most participants had an out-of-hospital cardiac arrest. From the pathogenesis of global cerebral ischaemias and theories as to why therapeutic hypothermia is effective, we could find no reason why therapeutic hypothermia should not be as effective in participants with asystole as the first cardiac rhythm or in those with 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).

The trial by Mori 2000 and colleagues was published as an abstract. In personal communications, we were able to receive information about the cooling method but not about quality criteria for this randomized controlled trial. Therefore, we have rated most of the quality criteria in our risk of bias assessment as 'unclear'.

The most recent study (Nielsen 2013) was the largest one in this field of research. Adding these data introduced considerable heterogeneity, which we had not observed with the existing studies. A clinical viewpoint suggests various reasons, the most obvious being the control group, which was kept at 36°C and not 'no cooling' as in other studies. The design of Nielsen 2013 was a pragmatic one (multi-centre, different methods of cooling, etc.), which may not be suitable as long as the cooling 'dose', which is mainly target temperature and cooling duration, is not unequivocally characterized in proof of concept studies. Additionally, Nielsen 2013 had a very short duration from collapse to resuscitation (one minute) compared with the other trials (around 10 minutes). Reports show that the effect of therapeutic hypothermia depends strongly on this no flow time (Testori 2012). Knowing whether the results of this study should be added to existing data, especially as they caused a high level of heterogeneity, was challenging. To provide the most informative picture of all levels of hypothermia, we have decided to present an ancillary analysis at the study level. Despite controversial arguments against and for pooling of all studies, a beneficial and statistically significant effect on neurological outcome was seen when all studies on conventional cooling were pooled (RR 1.53, 95% CI 1.02 to 2.29).

For the subgroup of participants with non-witnessed arrests, we observed an effect size substantially greater 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 participants only) and yielded large confidence intervals. Although it seems that participants benefited from the treatment provided, the result should be interpreted with caution.

Agreements and disagreements with other studies or reviews

We are aware of three other meta-analyses with similar objectives. The meta-analysis by Holzer 2005 is very similar to the one

performed in our review method-wise and in many ways was a predecessor to the first version of this 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 in 2011 (Nielsen 2011). The review authors judged the overall quality of the included studies to be at a lower level than we did in our review. From the available five studies, they combined four and five on the basis of 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 more conservative than ours. We found a third meta-analysis published recently, which focused on the safety effects of therapeutic hypothermia (Xiao 2013). Upon pooling randomized and non-randomized studies, review authors found overall better survival with therapeutic hypothermia with a slightly elevated incidence of arrhythmia and hypokalaemia.

AUTHORS' CONCLUSIONS

Implications for practice

Moderate-quality evidence suggests that conventional cooling methods to induce mild therapeutic hypothermia improve neurological outcome after cardiac arrest, specifically if compared with no temperature management. Available evidence was derived from studies in which the target temperature was 34°C or lower. This is in line with current best medical practice as recommended by international resuscitation guidelines (Callaway 2015; Soar 2015) on using hypothermia/targeted temperature management for survivors of cardiac arrest. We had insufficient evidence to determine the effects of therapeutic hypothermia on participants with in-hospital cardiac arrest, asystole or non-cardiac causes of arrest.

Implications for research

A considerable knowledge gap for what constitutes an optimal cooling protocol is ongoing. Available clinical trials on therapeutic hypothermia comprise a variety of patient populations and modes of hypothermia. It remains specifically unclear what the ideal target temperature should be. Likewise, it is unclear for what period of time targeted temperature management should be maintained. Whether cooling should be initiated prehospital or in-hospital needs further research. We expect that mild therapeutic hypothermia exerts its effects differently across subgroups of participants, but evidence is lacking. Evaluation of a possible dose-response effect of therapeutic hypothermia would shed some light on an optimal treatment regimen with ample room for cost-effectiveness analyses.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES
Characteristics of included studies [ordered by study ID]

Bernard 2002

Methods	Randomization: pre-hospital
Participants	<p>Total number of participants 77, mean age 66 years, 33% female</p> <p>Out-of-hospital cardiac arrest of cardiac cause, ventricular fibrillation as first cardiac rhythm, comatose after resuscitation</p> <p>Participating sites: Australian university and community hospitals</p> <p>Multi-centre: yes</p> <p>Language: English</p> <p>Allocation concealment: not applicable (odd and even days)</p> <p>Outcome assessor blind: yes</p> <p>Intention-to-treat analysis: yes</p> <p>Groups comparable: more females and more bystander CPR in hypothermia group</p> <p>Follow-up > 80% of randomly assigned participants: yes</p>
Interventions	<p>Therapeutic hypothermia vs standard pre-hospital treatment protocols and intensive care treatment</p> <p>Means of cooling: ice packs placed around head, neck, torso and limbs</p> <p>Cooling rate: time from ROSC to target temperature: 2 hours</p> <p>Target temperature: 33°C</p> <p>Duration of cooling: 12 hours after target temperature was reached</p> <p>Rewarming: passive after 12 hours, active after 18 hours</p>
Outcomes	<p>Survival with good neurological function to be sent home or to a rehabilitation facility at discharge</p> <p>In-hospital death</p> <p>Haemodynamic, biochemical and haematological effects of hypothermia</p> <p>For IPD analysis, best ever reached CPC during hospital stay and CPC discharge provided</p>

Bernard 2002 (Continued)

Notes Randomization: odd and even days

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Odd and even days
Allocation concealment (selection bias)	High risk	Odd and even days
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treating personnel not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up
Other bias	Low risk	No other major biases seen
Funding	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) Good neurologic outcome All outcomes	Low risk	Outcome assessment blinded
Blinding of outcome assessment (detection bias) Survival Survival	Low risk	Outcome assessment blinded

HACA 2002

Methods Randomization: in hospital

Participants Total number of participants 275, mean age 59 years, 24% female

In-hospital 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

Multi-centre: yes

Language: English

Allocation concealment: opaque envelopes

Outcome assessor blind: yes

Intention-to-treat analysis: yes

HACA 2002 (Continued)

Groups comparable: significantly more diabetes and coronary heart disease and bystander CPR in control group

Follow-up > 80% of randomly assigned participants: yes

Interventions	<p>Therapeutic hypothermia vs standard intensive care treatment</p> <p>Means of cooling: cooling blanket that covered the whole body and released cooled air</p> <p>Cooling rate: time from ROSC to target temperature: median of 8 hours</p> <p>Target temperature: 32°C to 34°C</p> <p>Duration of cooling: median 24 hours</p> <p>Rewarming: passive over 8 hours</p>
Outcomes	<p>Best CPC of 1, 2 vs CPC of 3, 4, 5 during 6 months</p> <p>Mortality at 6 months, rate of complication during first 7 days after cardiac arrest (bleeding of any severity)</p> <p>Pneumonia, sepsis, pancreatitis, renal failure, pulmonary oedema, seizures, arrhythmias and pressure sores</p> <p>For IPD analysis, best ever reached CPC during hospital stay and CPC discharge provided</p>
Notes	<p>Randomization: computer-generated random sequence</p> <p>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</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment assignments randomly generated by computer in blocks of 10, with stratification according to centre
Allocation concealment (selection bias)	Low risk	Sealed envelopes containing treatment assignments provided by biostatistics centre
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Personnel involved in care of patients during first 48 hours after cardiac arrest could not be blinded to treatment assignments
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two participants lost to follow-up, properly addressed
Other bias	Low risk	No other major biases seen
Funding	Low risk	Supported by grants of the Fourth RTD Framework Programme 1994–1998 of the European Union, the Austrian Ministry of Science and Transport and the Austrian Science Foundation
Blinding of outcome assessment (detection bias) Good neurologic outcome	Low risk	Personnel involved in care of patients during first 48 hours after cardiac arrest could not be blinded to treatment assignments. However, physicians respon-

HACA 2002 (Continued)

All outcomes		sible for assessing neurological outcome within first 6 months after the arrest unaware of treatment assignments
Blinding of outcome assessment (detection bias) Survival Survival	Low risk	Assessors of survival within first 6 months after arrest were unaware of treatment assignments

Hachimi-Idrissi 2001

Methods	Randomization: in-hospital	
Participants	Total number of participants 33, mean age 72 years, 39% female Out-of-hospital cardiac arrest of cardiac cause, pulseless electrical activity or asystole as first cardiac rhythm, comatose after resuscitation Participating site: Belgian university hospital Multi-centre: no Language: English Outcome assessor blind: yes Intention-to-treat analysis: yes Groups comparable: yes, although groups were small, no significant differences Follow-up > 80% of randomly assigned participants: yes	
Interventions	Therapeutic hypothermia vs standard post-resuscitation care protocol Means of cooling: helmet device placed around 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, 4 hours Rewarming: passive over 8 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 (OPCs) For IPD analysis, best ever reached CPC during hospital stay and CPC discharge provided	
Notes	Randomization: random number tables IPD included 33 participants; article reported on only 30, as follow-up was not completed at the time of submission	

Risk of bias

Bias	Authors' judgement	Support for judgement
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Hachimi-Idrissi 2001 (Continued)

Random sequence generation (selection bias)	Low risk	Random sequence generated with random number tables
Allocation concealment (selection bias)	Low risk	After stabilization and insertion of catheters, participants prospectively blindly randomly assigned to 2 groups (treatment allocation concealed by use of opaque envelopes)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treating personnel not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Differences between published report and IPD properly reported
Other bias	Low risk	No other major biases seen
Funding	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) Good neurologic outcome All outcomes	Low risk	Outcome assessors blind to the intervention
Blinding of outcome assessment (detection bias) Survival Survival	Low risk	Outcome assessors blind to the intervention

Laurent 2005

Methods	Randomization: pre-hospital
Participants	<p>Total number of participants 42, mean age 52 years in HF group, 56 years in HF+HT group, 19% female</p> <p>Out-of-hospital cardiac arrest of presumed cardiac cause, ventricular fibrillation or asystole as first cardiac rhythm, comatose after resuscitation</p> <p>Participating sites: French university and community hospital</p> <p>Multi-centre: yes</p> <p>Language: English</p> <p>Allocation concealment: opaque envelopes</p> <p>Outcome assessor blind: not stated</p> <p>Intention-to-treat analysis: yes</p> <p>Groups comparable: yes</p> <p>Follow-up > 80% of randomly assigned participants: yes</p>
Interventions	<p>High-flow haemofiltration vs high-flow haemofiltration + therapeutic hypothermia vs standard supportive care</p> <p>Means of cooling: direct external cooling of blood</p>

Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation (Review)

Laurent 2005 (Continued)

Cooling rate: 4 hours after ICU admission, median temperature 31.7°C

Target temperature: 32°C to 33°C

Duration of cooling: 24 hours

Rewarming: passive

Outcomes	Survival at 6 months Rate of death by intractable shock in participants who had a favourable Glasgow Coma Scale (M5 or M6) or who required sedation Survival at CPC 1, 2 vs all else at 6 months
Notes	Randomization pre-hospital to save time for haemofiltration We did not pool data from this study with data from the other 3 studies, as treatment schemes with haemofiltration are not comparable with treatment schemes with non-haemofiltration treatment (clinical heterogeneity)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated 1/1/1 randomization sequence prepared for each centre
Allocation concealment (selection bias)	Low risk	Participants randomly allocated to treatment by use of sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding to assigned treatment not feasible
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Other bias	Low risk	No other major biases seen
Funding	Unclear risk	For this study, haemofiltration circuits, catheters and replacement fluid concentrates provided by GAMBRO AB, with estimated cost of €120 per participant treated by haemofiltration
Blinding of outcome assessment (detection bias) Good neurologic outcome All outcomes	Unclear risk	Outcome assessor blind: not stated
Blinding of outcome assessment (detection bias) Survival Survival	Low risk	Outcome assessor blind: not stated, but for survival, risk of bias regarded as low

Mori 2000

Methods	Randomization: unknown
Participants	<p>Total number of participants 54, mean age unknown, gender distribution unknown</p> <p>Out-of-hospital cardiac arrest of unknown cause with Glasgow Coma Scale score < 8</p> <p>Participating site: Japanese university hospital</p> <p>Multi-centre: unknown</p> <p>Language of abstract: English</p> <p>Allocation concealment: unknown</p> <p>Outcome assessor blind: not stated</p> <p>Intention-to-treat analysis: unknown</p> <p>Groups comparable: unknown</p> <p>Follow-up > 80% of randomly assigned participants: yes</p>
Interventions	<p>"Brain-hypothermic treatment" vs "brain normothermic treatment"</p> <p>Means of cooling: water-circulating blankets above and below participant with another ice mounted blanket over participant</p> <p>Cooling rate: unknown</p> <p>Target temperature: 32°C to 34°C</p> <p>Duration of cooling: 3 days</p> <p>Rewarming: unknown</p>
Outcomes	Glasgow outcome scale at 1 month (5-point scale). Categories "moderate, mild, or no disabilities" defined as "good neurological outcome"
Notes	<p>Only abstract published</p> <p>Study now included in the pooled analysis, as we received information on the cooling method, whether cooling was applied locally or systemically</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information available from abstract and correspondence
Allocation concealment (selection bias)	Unclear risk	No information available from abstract and correspondence
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information available from abstract and correspondence
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information available from abstract and correspondence

Mori 2000 (Continued)

Other bias	Unclear risk	No information available from abstract and correspondence
Funding	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) Good neurologic outcome All outcomes	Unclear risk	No information available from abstract and correspondence

Nielsen 2013

Methods	Randomization: performed centrally with the use of a computer-generated assignment sequence	
Participants	<p>Total number of participants 950, mean age 64 years, 19% female</p> <p>Age \geq 18 years, out-of-hospital cardiac arrest of presumed cardiac cause, sustained return of spontaneous circulation comatose after resuscitation (GCS < 8)</p> <p>Participating sites: 36 intensive care units (ICUs) in Europe and Australia, university and community</p> <p>Multi-centre: yes</p> <p>Language: English</p> <p>Allocation concealment: centrally</p> <p>Outcome assessor blind: yes</p> <p>Intention-to-treat analysis: modified intention-to-treat analysis</p> <p>Groups comparable: higher incidence of previous AMI and ischaemic heart disease in 33°C group</p> <p>Follow-up > 80% of randomly assigned participants: yes</p>	
Interventions	<p>Group 1: target temperature 33°C</p> <p>Group 2: target temperature 36°C</p> <p>Means of temperature control: ice cold fluids, ice packs and intravascular or surface temperature-management devices at the discretion of sites</p>	
Outcomes	<p>All-cause mortality through the end of the trial</p> <p>CPC of 3 to 5 around 180 days</p> <p>Modified Rankin scale around 180 days</p> <p>Mortality at 180 days</p> <p>Individual neurological scores</p>	
Notes	Control group differs (36°) from control group of other studies (no cooling)	
Risk of bias		
Bias	Authors' judgement	Support for judgement

Nielsen 2013 (Continued)

Random sequence generation (selection bias)	Low risk	Randomization performed centrally with the use of a computer-generated assignment sequence
Allocation concealment (selection bias)	Low risk	Randomization performed centrally
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treating personnel not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	11 out of 950 participants excluded after randomization (for various reasons)
Other bias	Unclear risk	Time from collapse to resuscitation 1 minute - considerably shorter than in other trials Period between return of spontaneous circulation and start of therapy not defined, slow cooling rate Dose-finding study with pragmatic study design - risk of non-effect in both groups and misleading interpretation of equivalence
Funding	Low risk	Funded by the Swedish Heart–Lung Foundation and others
Blinding of outcome assessment (detection bias) Good neurologic outcome All outcomes	Low risk	Outcome assessment blinded
Blinding of outcome assessment (detection bias) Survival Survival	Low risk	Outcome assessment blinded

AMI = acute myocardial infarction
 CPC = cerebral performance category
 CPR = cardiopulmonary resuscitation
 GCS = Glasgow Coma Scale
 HF = haemofiltration
 HT = hypothermia
 ICU = intensive care unit
 IPD = individual patient data
 M5 = localizes painful stimuli
 M6 = obeys commands
 OPC = overall performance category
 ROSC = restoration of spontaneous circulation

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
CAEP/ACMU 2013	Substudy to Nielsen 2013 ; no outcome information on additional patients available
Lopez-de-Sa 2012	Intervention and control groups did not meet inclusion criteria; control group of 34°C and lower

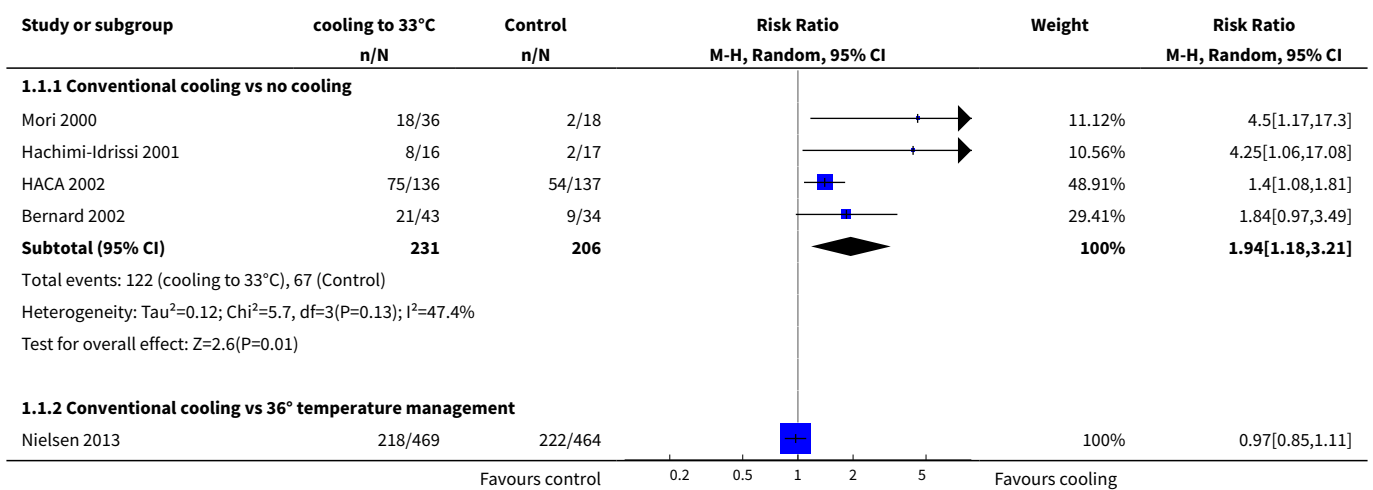
Study	Reason for exclusion
Takeda 2009	Intervention and control groups did not meet inclusion criteria, relevant numbers of participants in control and intervention groups not continuously cooled

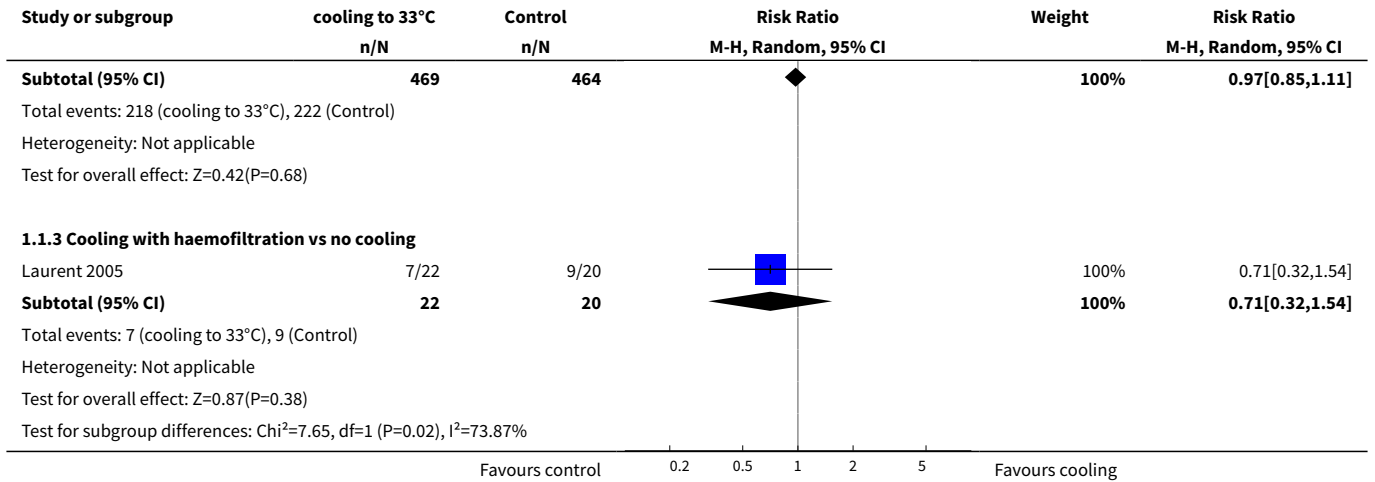
DATA AND ANALYSES

Comparison 1. Neurological outcome: therapeutic hypothermia versus no hypothermia

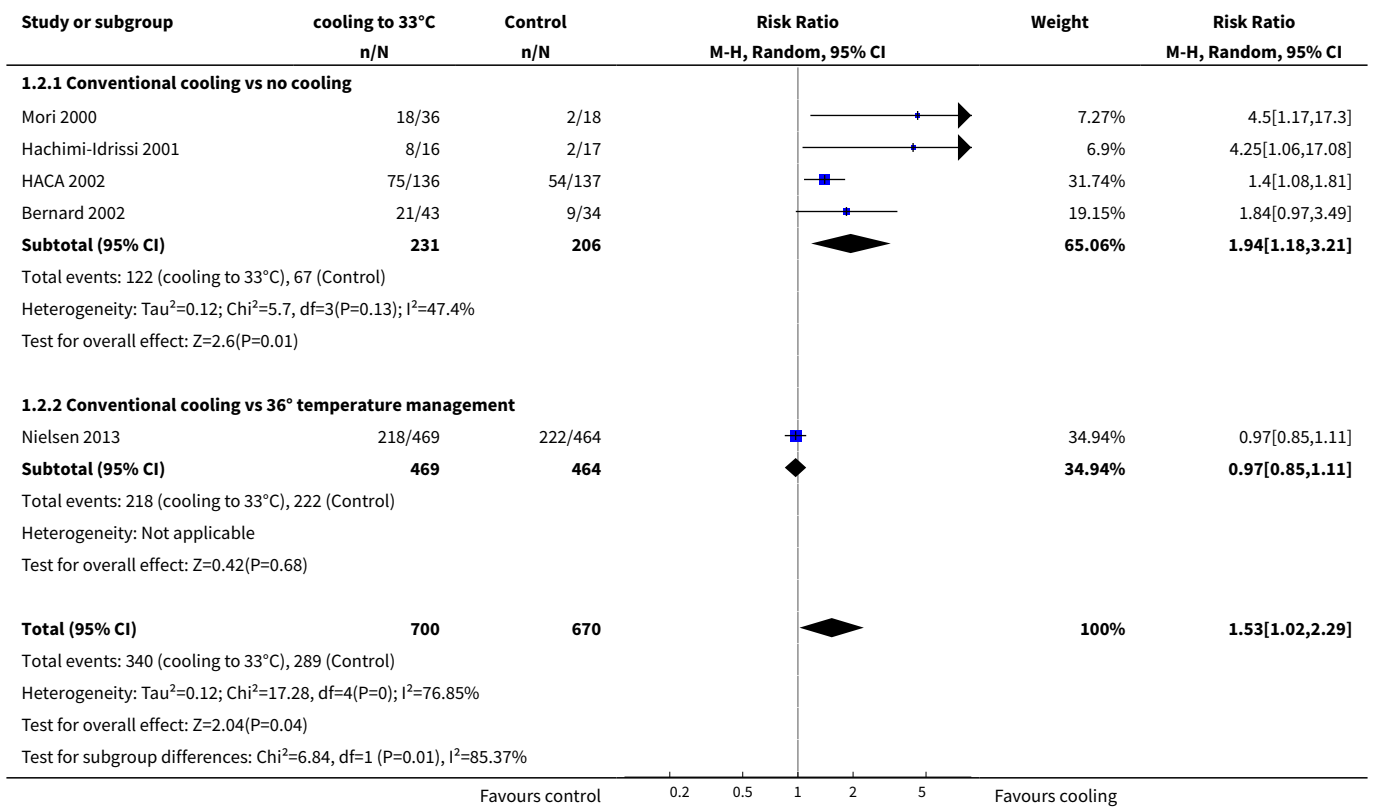
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All studies with subgroups	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Conventional cooling vs no cooling	4	437	Risk Ratio (M-H, Random, 95% CI)	1.94 [1.18, 3.21]
1.2 Conventional cooling vs 36° temperature management	1	933	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.85, 1.11]
1.3 Cooling with haemofiltration vs no cooling	1	42	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.32, 1.54]
2 Conventional cooling	5	1370	Risk Ratio (M-H, Random, 95% CI)	1.53 [1.02, 2.29]
2.1 Conventional cooling vs no cooling	4	437	Risk Ratio (M-H, Random, 95% CI)	1.94 [1.18, 3.21]
2.2 Conventional cooling vs 36° temperature management	1	933	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.85, 1.11]

Analysis 1.1. Comparison 1 Neurological outcome: therapeutic hypothermia versus no hypothermia, Outcome 1 All studies with subgroups.





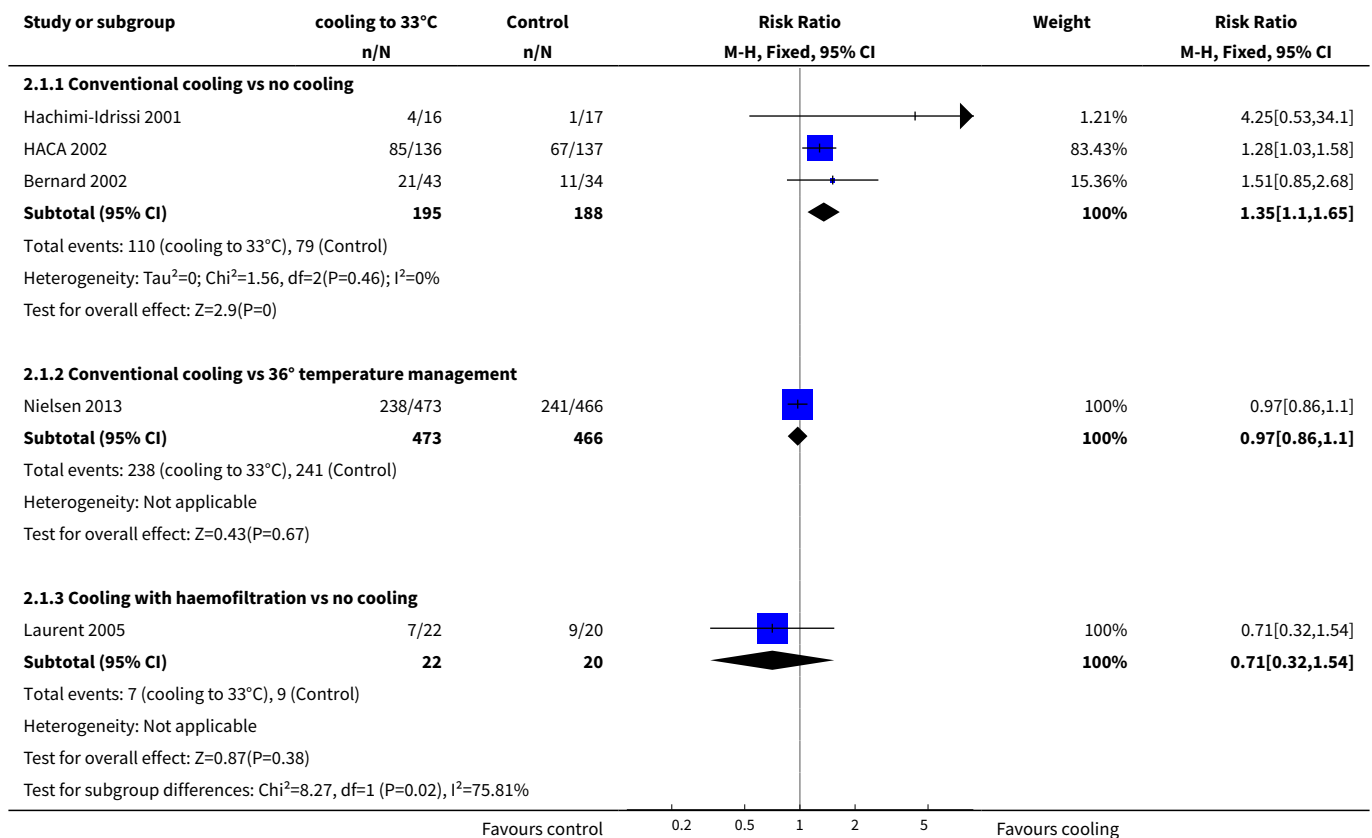
Analysis 1.2. Comparison 1 Neurological outcome: therapeutic hypothermia versus no hypothermia, Outcome 2 Conventional cooling.



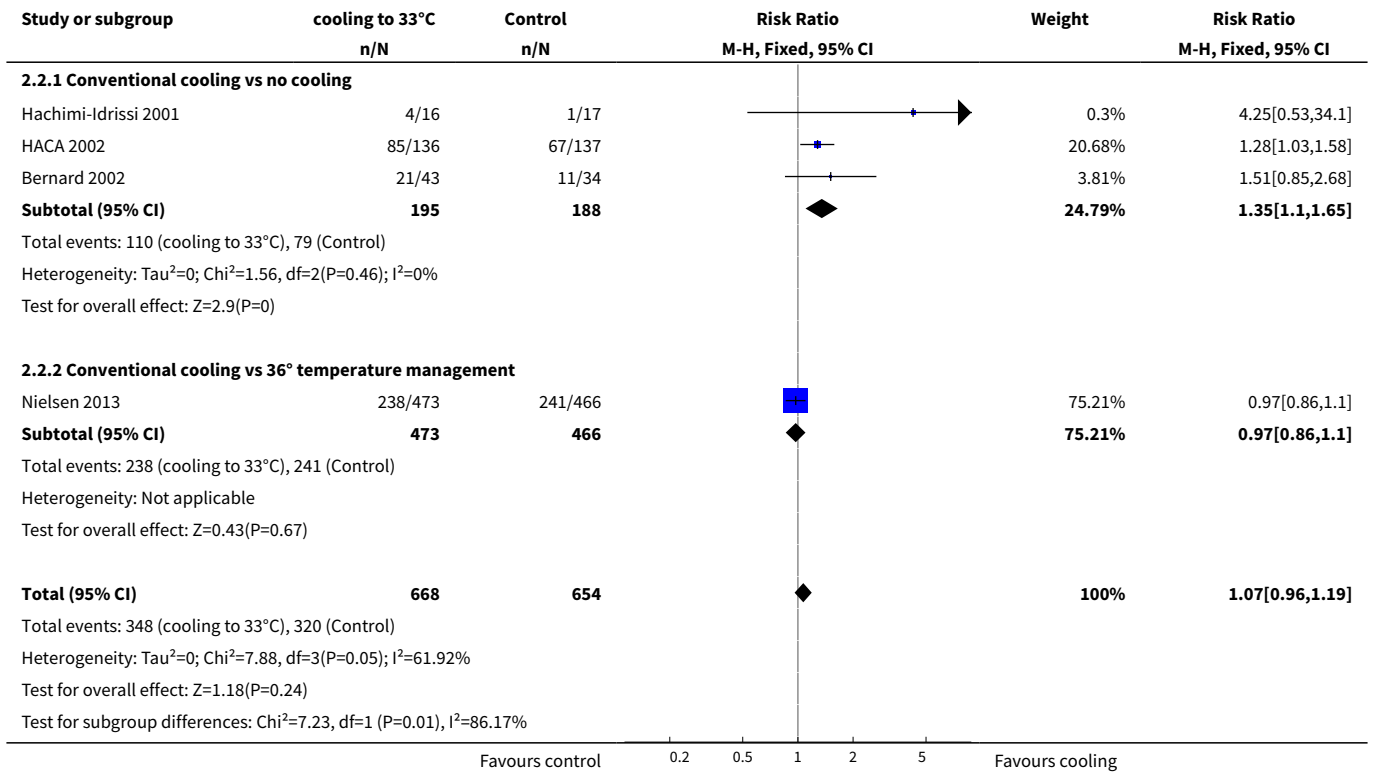
Comparison 2. Survival: therapeutic hypothermia versus no hypothermia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All studies with subgroups	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Conventional cooling vs no cooling	3	383	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [1.10, 1.65]
1.2 Conventional cooling vs 36° temperature management	1	939	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.86, 1.10]
1.3 Cooling with haemofiltration vs no cooling	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.32, 1.54]
2 Conventional cooling	4	1322	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.96, 1.19]
2.1 Conventional cooling vs no cooling	3	383	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [1.10, 1.65]
2.2 Conventional cooling vs 36° temperature management	1	939	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.86, 1.10]

Analysis 2.1. Comparison 2 Survival: therapeutic hypothermia versus no hypothermia, Outcome 1 All studies with subgroups.



Analysis 2.2. Comparison 2 Survival: therapeutic hypothermia versus no hypothermia, Outcome 2 Conventional cooling.



ADDITIONAL TABLES

Table 1. Subgroup analyses

Outcome or subgroup	Studies	Participants	Risk ratio (M-H, fixed, 95% CI)
Good neurological outcome by cardiac cause vs non-cardiac cause	3	383	1.54 (1.22 to 1.95)
Cardiac cause	3	372	1.51 (1.19 to 1.91)
Non-cardiac cause	2	11	3.80 (0.55 to 26.29)
Good neurological outcome by location of cardiac arrest	3	382	1.56 (1.23 to 1.98)
In-hospital	1	17	1.64 (0.47 to 5.73)
Out-of-hospital	3	365	1.56 (1.23 to 1.99)
Good neurological outcome by witnessed cardiac arrest	3	382	1.49 (1.18 to 1.88)
Witnessed cardiac arrest	3	360	1.43 (1.13 to 1.81)

Table 1. Subgroup analyses (Continued)

Non-witnessed cardiac arrest	3	22	5.31 (1.40 to 20.21)
Good neurological outcome by primary ECG rhythm	3	382	1.51 (1.19 to 1.91)
VF/VT rhythm	2	330	1.47 (1.15 to 1.88)
Non- VF/VT rhythm	2	52	2.17 (0.68 to 6.93)

ECG = electrocardiogram

VF/VT = ventricular fibrillation/ventricular tachycardia

Table 2. Sensitivity analysis

Outcome or subgroup	Studies	Participants	Risk ratio (M-H, Fixed, 95% CI)
Good neurological outcome for all studies with conventional cooling	4	437	1.94 (1.18 to 3.21)
Studies with conventional cooling and adequate or unknown allocation concealment	3	360	2.46 (0.96 to 6.28)
Studies with conventional cooling and adequate allocation concealment	2	445	1.97 (0.71 to 5.45)
Studies with other cooling methods and adequate allocation concealment	1	42	0.71 (0.32 to 1.54)

Table 3. Adverse effects

Outcome or subgroup	Studies	Participants	Risk ratio (M-H, Fixed, 95% CI)
Bleeding of any severity	2	1206	1.14 (0.96 to 1.35)
Need for platelet transfusion	1	273	5.11 (0.25 to 105.47)
Significant haemorrhagic complications	1	77	Not estimable
Pneumonia	2	1205	1.15 (1.02 to 1.30)
Pancreatitis	1	273	0.51 (0.05 to 5.57)
Sepsis	2	1206	1.14 (0.81 to 1.61)
Septic shock	1	933	0.87 (0.50 to 1.52)
Renal failure or oliguria	2	303	0.88 (0.48 to 1.61)
Haemodialysis	3	1288	1.16 (0.80 to 1.67)

Table 3. Adverse effects (Continued)

Seizures	2	1202	1.18 (0.98 to 1.42)
Lethal or long-lasting arrhythmia	2	315	1.21 (0.88 to 1.67)
Any arrhythmia	1	933	0.98 (0.93 to 1.04)
Pulmonary oedema	1	269	1.76 (0.61 to 5.12)
Cardiac complications	1		No totals
Hypokalaemia	2	975	1.38 (1.03 to 1.84)
Hypophosphataemia	2	975	1.10 (0.92 to 1.33)
Hypoglycaemia	1	933	1.12 (0.64 to 1.97)
Hypomagnesaemia	1	933	1.20 (0.88 to 1.65)
Pressure sores	1	269	Not estimable

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)

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 form

Data extraction sheet

Hypothermia for neuroprotection after cardiopulmonary resuscitation

Update review

Reviewer:

Date:

Decision:

- inclusion
- exclusion

Reasons for exclusion:

Study characteristics

Publication type:

Language

Setting

Multi-centre:

- yes
- no

Participating sites:

- university

(Continued)

- community hospitals
- other, please specify

Participants

Total number of patients:

Mean age:

Percentage female:

Cardiac arrest

- out-of-hospital
- in-hospital

Cause of cardiac arrest

- cardiac
- non-cardiac

Primary cardiac rhythm

- any
- ventricular fibrillation
- ventricular tachycardia
- asystole
- pulseless electrical activity

Quality

Allocation concealment

- adequate
- unclear
 - inadequate

Outcome assessor blind

- yes
- no
- if unclear, please explain

Intention-to-treat:

- yes
- no
- if unclear, please explain

Groups comparable:

- yes
- if not, please specify

Follow-up > 80% of randomly assigned participants:

- yes
- if not, please specify

Intervention

Type of intervention:

(Continued)

Controls:

Time from restoration of spontaneous circulation to target temperature:

Cooling rate:

Duration of cooling:

Rewarming:

Outcomes

Types of outcome measures:

- ..
- ..
- ..

Time point of assessment of outcome measures:

- ..
- ..
- ..

Funding

Notes

Risk of bias assessment

Allocation concealment

Short description:

rating

- low risk
- unclear risk
- high risk

Inclusion/exclusion explicitly reported:

Short description:

rating

- low risk
- unclear risk
- high risk

Intention-to-treat:

Short description:

rating

- low risk
- unclear risk
- high risk

Appropriate participant description

Short description:

rating

(Continued)

- low risk
- unclear risk
- high risk

Identical care

Short description:

rating

- low risk
- unclear risk
- high risk

Outcomes appropriately defined:

Short description:

rating

- low risk
- unclear risk
- high risk

Follow-up > 80%:

Short description:

rating

- low risk
- unclear risk
- high risk

Physician blinded:

Short description:

rating

- low risk
- unclear risk
- high risk

Outcome assessor blinded

Short description:

(outcomes other than mortality):

rating

- low risk
- unclear risk
- high risk

Other risks of bias

Short description:

Results primary:

Type of outcome:

Cooling

No cooling

Events (n)

Total (N)

Events (n)

Total (N)

Results secondary:

Type of outcome:			
Cooling		No cooling	
Events (n)	Total (N)	Events (n)	Total (N)

WHAT'S NEW

Date	Event	Description
13 December 2018	Amended	Editorial team changed to Cochrane Emergency and Critical Care

HISTORY

Protocol first published: Issue 2, 2003

Review first published: Issue 4, 2009

Date	Event	Description
15 February 2016	New search has been performed	We updated references (deleted Westfal 1996; added McNally 2011)
15 February 2016	New citation required but conclusions have not changed	<p>This review is the second update of a previous Cochrane systematic review (Arrich 2009) that included 4 trials and 1 abstract reporting on 481 participants. The first update of 2012 (Arrich 2012) included the same studies and participants</p> <p>In the previous version (Arrich 2012), we searched the databases until July 2011. In this updated version, we reran searches to May 2015. Since that time, 1 randomized controlled trial (RCT) was published (Nielsen 2013) and we have gained more information on another RCT (Mori 2000), so that we were able to include it in the main analysis</p> <p>We had to limit the individual patient data (IPD) analysis to subgroup analyses</p> <p>The conclusion for the primary outcome of "neurological outcome" has not changed substantially</p> <p>No review authors have joined or left the team</p>
31 July 2012	New search has been performed	This review is an update of a previous Cochrane systematic review (Arrich 2009) that included 4 trials and 1 abstract reporting on 481 participants

Date	Event	Description
		<p>In the previous version (Arrich 2009), we searched the databases until January 2009. In this updated version, we reran searches to July 2011</p> <p>We updated Methods, allocated all chapters, updated references and added a risk of bias table and a summary of findings table</p> <p>A typing error (survival instead of neurological outcome) in the Results section was spotted by a reader and was corrected accordingly</p>
31 July 2012	New citation required but conclusions have not changed	We added Christof Havel as a review author
28 June 2010	Amended	We updated contact details
29 October 2009	Amended	We corrected a typo in a co-review author's address (Müllner)

CONTRIBUTIONS OF AUTHORS

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

Co-ordinating the review: HH, Jasmin Arrich (JA).

Undertaking manual searches: MH, 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, JA.

Providing additional data about papers: MH, JA.

Obtaining and screening data on unpublished studies: MH, JA.

Managing data for the review: HH, JA, MM.

Entering data into Review Manager ([RevMan 5.3](#)): MH, JA.

Analysing RevMan statistical data: HH, MM, JA.

Performing other statistical analyses not using RevMan: HH, MM.

Performing double entry of data: MH, JA.

Interpreting data: MH, HH, JA, MM, CH.

Making statistical inferences: HH, MM, JA.

Writing the review: JA, MM, HH.

Securing funding for the review: not applicable.

Performing previous work that served as the foundation of the present study: MM, MH, CH.

Serving as guarantor for the review (one review author): JA.

Taking responsibility for reading and checking the review before submission: HH.

DECLARATIONS OF INTEREST

Jasmin Arrich has no conflicts of interest.

Michael Holzer received travel grants for scientific conferences and honoraria for lectures from Bard Medical, EmCools, Polimed Sp. z o.o. and Zoll Medical Österreich. He received honoraria for consulting from Zoll Medical Österreich and was responsible for studies for which the Department of Emergency Medicine received study grants from Velomedix and Philips.

Marcus Müllner, Michael Holzer and Christof Havel were involved in the design, conduct and publication of the [HACA 2002](#) trial. None of the authors of the [HACA 2002](#) trial extracted data from that 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

Update 2015

We did not search the PASCAL database, as it was no longer available at our institution. We additionally searched three trial registers ([EudraCT](#), [ClinicalTrials.gov](#) and the [International Clinical Trials Registry Platform](#)).

Update 2012 (Arrich 2012)

In our protocol ([Arrich 2003](#)), we aimed to include additional endpoints such as six-month and final CPC scores, long-term mortality, quality of life at six months, long-term dependency and cost-effectiveness. Retrieved studies provided no information on long-term mortality, quality of life or cost-effectiveness.

All studies included in the individual patient analysis provided data on both best and final neurological 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 such as worsening of body functions or re-arrests.

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

Documentation of adverse effects was overlooked in the original protocol. As they form a vital part of every review, we included adverse effects on 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 participants after cardiac arrest. neurological 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 neuroprotection in adults after cardiopulmonary resuscitation".

NOTES

May 2015: We adopted the GRADE approach for our review.

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 help and editorial advice provided during preparation of the earlier version of this 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 help and editorial advice provided during preparation of the protocol ([Arrich 2003](#)) for the systematic review.

INDEX TERMS**Medical Subject Headings (MeSH)**

Brain Diseases [*prevention & control]; Cardiopulmonary Resuscitation [*adverse effects]; Heart Arrest [*complications] [therapy]; Hypokalemia [etiology]; Hypothermia, Induced [adverse effects] [*methods]; Hypoxia, Brain [prevention & control]; Pneumonia [etiology]; Randomized Controlled Trials as Topic; Recovery of Function

MeSH check words

Adult; Humans