NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of therapeutic hypothermia following cardiac arrest

Reducing the development of brain injury after a cardiac arrest by lowering the body's temperature

People who have a cardiac arrest can sometimes develop neurological problems because of the lack of oxygen to the brain.

In this procedure, after resuscitation a cooling device is used to reduce the person's core temperature to 32–34°C to reduce the risk of developing neurological problems.

Introduction

The National Institute for Health and Clinical Excellence (NICE) has prepared this overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in October 2010.

Procedure name

- Therapeutic hypothermia following cardiac arrest

Specialty societies

- British Association of Emergency Medicine
- College of Emergency Medicine
- Intensive Care Society.

Description

Indications and current treatment

Cessation of normal circulation due to failure of the ventricles to contract effectively (cardiac arrest) leads to loss of consciousness and respiratory failure. Early cardiopulmonary resuscitation (CPR) is needed to prevent subsequent brain injury. The underlying abnormal cardiac rhythms are most commonly asystole, pulseless electrical activity (including electromechanical dissociation), ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT). Defibrillation may be used to treat VF and pulseless VT rhythms. Standard care also includes mechanical ventilation and drugs such as adrenaline.

After cardiac arrest, comatose patients who have return of spontaneous circulation (ROSC) can be cooled to a core temperature of 32 – 34°C with the aim of improving neurological outcome. The exact mechanism by which cooling confers cerebral protection is unknown. Postulated mechanisms include a reduction in metabolic demand, release of excitatory neurotransmitters, and inflammation after ischaemia.

What the procedure involves

The patient's temperature is measured on admission. Mild hypothermia is induced by using either surface techniques (for example heat-exchange cooling pads or ice packs), internal techniques (for example endovascular cooling device), or a combination of cooling methods. Core body temperature is monitored using a bladder temperature probe. In addition to cooling, patients generally receive standard critical care measures, together with intravenous sedation and muscle relaxants (to prevent shivering).

The aim is to reach the target bladder temperature within 4 hours after ROSC. If this goal is not achieved, extra ice packs may be applied. The temperature is maintained at 32–34°C for 12–24 hours from the start of cooling, followed by passive re-warming, usually done slowly.

Instruments to assess efficacy

A range of validated instruments are used to evaluate neurological outcome including:

- Cerebral performance categories (CPC). This is a 5-category measure used to assess neurological outcome. Categories 1 (good cerebral performance: conscious, alert, capable of normal life) and 2 (moderate cerebral disability: conscious, alert, sufficient cerebral function for activities of daily life) are considered to indicate a good neurological outcome. Categories 3 (severe cerebral disability), 4 (coma/vegetative state) and 5 (certified brain death) are considered to be a poor neurological outcome.

- Overall performance category (OPC). This is a 5-category measure used to assess disability. Categories 1 (good overall capability) and 2 (moderate overall disability) are considered to indicate a good outcome. Categories 3 (severe disability), 4 (coma) and 5 (death) are considered to be a poor outcome.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to therapeutic hypothermia following cardiac arrest. Searches were conducted of the following databases, covering the period from their commencement to 15 June 2010 and updated 25 October 2010: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with cardiac arrest.
Intervention/test	Therapeutic hypothermia.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on 7450 patients from 2 systematic reviews[1,2], 10 randomised controlled trials (RCTs)[3,4,5,6,7,8,9,10,11,12], 1 non-randomised controlled study[13] and 1 case series (register)[14]. A further 217 patients from 1 non-randomised comparative study[15], 4 case series[16,17,18,19] and 3 case reports[20,21,22] are included to report safety outcomes not included in the RCTs.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on therapeutic hypothermia following cardiac arrest

Abbreviations used: CHD, coronary heart disease; CI, confidence interval; CPC, cerebral performance categories; CPR: cardiopulmonary resuscitation; ICU, intensive care unit; NR, not reported; NS, not significant; OHCA, out of hospital cardiac arrest; OPC, overall performance category; OR, odds ratio; PEA, pulseless electrical activity; RCT, randomised controlled trial; ROSC, return of spontaneous circulation; RR, risk ratio; VF, ventricular fibrillation; VT, ventricular tachycardia

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Arrich J (2007)[1]

Systematic review (meta analysis)
International
Recruitment period: randomised controlled trials published up to 25 January 2007.
Includes 5 RCTs:
Bernard 2002
HACA 2002
Hachimi-Idrissi 2001
Laurent 2005
Mori 2000.
Study population: patients who had suffered a cardiac arrest (in or out of hospital) and were successfully resuscitated.

n = 481 (255 vs 226)

Age: not reported
Sex: not reported
Patient selection criteria: excluded studies on children and adolescents aged < 18 years.
Technique: therapeutic hypothermia (body</td>
<td>Number of patients analysed: 479 (253 vs 226)

<table>
<tr><th></th><th>Good neurological outcome</th><th>Survival to hospital discharge</th></tr>
<tr><td>Conventional cooling methods vs standard care [3 studies, 195 vs 188 patients]</td><td>RR: 1.55 (95% CI: 1.22 to 1.96) [I^2 = 32% indicating no significant heterogeneity]</td><td>RR: 1.35 (95% CI: 1.10 to 1.65) [I^2 = 0% indicating no heterogeneity]</td></tr>
<tr><td>Hypothermia + haemofiltration vs haemofiltration only [1 study, 22 vs 20 patients]</td><td>RR: 0.71 (95% CI: 0.32 to 1.54)</td><td>RR: 0.71 (95% CI: 0.32 to 1.54)</td></tr>
<tr><td>Unknown cooling method vs standard care [1 study, 36 vs 18 patients]</td><td>RR: 4.5 (95% CI: 1.17 to 17.3)</td><td>-</td></tr>
<tr><td>All studies</td><td>RR: 1.55 (95% CI: 1.24 to 1.94)</td><td>Not reported</td></tr>
</table>

The results above indicate that a significantly higher proportion of patients in the hypothermia group have a good neurological outcome compared to patients in the standard group.
In addition, a significantly higher proportion of patients in the conventional cooling methods group survive to hospital discharge than do patients in the standard care group.</td>
<td>
<table>
<tr><th>Adverse event</th><th>Studies (participants)</th><th>RR (95% CI)</th></tr>
<tr><td>Bleeding of any severity</td><td>1 (273 patients)</td><td>1.38 (0.88 to 2.16)</td></tr>
<tr><td>Need for platelet transfusion</td><td>1 (273 patients)</td><td>5.11 (0.25 to 05.47)</td></tr>
<tr><td>Pneumonia</td><td>1 (273 patients)</td><td>1.27 (0.90 to 1.78)</td></tr>
<tr><td>Sepsis</td><td>1 (273 patients)</td><td>1.93 (0.89 to 1.78)</td></tr>
<tr><td>Pancreatitis</td><td>1 (273 patients)</td><td>0.51 (0.05 to 5.57)</td></tr>
<tr><td>Renal failure or oliguria</td><td>2 (303 patients)</td><td>0.88 (0.48 to 1.61)</td></tr>
<tr><td>Haemodialysis</td><td>2 (350 patients)</td><td>1.11 (0.41 to 3.01)</td></tr>
<tr><td>Pulmonary oedema</td><td>1 (273 patients)</td><td>1.76 (0.61 to 5.12)</td></tr>
<tr><td>Seizures</td><td>1 (273 patients)</td><td>0.89 (0.39 to 2.02)</td></tr>
<tr><td>Lethal or long lasting arrhythmia</td><td>2 (315 patients)</td><td>1.21 (0.88 to 1.67)</td></tr>
<tr><td>Cardiac complications</td><td>1 (77 patients)</td><td>0.16 (0.01 to 3.21)</td></tr>
<tr><td>Hypokalaemia</td><td>1 (42 patients)</td><td>0.91 (0.3 to 2.68)</td></tr>
<tr><td>Hypo-phosphataemia</td><td>1 (42 patients)</td><td>1.12 (0.65 to 2.25)</td></tr>
</table>

Timing and treatment of adverse events is not reported. All the outcomes above indicate no significant difference between groups.</td>
<td>Follow-up issues:
• One study lost information for 2 patients on the primary endpoint (good neurological outcome). All other studies had complete follow-up.

Study design issues:
• Cochrane study including thorough literature search.
• Quality assessment indicates that 3 (Bernard 2002, HACA 2002 and Hachimi-Idrissi 2001) of the 5 included studies are of good quality (covering randomisation, allocation concealment, blinding, loss to follow-up, comparability of groups and use of measures to account for</td>
</tr>
</table>

Abbreviations used: CHD, coronary heart disease; CI, confidence interval; CPC, cerebral performance categories; CPR: cardiopulmonary resuscitation; ICU, intensive care unit; NR, not reported; NS, not significant; OHCA, out of hospital cardiac arrest; OPC, overall performance category; OR, odds ratio; PEA, pulseless electrical activity; RCT, randomised controlled trial; ROSC, return of spontaneous circulation; RR, risk ratio; VF, ventricular fibrillation; VT, ventricular tachycardia			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
target temperature < 35°C), regardless of how body temperature was reduced, applied within 6 hours of arrival at hospital vs standard treatment following cardiac arrest. Follow-up: **up to 6 months** Conflict of interest/source of funding: key author had an unrestricted grant from a manufacturer.			differences between groups). • Good neurological outcome defined as a CPC score of 1 or 2. If studies reported 'good neurological outcome' this was also accepted.

Abbreviations used: CHD, coronary heart disease; CI, confidence interval; CPC, cerebral performance categories; CPR: cardiopulmonary resuscitation; ICU, intensive care unit; NR, not reported; NS, not significant; OHCA, out of hospital cardiac arrest; OPC, overall performance category; OR, odds ratio; PEA, pulseless electrical activity; RCT, randomised controlled trial; ROSC, return of spontaneous circulation; RR, risk ratio; VF, ventricular fibrillation; VT, ventricular tachycardia			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Cheung KW (2006)[2] **Systematic review (meta analysis)** International Recruitment period: randomised controlled trials published up to November 2005. Includes 4 RCTs: Bernard 2002 HACA 2002 Hachimi-Idrissi 2001 Mori 2000. Study population: patients who had a primary cardiac arrest and were comatose (Glasgow Coma Scale score < 8) after ROSC. n = **436 (232 vs 204)** Age: not reported Sex: not reported Patient selection criteria: included studies of adults > 18 years. Technique: mild	Number of patients analysed: **434 (231 vs 203)** **Poor neurological outcome** [4 studies, 231 vs 203 patients] RR: 0.72 (95% CI: 0.62 to 0.84) [I^2 = 0% indicating no heterogeneity]. This result indicates that a significantly lower proportion of patients in the hypothermia group had a poor neurological outcome compared to the normothermia group. Number needed to treat to improve neurological outcome = 5 (95% CI: 4 to 10) Number needed to treat to save 1 life = 7.	**In-hospital mortality** [3 studies, 196 vs 186 patients] RR: 0.75 (95% CI: 0.62 to 0.92) [I^2 = 51% indicating moderate heterogeneity]. This result indicates that a significantly lower proportion of patients in the hypothermia group died in hospital compared to the normothermia group.	**Follow-up issues**: • Completeness of follow-up not reported. **Study design issues**: • Quality of each included study was assessed and 2 studies were reported to be of good quality (Jadad score = 3) and 2 studies had unclear or inadequate allocation concealment (poor quality, Jadad score = 1) • Presenting cardiac rhythms included ventricular arrhythmias, asystole and pulseless electrical activity. • Poor neurological outcome defined as CPC categories 3, 4 or 5 in 2 studies. One study

Abbreviations used: CHD, coronary heart disease; CI, confidence interval; CPC, cerebral performance categories; CPR: cardiopulmonary resuscitation; ICU, intensive care unit; NR, not reported; NS, not significant; OHCA, out of hospital cardiac arrest; OPC, overall performance category; OR, odds ratio; PEA, pulseless electrical activity; RCT, randomised controlled trial; ROSC, return of spontaneous circulation; RR, risk ratio; VF, ventricular fibrillation; VT, ventricular tachycardia			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
induced hypothermia (32–34°C) versus normothermia within 24 hours of presentation with assessment and description of neurological outcome and mortality. Follow-up: **up to 6 months** Conflict of interest/source of funding: none.			reported poor neurological outcome as discharge to a long-term nursing facility or death. Another study used the Glasgow Outcome Scale.
Abbreviations used: CHD, coronary heart disease; CI, confidence interval; CPC, cerebral performance categories; CPR: cardiopulmonary resuscitation; ICU, intensive care unit; NR, not reported; NS, not significant; OPC, overall performance category; OR, odds ratio; PEA, pulseless electrical activity; RCT, randomised controlled trial; ROSC, return of spontaneous circulation; RR, risk ratio; VF, ventricular fibrillation; VT, ventricular tachycardia			

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>HACA (2002)[3]

RCT
Europe
Recruitment period: 1996–2001

Study population: patients aged 18–75 in whom spontaneous circulation had been restored after a witnessed cardiac arrest due to ventricular fibrillation or non-perfusing ventricular tachycardia.

n = 275 (137 vs 138)

Age: hypothermia group: 59 years (median); normothermia group: 59 years (median).
Sex: hypothermia group: 75.9% (104/137) male; normothermia group: 76.8% (106/138) male.

Patient selection criteria: interval of only 5–15 minutes from the patient’s collapse to first attempt at resuscitation and an interval of no more than 60 minutes from collapse to ROSC. Patients excluded if they had a tympanic</td>
<td>Number of patients analysed: 273 (136 vs 137)

Favourable neurological outcome at 6 months:
Hypothermia (n = 136): 55.1% (75/136)
Normothermia (n = 137): 39.4% (54/137) (p = 0.009)
RR (95% CI): 1.40 (1.08 to 1.81)
RR after adjusting for baseline variables: 1.47 (1.09 to 1.82)

Number needed to treat to prevent 1 unfavourable neurological outcome = 6 (95% CI: 4 to 25)</td>
<td>Number of patients analysed: 275 (137 vs 138)
<table>
<tr><th></th><th>Hypo-thermia</th><th>Normo-thermia</th><th>RR (95% CI)</th><th>p value</th></tr>
<tr><td>Mortality at 6 months</td><td>40.9% (56/137)</td><td>55.1% (76/138)</td><td>0.74 (0.58 to 0.95)

0.62 (0.36 to 0.95) after adjusting for baseline variables</td><td>0.02</td></tr>
<tr><td>Mortality in hospital</td><td>36.5% (50/137)</td><td>50% (69/138)</td><td>NR</td><td>NR</td></tr>
</table>
Number needed to treat to prevent 1 death = 7 (95% CI: 4 to 33)

<table>
<tr><th>Complications in first 7 days</th><th>Hypo-thermia</th><th>Normo-thermia</th><th>p value</th></tr>
<tr><td>Any complication</td><td>72.6% (98/135)</td><td>70.5% (93/132)</td><td>0.70</td></tr>
<tr><td>Bleeding of any severity</td><td>25.9% (35/135)</td><td>18.8% (26/138)</td><td>NS</td></tr>
<tr><td>Need for platelet transfusion</td><td>1.5% (2/135)</td><td>0</td><td>NS</td></tr>
<tr><td>Pneumonia</td><td>37.0% (50/135)</td><td>29.2% (40/137)</td><td>NS</td></tr>
<tr><td>Sepsis</td><td>12.6% (17/135)</td><td>6.5% (9/138)</td><td>NS</td></tr>
<tr><td>Pancreatitis</td><td>0.7% (1/135)</td><td>1.5% (2/138)</td><td>NS</td></tr>
<tr><td>Renal failure</td><td>9.6% (13/135)</td><td>10.1% (14/138)</td><td>NS</td></tr>
<tr><td>Haemodialysis</td><td>4.4% (6/135)</td><td>4.3% (6/138)</td><td>NS</td></tr>
<tr><td>Pulmonary oedema</td><td>6.6% (9/136)</td><td>3.8% (5/133)</td><td>NS</td></tr>
<tr><td>Seizures</td><td>7.4% (10/136)</td><td>8.3% (11/133)</td><td>NS</td></tr>
<tr><td>Lethal or long lasting arrhythmia</td><td>36.3% (49/135)</td><td>31.9% (44/138)</td><td>NS</td></tr>
</table>
</td>
<td>Included in Arrich 2007 and Cheung 2005
Follow-up issues:
One patient in each group was lost to follow-up for neurological outcome at 6 months.
Study design issues:
Prospective multicentre study.
91.4% (3246/3551) of patients assessed for eligibility did not meet the inclusion criteria. In addition, 30 patients were not included for logistical reasons.
Appropriate randomisation (done at the hospital) and allocation concealment (computer generated blocks of 10 and sealed envelopes).
Outcome assessors at 6 months were blind to treatment allocation.
Favourable neurological outcome defined</td>
</tr>
</table>

Abbreviations used: CHD, coronary heart disease; CI, confidence interval; CPC, cerebral performance categories; CPR: cardiopulmonary resuscitation; ICU, intensive care unit; NR, not reported; NS, not significant; OHCA, out of hospital cardiac arrest; OPC, overall performance category; OR, odds ratio; PEA, pulseless electrical activity; RCT, randomised controlled trial; ROSC, return of spontaneous circulation; RR, risk ratio; VF, ventricular fibrillation; VT, ventricular tachycardia

Study details	Key efficacy findings	Key safety findings	Comments
membrane temperature < 30°C on admission, comatose before cardiac arrest, pregnant, responsive to verbal commands after ROSC and before randomisation, hypotension for more than 30 minutes after ROSC, hypoxemia for more than 15 minutes after ROSC, terminal illness prior to cardiac arrest, cardiac arrest after the arrival of medical personnel or known pre-existing coagulopathy. Technique: mild induced hypothermia (32–34°C) using Theracool (cooling mattress) and ice packs where required (median duration of cooling: 24 hours, median interval between ROSC and initiation of cooling: 105 minutes) vs			as CPC categories 1 or 2. • Temperature monitored with a bladder temperature probe (Foley catheter). • Hypothermia was discontinued early in 14 patients because of arrhythmia and haemodynamic instability

Abbreviations used: CHD, coronary heart disease; CI, confidence interval; CPC, cerebral performance categories; CPR: cardiopulmonary resuscitation; ICU, intensive care unit; NR, not reported; NS, not significant; OPC, overall performance category; OR, odds ratio; PEA, pulseless electrical activity; RCT, randomised controlled trial; ROSC, return of spontaneous circulation; RR, risk ratio; VF, ventricular fibrillation; VT, ventricular tachycardia

Study details	Key efficacy findings	Key safety findings	Comments
normothermia (standard care). Follow-up: **6 months** Conflict of interest/source of funding: grants from Biomedicine and health programme (BIOMED 2), the European Union, the Austrian Ministry of Science and Transport and the Austrian Science Foundation.			• (3 patients), technical problems with device (2 patients), liver rupture (1 patient), previous random assignment to cooling (1 patient), error in duration of cooling (1 patient) and death (6 patients). This is an Intention to treat analysis. **Study population issues** • Median Glasgow Coma Scale was 3 in both groups and pupillary light reflexes were present in 59.3% (73/123) of hypothermia patients and 52% (65/125) of normothermia patients on admission (data provided in response to a letter to the editor). This indicates that patients in the 2 groups had a similar neurological profile on

Abbreviations used: CHD, coronary heart disease; CI, confidence interval; CPC, cerebral performance categories; CPR: cardiopulmonary resuscitation; ICU, intensive care unit; NR, not reported; NS, not significant; OHCA, out of hospital cardiac arrest; OPC, overall performance category; OR, odds ratio; PEA, pulseless electrical activity; RCT, randomised controlled trial; ROSC, return of spontaneous circulation; RR, risk ratio; VF, ventricular fibrillation; VT, ventricular tachycardia			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
			admission. • Target temperature not reached in 13.9% (19/137) patients.

Abbreviations used: CHD, coronary heart disease; CI, confidence interval; CPC, cerebral performance categories; CPR: cardiopulmonary resuscitation; ICU, intensive care unit; NR, not reported; NS, not significant; OHCA, out of hospital cardiac arrest; OPC, overall performance category; OR, odds ratio; PEA, pulseless electrical activity; RCT, randomised controlled trial; ROSC, return of spontaneous circulation; RR, risk ratio; VF, ventricular fibrillation; VT, ventricular tachycardia

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Bernard SA (2010)[4]

RCT
Australia
Recruitment period: 2005 to 2007

Study population: patients with OHCA with initial cardiac rhythm VF, return of spontaneous circulation, systolic blood pressure > 90 mmHg, cardiac arrest >10 mins, age > 15 years.

n = 234 (118 immediate paramedic cooling vs 116 hospital cooling.)

Age: 63 years (mean)
Sex: 85 % male

Patient selection criteria: patients excluded if they were not intubated, care dependent, or already hypothermic.

Technique: paramedic cooling after administration of midazolam and pancuronium using infusion of 2 litres of ice-cold Ringer’s solution at 100 ml/minute vs hospital care on arrival with rapid infusion of 40 ml/kg ice-cold Ringer’s solution. Surface cooling commenced in both groups with target temperature 33°C.

Follow-up: discharge

Conflict of interest/source of</td>
<td>Number of patients analysed: 234 (118 vs 116)

Outcome following discharge
Group %
<table>
<tr><th></th><th>Paramedic cooling</th><th>Hospital cooling</th><th>p=</th></tr>
<tr><td>Favourable outcome*</td><td>47.5% (56/118)</td><td>52.6% (61/116)</td><td>0.433</td></tr>
<tr><td>Discharged home</td><td>20.3% (24/118)</td><td>29.3% (34/116)</td><td>NR</td></tr>
<tr><td>Discharged to rehabilitation</td><td>27.1% (32/118)</td><td>23.3% (27/116)</td><td>NR</td></tr>
<tr><td>Dead</td><td>52.5% (62/118)</td><td>46.6% (54/116)</td><td>NR</td></tr>
</table>
* patients who died or were discharged to a long term nursing facility were defined as having an unfavourable outcome.
NR = not reported.</td>
<td>Safety outcomes are not reported on.</td>
<td>Follow-up issues:
One patient in the hospital cooling group received paramedic cooling due to protocol violation.
Study design issues:
Randomisation by computer generation in blocks of ten per paramedic. Allocation concealment by opaque envelopes.
After interim analysis steering committee stopped the trial as no difference in the primary outcome measure.
All outcomes assessed on intention-to-treat basis.
Study also reported differences in body temperatures on arrival; however, this outcome is directly related to group allocation.
Other emergency clinicians not blinded to treatment allocation.
Only half the patients in the paramedic cooling arm received full amount of cooling due to short transfer to hospital.
Study population issues
No statistically significant difference between the groups in terms of demographics, response time, number of defibrillations, and total cardiac arrest time.</td>
</tr>
</table>

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Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
funding: supported by national grant			

Abbreviations used: CHD, coronary heart disease; CI, confidence interval; CPC, cerebral performance categories; CPR: cardiopulmonary resuscitation; ICU, intensive care unit; NR, not reported; NS, not significant; OHCA, out of hospital cardiac arrest; OPC, overall performance category; OR, odds ratio; PEA, pulseless electrical activity; RCT, randomised controlled trial; ROSC, return of spontaneous circulation; RR, risk ratio; VF, ventricular fibrillation; VT, ventricular tachycardia

Study details	Key efficacy findings	Key safety findings	Comments

Castrén M (2010)[5]

RCT
European
Recruitment period: 2008 to 2009

Study population: patients with out-of-hospital cardiac arrest.

n = 200 (96 nasal cooling vs 104 standard care)

Age: 65 years (mean)
Sex: 73% male

Patient selection criteria: patients >18 years, with CPR within 20 minutes of collapse. Patients excluded if suffered trauma, overdose, cerbrovascular accident, electrocution, had known coagulopathy, asphyxia, or were very cold on arrival.

Technique: nasal cooling with coolant via nasal catheter for 22.5 minutes at 40litres/min plus standard care protocol vs standard care protocol alone).

Follow-up: discharge

Conflict of interest/source of funding: supported by manufacturer

Number of patients analysed: **n = 194 (93 vs 101)**

Outcome
Group %

	Nasal cooling	Standard care	p=
Achieved ROSC	37.6% (35/93)	42.6% (43/101)	0.48
Survival – all patients	43.8% (14/32)	31.0% (13/42)	0.26
Survival – patients who received CPR within 10 minutes	56.5% (13/23)	29.4% (10/34)	0.04
Survival – VF	62.5% (10/16)	47.6% (10/21)	0.37

Complications
Adverse events related to the nasal cooling

Outcomes	Rate
Nasal whitening	14.0% (13/93)
Epistaxis (serious in 1 patient)	3.2% (3/93)
Periorbital emphysema (occurred 75 minutes into the treatment and resolved spontaneously within 24 hours)	1.1% (1/93)

Total serious adverse events to 7 days follow-up occurred in 7 patients in the nasal cooling group and 14 patients in the standard care group (p = 0.23)

Serious adverse events (number of patients)

Outcome	Nasal cooling	Standard care
Acidosis	0	2
Acute myocardial infarction	0	1
Bleeding	1	1
New cardiac arrest	3	2
Convulsions	1	1
Arrhythmia	1	2
Renal failure	1	2
Sepsis	0	3

Follow-up issues:
- Prospective study. 3 patients in each group lost to follow-up before ROSC
- Intention-to-treat analysis including patients who were found to have exclusion criteria following randomisation.

Study design issues:
Other
- 15 participating sites.
- Randomisation by computer generation in blocks of 8 per site on 1:1 ratio. Allocation concealment by opaque envelopes.
- Patients in both groups may have received other cooling according to protocol at each site.
- No blinding of emergency clinicians or outcome assessors.
- Study not powered to address clinical outcome.
- Analysis of efficacy outcome based on subgroups is not defined a priori.

Study population issues
- No significant differences between groups at baseline in demographics or emergency treatment except for longer time to airway establishment in the nasal cooling group.

Other
- Atypical method of cooling intervention.

Abbreviations used: CHD, coronary heart disease; CI, confidence interval; CPC, cerebral performance categories; CPR: cardiopulmonary resuscitation; ICU, intensive care unit; NR, not reported; NS, not significant; OHCA, out of hospital cardiac arrest; OPC, overall performance category; OR, odds ratio; PEA, pulseless electrical activity; RCT, randomised controlled trial; ROSC, return of spontaneous circulation; RR, risk ratio; VF, ventricular fibrillation; VT, ventricular tachycardia

Study details	Key efficacy findings	Key safety findings	Comments

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Study details

Kim F (2007)[6]

RCT
USA
Recruitment period: 2004–2006

Study population: patients resuscitated by paramedics following an out-of-hospital cardiac arrest.

n = **125 (63 vs 62)**

Age: hypothermia group: 67 years; control group: 65 years (mean)
Sex: hypothermia group: 66.7% (42/63) male; control group: 74.2% (46/62) male.

Patient selection criteria: patients must have return of pulse, tracheal intubation, intravenous access, have an oesophageal temperature probe and be unconscious. Patients excluded if a traumatic cardiac arrest, age < 18 years, able to follow commands or temperature < 34°C.

Technique: therapeutic hypothermia using 4°C saline infusion (up to 2 litres) administered as soon as possible after resuscitation in the field vs normothermia (standard care).

Follow-up: **discharge**

Conflict of interest/source of funding: funded by grant from Medic One Foundation and National Institutes of Health.

Key efficacy findings

Number of patients analysed: **125 (63 vs 62)**
Mean temperature on arrival at hospital 34.7°C

	Pre-hospital hypothermia (n = 63)	**Normo thermia (n = 62)**
Initial rhythm – asystole	28.6% (18/63)	33.9% (21/62)
Initial rhythm – pulseless electrical activity	23.8% (15/63)	30.6% (19/62)
Initial rhythm – VF	46% (29/63)	35.5% (22/62)
Initial rhythm – unknown	1.6% (1/63)	0

	Discharged alive
Hypothermia group – VF rhythm	65.5% (19/29) [2 patients with severe neurological deficit]
Hypothermia group – non-VF rhythm	5.9% (2/34)
Standard care – VF rhythm	45.5% (10/22) [1 patient with severe neurological deficit]
Standard care – non-VF rhythm	20% (8/40) [1 patient with severe neurological deficit]

Authors report a trend toward improved survival to discharge when the initial rhythm is VF but this was not statistically significant (no p values given).

Survival to hospital discharge after adjusting for the effects of hospital cooling: OR 1.38 (95% CI: 0.58 to 3.29)

Key safety findings

	Deaths before admission	**In-hospital death**	**Total deaths**
Hypothermia group – VF rhythm	10.3% (3/29)	24.1% (7/29)	34.5% (10/29)
Hypothermia group – non-VF rhythm	32.4% (11/34)	61.8% (21/34)	94.1% (32/34)
Standard care – VF rhythm	13.6% (3/22)	40.9% (9/22)	54.5% (12/22)
Standard care – non-VF rhythm	27.5% (11/40)	20% (8/40)	47.5% (19/40)

Authors report pre-hospital and in-hospital deaths in both treatment groups were similar (no p values reported).

	Pre-hospital hypothermia	**Normo thermia (n = 62)**	**p value**
Median time to death	1.01 days (n = 42)	0.46 days (n = 44)	0.59

Pulmonary oedema:
Pre-hospital hypothermia group: 44% (24/54)
Normothermia group: 55% (27/49) (p = 0.28)

Comments

Follow-up issues:
- 34.2% (65/190) eligible patients were not randomised (24 haemodynamically unstable, 10 equipment problems, 8 during a temporary suspension of the study to renew the university application and 23 were missed or staff forgot to enrol them).
- Complete follow-up reported for remaining 125 patients.

Study design issues:
- Patients randomised in the field. Paramedics phoned an emergency room physician who opened sequentially numbered envelopes that randomised patients to treatment or standard care alone. Randomisation was in balanced blocks of 4. Unclear how random numbers were generated.
- Core body temperature monitored by oesophageal temperature probe prior to hospital admission.
- In-hospital use of hypothermia was at the discretion of the treating physician.
- 12.9% (8/62) patients in the hypothermia group did not receive any cooling

Abbreviations used: CHD, coronary heart disease; CI, confidence interval; CPC, cerebral performance categories; CPR: cardiopulmonary resuscitation; ICU, intensive care unit; NR, not reported; NS, not significant; OPC, overall performance category; OR, odds ratio; PEA, pulseless electrical activity; RCT, randomised controlled trial; ROSC, return of spontaneous circulation; RR, risk ratio; VF, ventricular fibrillation; VT, ventricular tachycardia

Study details	Key efficacy findings	Key safety findings	Comments
	<table><tr><th></th><th>Pre-hospital hypothermia</th><th>Normo thermia (n = 62)</th><th>p value</th></tr><tr><td>Median time to awakening</td><td>1.52 days (n = 22)</td><td>1.05 days (n = 17)</td><td>0.21</td></tr><tr><td>Median time to discharge</td><td>12.2 days (n = 21)</td><td>9.9 days (n = 18)</td><td>0.71</td></tr></table>		saline, 9.5% (6/63) received < 500mL, 58.7% (37/63) received 500mL – 2L and 19% (12/63) received the full 2L. Incomplete fluid administration due to recurrent arrest, death or lack of time before arrival at hospital. **Study population issues** • Core temperature of hypothermia group was significantly lower at time of hospital admission in comparison to the standard care group (34.7° vs 35.7°C, p < 0.0001).

Abbreviations used: CHD, coronary heart disease; CI, confidence interval; CPC, cerebral performance categories; CPR: cardiopulmonary resuscitation; ICU, intensive care unit; NR, not reported; NS, not significant; OPC, overall performance category; OR, odds ratio; PEA, pulseless electrical activity; RCT, randomised controlled trial; ROSC, return of spontaneous circulation; RR, risk ratio; VF, ventricular fibrillation; VT, ventricular tachycardia

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Bernard SA (2002)[7]

RCT
Australia
Recruitment period: 1996–1999

Study population: comatose patients in whom spontaneous circulation had been restored after cardiac arrest due to ventricular fibrillation.

n = 77 (43 vs 34)

Age: hypothermia group: 66.8 years (median); normothermia group: 65 years (median).
Sex: hypothermia group: 58% male; normothermia group: 79% male (p = 0.05).

Patient selection criteria: patients excluded if < 18 year old male and < 50-year-old female (due to possibility of pregnancy), in cardiogenic shock or coma possibly due to a cause other than cardiac arrest. Patients also excluded if an intensive care bed was not available at the participating centre.

Technique: mild induced hypothermia (33°C) using cool packs (CoolCare) to the head, neck, torso and limbs initiated by paramedics in the field (cooling maintained for 12 hours after arrival at hospital) vs normothermia (standard care).

Follow-up: discharge

Conflict of interest/source of funding: not reported.</td>
<td>Number of patients analysed: 77 (43 vs 34)

<table>
<tr><th></th><th>Hypo-thermia</th><th>Normo-thermia</th><th>p value</th></tr>
<tr><td>Survival to hospital discharge with a good neurological outcome</td><td>48.8% (21/43)</td><td>26.5% (9/34)</td><td>0.046</td></tr>
<tr><td>Survival to hospital discharge with normal or minimal disability</td><td>34.9% (15/43)</td><td>20.6% (7/34)</td><td>NR</td></tr>
<tr><td>Survival to hospital discharge with moderate disability</td><td>13.9% (6/43)</td><td>5.9% (2/34)</td><td>NR</td></tr>
<tr><td>Survival to hospital discharge with severe disability, awake but completely dependent</td><td>0%</td><td>2.9% (1/34)</td><td>NR</td></tr>
<tr><td>Survival to hospital discharge with severe disability, unconscious</td><td>0%</td><td>2.9% (1/34)</td><td>NR</td></tr>
</table>
For each 2-year increase in age there was a 9% decrease in likelihood of a good outcome. OR: 0.91 (95% CI: 0.84 to 0.98; p = 0.014).

For each additional 15 minutes from collapse to ROSC there was a 14% decrease in likelihood of a good outcome. OR: 0.856 (95% CI: 0.78 to 0.94; p = 0.001).

Good outcome (unadjusted): OR: 2.65 (95% CI: 1.02 to 6.88; p = 0.046).
Good outcome (adjusted for baseline differences and time from collapse to ROSC): OR: 5.25 (95% CI: 1.47 to 18.76; p = 0.011). Both results indicate that patients in the hypothermia group were significantly more likely to have a good outcome than patients in the normothermia group.</td>
<td>Mortality in hospital
Hypothermia group: 51.2% (22/43)
Normothermia group: 67.6% (23/34) (p = 0.145)

Cause of death:
Hypothermia group:
Cardiac failure: 22.7% (5/22)
Brain death: 4.5% (1/22)
Severe neurological injury and withdrawal of all active therapy: 72.7% (16/22)

Normothermia group:
Cardiac failure: 17.4% (4/23)
Brain death: 4.3% (1/23)
Severe neurological injury and withdrawal of all active therapy: 78.3% (18/23)</td>
<td>Included in Arrich 2007 and Cheung 2005

Follow-up issues:
• 7.2% (6/83) of patients assessed as eligible for the study were excluded form the analysis (5 because they were transferred to a non-participating ICU and 2 because the next of kin refused consent for data collection).
• Complete follow-up reported for remaining 77 patients.
Study design issues:
• Prospective single-centre study.
• Patients randomised immediately after ROSC if eligible.
• Inadequate randomisation technique (assigned according to day of month – odd numbers for hypothermia group).
• 4 patients assigned to hypothermia did not receive the treatment (3 physician error and 1 inadvertently re-warmed shortly after admission to ICU) and 1 patient in the normothermia group was hypothermic for 4 hours during emergency angioplasty. Intention to treat analysis.
• Outcome assessor at discharge was blind to treatment allocation.
• Good neurological outcome defined as discharge home or to a rehabilitation facility (normal/minimal or moderate disability).
• Core body temperature monitored via tympanic membrane or bladder until a pulmonary artery catheter was put in place on admission to ICU.</td>
</tr>
</table>

Abbreviations used: CHD, coronary heart disease; CI, confidence interval; CPC, cerebral performance categories; CPR: cardiopulmonary resuscitation; ICU, intensive care unit; NR, not reported; NS, not significant; OPC, overall performance category; OR, odds ratio; PEA, pulseless electrical activity; RCT, randomised controlled trial; ROSC, return of spontaneous circulation; RR, risk ratio; VF, ventricular fibrillation; VT, ventricular tachycardia

Study details	Key efficacy findings	Key safety findings	Comments
Heard KJ (2010)[8] **RCT** USA Recruitment period: 2004–2007 Study population: comatose patients aged 18+ years that had ROSC after an out of hospital cardiac arrest from a presumed cardiac cause. n = **64 (34 vs 30)** Age: gel pads with feedback control group: 57 years (mean); blankets and ice group: 64 years (mean) Sex: gel pads with feedback control group: 61.8% (21/34) male; blankets and ice group: 73.3% (22/30) male. Patient selection criteria: patients included if 1st attempt at resuscitation started within 15 minutes of collapse and ROSC within 60 minutes of collapse and time from ROSC to initiation of cooling ≤ 6hrs. Patients excluded if temp < 35°C on admission, comatose prior to cardiac arrest, pregnant, responsive to verbal comments after ROSC prior to initiation of hypothermia, hypotensive, hypoxic, terminal illness, in cardiogenic shock, continuing refractory ventricular arrhythmias at enrolment, 2+ high-dose vasopressors, active bleeding, history of agglutinin disease, Raynaud's disease, sickle cell disease, compromised skin integrity and weight ≥ 114kg or < 50kg. Technique: therapeutic hypothermia (target temperature 33.5°C) using temperature controlled external gel pad system on legs on torso (Arctic Sun) versus therapeutic hypothermia using 2 cooling blankets (1 on upper torso and 1 on lower torso and thighs) and ice bags on the axillae and groin (target temperature 33.5°C). Follow-up: **90 days** Conflict of interest/source of funding: one of the authors is a paid consultant for the Arctic Sun manufacturer.	Number of patients analysed: **61 (32 vs 29)** **Good neurological outcome at 90 days:** gel pads with feedback control group: 46.9% (15/32). Blankets and ice group: 37.9% (11/29) (p = 0.6). Median time to target temperature was 54 minutes faster in the Arctic Sun group compared to blankets and ice group (p < 0.01).	**Serious adverse events** [Timing and treatment of events is not reported.] **Gel pads with feedback control (n = 32)** **Blankets and ice (n = 29)** Any event: 84.4% (27/32); 86.2% (25/29) Death: 50% (16/32); 55.2% (16/29) Seizures/status epilepticus: 18.8% (6/32); 17.2% (5/29) Pneumonia: 21.9% (7/32); 10.3% (3/29) Significant arrhythmias: 6.3% (2/32); 17.2% (5/29) Renal failure: 6.3% (2/32); 10.3% (3/29) Stroke: 12.5% (4/32); 3.4% (1/29) Sepsis/septic shock: 9.4% (3/32); 3.4% (1/29) Cardiac arrest: 0; 6.9% (2/29) Bleed (gastrointestinal): 0; 6.9% (2/29) Fever: 3.1% (1/32); 3.4% (1/29) Infection, UTI: 6.3% (2/32); 0 Cardiogenic shock: 0; 6.9% (2/29) Anaemia: 6.3% (2/32); 0 Bacteraemia: 3.1% (1/32); 0 Bleed (haematuria): 0; 3.4% (1/29) Acute myocardial infarction: 3.1% (1/32); 0 Pneumothorax: 0; 3.4% (1/29) Respiratory failure: 0; 3.4% (1/29) ECG changes / ST elevation: 0; 3.4% (1/29) Deep vein thrombosis: 3.1% (1/32); 0 Pleural effusion: 3.1% (1/32); 0 Infection, sinusitis: 3.1% (1/32); 0 Heparin induced thrombocytopenia: 3.1% (1/32); 0 Authors report the proportion of serious adverse events was similar between the 2 groups.	**Follow-up issues**: • 3 patients were removed from the study after randomisation but before initiation of cooling. • Complete follow-up reported for remaining 61 patients. **Study design issues**: • Prospective multicentre study (6 centres). • Appropriate randomisation technique (centralised telephone system using a fixed-block randomisation scheme with an allocation ratio of 1:1 for each centre). • Outcome assessors at 90 days were not blind to treatment allocation. • Good neurological outcome defined as CPC of 1 or 2. • Hypothermia terminated early in 2 patients: 1 in each group. One due to arrhythmias/hypotension and family request. • Core body temperature monitored via bladder temperature probe.

Abbreviations used: CHD, coronary heart disease; CI, confidence interval; CPC, cerebral performance categories; CPR: cardiopulmonary resuscitation; ICU, intensive care unit; NR, not reported; NS, not significant; OPC, overall performance category; OR, odds ratio; PEA, pulseless electrical activity; RCT, randomised controlled trial; ROSC, return of spontaneous circulation; RR, risk ratio; VF, ventricular fibrillation; VT, ventricular tachycardia

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Kämäräinen A (2009)[9]

RCT
Finland
Recruitment period: 2005–2008

Study population: comatose patients who had an out of hospital cardiac arrest treated by physician staffed Helsinki Area Helicopter Emergency Medical Air Service (HEMS).

n = 43 (23 vs 20)

Age: hypothermia group: 59 years; control group: 63 years
Sex: hypothermia group: 94.7% (18/19) male; control group: 94.4% (17/18) male.

Patient selection criteria: patients must be aged ≥ 18 years, with time to ROSC exceeding 9 minutes and Glasgow Coma Scale ≤ 5. Patients excluded if pregnant, cardiac arrest due to trauma or intoxication or persistently hypotensive after ROSC.

Technique: therapeutic hypothermia (target temp 33°C) using +4°C Ringer’s IV solution (100 ml/min up to a maximum of 30 ml/kg, mean delay from ROSC to initiation of treatment: 26 minutes) versus controls (standard care). This only relates to techniques used prior to hospital admission.

Follow-up: discharge
Conflict of interest/source of funding: none.</td>
<td>Number of patients analysed: 37 (19 vs 18)

<table>
<tr><th></th><th>Pre-hospital hypothermia (n = 19)</th><th>Control (n = 18)</th><th>p value</th></tr>
<tr><td>Hypothermia administered in hospital</td><td>52.6% (10/19)</td><td>72.2% (13/18)</td><td>NS</td></tr>
<tr><td>Survival to discharge</td><td>42.1% (8/19)</td><td>44.4% (8/18)</td><td>NS</td></tr>
<tr><td>Survival to discharge: CPC 1</td><td>36.8% (7/19)</td><td>38.9% (7/18)</td><td>NS</td></tr>
<tr><td>Survival to discharge: CPC 2</td><td>5.3% (1/19)</td><td>5.6% (1/18)</td><td>NS</td></tr>
</table>
Core temperature of hypothermia group was significantly lower at time of hospital admission in comparison with the control group (34.1°C vs 35.2°C, p < 0.001).</td>
<td>None reported</td>
<td>Follow-up issues:
• 2 patients in the control group were lost to follow-up after randomisation and 4 patients in the hypothermia group were also not included in the analysis (1 due to protocol violation, 1 withdrew consent during follow-up and 2 patients re-arrested and died before treatment initiated).
• Complete follow-up reported for remaining 37 patients.

Study design issues:
• Patients randomised in the field. Appropriate allocation concealment using unmarked sealed opaque envelopes. Unclear how random numbers were generated.
• Core body temperature monitored by nasopharyngeal temperature probe prior to hospital admission.
• In-hospital use of hypothermia was at the discretion of the treating physician. Not all patients in the hypothermia group continued to receive this therapy in hospital and a high proportion of the control group were cooled after admission.

Study population issues
• Baseline characteristics similar for both groups except higher rate of bystander CPR in the hypothermia group (58% vs 22%, p = 0.027).</td>
</tr>
</table>

Abbreviations used: CHD, coronary heart disease; CI, confidence interval; CPC, cerebral performance categories; CPR: cardiopulmonary resuscitation; ICU, intensive care unit; NR, not reported; NS, not significant; OPC, overall performance category; OR, odds ratio; PEA, pulseless electrical activity; RCT, randomised controlled trial; ROSC, return of spontaneous circulation; RR, risk ratio; VF, ventricular fibrillation; VT, ventricular tachycardia

Study details	Key efficacy findings	Key safety findings	Comments
Laurent I (2005)[10] **RCT** France Recruitment period: 2000–2002 Study population: patients who had a cardiac arrest related to heart disease. n = **61 (20 vs 22 vs 19)** Age: haemofiltration-only group: 52 years; hypothermia + haemofiltration group: 56 years; control group: 58 years (median) Sex: haemofiltration only group: 80% (16/20) male; hypothermia + haemofiltration group: 81.8% (18/22) male; control group: 78.9% (15/19) male. Patient selection criteria: patients must be aged 18–75 years, initial ventricular fibrillation or asystole, < 10 minutes from cardiac arrest to ROSC and < 50 minutes from initiation of CPR to ROSC. Exclusions: pregnancy, response to verbal commands after ROSC or a terminal illness before cardiac arrest. Technique: isovolumic high-volume haemofiltration using Gambro AL200-Ultra machine (200 ml/kg/h over 8 hours) only versus therapeutic hypothermia (target temp 32–33°C) using ice packs plus haemofiltration with fluid set at 30°C versus controls (standard care). Follow-up: **6 months** Conflict of interest/source of funding: haemofiltration equipment provided by manufacturer.	Number of patients analysed: **61 (20 vs 22 vs 19)** **In hospital survival** Haemofiltration only group: 45% (9/20) Hypothermia + haemofiltration group: 45.5% (10/22) Control group: 26.3% (5/19) (p = 0.16 compared to the other 2 groups) **6 months survival** Haemofiltration only group: 45% (9/20). Hypothermia + haemofiltration group: 31.8% (7/22) Control group: 21.1% (4/19) (p = 0.28 compared to the other 2 groups) **6 month Kaplan-Meier survival curves:** Haemofiltration only group vs control group: p = 0.026 Hypothermia + haemofiltration group versus control group: p = 0.018 Neurological outcome was favourable in all survivors at 6 months.	**Death by intractable shock** Haemofiltration only group: 10% (2/20) RR: 0.21 (95% CI: 0.05 to 0.85) Hypothermia + haemofiltration group: 13.6% (3/22) RR: 0.29 (95% CI: 0.09 to 0.91) Control group: 47.4% (9/19) (p = 0.009 compared to the other 2 groups) **Hypokalemia:** Haemofiltration-only group: 25% (5/20) Hypothermia + haemofiltration group: 22.7% (5/22) This was corrected by adding potassium chloride to the substitution fluid. **Hypophophataemia:** Haemofiltration-only group: 45% (9/20) Hypothermia + haemofiltration group: 54.5% (12/22) This was corrected by intravenous infusion of disodium phosphate. Timing of events is not reported.	**Included in Arrich 2007** **Follow-up issues**: • 75% (183/244) patients assessed did not meet the inclusion criteria. • Complete follow-up reported for all included patients. **Study design issues**: • Prospective 2-centre study. • Appropriate randomisation using computer generated 1:1:1 randomisation sequence at each hospital. Appropriate allocation concealment using sealed opaque envelopes. • Core body temperature monitored by bladder temperature probe. • Favourable neurological outcome defined as CPC of 1 or 2. **Study population issues** • Baseline characteristics similar for both groups although the authors report a trend towards greater severity seen in the haemofiltration-only group. • 2 patients in the haemofiltration-only group died before the intervention was initiated. They are included in the analysis.

Abbreviations used: CHD, coronary heart disease; CI, confidence interval; CPC, cerebral performance categories; CPR: cardiopulmonary resuscitation; ICU, intensive care unit; NR, not reported; NS, not significant; OPC, overall performance category; OR, odds ratio; PEA, pulseless electrical activity; RCT, randomised controlled trial; ROSC, return of spontaneous circulation; RR, risk ratio; VF, ventricular fibrillation; VT, ventricular tachycardia

Study details	Key efficacy findings	Key safety findings	Comments
Mori K (2000)[11] **RCT** Japan Recruitment period: not reported. Study population: patients successfully resuscitated from out of hospital cardiac arrest with post resuscitation Glasgow Coma Scale < 8. n = **54 (36 vs 18)** Age: not reported. Sex: not reported. Patient selection criteria: see above Technique: brain hypothermic therapy (32–34°C) using an unspecified device vs brain normothermic therapy (36°C). Treatment given for 3 days after resuscitation. Follow-up: **1 month** Conflict of interest/source of funding: not reported.	Number of patients analysed: **54 (36 vs 18)** **Good neurological outcome at 1 month:** Hypothermic group: 50% Normothermic group: 11% (p < 0.05) Multivariate analysis of patient characteristics showed that relative improvement in patients with arrest time < 20 minutes and Glasgow Coma Scale > 5. **Good neurological outcome for patients with arrest time < 20 minutes and Glasgow Coma Scale > 5:** Hypothermic group: 79% Normothermic group: 25% (p < 0.05) [no absolute numbers provided in the abstract]	Not reported.	**Included in Arrich 2007 and Cheung 2005** **Follow-up issues**: • Completeness of follow-up not reported. **Study design issues**: • Very little detail included as this study is only reported in an abstract. • Patients randomised 2:1. Method of randomisation and allocation concealment is not reported. • Good neurological outcome defined as Glasgow Coma Scale indicating mild moderate or no disabilities.

Abbreviations used: CHD, coronary heart disease; CI, confidence interval; CPC, cerebral performance categories; CPR: cardiopulmonary resuscitation; ICU, intensive care unit; NR, not reported; NS, not significant; OPC, overall performance category; OR, odds ratio; PEA, pulseless electrical activity; RCT, randomised controlled trial; ROSC, return of spontaneous circulation; RR, risk ratio; VF, ventricular fibrillation; VT, ventricular tachycardia

Study details	Key efficacy findings	Key safety findings	Comments
Hachimi-Idrissi S (2001)[12] **RCT** Belgium Recruitment period: not reported Study population: patients with asystole or pulseless electrical activity of presumed cardiac origin who achieved ROSC after out of hospital cardiac arrest. n = **30 (16 vs 14)** Age: hypothermia group: 76.5 years (median); normothermic group: 74 years (median) Sex: hypothermia group: 56.3% (9/16) male; normothermic group: 64.3% (9/14) male. Patient selection criteria: patients had to be over 18 years with tympanic temperature > 30°C on admission to emergency room and Glasgow Coma Scale < 7. Patients were excluded if pregnant had a known coagulopathy, history of central nervous system depressant drug medication. All patients had to be haemodynamically stable to be included. Technique: therapeutic mild hypothermia (34°C) using the Frigicap® (cooling device for the head, median time from collapse to start of cooling: 102 minutes) vs normothermia (standard care). Follow-up: **2 weeks** Conflict of interest/source of funding: not reported.	Number of patients analysed: **30 (16 vs 14)** **Survival:** Hypothermia group:18.8% (3/16) Normothermia group:7.1% (1/14) **OPC of survivors:** Hypothermia group: 2 patients had an OPC of 1, and 1 patient had an OPC of 3. Normothermia group: the 1 surviving patient had an OPC of 3.	**Mortality:** Hypothermia group: 81.3% (13/16) Normothermia group: 92.9% (13/14) 5 patients died due to refractory cardiogenic shock a few hours after admission to ICU. The remaining 21 patients died due to neurological failure within 2 weeks of admission. **Oliguria:** Hypothermia group: 25% (4/16) Normothermia group: 35.7% (5/14)	**Included in Arrich 2007 and Cheung 2005** **Follow-up issues**: • Follow-up is complete for all patients. **Study design issues**: • Prospective single centre study. • Appropriate randomisation using random number tables occurred after arrival at hospital. Method of allocation concealment is not reported. • OPC of 1 indicates a good functioning and OPC of 3 indicates severe disability. • Core body temperature monitored via bladder and tympanic thermometers. **Study population issues** • Baseline characteristics similar for both groups. • Study included 1 patient who had a massive brain stem haemorrhage. All other patients had a cardiac arrest of cardiac origin.

Abbreviations used: CHD, coronary heart disease; CI, confidence interval; CPC, cerebral performance categories; CPR: cardiopulmonary resuscitation; ICU, intensive care unit; NR, not reported; NS, not significant; OPC, overall performance category; OR, odds ratio; PEA, pulseless electrical activity; RCT, randomised controlled trial; ROSC, return of spontaneous circulation; RR, risk ratio; VF, ventricular fibrillation; VT, ventricular tachycardia

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Van der Wal G (2010)[13]

Non-randomised controlled study

Holland

Recruitment period: 1999 to 2009.

Study population: patients having cardiac arrest up to 24 hours before admission to ICU.

n = 5317 (3770 cooling vs 1547 no cooling)

Age:64 years (mean)
Sex 64% male

Patient selection criteria: patients were excluded if defibrillation or cardioversion without chest compression, cardiopulmonary resuscitation in ICU, or Glasgow Coma Scale score >8.

Technique. Protocol to use mild therapeutic hypothermia (32–34°C) for 12 to 24 hours in comatose patients after out-of-hospital cardiac arrest (<15 mins) following VF, with cooling as soon as possible after ROSC.

Follow-up: to discharge

Conflict of interest/source of funding: none.</td>
<td>Number of patients analysed: 5317 (3770 cooling vs 1547 no cooling)

Survival
Hospital mortality was significantly reduced among patients treated with cooling compared with those with no cooling OR 0.8 (95% CI 0.654 to 0.978) (p = 0.029).

Length of stay
Overall group median length of stay (and interquartile range) days
<table>
<tr><td></td><td>Cooling</td><td>No cooling</td><td>p=</td></tr>
<tr><td>ICU</td><td>3.0 (1.3 to 5.8)</td><td>2.6 (0.9 to 5.3)</td><td>< 0.001</td></tr>
<tr><td>Hospital</td><td>6.0 (2.4 to 17.0)</td><td>5.0 (2.2 to 15.0)</td><td>< 0.001</td></tr>
</table>
Survivors group median length of stay (and interquartile range) days
<table>
<tr><td></td><td>Cooling</td><td>No cooling</td><td>p=</td></tr>
<tr><td>ICU</td><td>4.8 (2.7 to 7.9)</td><td>3.7 (1.6 to 7.0)</td><td>< 0.001</td></tr>
<tr><td>Hospital</td><td>19.0 (10.0 to 33.0)</td><td>18.0 (9.0 to 35.5)</td><td>N/S</td></tr>
</table>
</td>
<td>Safety outcomes were not reported on</td>
<td>Follow-up issues:
• Retrospective follow-up of national database.

Study design issues:
• Historical control of patients treated before cooling was introduced in Holland.
• 59 participating sites.
• Patients treated within 3 months of introducing cooling protocol at each site were excluded from analysis.

Study population issues:
• No analysis undertaken to compare potential differences between groups at baseline. However, characteristics appear to be broadly similar.
Other issues:
• Introduction of cooling significantly increased length fo stay outcomes.</td>
</tr>
</table>

Abbreviations used: CHD, coronary heart disease; CI, confidence interval; CPC, cerebral performance categories; CPR: cardiopulmonary resuscitation; ICU, intensive care unit; NR, not reported; NS, not significant; OPC, overall performance category; OR, odds ratio; PEA, pulseless electrical activity; RCT, randomised controlled trial; ROSC, return of spontaneous circulation; RR, risk ratio; VF, ventricular fibrillation; VT, ventricular tachycardia

Study details

Nielsen N (2009)[14]

Case series (register)

Scandinavia

Recruitment period: 2004–2008.

Study population: unconscious (Glasgow Coma Scale < 8) patients with ROSC admitted to ICU following an out-of-hospital cardiac arrest (all causes).

n = **986**

Age: 63 years (median)
Sex: 74.3% (733/986)

Patient selection criteria: patients aged 18+ years.

Technique: therapeutic mild hypothermia using a variety of methods/devices (median time from arrest to initiation of hypothermia was 90 minutes).

Follow-up: **6–12 months**

Conflict of interest/source of funding: supported by non-manufacturer grants.

Key efficacy findings

Number of patients analysed: **986 at discharge, 975 long term**

	Initiation of hypothermia	**Maintenance of hypothermia**
Ice packs	42.6% (420/986)	17.3% (171/986)
Cold fluid infusion	79.9% (788/986)	-
Air cooling	9.4% (93/986)	7.9% (78/986)
Circulating water blankets	4.6% (460/986)	63.4% (625/986)
Intravascular devices	9.9% (98/986)	15.9% (157/986)
Other	6.2% (61/986)	7.9% (78/986)

More than 1 technique used for some patients.

	All patients (n = 986)	VT/VF patients (n = 686)	Asystole patients (n = 217)	PEA patients (n = 66)	Unknown rhythm (n = 17)
Survival at ICU discharge	68.6% (676/986)	77.8% (534/686)	47.5% (103/217)	47.0% (31/66)	47.1% (8/17)
Survival at ICU discharge with a good outcome:	40.1% (401/986)	49.3% (338/686)	18.9% (41/217)	21.2% (14/66)	47.1% (8/17)
Survival at hospital discharge:	56.4% (556/986)	67.5% (463/686)	30.0% (65/217)	28.8% (19/66)	47.1% (8/17)
Survival at hospital discharge with a good outcome:	44.0% (434/986)	53.1% (364/686)	21.7% (47/217)	21.2% (14/66)	47.1% (8/17)
6–12 months survival:	50.3% (490/975)	60.9% (412/677)	25.1% (54/215)	27.3% (18/66)	47.1% (8/17)
6–12 months survival with a good outcome:	45.8% (447/975)	56.1% (380/677)	21.4% (46/215)	22.7% (15/66)	47.1% (8/17)

Of those alive with a poor outcome at long term follow-up, 39 had CPC 3 and 4 had CPC 4. Patients who died after discharge from ICU died at a median of 1

Key safety findings

Bradycardia: 12.9% (127/986)
Tachycardia: 5.8% (57/986)
Atrial fibrillation: 8.9% (88/986)
VT: 9.0% (89/986)
VF: 7.2% (71/986)
Any combination of arrhythmia: 32.9% (325/986)
Pneumonia: 41.3% (407/986)
Sepsis: 4.1% (35/986)
Other infection: 4.1% (41/986)
Bleeding requiring transfusion: 4.5% (44/986).
Significantly higher risk of bleeding if angiography or percutaneous coronary intervention performed (2.8% vs 6.2%, p = 0.02)
Intracerebral bleeding: 0.2% (2/986)
Seizures: 23.6% (233/986)
Hypokalaemia, hypomagnesaemia and hypophosphataemia present in approximately 20% of patients.

Comments

Follow-up issues:
- 1.1% (11/986) lost at 6-12 months follow-up.

Study design issues:
- Prospective register in 7 countries.
- Good outcome defined as CPC of 1 or 2.

Study population issues
- Type of cardiac arrest: asystole: 22.0% (217/986), pulseless electrical activity: 6.7% (66/986) and VF/VT: 69.6% (686/986).
- 48.6% (479/986) had emergency coronary angiography and 30.3% (299/986) had percutaneous coronary intervention.

Abbreviations used: CHD, coronary heart disease; CI, confidence interval; CPC, cerebral performance categories; CPR: cardiopulmonary resuscitation; ICU, intensive care unit; NR, not reported; NS, not significant; OPC, overall performance category; OR, odds ratio; PEA, pulseless electrical activity; RCT, randomised controlled trial; ROSC, return of spontaneous circulation; RR, risk ratio; VF, ventricular fibrillation; VT, ventricular tachycardia			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
	week after discharge. Median length of stay in ICU: 100 hours		

Abbreviations used: CHD, coronary heart disease; CI, confidence interval; CPC, cerebral performance categories; CPR: cardiopulmonary resuscitation; ICU, intensive care unit; NR, not reported; NS, not significant; OPC, overall performance category; OR, odds ratio; PEA, pulseless electrical activity; RCT, randomised controlled trial; ROSC, return of spontaneous circulation; RR, risk ratio; VF, ventricular fibrillation; VT, ventricular tachycardia	
Study details	**Key safety findings (This table describes serious safety outcomes taken from smaller non randomised controlled trials, case series and case reports that have not occurred in the previous 9 studies in table 2)**
Batista LM (2010)[15] Laish-Farkash A (2007)[16] Park E (2009)[17] Busch M (2006)[18] Al-Senani FM (2004)[19] Goto T (2009)[20] Bergman R (2008)[21] Wible EF (2010)[22]	**Batista 2010** Non-randomised comparative study of 90 patients (20 hypothermia + percutaneous coronary intervention vs 70 hypothermia only). Mortality: 67.8% (61/90) died during hospitalisation but the rates of mortality were not significantly different between the 2 group (60% vs 70 %, p = 0.4). Any adverse events: 55.0% (11/20) in the PCI + hypothermia group vs 31.4% (22/70) in the hypothermia only group [OR: 2.6 (95% CI: 1.0 to 7.3)]. Dysrhythmia (any): 30% (6/20) vs 18.6% (13/70) [OR: 1.9 (95% CI: 0.6 to 5.8)]. Serious dysrhythmia: 15.0% (3/20) vs 12.8% (9/70) [OR: 1.2 (95% CI: 0.3 to 5.0)]. **Laish-Farkash (2007)** Case series of 51 patients. Mortality: 37.3% (19/51), pneumonia: 52.9% (27/51), sepsis: 23.5% (12/51), cardiogenic shock: 25.5% (13/51), any bleeding: 15.7% (8/51), acute renal failure: 17.6% (9/51), pancreatitis: 2.0% (1/51), pulmonary oedema: 9.8% (5/51), seizures: 17.6% (9/51), significant prolonged or lethal arrhythmia: 9.8% (5/51). **Park (2009) [abstract]** Case series of 34 patients. Systemic inflammatory response syndrome: 26.5% (9/34). All of these patients had been rewarmed to a temperature of 38°C or more. **Busch (2006)** Case series of 27 patients. Median length of stay in ICU: 4 days, death or CPC of 3 or 4 at discharge: 59.3% (16/27), pneumonia: 70.4% (19/27), hypokalaemia: 81.5% (22/27), arrhythmia: 25.9% (7/27), insulin resistance: 18.5% (5/27), elevated amylase: 59.3% (16/27), platelet reduction > 30%: 11.1% (3/27). **Al-Senani (2004)** Case series of 13 patients. Mortality: 30.8% (4/13), sepsis: 23.1% (3/13), recurrent ventricular tachycardia/cardiac arrest: 30.8% (4/13), pneumonia: 7.7% (1/13), pneumothorax: 7.7% (1/13), lower lung lobe collapse: 7.7% (1/13), hypertension/hypotension: 23.1% (3/13), seizures : 7.7% (1/13), respiratory distress: 7.7% (1/13), worsening renal insufficiency requiring dialysis: 7.7% (1/13), bradycardia: 7.7% (1/13), renal failure: 7.7% (1/13), thrombocytopenia:7.7% (1/13). **Goto (2009)** Case report in a letter describing a patient who developed septic shock from Klebsiella pneumonia. Bacterial translocation is the suspected cause of septic shock. Treatment and outcome of septic shock are not reported. **Bergman (2008)** Case report describing a patient with unexpected fatal neurological deterioration after therapeutic hypothermia. 24 hours after rewarming, the patient developed a high fever and episodes of bradypnoea requiring renewed controlled mechanical ventilation. The patient then developed hypertension followed by hypotension and relative bradycardia with pupils dilated and fixed and a deterioration of GCS. The patient also developed polyuria and diabetes insipidus was diagnosed. A CT scan showed massive diffuse cerebral oedema with complete compression of the fourth ventricle and supratentorial herniation. Clinical brainstem death was then reported. **Wible EF (2010)** Case report describing a pregnant 44-year-old female (20 week gestation) treated with therapeutic hypothermia following out-of-hospital cardiac arrest delivered a stillborn foetus 1 day after admission. The patient made a good neurological recovery and was discharged home at day 42. She was able to perform activities of daily living at 1 year follow-up.

Efficacy

SurvivalA systematic review of 481 patients reported that a significantly higher proportion of patients in the hypothermia group survived to hospital discharge in comparison with patients in the standard care group (risk ratio [RR]: 1.35, 95% confidence interval [CI]:1.10 to 1.65, 3 studies)[1].A randomised controlled trial (RCT) of 200 patients (96 nasal cooling vs 104 standard care) reported that a significantly higher proportion of patients in the nasal cooling group survived to hospital discharge compared with patients in the standard care group where patients had received cardiopulmonary resuscitation within 10 minutes of out of hospital cardiac arrest (57% [13/23] vs 29% [10/34], p = 0.04)[5].

An RCT of 125 patients (63 hypothermia vs 62 normothermia) reported survival at discharge in 66% (19/29) of VF rhythm hypothermia patients, 6% (2/34) of non-VF rhythm hypothermia patients, 46% (10/22) of VF rhythm normothermia patients and 20% (8/40) of non-VF rhythm normothermia patients[6].

An RCT of 77 patients (43 hypothermia vs 34 normothermia) reported a significantly higher proportion of patients in the hypothermia group survived to hospital discharge with a good neurological outcome (defined as discharge home or to a rehabilitation facility) in comparison to patients in the normothermia group (49% [21/43] vs 27% [9/34], p = 0.046)[7].

An RCT of 43 patients (23 hypothermia vs 20 normothermia) reported similar rates of survival to discharge in both groups (42% [8/19] vs 44% [8/18], p = not significant)[9].

An RCT of 61 patients (20 haemofiltration only vs 22 hypothermia plus haemofiltration vs 19 controls) reported higher rates of 6-month survival in the haemofiltration-only and hypothermia plus haemofiltration groups than the control group; but this result was not statistically significant (45% [9/20] vs 32% [7/22] vs 24% [5/19], p = 0.28)[10].

An RCT of 30 patients (16 hypothermia vs 14 normothermia) reported similar survival rates at 2 weeks in both groups (19% [3/16] vs 7% [1/14])[12].

A non-randomised comparative study of 5317 patients (3770 hypothermia vs 1547 no cooling) reported that hospital mortality was significantly reduced among patients treated with hypothermia compared with those who were not (odds ratio (OR) 0.8 [95% confidence interval (CI) 0.654 to 0.978, p = 0.029])[13]

A case series of 986 patients reported 6–12 months survival in 50% (490/975) of all patients and 61% (412/677) patients with a VF/VT rhythm, 25% (54/215) patients with an asystole rhythm and 27% (18/66) patients with a PEA rhythm[14].

Neurological outcome

A systematic review of 481 patients reported that a significantly higher proportion of patients in the hypothermia group had a good neurological outcome (defined as CPC score of 1 or 2 or where authors had reported a good neurological outcome) at hospital discharge in comparison to patients in the standard care group (RR: 1.55, 95% CI: 1.24 to 1.94, 5 studies)[1].

A systematic review of 436 patients reported that a significantly lower proportion of patients in the hypothermia group had a poor neurological outcome (defined as

either CPC categories 3, 4 or 5; poor outcome on the Glasgow Outcome Scale or discharge to a long term nursing facility or death) in comparison to patients in the standard care group (RR: 0.72, 95% CI: 0.62 to 0.84, 4 studies)[2].

An RCT of 275 patients (137 hypothermia vs 138 normothermia) reported a significantly higher proportion of patients in the hypothermia group with a favourable neurological outcome at 6 months (defined as CPC 1 or 2) in comparison with patients in the normothermia group after adjusting for baseline variables (RR: 1.47 (95% CI: 1.09 to 1.82)[3].

An RCT of 234 patients (118 immediate paramedic cooling vs 116 hospital cooling) reported a similar proportion of patients with a favourable outcome (defined as patients who did not die/discharged to a long-term nursing facility) at discharge (48% [56/118 vs 53% [61/116], p = 0.433)[4].

An RCT of 64 patients (34 hypothermia using gel pads with feedback control vs 30 hypothermia using blankets and ice) reported that a higher proportion of patients in the gel pads with feedback control group had a good neurological outcome at 90 days (defined as CPC of 1 or 2) than patients in the blankets and ice group but this result was not statistically significant (47% [15/32] vs 38% [11/29], p = 0.6)[8].

An RCT of 54 patients (36 hypothermia vs 18 normothermia) reported a significantly higher proportion of patients in the hypothermia group had a good neurological outcome at 1 month (defined as Glasgow Coma Scale showing mild, moderate or no disabilities) in comparison with patients in the normothermia group (50% vs 11%, p < 0.05)[11].

A case series of 986 patients reported 6-–12 months survival with a good neurological outcome (defined as CPC 1 or 2) in 456% (447/975) of all patients and 56% (380/677) patients with a VF/VT rhythm, 21% (46/215) patients with an asystole rhythm and 23% (15/66) patients with a PEA rhythm[14].

Safety

Infection

A systematic review of 481 patients reported higher rate of pneumonia in the hypothermia group but this result was not statistically significant (RR: 1.27, 95% CI: 0.90 to 1.78, 1 study)[1].

A systematic review of 481 patients reported higher rate of sepsis in the hypothermia group, but this result was not statistically significant (RR: 1.93, 95% CI: 0.89 to 1.78, 1 study)[1].

A case series of 986 patients reported sepsis and pneumonia rates of 4% (35/986) and 41% (407/986) respectively at 6–12-month follow-up[14].

Metabolic changes: hypokalaemia and hypophosphataemia

The systematic review of 481 patients reported a higher rate of hypophosphataemia in the hypothermia group, but this result was not statistically significant (RR: 1.12, 95% CI: 0.65 to 2.25, 1 study). The same study reported a lower rate of hypokalaemia in the hypothermia group, but this result was not statistically significant (RR: 0.91, 95% CI: 0.3 to 2.68, 1 study)[1].

The RCT of 61 patients (20 haemofiltration only vs 22 hypothermia plus haemofiltration vs 19 controls) reported similar 6-month hypokalaemia rates of 25% (5/20) in the haemofiltration only group and 23% (5/22) in the hypothermia plus haemofiltration group. The same study reported similar 6-month hypophosphataemia rates of 45% (9/20) in the haemofiltration only group and 55% (12/22) in the hypothermia plus haemofiltration group[10].

Haematological: thrombocytopenia, bleeding, platelet transfusion

The systematic review of 481 patients reported a higher rate of bleeding requiring platelet transfusion in the hypothermia group, but this result was not statistically significant (RR: 5.11, 95% CI: 0.25 to 5.47, 1 study)[1].

The RCT of 64 patients (34 hypothermia using gel pads with feedback control vs 30 hypothermia using blankets and ice) reported heparin-induced thrombocytopenia within 90 days in 1 patient in the gel pads with feedback control group and no patients in the blankets and ice group. The same study reported 2 patients with a gastrointestinal bleed within 90 days in the blankets and ice group and no patients in the gel pads with feedback control group[8].

A case series of 986 patients reported bleeding requiring transfusion in 5% (44/986) of patients[14].

Seizures

The systematic review of 481 patients reported fewer seizures in the hypothermia group, but this result was not statistically significant (RR: 0.89, 95% CI: 0.39 to 2.02, 1 study)[1].

The RCT of 64 patients (34 hypothermia using gel pads with feedback control vs 30 hypothermia using blankets and ice) reported similar 90-day seizures and/or status epilepticus rates in both groups (19% [6/32] vs 17% [5/29])[8].

A case series of 986 patients reported seizures in 24% (233/986) of patients[14].

Bradyarrhythmias

The systematic review of 481 patients reported a higher rate of lethal or long-lasting arrhythmias in the hypothermia group, but this result was not statistically significant (RR: 1.21, 95% CI: 0.88 to 1.67, 1 study)[1].

The RCT of 64 patients reported significant arrhythmia in 6% (2/32) of patients in the gel pads with feedback control group and 17% (5/29) in the blankets and ice group[8].

A case series of 986 patients reported bradycardia in 13% (127/986) of patients[14].

Validity and generalisability of the studies

- All key papers presented are either systematic reviews including meta-analysis or RCTs.
- No long-term data greater than 6 months is available.
- A variety of devices were used in the reported studies to achieve cooling to 32–34°C. The length of therapeutic mild hypothermia also varied between the studies and was not reported in all the papers.

Existing assessments of this procedure

Eleven existing assessments of this procedure were found in the published literature:

1. Resuscitation Council (UK) published guidelines on Adult Advanced Life Support in 2005. The following recommendations relate to therapeutic hypothermia:
    - Unconscious adult patients with spontaneous circulation after out-of-hospital VF cardiac arrest should be cooled to 32–34°C for 12–24 hours.
    - Mild hypothermia may also benefit unconscious patients with spontaneous circulation after out-of-hospital cardiac arrest due to a non-shockable rhythm, or after cardiac arrest in hospital.
    - Treat shivering by ensuring adequate sedation and giving neuromuscular blocking drugs. Bolus doses of neuromuscular blockers are usually adequate but infusions are occasionally necessary.
    - Re-warm the patient slowly (0.25–0.5°C per hour) and avoid hyperthermia. The optimum target temperature, rate of cooling, duration of hypothermia, and rate of re-warming have yet to be determined; further studies are essential.External or internal cooling techniques or both can be used to initiate treatment. An infusion of 30 ml kg^{-1} saline at 4°C decreases core temperature by 1.5°C. Intravascular cooling enables more precise control of core temperature than external methods, but it is unknown whether this improves outcomes[23].

2. The American Heart Association published a guideline in 2010 on post-cardiac arrest care. The Association recommends surface or endovascular cooling (32–34°C) for 24 hours. After 24 hours, re-warm at 0.25°C per hour[24].
3. The International Liaison Committee on Resuscitation and the American Heart Association published a pathway for the management of survivors of out-of hospital cardiac arrest in 2010. The pathway includes

recommendations for a three-phase hypothermia protocol: 1) invasive cooling in first 24 hours to reach 33°C; 2) re-warming phase after 24 hours (0.25°C per hour up to 37°C); 3) normothermia maintenance including antibiotic therapy if necessary and consideration for additional cooling. Inclusion criteria for induced hypothermia protocol: 1) aged > 18 years; 2) coma at time of cooling (defined as not following commands, no purposeful movement, reflex and pathological posturing movements are permissible)[25]

4. The Scandinavian guideline for therapeutic hypothermia and post-resuscitation care after cardiac arrest (Castren, Silfvast, Rubertsson S et al 2009) recommendation summary reports that although proven beneficial only for patients with initial VF, mild therapeutic hypothermia is also recommended after ROSC, if active treatment is decided in patients with initial pulseless electrical activity and asystole. Normal ethical considerations, pre-morbid status, total anoxia time and general condition should also decide whether active treatment is required. Mild therapeutic hypothermia should be part of a standardised treatment protocol and initiated as early as possible. There is insufficient evidence to make definitive recommendations among techniques to induce mild therapeutic hypothermia[26].
5. Northwest Community Hospital (Illinois, USA) published an evidence-based emergency department protocol for therapeutic hypothermia in the post-resuscitation patient in 2009. The protocol provides a detailed explanation on how to initiate therapeutic hypothermia using cold saline, ice packs and cooling blankets and states that it should be used for patients who have had a cardiac arrest with return of spontaneous circulation. The following are contraindications: pregnancy, paediatrics, trauma and rapidly improving neurological deficits[27].

6. The National Association of Emergency Medical Service Physicians in the USA published a position paper on induced therapeutic hypothermia in

resuscitated cardiac arrest patients in 2008. The Association states that a lack of evidence on induced hypothermia in the pre-hospital setting precludes recommending this treatment modality for emergency medical services patients resuscitated from cardiac arrest. Further research is needed to examine the ideal time of initiation of induced hypothermia, types of patients likely to benefit, and most practical and effective means of cooling[28].

7. The Australian Resuscitation Council published guidelines on adult advanced life support in 2006. The following recommendations are made with regards to therapeutic hypothermia following cardiac arrest:
    - Unconscious adult patients with return of spontaneous circulation after out-of-hospital cardiac arrest, when the initial rhythm was ventricular fibrillation (VF) should be cooled to 32–34°C for 12–24 hours.
    - Unconscious adult patients with return of spontaneous circulation after out-of-hospital cardiac arrest, when the initial rhythm was other than VF or cardiac arrest in hospital, such cooling may also be beneficial[29].

8. The CAEP Critical Care Committee in Canada published an algorithm for emergency physicians regarding hypothermic modulation of anoxic brain injury in adult survivors of cardiac arrest in 2005. The inclusion criteria are primary cardiac arrhythmia, time from collapse to advanced cardiac life support < 15 minutes, time from collapse to ROSC < 60 minutes, persistent coma (Glasgow Coma Score < 10) and adults > 18 years[30]. A guideline for the use of hypothermia after cardiac arrest was published by the same organisation in 2006 and recommended that:
    - Cardiac arrest patients who present with non-perfusing ventricular tachycardia or ventricular fibrillation are resuscitated to

haemodynamic stability but remain unresponsive should undergo therapeutic hypothermia.

- Cardiac arrest patients who present with asystole or pulseless electrical activity felt to be of cardiac origin and resuscitated to haemodynamic stability should be considered for therapeutic hypothermia.
- Patients under 18 years of age and pregnant women may benefit from this therapy, but its role is unproven. Consideration in these populations should be on a case-by-case basis[31].

9. The 2005 European Guidelines for cardiopulmonary resuscitation does not specify a cooling technique but does recommend mild therapeutic hypothermia (cooling to 32–34°C) for 12–24 hours in all comatose survivors of out-of-hospital cardiac arrest when the initial recorded rhythm was ventricular fibrillation. Cooling should be initiated as soon as possible. The use of therapeutic hypothermia should be considered in comatose survivors of out-of-hospital non VF/VT cardiac arrest or after in-hospital cardiac arrest[32].
10. The Australia and New Zealand Horizon Scanning Network published a prioritising summary on the CoolGard™ 3000 Catheter Thermal Regulation System: endovascular hypothermia induction for treatment of comatose survivors of ventricular fibrillation cardiac arrest in 2005. The report concludes that “there is currently insufficient high level evidence to assess the effectiveness of hypothermia induction with the CoolGard™. However, there is recognition of the benefits of hypothermia for improved neurological outcomes”[33].
11. The Advance Life Support Task force of the International Liaison Committee on Resuscitation recommended the following with regards to therapeutic hypothermia in 2003:

- Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32–34°C for 12–24 hours when the initial rhythm was VF.
- Such cooling may also be beneficial for other rhythms or in-hospital cardiac arrest[34].

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury. NICE interventional procedures guidance 347 (2010). Available from www.nice.org.uk/guidance/IPG347

Specialist Advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

Mr Adam Wolverson and Mr Jerry Nolan (Intensive Care Society), Mr Bill Hulse, Mr Robin Roop, Mr Dominic Williamson and Mr Simon Smith (College of Emergency Medicine)

- Five Specialist Advisers perform this procedure regularly and 1 has performed the procedure at least once.
- Four Specialist Advisers consider it to be established practice, 1 considers it to be a minor variation on an existing procedure and 1 considers this to be the first in a new class of procedure. Four Specialist Advisers state that 10–50% of specialists are engaged in this area of work. One Specialist Adviser states that the procedure is being used in 85% of intensive care units (ICU) in the UK.
- Theoretical adverse events: ileus, hepatic failure and renal failure.
- Anecdotal/reported adverse events: over-cooling, difficulty maintaining temperature or failing to cool patients quickly enough, inability to re-warm slowly, danger of inducing moderate hypothermia causing effects on coagulation and immune modulation, thermal injury to skin from cooling devices, arrhythmias, secondary infections, shivering, electrolyte imbalance, pancreatitis, bradycardia, peripheral vasoconstriction and trauma thrombosis.
- Comparator: normothermia (standard care).

- Key efficacy outcomes: survival/mortality rates and reduced long-term neurological disability, measure of independent living, quality of life (SF-36, Health Utility Index 3), time to target temperature, time spent in target temperature range, reduction in ICU and hospital length of stay.
- Training and facilities: level 3 critical care facilities where staff have training and experience in the procedure. Training and guidelines for staff in emergency medicine, acute and general medicine and cardiology are important to ensure that suitable patients are identified early on and referred appropriately.
- One Specialist Adviser states that the procedure is not yet proven in paediatric patients, trauma or septic patients.
- Two Specialist Advisers state that the optimum method, timing, duration of cooling and rate of re-warming remain uncertain and guidelines to clarify this would be useful in spreading the use of this procedure.
- One Specialist Adviser states that the evidence base supports cooling for post-VF cardiac arrest (and not pulseless electrical activity cardiac arrest) and for patients in coma post arrest (and not those who make a rapid recovery to consciousness).
- One Specialist Adviser states that there is uncertainty if this procedure is of benefit in all types of cardiac arrest and if hypothermia should be started before the patient reaches hospital. Another Specialist Adviser states that one unresolved topic is whether any particular cooling devices are safer or produce better outcomes.
- Two Specialist Advisers state that acceptance of this procedure is not universal and application of it outside of the areas in the published literature remains controversial. One of these Specialist Advisers states that significant numbers of patients who might benefit from the procedure do not currently receive it.

Patient Commentators' opinions

This is an emergency procedure. Patients are comatose and therefore unable to consent to treatment, therefore patient commentary was not sought for this procedure.

Issues for consideration by IPAC

- Title: should the title include the type of cardiac arrest (that is ventricular fibrillation) and/or specify that it is only for use in patients who are comatose after ROSC?
- Future studies awaiting publication:
  - The Rhinocoll study (first study in Appendix A) will be published shortly.
  - A German RCT of 120 patients "clinical and neurological outcome with two different cooling methods (invasive and non-invasive) after sudden cardiac arrest" was completed in January 2010. The phase IV trial (known as the COOL trial) compares Coolgard vs Arctic Sun vs sham treatment. Primary outcome measures: time to reach the target temperature and neuron specific enolase (NSE) as a parameter for cerebral damage. Secondary outcome measures are neurological outcome, survival and periprocedural complications. Inclusion criteria: ROSC after sudden cardiac arrest due to VF/VT or PEA/asystolia with Glasgow Coma Scale 3. Exclusion criteria: non-cardiac sudden cardiac arrest, pregnancy, unstable circulation instead of high-dose inotropics and life-expectancy reducing concomitant illness.
  - A French RCT sponsored by a manufacturer: 'Clinical interest of endovascular cooling in the management of cardiac arrest: impact on mortality in a randomised medico-economical trial (the ICEREA Study)' was completed in November 2009. The study recruited 389 patients and compares Coolguard and another cooling system. Outcomes include CPC, length of stay in ICU and survival at 90 days. Inclusion criteria: 18–79 years

old, out-of-hospital cardiac arrest due to a presumed cardiac aetiology, delay between cardiac arrest and ROSC < 60 minutes, delay between ROSC and starting cooling < 240 minutes, patient not obeying verbal command after ROSC and prior to starting cooling.

- Future trials still recruiting patients:
  - A Taiwanese non-randomised comparative study ‘The therapeutic effect of induced hypothermia in cardiac arrest patients rescued by extracorporeal cardiopulmonary resuscitation (ECPR)’ is currently recruiting patients. The study aims to recruit 45 patients and compares hypothermia to standard care. Outcomes include survival to discharge and brain injury. Inclusion criteria: aged 16+ years, out-of-hospital cardiac arrest that necessitated external or open-chest cardiac massage and a large amount of epinephrine (>5 mg) during CPR and could not be returned to spontaneous circulation within 10 to 20 min.
  - A Japanese case series ‘Multicenter registry study with therapeutic hypothermia after cardiac arrest in Japan’ is currently recruiting patients. The study aims to recruit 500 patients. Outcomes: 3 month survival and CPC. Inclusion criteria: adult patients who remained unconscious after resuscitation from out-of-hospital or in-hospital cardiac arrest who presented the stable haemodynamics with drug treatments or mechanical supporting system including IABP or PCPS.
  - A German RCT ‘Hypothermia after in-hospital cardiac arrest’ is currently recruiting patients. The study aims to recruit 440 patients and compares hypothermia to standard care. Outcomes: 6-month mortality, in hospital mortality and 6-month Glasgow-Pittsburgh cerebral performance scale. Inclusion criteria: in-hospital cardiac arrest, ROSC, unconsciousness, age

over 18 and initiation of mild therapeutic hypothermia is possible within 4 hours after resuscitation.

- A Singapore RCT ‘Prospective clinical study comparing controlled therapeutic hypothermia post cardiac arrest using external and internal cooling to standard intensive care unit therapy’ is currently recruiting patients. The study aims to recruit 51 patient and compares Alsius Thermogard (internal device) versus Arctic Sun (external device). Outcomes: survival to discharge and neurological status. Inclusion criteria: ROSC after cardiac arrest for more than 30 mins, aged 18 to 80 years, haemodynamically stable, BP > 90 mmHg with or without inotropic support; patients comatose or unresponsive post-resuscitation.
- An American case series ‘A prospective analysis of the effect of therapeutic hypothermia after cardiac arrest’ is currently recruiting patients. The study aims to recruit 40 patients. Outcomes include survival and neurological outcome. Inclusion criteria: any adult non-pregnant patient who is unresponsive after resuscitation from cardiac arrest regardless of presenting rhythm and who survives to hospital admission.

References

1 . Arrich J, Holzer M, Herkner H et al. (2009) Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. [Review] [69 refs]. Cochrane Database of Systematic Reviews CD004128.

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Appendix A: Additional papers on therapeutic hypothermia following cardiac arrest

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
BJCardio editorial staff (2010) Early cooling in cardiac arrest may improve survival. British Journal of Cardiology 17:16-7.	RCT n = 182 Follow-up = discharge	Swedish RCT (PRINCE – pre-resuscitation intra-nasal cooling effectiveness) compares standard resuscitation + Rhinochill (introduces coolant through nasal prongs) to standard resuscitation only. 46.7% of those cooled survived to hospital discharge vs 31% who received standard resuscitation only.	News article – no detail on study methods provided.
Damian MS, Ellenberg D, Gildemeister R et al. (2004) Coenzyme Q10 combined with mild hypothermia after cardiac arrest: a preliminary study. Circulation 110: 3011-6.	RCT n = 49 (25 vs 24) Follow-up = 3 months	3 month survival: Hypothermia + Q10: 68% (17/25) Hypothermia + placebo only: 29% (7/24) GOS of 4 or 5: Hypothermia + Q10: 9 patients Hypothermia + placebo only: 5 patients	Both group receive hypothermia – Coenzyme Q10 is the component being studied here.
Heradstveit BE, Guttormsen AB, Langorgen J et al. (2010) Capillary leakage in post-cardiac arrest survivors during therapeutic hypothermia - a prospective, randomised study. Scandinavian Journal of Trauma, Resuscitation & Emergency Medicine 18: 29.	RCT n = 19 (10 hypertonic saline vs 9 standard fluid) Follow-up =1 year	Survival: Hypertonic group: 80% (8/10) Standard group: 77.8% (7/9) Adverse events: 2 patients in the hypertonic group later developed renal failure (timing / treatment unknot specified)	Small trial. No other relevant clinical outcomes reported.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Werling M, Thoren AB, Axelsson C et al. (2007) Treatment and outcome in post-resuscitation care after out-of-hospital cardiac arrest when a modern therapeutic approach was introduced. Resuscitation 73: 40-5.	Non randomised comparative study n = 1395 (85 vs 1310) Follow-up: discharge	Alive at discharge: Hypothermia group: 31.7% (27/85) Normothermia: 36% (472/1310)	Randomised studies in Table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Holzer M, Mullner M, Sterz F et al. (2006) Efficacy and safety of endovascular cooling after cardiac arrest: cohort study and Bayesian approach. Stroke 37:1792-7.	Non randomised comparative study n = 1038 (97 vs 941) Follow-up: 30 days or discharge	Patients in the endovascular group were significantly more likely to survive OR:2.28 (95% CI: 1.45 to 3.57, p <0.001) Survived with favourable neurological outcome: Endovascular group: 52.5% (51/97) Control group: 34% (320/941) OR:2.15 (95% CI: 1.38 to 3.35, p=0.0003) No difference in rate of complications except bradycardia (15% vs 3%, p=0.025)	Randomised studies in Table 2
Arrich J and European Resuscitation Council Hypothermia After Cardiac Arrest Registry Study Group. (2007) Clinical application of mild therapeutic hypothermia after cardiac arrest. Critical Care Medicine 35:1041-7.	Non randomised comparative study n = 587 (462 vs 123) Follow-up: discharge	75% (347/462) cooled using an endovascular device, 25% (114/462) with blankets, ice and cold fluids in the hypothermia group. Died during hospital stay: Hypothermia group: 43% (195/462) Normothermia group: 68% (84/123) (p <0.001) 3% (15/462) in the hypothermia group had a haemorrhage and 6% (28/462) had at least 1 arrhythmia within 7 days.	Randomised studies in Table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Don CW, Longstreth WT, Jr., Maynard C et al. (2009) Active surface cooling protocol to induce mild therapeutic hypothermia after out-of-hospital cardiac arrest: a retrospective before-and-after comparison in a single hospital. Critical Care Medicine 37: 3062-9.	Non randomised comparative study n = 491 (204 vs 287) Follow-up: discharge	Patients in the hypothermia group significantly more likely to survive to discharge: OR: 1.88, 95% CI: 1.03 to 3.45) although this is not the case for patients with non-ventricular fibrillation: OR: 1.17, 95% CI: 0.85 to 3.46). Patients in the hypothermia group significantly more likely to have a favourable neurological outcome : OR: 2.62, 95% CI: 1.1 to 6.27)	Randomised studies in Table 2
Prior J, Lawhon-Triano M, Fedor D et al. (2010) Community-based application of mild therapeutic hypothermia for survivors of cardiac arrest. Southern Medical Journal 103: 295-300.	Non randomised comparative study n = 412 (44 vs 368 controls) Follow-up = discharge	Survival until hospital discharge with good neurological outcome: Hypothermia group: 43% (19/44) Controls: 13%(13/368) p <0.001 Complications in hypothermia group: Acute kidney injury: 50% Bleeding: 9% Skin breakdown: 7%	Randomised studies in Table 2
Kagawa E, Inoue I., Kawagoe T. et al. (2010) Who benefits most from mild therapeutic hypothermia in coronary intervention era? A retrospective and propensity-matched study. Critical Care (London, England) 14: R155.	Non randomised comparative study n = 400 (110 hypothermia vs 290 matched controls) Follow-up = 30 days	Favourable neurological outcome: (27% hypothermia vs 4% matched controls, p <0.001)	Randomised studies in Table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Storm C, Nee J, Krueger A et al. (2010) 2-year survival of patients undergoing mild hypothermia treatment after ventricular fibrillation cardiac arrest is significantly improved compared to historical controls. Scandinavian Journal of Trauma, Resuscitation & Emergency Medicine 18: 2-5	Non randomised comparative study n = 205 (107 vs 98) Follow-up:2 years	Patients in the hypothermia group were significantly more likely to have a good neurological outcome (PC 1or 2): 59.8% vs 24.5%, p <0.01) Kaplan-Meier survival analysis reported significantly improved 2 year probability of survival for patients in the hypothermia group: 55% vs 34%,p=0.029	Randomised studies in Table 2
Bro-Jeppesen J, Kjaergaard J, Horsted TI et al. (2009) The impact of therapeutic hypothermia on neurological function and quality of life after cardiac arrest. Resuscitation 80: 171-6.	Non randomised comparative study n = 156 (79 vs 77) Follow-up: 6 months	CPC 1 or 2 in patients alive at hospital discharge: Hypothermia group: 97% Control group: 71% (p=0.003)	Randomised studies in Table 2
Rittenberger JC, Guyette FX, Tisherman SA et al. (2008) Outcomes of a hospital-wide plan to improve care of comatose survivors of cardiac arrest. Resuscitation 79:198-204.	Non randomised comparative study n = 140 (69 vs 71) Follow-up: unclear	Patients with ventricular dysrhythmia were more likely to have a good outcome if they had hypothermia (57% vs 8%, p=0.005)	Randomised studies in Table 2
Storm C, Steffen I, Schefold JC et al. (2008) Mild therapeutic hypothermia shortens intensive care unit stay of survivors after out-of-hospital cardiac arrest compared to historical controls. Critical Care (London, England) 12: R78.	Non randomised comparative study n = 126 (52 vs 74) Follow-up: 1 year	Kaplan-Meier analysis showed improved probability for 1 year survival in the hypothermia group compared with controls (55% vs 31%, p=0.013)	Randomised studies in Table 2
Whitfield AM, Coote S, and Ernest D. (2009) Induced hypothermia after out-of-hospital cardiac arrest: one hospital's experience. Critical Care & Resuscitation 11: 97-100.	Non randomised comparative study n =123 (75 vs 48) Follow-up: discharge	Patients with VF or unstable VT had significantly greater chance of survival: OR:2.51, 95% CI: 1.06 to 5.95, p=0.03) and better neurological outcome: OR: 2.85, 95% CI: 1.19 to 6.86, p=0.02)	Randomised studies in Table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Sunde K, Pytte M, Jacobsen D et al. (2007) Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. Resuscitation 73: 29-39.	Non randomised comparative study n = 119 (61 vs 58) Follow-up: 1 year	Patients in the hypothermia group had significantly better neurological outcome: OR: 3.61, 95% CI: 1.66 to 7.84, p=0.001)	Randomised studies in Table 2
Oddo M, Schaller MD, Feihl F et al. (2006) From evidence to clinical practice: effective implementation of therapeutic hypothermia to improve patient outcome after cardiac arrest. Critical Care Medicine 34: 1865-73.	Non randomised comparative study n = 109 (55 vs 54) Follow-up: discharge	Patients with VF had a significantly better outcome (p=0.027) No difference in outcome for patients with non-VF cardiac arrest	Randomised studies in Table 2
Hammer L, Vitrat F, Savary D et al. (2009) Immediate prehospital hypothermia protocol in comatose survivors of out-of-hospital cardiac arrest. American Journal of Emergency Medicine 27: 570-3.	Non randomised comparative study n = 99 (22 vs 77) Follow-up: 1 year	Good outcome at 1 year: Hypothermia group: 27% (6/22) Control group: 39% (30/77)	Randomised studies in Table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Gillies MA, Pratt R., Whiteley C. et al. (2010) Therapeutic hypothermia after cardiac arrest: a retrospective comparison of surface and endovascular cooling techniques. Resuscitation 81: 1117-22.	Non randomised comparative study n = 83 (42 endovascular cooling vs 41 surface cooling) Follow-up = discharge	Poor neurological outcome: Endovascular group: 57.1% (24/42) Surface cooling group:61% (25/41) Hospital mortality: Endovascular group: 50% (21/42) Surface cooling group:58.5% (24/41) Complications (any type): Endovascular group: 91% (38/42) Surface cooling group:85% (35/41) p=0.52 Overcooling: Endovascular group: 10% (4/42) Surface cooling group: 27% (11/41) p=0.049 Target temperature not reached: Endovascular group: 7% (3/42) Surface cooling group: 24% (10/41) p=0.04	Randomised studies in Table 2
Flemming K, Simonis G, Ziegs E et al. (2006) Comparison of external and intravascular cooling to induce hypothermia in patients after CPR. German Medical Science 4: Doc04.	Non randomised comparative study n = 80 (49 conventional cooling vs 31 intravascular cooling) Follow-up = discharge	In hospital mortality: Conventional cooling: 22.4% (11/49) Intravascular cooling: 25.8% (8/31) p=0.2	Randomised studies in Table 2
Ferreira I, Schutte M., Oosterloo E. et al. (2009) Therapeutic mild hypothermia improves outcome after out-of-hospital cardiac arrest. Netherlands Heart Journal 17: 378-84.	Non randomised comparative study n = 75 (49 hypothermia vs 26 controls) Follow-up = discharge	Survival: OR: 0.36 (95% CI: 0.13 to 0.95) p <0.05 Neurological outcome: OR: 0.23 (95% CI: 0.07 to 0.70) p <0.01	Randomised studies in Table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Andrade F, I, Schutte M, Oosterloo E et al. (2009) Therapeutic mild hypothermia improves outcome after out-of-hospital cardiac arrest. Netherlands Heart Journal 17: 378-84.	Non randomised comparative study n = 75 (49 vs 26) Follow-up: discharge	Hypothermia significantly improved survival (OR: 0.36, 95% CI: 0.13 to 0.95, p <0.05) and neurological outcome (OR:23, 95% CI: 0.07 to 0.70, p <0.01)	Randomised studies in Table 2
Fries M, Stoppe C, Brucken D et al. (2009) Influence of mild therapeutic hypothermia on the inflammatory response after successful resuscitation from cardiac arrest. Journal of Critical Care 24: 453-7.	Non randomised comparative study n = 70 (39 vs 31) Follow-up: 14 days	Hypothermia patients showed a strong trend towards reduced mortality. Hypothermia had no influence on neurological recovery.	Randomised studies in Table 2
Castrejon S, Cortes M, Salto ML et al. (2009) Improved prognosis after using mild hypothermia to treat cardiorespiratory arrest due to a cardiac cause: comparison with a control group. Revista Espanola de Cardiologia 62: 733-41.	Non randomised comparative study n = 69 (41 vs 28) Follow-up: 6 months	Good neurological status at 6 months: Hypothermia group: 46.3% (19/41) Control group: 21.4% (6/28) RR: 2.16 (95% CI: 1.05 to 3.36, p=0.038)	Randomised studies in Table 2
Belliard G, Catez E, Charron C et al. (2007) Efficacy of therapeutic hypothermia after out-of-hospital cardiac arrest due to ventricular fibrillation. Resuscitation 75: 252-9.	Non randomised comparative study n = 68 (32 vs 36) Follow-up: unclear	Survival was significantly higher in the hypothermia group (56% vs 36%, p=0.04) Glasgow outcome of 5 in survivors: Hypothermia group: 72.2% (13/18) Control group: 46.2% (6/13) (p=0.02)	Randomised studies in Table 2
Zeiner A, Sunder-Plassmann G, Sterz F et al. (2004) The effect of mild therapeutic hypothermia on renal function after cardiopulmonary resuscitation in men. Resuscitation 60: 253-61.	Non randomised comparative study n = 60 (32 vs 28) Follow-up: 28 days	No difference was found in the groups in the development of acute renal failure or need for renal supportive therapy.	Randomised studies in Table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Cariou A, Claessens YE, Pene F et al. (2008) Early high-dose erythropoietin therapy and hypothermia after out-of-hospital cardiac arrest: a matched control study. Resuscitation 76: 397-404.	Non randomised comparative study n = 58 (18 Epo vs 40 hypothermia) Follow-up: 28 days	Survival at 28 days similar in both groups (55% vs 47.5%, p=0.17) Rates of full neurological recovery not significantly different (55% vs 37.5%) Thrombocytosis: Epo group: 15% Hypothermia group: 5%	Randomised studies in Table 2
Bryant Nguyen H, Morawski K, Ramsingh D (2009) Implementation of a post-cardiac arrest care bundle including therapeutic hypothermia and early goal-directed therapy: A feasibility study. Critical Care Medicine (Baltimore) 37: A254	Non randomised comparative study n =55 (29 vs 26) Follow-up: 1 year	Mortality: Hypothermia and early goal directed therapy: 55.2% No hypothermia: 69.2% (p=0.29) Glasgow –Pittsburgh Cerebral performance category in survivors: Hypothermia and early goal directed therapy: 2.1 No hypothermia: 2.6	Randomised studies in Table 2
Nagao K, Hayashi N, Kanmatsuse K (2000) Cardiopulmonary cerebral resuscitation using emergency cardiopulmonary bypass, coronary reperfusion therapy and mild hypothermia in patients with cardiac arrest outside the hospital. Journal of the American College of Cardiology 36: 776-83	Non randomised comparative study n = 50 (23 vs 27) Follow-up: discharge	53% (12/23) of hypothermia patients had a good recovery.	Randomised studies in Table 2
Bernard SA, Jones BM, Horne MK. (1997) Clinical trial of induced hypothermia in comatose survivors of out-of-hospital cardiac arrest. Annals of Emergency Medicine 30: 146-53.	Non randomised comparative study n =44 (22 vs 22) Follow-up: discharge	Significantly better outcome in hypothermia group (GOCS 1 or 2): 50% (11/22) vs 13.6% (3/22), p <0.05.	Randomised studies in Table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Flint AC, Hemphill JC, Bonovich DC. (2007) Therapeutic hypothermia after cardiac arrest: performance characteristics and safety of surface cooling with or without endovascular cooling. Neurocritical Care 7: 109-18.	Non randomised comparative study n = 42 (23 vs 19) Follow-up: unclear	Bradycardia: Surface cooling group: 60.9% Endovascular group: 42.1% (p <0.35)	Larger studies in Table 2
Gaieski DF, Band RA, Abella BS et al. (2009) Early goal-directed hemodynamic optimization combined with therapeutic hypothermia in comatose survivors of out-of-hospital cardiac arrest. Resuscitation 80: 418-24.	Non randomised comparative study n = 38 (20 vs 18) Follow-up: not reported	Mortality: Hypothermia: 50% (9/18) Controls: 78% (14/18)	Randomised studies in Table 2
Hachimi-Idrissi S, Zizi M, Nguyen DN et al. (2005) The evolution of serum astroglial S-100 beta protein in patients with cardiac arrest treated with mild hypothermia. Resuscitation 64: 187-92.	2 Non randomised comparative study 1st study: n = 33 (16 vs 17) Follow-up: unclear 2nd study: n = 28 (14 vs14) Follow-up: unclear	1st study: Mortality: Hypothermia:75% (12/16) Normothermia: 88.2% (15/17) Good outcome (CPC 1 or 2): Hypothermia:12.5% (2/16) Normothermia: 0 2nd study: Mortality: Hypothermia:42.9% (6/14) Normothermia: 57.1% (8/14) Good outcome (CPC 1 or 2): Hypothermia:42.9% (6/14) Normothermia: 21.4% (3/14)	Randomised studies in Table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Yanagawa Y, Ishihara S, Norio H et al. (1998) Preliminary clinical outcome study of mild resuscitative hypothermia after out-of-hospital cardiopulmonary arrest. Resuscitation 39: 61-6.	Non randomised comparative study n = 28 (13 vs 15) Follow-up: discharge	Survival: Hypothermia: 53.8% (7/13) Control: 33.3% (5/15) Fully recovered: Hypothermia: 23.1% (3/13) Control: 6.7% (1/15) Pneumonia: Hypothermia: 84.6% (11/13) Control: 40% (6/15)	Randomised studies in Table 2
Bierer P, Bersten A. (2010) Audit of active cooling methods in induced therapeutic hypothermia. ANZICS/ACCCN Intensive Care ASM 2009 Perth 34th Australian and New Zealand Annual Scientific Meeting on Intensive Care 2009, incorporating the 15th Australian and New Zealand Paediatric and Neonatal Intensive Care Conference. Australian Critical Care 23: 33-4.	Non randomised comparative study n = 18 (14 vs 4) Follow-up: 12 months	Mortality: Surface cooling: 85.7% (12/14) Intravascular cooling: 50% (2/4)	Randomised studies in Table 2
Hinchey PR, Myers JB, Lewis R et al. (2010) Improved out-of-hospital cardiac arrest survival after the sequential implementation of 2005 AHA guidelines for compressions, ventilations, and induced hypothermia: The wake county experience. Annals of Emergency Medicine 56: 348-57.	Case series n = 1365 Follow-up: discharge	Absolute increase in survival from baseline to full implementation of AHA guidelines (include therapeutic hypothermia) is 7.3% (95% CI: 3.7% to 10.9%) Increased survival in witnessed VF/VT survival: 27% (95% CI: 13.6% to 40.4%)	Randomised studies in Table 2
Oksanen T, Pettila V, Hynynen M et al. (2007) Therapeutic hypothermia after cardiac arrest: implementation and outcome in Finnish intensive care units. Acta Anaesthesiologica Scandinavica 51: 866-71.	Case series n = 407 Follow-up: 6 months	In hospital mortality: 32.7% 6 month survival: 55.3% Length of stay in ICU: 3.7 days	Larger studies in Table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Funk G-C, Doberer D, Sterz F et al. (2009) The strong ion gap and outcome after cardiac arrest in patients treated with therapeutic hypothermia: A retrospective study. Intensive Care Medicine 35: 232-9.	Case series n = 288 Follow-up: 6+ months	Survival > 6 months with CPC 1 or 2: 48% (137/288)	Larger studies in Table 2
Nagao K, Kikushima K, Watanabe K et al. (2010) Early induction of hypothermia during cardiac arrest improves neurological outcomes in patients with out-of-hospital cardiac arrest who undergo emergency cardiopulmonary bypass and percutaneous coronary intervention. Circulation Journal 74: 77-85.	Case series n = 171 Follow-up: discharge	Favourable neurological outcome at discharge: 12.3% (21/171)	Larger studies in Table 2
Falkenbach P, Kamarainen A, Makela A et al. (2009) Incidence of iatrogenic dyscarbia during mild therapeutic hypothermia after successful resuscitation from out-of-hospital cardiac arrest. Resuscitation 80: 990-3.	Case series n = 154 Follow-up: 6 months	ICU mortality: 17.2% 6 month mortality: 50.8%	Larger studies in Table 2
Hay AW, Swann DG, Bell K et al. (2008) Therapeutic hypothermia in comatose patients after out-of-hospital cardiac arrest. Anaesthesia 63:15-9.	Case series n = 139 Follow-up: 33 days after ICU discharge	UK study Favourable outcome (discharged home or to rehabilitation): 27% (37/139)	Larger studies in Table 2
Rossetti AO, Oddo M, Logroscino G et al. (2010) Prognostication after cardiac arrest and hypothermia: a prospective study. Annals of Neurology 67:301-307.	Case series n = 111 Follow-up: discharge	Survival at discharge: 40.5% (45/111)	Larger studies in Table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Busch H-J, Eichwede F, Fodisch M et al. (2010) Safety and feasibility of nasopharyngeal evaporative cooling in the emergency department setting in survivors of cardiac arrest. Resuscitation 81: 943-9.	Case series n = 84 Follow-up = discharge	Survival: 40% (34/84) 76.5% (26/34) had a favourable neurological outcome (CPC 1 or 2) at discharge Epistaxis: 2 patients Periorbital gas emphysema: 1 patient	Larger studies in Table 2
Oddo M, Ribordy V, Feihl F et al. (2008) Early predictors of outcome in comatose survivors of ventricular fibrillation and non-ventricular fibrillation cardiac arrest treated with hypothermia: a prospective study. Critical Care Medicine 36: 2296-2301.	Case series n = 74 Follow-up: discharge	Survival with time to ROSC > 25 mins: 3.1% Survival with time to ROSC ≤ 25 mins: 65.7%	Larger studies in Table 2
Schefold JC, Storm C, Kruger A et al. (2009) The Glasgow Coma Score is a predictor of good outcome in cardiac arrest patients treated with therapeutic hypothermia. Resuscitation 80: 658-61.	Case series n = 72 Follow-up: discharge	61% (44/72) discharged with a favourable neurological outcome (CPC 1 or 2).	Larger studies in Table 2
Jacobshagen C, Pax A, Unsold BW et al. (2009) Effects of large volume, ice-cold intravenous fluid infusion on respiratory function in cardiac arrest survivors. Resuscitation 80: 1223-8.	Case series n = 52 Follow-up: discharge	Alive at discharge: 67.3% (35/52)	Larger studies in Table 2
Scott BD, Hogue T, Fixley MS et al. (2006) Induced hypothermia following out-of-hospital cardiac arrest; initial experience in a community hospital. Clinical Cardiology 29: 525-9.	Case series n = 49 Follow-up: 12.5 months	Survival at discharge: 38.8% (19/49) 3 of these patients had significant residual neurological injury.	Larger studies in Table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Wolff B, Machill K, Schumacher D et al. (2009) Early achievement of mild therapeutic hypothermia and the neurologic outcome after cardiac arrest. International Journal of Cardiology 133: 223-8.	Case series n = 49 Follow-up: discharge	Discharged with a good outcome: 57.1% (28/49)	Larger studies in Table 2
Stammet P, Werer C, Mertens L et al. (2009) Bispectral index (BIS) helps predicting bad neurological outcome in comatose survivors after cardiac arrest and induced therapeutic hypothermia. Resuscitation 80: 437-42.	Case series n = 45 Follow-up: 6 months	6 month mortality: 48.9% (22/45) Good neurological outcome (CPC 1 or 2): 37.8% (17/45)	Larger studies in Table 2
Gal R, Slezak M, Zimova I et al. (2009) Therapeutic hypothermia after out-of-hospital cardiac arrest with the target temperature 34-35 degrees C. Bratislavske Lekarske Listy 110: 222-5.	Case series n = 43 Follow-up: 6 months	Good outcome at hospital discharge: 48.8% (21/43) 6-month mortality: 28%	Larger studies in Table 2
Vanston VJ, Lawhon-Triano M, Getts R et al. (2010) Predictors of poor neurologic outcome in patients undergoing therapeutic hypothermia after cardiac arrest. Southern Medical Journal 103: 301-6.	Case series n = 41 Follow-up: discharge	Survival at hospital discharge: 41.5% (17/41) Good CPS: 41.5% (17/41)	Larger studies in Table 2
Pichon N, Amiel JB, Francois B et al. (2007) Efficacy of and tolerance to mild induced hypothermia after out-of-hospital cardiac arrest using an endovascular cooling system. Critical Care 11: R71.	Case series n = 40 Follow-up: not reported	Mortality: 15% (6/40) Rebound hyperthermia (temp ≥ 38.5°C): 74% (25/40) Infection: 45% (18/40)	Larger studies in Table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Larsson I-M, Wallin E, Rubertsson S. (2010) Cold saline infusion and ice packs alone are effective in inducing and maintaining therapeutic hypothermia after cardiac arrest. Resuscitation 81: 15-9.	Case series n = 38 Follow-up: 6 months	CPC 1 or 2 at 6 months: 44.7% (17/38) Mean length of stay in ICU: 4.4 days	Larger studies in Table 2
Al Thenayan E, Savard M, Sharpe M et al. (2008) Predictors of poor neurologic outcome after induced mild hypothermia following cardiac arrest. Neurology 71: 1535-7.	Case series n = 37 Follow-up: 3 months	None of the 6 patients without papillary reactivity, 6 patients without corneal reflexes on day 3 or 8 patients with myoclonus status epilepticus recovered awareness.	Larger studies in Table 2
Wennervirta JE, Ermes MJ, Tiainen SM et al. (2009) Hypothermia-treated cardiac arrest patients with good neurological outcome differ early in quantitative variables of EEG suppression and epileptiform activity. Critical Care Medicine 37: 2427-35.	Case series n = 33 Follow-up: unclear	Mortality: 27.3% (9/33) CPC 1 or 2: 60.6% (20/33)	Larger studies in Table 2
Bruel C, Parienti JJ, Marie W et al. (2008) Mild hypothermia during advanced life support: a preliminary study in out-of-hospital cardiac arrest. Critical Care 12: R31.	Case series n = 33 Follow-up: 6 months	Survival at 6 months: 12.1% (4/33) CPC 1 or 2 at 6 months: 9.1% (3/33) 1 patient had pulmonary oedema	Larger studies in Table 2
Merchant RM, Abella BS, Peberdy MA et al. (2006) Therapeutic hypothermia after cardiac arrest: unintentional overcooling is common using ice packs and conventional cooling blankets. Critical Care Medicine 34 (Suppl 4).	Case series n = 32 Follow-up: discharge	Overcooling (< 32°C) lasting > 1 hour: 62.5% (20/32) Of those overcooled, 30% (6/20) survived to discharge Of those not overcooled, 58% (7/12) survived to discharge (p = non significant)	Larger studies in Table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Hokanson J, Edelstein K, Unger B et al. (2007) Therapeutic hypothermia for resuscitated cardiac arrest patients with anoxic encephalopathy-neurologic and survival results after the implementation of an inter-disciplinary protocol. 2007 Society for Academic Emergency Medicine Annual Meeting. Academic Emergency Medicine 14: S173.	Case series n = 30 Follow-up: discharge	Survival: 46.7% (14/30)	Larger studies in Table 2
Benson DW, Williams GR, Jr., Spencer FC et al. (1959) The use of hypothermia after cardiac arrest. Anesthesia & Analgesia 38: 423-8.	Case series n = 27 Follow-up: up to 35 days	Mortality: 44.4% (12/27) Survival with no residual damage: 48% (13/27)	Larger studies in Table 2
Kliegel A, Janata A, Wandaller C et al. (2007) Cold infusions alone are effective for induction of therapeutic hypothermia but do not keep patients cool after cardiac arrest. Resuscitation 73: 46-53.	Case series n = 27 Follow-up: discharge	Survival at discharge: 29.6% (8/27) Favourable neurological outcome at discharge: 25.9% (7/27)	Larger studies in Table 2
Zeiner A, Holzer M, Sterz F et al. (2000) Mild resuscitative hypothermia to improve neurological outcome after cardiac arrest. A clinical feasibility trial. Hypothermia After Cardiac Arrest (HACA) Study Group. Stroke 31: 86-94.	Case series n = 27 Follow-up: unclear	CPC 1 or 2: 37.8% (14/27)	Larger studies in Table 2
Torgersen J, Strand K, Bjelland TW et al. (2010) Cognitive dysfunction and health-related quality of life after a cardiac arrest and therapeutic hypothermia. Acta Anaesthesiologica Scandinavica 54: 721-8.	Case series n = 26 Follow-up: 13-28 months	Cognitive dysfunction: 52% (13/25)	Larger studies in Table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Kliegel A, Losert H, Sterz F et al. (2005) Cold simple intravenous infusions preceding special endovascular cooling for faster induction of mild hypothermia after cardiac arrest--a feasibility study. Resuscitation 64: 347-51.	Case series n = 26 Follow-up: 6 months	Survival with favourable neurological outcome: 50% (13/26)	Larger studies in Table 2
Freeman WD, Barrett KM, Biewend ML et al. (2009) Predictors of poor neurologic outcome after induced mild hypothermia following cardiac arrest. Neurology 73: 997-8.	Case series n = 25 Follow-up: discharge	Recovery of awareness at hospital discharge: 28% (7/25) 50% (7/14) of patients with preserved pupillary reflexes and 36% (4/11) with preserved motor responses died or remained vegetative.	Larger studies in Table 2
Kilgannon JH, Roberts BW, Stauss M et al. (2008) Use of a standardized order set for achieving target temperature in the implementation of therapeutic hypothermia after cardiac arrest: a feasibility study. Academic Emergency Medicine 15: 499-505.	Case series n = 23 Follow-up: discharge	In hospital mortality: 78.3% (18/23) Clinically significant bleeding: 1 patient Arrhythmia requiring treatment: 1 patient	Larger studies in Table 2
Howes D, Ohley W, Dorian P et al. (2010) Rapid induction of therapeutic hypothermia using convective-immersion surface cooling: safety, efficacy and outcomes. Resuscitation 81: 388-92.	Case series n = 22 Follow-up: 6 months	Survival at 6 months: 68% (87% of survivors living independently)	Larger studies in Table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Bernard S, Buist M, Monteiro O et al. (2003) Induced hypothermia using large volume, ice-cold intravenous fluid in comatose survivors of out-of-hospital cardiac arrest: a preliminary report. Resuscitation 56: 9-13.	Case series n = 22 Follow-up: discharge	Survival: 45.5% (10/22)	Larger studies in Table 2
Vourlekis JS (2008) Community hospital experience with therapeutic hypothermia after cardiac arrest. Critical Care Medicine (Baltimore) 36: A145	Case series n = 21 Follow-up: discharge	Survival to discharge: 57.1% (12/21) Favourable neurological outcome (CC 1 or 2): 52.4% (11/21)	Larger studies in Table 2
Hoedemaekers CW, Ezzahti M, Gerritsen A et al. (2007) Comparison of cooling methods to induce and maintain normo- and hypothermia in intensive care unit patients: a prospective intervention study. Critical Care (London, England) 11: R91	Case series n = 19 Follow-up: discharge from ICU (only reporting hypothermia group – controls did not have cardiac arrest)	Survival to discharge from ICU: 57.9% (11/19) Hypotension:47.4% (9/19) Arrhythmia: 47.4% (9/19)	Larger studies in Table 2
Kamarainen A, Virkkunen I, Tenhunen J et al. (2008) Induction of therapeutic hypothermia during prehospital CPR using ice-cold intravenous fluid. Resuscitation 79: 205-11.	Case series n = 17 Follow-up: 6 months	Survival to hospital discharge : 1 patient Hypotension: 5 patients	Larger studies in Table 2
Uray T, Malzer R, and Vienna Hypothermia After Cardiac Arrest (HACA) Study Group. (2008) Out-of-hospital surface cooling to induce mild hypothermia in human cardiac arrest: a feasibility trial. Resuscitation 77: 331-38.	Case series n = 15 Follow-up: 6 months	Survival to hospital discharge: 33.3% (5/15) all showing normal cerebral and overall recovery at 6 months. Pneumonia: 2 patients	Larger studies in Table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Virkkunen I, Yli-Hankala A, Silfvast T. (2004) Induction of therapeutic hypothermia after cardiac arrest in prehospital patients using ice-cold Ringer's solution: a pilot study. Resuscitation 62: 299-302.	Case series n = 13 Follow-up: not reported	Survival: 30.8% (4/13)	Larger studies in Table 2
Felberg RA, Krieger DW, Chuang R et al. (2001) Hypothermia after cardiac arrest: feasibility and safety of an external cooling protocol. Circulation 104: 1799-1804.	Case series n = 9 Follow-up: not clear	3 patients completely recovery and 1 patient had partial neurological recovery. 1 patient developed unstable cardiac dysrhythmia.	Larger studies in Table 2
Aghenta A, Osowo A, Das V et al. (2008) Therapeutic hypothermia in cardiac arrest: feasible? Case series in a community hospital. Journal of Hospital Medicine (Online) 3: 489-92.	Case series n = 8 Follow-up: discharge	Mortality: 75% (6/8) The other 2 patients had a good recovery. Complications by day 5: Hypokalaemia: 62.5% (5/8) Pneumonia: 1 patient Seizures:21 patients Elevated creatinine: 3 patients	Larger studies in Table 2
Kamarainen A, Virkkunen I, Tenhunen J et al. (2008) Prehospital induction of therapeutic hypothermia during CPR: a pilot study. Resuscitation 76: 360-3.	Case series n = 5 Follow-up: to death	4 patients died before they reached hospital. The other patient died in hospital.	Larger studies in Table 2
Yannopoulos D, Kotsifas K, Aufderheide TP et al. (2007) Cardiac arrest, mild therapeutic hypothermia, and unanticipated cerebral recovery. Neurologist 13: 369-75.	Case report n = 4 Follow-up: 1 month (2 patients), 3 days (1 patient) and 4 days (1 patient)	Patient 1: survival at 1 month with normal neurological examination. Patient 2: survival at 1 month with no neurological deficit Patient 3: discharge at day 3 with normal neurological evaluation Patient 4: discharge at day 3 with normal neurological evaluation.	Larger studies in Table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Silfvast T, Tiainen M, Poutiainen E et al. (2003) Therapeutic hypothermia after prolonged cardiac arrest due to non-coronary causes. Resuscitation 57: 109-12.	Case report n = 3 Follow-up: discharge (patients) and 3 months (1 patient)	Patient 1: survival with normal neurological examination at discharge. Patient 2: survival without obvious neurological sequelae at discharge at 17 days. Patient 3: moderate deficits in flexible verbal processing requiring neuropsychological rehabilitation at 3 months.	Larger studies in Table 2
Kozik T. (2009) Achieving neuroprotection for cardiac arrest patients through induced hypothermia. Nevada RNformation 18: 19-20.	Case report n = 3 Follow-up: discharge	Patient 1: walked from hospital on day 11 neurologically intact and has since returned to work Patient 2: discharged shortly after day 3 with no neurological deficits and has since returned to work. Patient 3: discharge d at day 4 with no neurological damage.	Larger studies in Table 2
Guenther U, Varelmann D, Putensen C et al. (2009) Extended therapeutic hypothermia for several days during extracorporeal membrane-oxygenation after drowning and cardiac arrest Two cases of survival with no neurological sequelae. Resuscitation 80: 379-81.	Case report n = 2 Follow-up: discharge and transfer to a general ward	Patient 1: complications: delirium, gastric haemorrhage, oedematous pancreatitis and ventilator associated pneumonia. Patient discharged at 27 days with no signs of neurological deficit except for a general muscular weakness. Patient 2: Transferred to a general ward at day 10 without neurological impairment.	Larger studies in Table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Tilney P Kendall K. (2009) Cold hearts: a case study of therapeutic hypothermia in helicopter emergency medical services (HEMS). Air Medical Journal 28:154-7.	Case report n = 1 Follow-up: 2 weeks	Cooled with Riger's solution. Patient discharged at day 9 and returned to work at 2 weeks without any neurological or cardiovascular deficits.	Larger studies in Table 2
Nichols R, Zawada E. (2008) A case study in therapeutic hypothermia treatment post-cardiac arrest in a 56-year-old male. South Dakota Medicine: The Journal of the South Dakota State Medical Association 61: 371-3.	Case report n = 1 Follow-up: discharge	Patient discharged at day 4 neurologically intact.	Larger studies in Table 2
Kurisu S, Inoue I, Kawagoe T et al. (2008) Therapeutic hypothermia after out-of-hospital cardiac arrest due to Brugada syndrome. Resuscitation 79: 332-5.	Case report n = 1 Follow-up: discharge	Patient diagnosed with Brugada syndrome and received an implantable cardioverter/defibrillator at day 25. He made a full recovery and was discharged at day 54.	Larger studies in Table 2
Kurisu S, Inoue I, Kawagoe T et al. (2009) Therapeutic hypothermia in combination with percutaneous coronary intervention in out-of-hospital cardiac arrest due to left main coronary artery disease. Heart and Vessels 24: 376-9.	Case report n = 1 Follow-up: discharge	Echocardiogram at day 9 showed mild hypokinesia of the anterior wall with an ejection fraction of 77%. Patient discharged at day 18 with no neurological complications.	Larger studies in Table 2
Rittenberger JC, Kelly E, Jang D et al. (2008) Successful outcome utilizing hypothermia after cardiac arrest in pregnancy: a case report. Critical Care Medicine 36: 1354-6.	Case report n = 1 Follow-up: 34 weeks	13-week pregnant woman who had an out-of-hospital VF cardiac arrest and was discharged from hospital at day 6 with mild neurological deficit (CPC 2). Infant delivered at 39 weeks with Apgar and neurodevelopmental testing appropriate for age at both and at 2 months.	Larger studies in Table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Bernard SA and Rosalion A. (2008) Therapeutic hypothermia induced during cardiopulmonary resuscitation using large-volume, ice-cold intravenous fluid. Resuscitation 76: 311-3.	Case report n = 1 Follow-up: discharge	Patient was alert and orientated at discharge on day 20.	Larger studies in Table 2
Bader MK, Rovzar M, Baumgartner L et al. (2007) Keeping cool: a case for hypothermia after cardiopulmonary resuscitation. American Journal of Critical Care 16: 636-5.	Case report n = 1 Follow-up: 6 weeks	Complications: pulmonary infarcts, prolonged mechanical ventilation, and mediastinal and rectus sheath hematomas requiring blood transfusion Patient discharged at 3 weeks with no neurological impairment. Returned to work at 6 weeks with no neurological deficits.	Larger studies in Table 2
Busch M, Soreide E. (2010) Successful use of therapeutic hypothermia in an opiate induced out-of-hospital cardiac arrest complicated by severe hypoglycaemia and amphetamine intoxication: a case report. Scandinavian journal of trauma, resuscitation and emergency medicine 18:4.	Case report n = 1 Follow-up: 6 months	Patient discharged after day 7 with CPC 1. 6 month follow-up showed no neurological or cardiovascular sequelae.	Larger studies in Table 2
Minambres E, Gonzalez-Castro A, Ots E et al. (2007) Mild hypothermia induction after cardiac arrest using water-circulating cooling device. American Journal of Emergency Medicine 25: 730-2.	Case report n = 1 Follow-up: discharge	Complication: acute renal failure. Patient discharged at day 10 without neurological sequelae.	Larger studies in Table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Sunde K, Dunlop O, Rostrup M et al. (2006) Determination of prognosis after cardiac arrest may be more difficult after introduction of therapeutic hypothermia. Resuscitation 69: 29-32.	Case report n = 1 Follow-up: 1 year	Complications: status epilepticus, severe sepsis. Patient received intensive care with respiratory support for 42 days. Normal function and memory on neurophysiological exam at 9 months. Returned to work at 1 year.	Larger studies in Table 2
Ball RE. (2010) In my own words: a prehospital provider's chilling experience with therapeutic hypothermic resuscitation. JEMS: Journal of Emergency Medical Services 35: 8-10.	Case report n = 1 Follow-up: discharge	Patient reported his own experience in a journal article. Patient discharged at 8 days with short term memory problems and minor balance problems. Patient able to return to work.	Larger studies in Table 2
Koutouzis M, Nikolaou N, Lazaris E et al. (2007) Interventional hypothermia and primary percutaneous coronary intervention in a patient with anterior wall ST elevation myocardial infarction and aborted sudden death. Hjc Hellenic Journal of Cardiology 48: 377-9.	Case report n = 1 Follow-up: discharge	Patient discharged at day 8 with a fully preserved mental status.	Larger studies in Table 2
Bartels M, Tjan DH, Reussen EM et al. (2007) Therapeutic hypothermia after prolonged cardiopulmonary resuscitation for pulseless electrical activity. Netherlands Journal of Medicine 65: 38-41.	Case report n = 1 Follow-up: discharge	Patient discharged at day 14 with CPC 1.	Larger studies in Table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Hammell CL, Sulaiman L. (2010) Brachial plexopathy as a complication of induced hypothermia following cardiac arrest. Anaesthesia 65 (10): 1034-1036. .	Case report n = 1 Follow-up = 4 weeks	Safety report. – patient developed brachial plexopathy diagnosed 4 days after re-warming (therapeutic hypothermia achieved by cold saline infusion and ice packs).	Larger studies in Table 2

Appendix B: Related NICE guidance for therapeutic hypothermia following cardiac arrest

Guidance	Recommendations
Interventional procedures	**Therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury. NICE interventional procedures guidance 347 (2010)** 1 Guidance 1.1 Current evidence on the safety and efficacy of therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury is adequate to support the use of this procedure in carefully selected neonates provided that normal arrangements are in place for clinical governance, consent and audit (See section 2.5.1 for comments on selection). 1.2 This procedure should only be carried out in units experienced in the care of severely ill neonates, by staff who have been specifically trained in the use of therapeutic hypothermia. 1.3 NICE encourages clinicians to enter details about all neonates undergoing this procedure into the UK TOBY cooling register (www.npeu.ox.ac.uk/tobyregister). The register provides a suggested management algorithm. Submitting data to the register will contribute to the evidence on long-term follow-up and may lead to improvements in the management algorithm.

Appendix C: Literature search for therapeutic hypothermia following cardiac arrest

Database	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	25/10/2010	October 2010
Database of Abstracts of Reviews of Effects – DARE (CRD website)	25/10/2010	n/a
HTA database (CRD website)	25/10/2010	n/a
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)		October 2010
MEDLINE (Ovid)	25/10/2010	1950 to Week 2, October 2010
MEDLINE In-Process (Ovid)	25/10/2010	October 22, 2010
EMBASE (Ovid)	25/10/2010	1980 to Week 42, 2010
CINAHL (NLH Search 2.0)	25/10/2010	n/a
Zetoc	25/10/2010	n/a

Websites	Date searched	Title, year and link
NICE ('published' and 'in development' guidance)	15/06/2010	IPG347 Therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury. (May 2010)
FDA (MAUDE database)	15/06/2010	GAYMAR INDUSTRIES RAPRROUND HYPOTHERMIA VEST (2010) GAYMAR HYPO/HYPERTHERMIA MACHINE (2008) INNERCOOL THERAPIES, INC. CELSIUS CONTROL SYSTEM CATHETER CCS CATHETER (2007) Alsius CoolGard™ 3000 Catheter Thermal Regulation System (2005)

ASERNIP	15/06/2010	
ANZHSN	15/06/2010	Coolgard™ 3000 Catheter Thermal Regulation System: Endovascular hypothermia induction for treatment of comatose survivors of ventricular fibrillation cardiac arrest. (2005)
National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database	15/06/2010	None found
Current Controlled Trials *meta*Register of Controlled Trials - *m*RCT	15/06/2010	All listed below
Clinicaltrials.gov	15/06/2010	**Completed** COOL-Trial: Outcome With Invasive and Non-invasive Cooling After Cardiac Arrest (2010) Neuron Specific Enolase (NSE) as Outcome Parameter of Cooling Therapy After Survived Sudden Cardiac Death (2010) Clinical and Economical Interest of Endovascular Cooling in the Management of Cardiac Arrest (ICEREA Study) (2009) Fluid Shifts in Patients Treated With Therapeutic Hypothermia After Cardiac Arrest (2009) Induction of Mild Hypothermia in Resuscitated Cardiac Arrest Patients (2006) **Ongoing** Induced Hypothermia in Cardiac Arrest Patients Rescued by Extracorporeal Cardiopulmonary Resuscitation (expected completion date

		December 2009) Multicenter Registry Study With Therapeutic Hypothermia After Cardiac Arrest in Japan (J-PULSE-HYPO) (expected completion March 2010) Hypothermia After in-Hospital Cardiac Arrest (HACAinhospital) (expected completion date March 2010) Comparing Therapeutic Hypothermia Using External and Internal Cooling for Post-Cardiac Arrest Patients (expected completion date September 2010) A Prospective Analysis of the Effect of Therapeutic Hypothermia After Cardiac Arrest (expected completion date December 2010) Effect of Xenon and Therapeutic Hypothermia, on the Brain and on Neurological Outcome Following Brain Ischemia in Cardiac Arrest Patients (Xe-hypotheca) (expected completion date December 2013) **Not yet recruiting** Clinical Study of the LRS ThermoSuit™ System in Post Arrest Patients With Intravenous Infusion of Magnesium Sulfate
General internet search	15/06/2010	Resuscitation Council: Hypothermia, therapeutic (in Adult Advanced Life Support Guidelines)

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

The MEDLINE search strategy was adapted for use in the other sources.

1	exp hypothermia, induced/
2	(induce* adj3 hypothermi*).tw.
3	((cold or chill* or cool* or hypother*) adj3 therap*).tw.
4	cryotherapy/
5	cryotherap*.tw.
6	(cool* adj3 (blanket* or pad* or device*)).tw.
7	(cool* adj3 (endovascular* or intravascular*)).tw.
8	(ice* adj3 pack*).tw.
9	(blanketrol or caircooler or alsius or coolgard or medicool or (arctic adj3 sun) or (celsius and control and system)).tw.
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11	heart arrest/
12	((heart* or cardiac* or cardiopulmonar* or circulat*) adj3 arrest*).tw.
13	11 or 12
14	10 and 13
15	Animals/ not Humans/
16	14 not 15