WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care

Worksheet author(s)

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Clinical question.

In post-cardiac arrest patients with ROSC (P), does therapeutic hypothermia (I) compared with usual care (C), improve morbidity or mortality (O)?
Is this question addressing an intervention/therapy, prognosis or diagnosis: Intervention/therapy**.**
State if this is a proposed new topic or revision of existing worksheet: Revision

Search strategy (including electronic databases searched).

PubMed ("heart arrest" or "cardiopulmonary resuscitation") AND "hypothermia, induced" using 'Clinical Queries' search strategy = 1185 hits
EMBASE (heart arrest) OR (cardiopulmonary resuscitation) AND hypothermia (limited to Title and abstract) – 692 hits – just 3 new relevant reference
ECC EndNote Library 4Nov09: "hypothermia" in abstract OR title = 1016 hits
Cochrane database for systematic reviews "hypothermia" = 1 review (Arrich 2009).
Review of references from articles.
References from pdfs stored by Nolan and Morley.

- State inclusion and exclusion criteria

The following studies were excluded: animal studies, reviews and editorials, surveys of implementation, analytical models, reports of single cases, pre-arrest or during arrest cooling, intervention group not hypothermia alone (eg. combined with haemofiltration or resuscitation with cardiopulmonary bypass instead of CPR).

- Number of articles/sources meeting criteria for further review:

72 studies met criteria for further review. Of these three were Level 1 (meta-analyses), seven were Level 1 (RCTs), eight Level 2 (non-randomised, concurrent controls), fifteen Level 3 (retrospective controls), thirty-eight Level 4 (no controls) and one Level 5 (extrapolated from non-cardiac arrest group).

Summary of evidence

Evidence Supporting Clinical Question

Good	Arrich 2009 CD[#] Hypothermia After Cardiac Arrest Study Group, 2002 CD* Tiainen, 2003 E*		Bernard, 1997 C, D	Hovdenes, 2007 CD Wolff, 2009 DE Nielsen, 2009 CD	
Fair	Holzer, 2005 CD[#]	Bernard, 2002 D Holzer, 2006 CD	Knafelj, 2007 CD Busch, 2006 C Belliard, 2007 CD Oddo, 2006 D Sunde, 2007 CD Storm, 2008 CDE Don, 2009 CD Bro-Jeppesen, 2009 D	Oksanen, 2007 C Sagalyn, 2009 #	
Poor	Hachimi-Idrissi, 2001 E Cheung, 2006 CD[#]	Arrich, 2007 CD	Castrejon, 2009 D	Williams, 1958 D	
	1	**2**	**3**	**4**	**5**
Level of evidence					

A = Return of spontaneous circulation
B = Survival of event
C = Survival to hospital discharge
D = Intact neurological survival
E = Other endpoint
# = meta-analysis
* = overlapping patients

Evidence Neutral to Clinical question

Good	Tiainen, 2003 D* Tiainen, 2007 E* Tiainen, 2009 D, E* Koreny, 2009 E*			Damian, 2004 CD Cronberg, 2009 D	
Fair	Zeiner, 2004 E*	Bernard, 2002 C Doherty, 2009 CDE (P) Hammer, 2009 CD	Yanagawa, 1998 CDE Oddo, 2006 C Wolfrum, 2008 CDE Gaieski, 2009 CD Bro-Jeppesen, 2009 C Busch, 2006 D	Bernard, 2003 E Merchant, 2006 C Virkkunen, 2004 E Kliegel, 2005 CDE Kliegel, 2007 CDE Feuchtl, 2007 CD Haughk, 2007 E Pichon, 2007 CDE Kim, 2005 E Kim, 2007 C Uray, 2008 CDE Skulec, 2008 D Jimmink, 2008 E Heard, 2010 E Larsson, 2010 E Jacobshagen, 2009 E Spiel, 2009 E Gal, 2009 CD Kamarainen, 2009 CDE	
Poor	Hachimi-Idrissi, 2001 C	Benson, 1959C Derwall, 2009 E (S100) Fries, 2009 CD	Werling, 2007 CD Borgquist, 2009 CD Castrejon, 2009 C	Al-Senani, 2004 CDE Felberg, 2001 Nagao, 2000 Silfvast, 2003 Zeiner, 2000 Scott, 2006 CD Aberle, 2006 E Hoedemaekers, 2007 E Flint, 2007 E Hay 2008 D Kamarainen, 2008a CE Kamarainen, 2008b CE Kilgannon, 2008 E	
	1	**2**	**3**	**4**	**5**
Level of evidence					

A = Return of spontaneous circulation
B = Survival of event
C = Survival to hospital discharge
D = Intact neurological survival
E = Other endpoint
(P) = paediatric patients
* = overlapping patients

Evidence Opposing Clinical Question

Good					
Fair			Yanagawa, 1998 E		
Poor		Fries, 2009 E (bact. colon.)			Simosa, 2007 E (DVT with intravasc. cooling)
	1	**2**	**3**	**4**	**5**
Level of evidence					

A = Return of spontaneous circulation
B = Survival of event
C = Survival to hospital discharge
D = Intact neurological survival
E = Other endpoint

REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

DISCUSSION:
Who to cool?
The definitive study to date is that performed by the Hypothermia After Cardiac Arrest (HACA) Study Group (HACA, 2002) which performed a methodologically good prospective randomized study, and confirmed that the induction of hypothermia in comatose survivors of out-of-hospital cardiac arrest caused by ventricular fibrillation (VF) improves neurological outcome and mortality at 6 months. Hypothermia patients were sedated, paralysed, ventilated and cooled with surface cooling to 32-34^{o}C for 24 hours. Major limiting factors include the inability of the investigators to blind the treating team to the study group, the limited proportion of patients finally included (8% of those assessed; limiting extrapolations), and the relative hyperthermia in the control group. There were more complications in the hypothermia group but these (individually or collectively) were not statistically significant.

The other landmark study was performed in Melbourne Australia, also in comatose survivors of out-of-hospital cardiac arrest caused by VF, was statistically underpowered to confirm the measured benefit (Bernard, 2002). Hypothermia patients were sedated, paralysed, ventilated and cooled with surface cooling to 33^{o}C for 12 hours. Major limitations of this study included the pseudo-randomisation of patients, the inability of the investigators to blind the treating team to the study group, and the limited number of patients finally included.

In a Level 3 study of patients with out-of-hospital VF cardiac arrest associated with ST-elevation MI, the neurological outcome of patients treated with primary PCI and cooling after was improved compared with an historical control group treated with primary PCI alone (Knafleji, 2007).

There is good evidence supporting the use of induced hypothermia in comatose survivors of out-of-hospital cardiac arrest caused by VF.

Two studies with historical control groups (Level 3) showed improvement in neurological outcome after therapeutic hypothermia for comatose survivors of VF cardiac arrest (Belliard, 2007, 252; Castrejon, 2009, 733)
Extrapolation of these data to other cardiac arrests (e.g., other initial rhythms, in-hospital arrests, paediatric patients) seems reasonable but is supported by only lower level data:

Six studies with historical control groups (Level 3) showed benefit after therapeutic hypothermia in comatose survivors of OHCA after all rhythm arrests (Bernard, 2007; Oddo, 2006; Busch, 2006; Sunde, 2007; Storm, 2008; Don 2009). One studies with historical controls showed better neurological outcome after VF cardiac arrest but no difference after cardiac arrest from other rhythms (Bro-Jeppesen, 2009). Two non-randomised studies with concurrent controls (Arrich, 2007; Holzer, 2006) indicate possible benefit of hypothermia following cardiac arrest from other initial rhythms in- and out-of-hospital.

Statistical summary of critical studies: HACA 2002; Bernard 2002
Summary of HCASG 2002:
- 3551 assessed 275 enrolled
- Good neurological outcome at 6 months 75/136 [55% in hypo group] vs 54/137 [39%] (RR 1.40, 95% CI 1.08-1.81; Number Needed to Treat = 6)
- Deaths by 6 months 56/137 [41% in hypothermia group] vs 76/138 [55%] (RR 0.74, 95% CI 0.58-0.95; NNT = 7)
- Non-significant trend to more complications in hypothermia group (22% more overall): more pneumonia (NNH = 12), bleeding (NNH = 14) and sepsis (NNH = 16).

Summary of Bernard 2002:
- Unknown number assessed, 77 enrolled
- Good neurological outcome at discharge 21/43 [49%] vs 9/34 [26%]
- (*OR 2.7 [1.0-7.0]; NNT 4.5 [2.3 - 76]; Chi square P=0.046; FE, P=0.061*)
- Mortality 22/43 [51% in hypo group] vs 23/34 [68%]
- (*ChiSq P=0.145*) (NNT = 6)

How to cool?
Cooling should be initiated as soon as possible after return of spontaneous circulation (Wolff, 2008), but appears successful even if it is delayed (e.g., 4-6 hours). Cooling should be to 32-34^{o}C for 24 hours, and rewarming should be passive over at about 0.25^{o}C h^{-1}.
The practical approach of therapeutic hypothermia can be divided into three parts: induction, maintenance, and rewarming.
Induction can be induced easily and inexpensively with intravenous ice-cold fluids (30 ml/kg of saline 0.9% or Ringer's lactate)

(Kliegel, 2005; Bernard, 2003; Virkkunen, 2004; Kim, 2007; Jacobshagen, 2009; Kilgannon, 2008; Spiel, 2009; Larsson, 2010;) or traditional ice packs, placed in the groins, armpits and around the neck and head. Cooling with IV cold saline can be initiated in the pre-hospital phase (Hammer, 2009; Kamarainen, 2008a; Kamarainen, 2008b; Kamarainen, 2009). Out-of-hospital cooling can also be initiated with cooling pads (Uray, 2008). Initial cooling is facilitated by concomitant neuromuscular blockade with sedation to prevent shivering. If indicated, the patient can be transferred to the angiography laboratory with ongoing cooling, using these easily applied methods (Sunde, 2007; Knafelj, 2007) Surface or internal cooling devices can also be used alone or in combination with the above measures to facilitate induction (Holzer, 2006; Haugk, 2007).

In the maintenance phase, a cooling method with effective temperature monitoring that avoids temperature fluctuations is preferred. This is best achieved with external or internal cooling devices that include continuous temperature feedback to achieve a set target temperature (Hoedemaekers, 2007). Typical external devices are cooling blankets (Gal, 2009) or pads with water-filled circulating systems (Haugk, 2007; Heard, 2010). Typical internal cooling devices include intravascular cooling catheters (Al-Senani, 2004; Pichon, 2007), placed usually in the femoral or subclavian veins. However, less sophisticated methods such as cold wet, blankets on the torso and around the extremities, or icepacks, combined with ice cold fluids, can also be effective; however, these methods may be more time consuming for nursing staff, may result in greater temperature fluctuations, and do not enable controlled rewarming (Merchant, 2006). Ice cold fluids alone cannot be used to maintain hypothermia (Kliegel, 2007), but even the addition of simple ice packs may control the temperature adequately (Larsson, 2010).
The rewarming phase can be achieved with either external or internal cooling devices (if these are used), or with other heating systems. The optimal rate of rewarming is not known, but the consensus is currently about 0.25-0.5 ºC of warming per hour (Arrich, 2007). Particular care should be taken during the cooling and rewarming phases because metabolic rate, plasma electrolyte concentrations and haemodynamics may change rapidly.

If therapeutic hypothermia is not feasible or contraindicated, then, at a minimum, pyrexia must be prevented.

Harm from cooling?
One study (Yanagawa, 1998) reported more pneumonia in a 48-hour hypothermia group and another reported higher levels of inflammatory markers (IL-6) and bacterial colonization with hypothermia compared with controls (Fries, 2009).

REVIEWER'S CONFLICTS OF INTEREST:

Peter Morley - Intensive Care Specialist/Internist/Anesthesiologist. No intellectual or commercial conflicts. Reimbursed consultant for E3 position with ILCOR/AHA. No other conflicts.
Jerry Nolan - Consultant in Anaesthesia and Critical Care Medicine. Co-chair ILCOR, Chair Resuscitation Council (UK) and member of the Executive Committee of the ERC. No other conflicts.

Acknowledgements:
Nil

Citation List

Aberle J, Kluge S, Prohl J, et al. Hypothermia after CPR through conduction and convection - Initial experience on an ICU. Intensivmedizin und Notfallmedizin 2006; 43: 37-43.

Level 4, poor, neutral. Case series of 20 patients cooled on ITU – no outcome data but full paper not reviewed (German)

Al-Senani FM, Graffagnino C, Grotta JC, et al. A prospective, multicenter pilot study to evaluate the feasibility and safety of using the CoolGard trade mark System and Icy trade mark catheter following cardiac arrest. Resuscitation 2004; 62: 143-50.

Level 4 study, neutral. Intravascular cooling with this device resulted in very tight control of body temperature.

Arrich J. Clinical application of mild therapeutic hypothermia after cardiac arrest. Crit Care Med 2007; 35: 1041-7.

Level 2 Study, poor, supportive. Patients entered on to cardiac arrest registry run by Alsius and ERC. A few centres contributed most patients. Most of those cooled were cooled endovascularly. Controls not matched and significant baseline differences (e.g. far more in-hospital, non-cardiac aetiology arrests in normothermic group. Survival to discharge hypothermia 267 (57%) versus normothermia 39 (32%) but impossible to draw conclusions because of selection bias. 16 patients who were cooled in the PEA/Asystole group survived with a CPC of > 2. All those with PEA/asystole in the normothermia group who survived had a favourable CPC.

Arrich J, Holzer M, Herkner H, Müllner M. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. Cochrane Database of Systematic Reviews. 2009(4):Art. No.: CD004128.

LOE 1 , good, supportive (survival, neurology). Meta-analysis of RCTs. Search to Jan 2007. Included Bernard 2002; HACA 2002; Hachimi-Idrissi 2001; Laurent 2005 (no hypothermia group by itself, only combined with haemofiltration); Mori 2000 (abstract only). Results :
- Survival: Conventional cooling without extracorporal methods (survival to discharge) N = 383. Risk Ratio (M-H, Fixed, 95% CI) 1.35 [1.10, 1.65]
- Good neurological outcome: Conventional cooling without extracorporal methods: N = 383. Risk Ratio (M-H, Fixed, 95% CI) 1.55 [1.22, 1.96]
- No significant differences between groups for adverse effects.

Belliard G, Catez E, Charron C, et al. Efficacy of therapeutic hypothermia after out-of-hospital cardiac arrest due to ventricular fibrillation. Resuscitation 2007; 75: 252-9.

Level 3 study, fair, supportive. 76 patients after OHCA from VF. 8 moribund patients excluded from the analysis (4 in control and 4 in hypothermia group) – validity of this? Survival to discharge: historical 13/36 (36%) versus hypothermia 18/32 (56%) P = 0.04. Neurological status at least 1 year after discharge was good (GOS 5) in 6/13 in historical versus 13/18 in hypothermia group (P=0.02)

Benson, D. W., G. R. Williams, et al. (1959). "The use of hypothermia after cardiac arrest." Anesth Analg 38: 423-28.
No abstract available.
Level 2. Poor. Neutral (underpowered).
27 in-hospital arrests at Johns Hopkins University (Baltimore), excluded 2 failed resuscitations and 6 good neurological outcome. 19 patients with neurological insult after successful resuscitation (internal cardiac massage) were either cooled or not. Concurrent controls. Not randomised. 12 cooled to 30-32°C within 1 to 6 hours (for 3hrs to 8 days). 7 not cooled. Survival in 1/7 vs 6/12 (FE, P=0.17). Included all four cases reported in Williams and Spencer Ann Surg 1958.

Bernard SA, Jones BM, Horne MK. Clinical trial of induced hypothermia in comatose survivors of out-of-hospital cardiac arrest. Ann Emerg Med. 1997 Aug;30(2):146-53.

Level 3. Good. Supportive (GOCS/neurological and mortality).
Prospective interventional study of hypothermia using retrospective controls, single centre, Melbourne Australia. Consecutive patients comatose on arrival at ED, after out-of-hospital cardiac arrest (but not hypotensive despite dopamine/adrenaline, other causes of coma, <16 years or possibly pregnant). Surface cooled with ice packs and paralysed, maintained at 33°C for 12 hours then actively rewarmed over 6 hours. Goals of PaCO2 of 40 mmHg, MAP 90-100, lidocaine if VF. 22 consecutive historical controls, same inclusion and exclusion criteria. Similar groups (17/22 in each group initially VF)). Similar protocols for therapy and

withdrawal. Better good Glasgow Outcome Coma Scale (1 or 2; 11/22 [50%] vs 3/22 [14%], FE P=0.02) and mortality (10/22 [45%] vs 17/22 [77%], Chi square P = 0.03; FE P=0.06). No increased bleeding, sepsis, coagulopathy, thrombocytopenia.

Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med. 2002 Feb 21;346(8):557-63.

Level 2, supportive (intact neurology), neutral (mortality). Fair. Underpowered, stopped early, unadjusted P value, not randomised, randomisation not blinded, treatment (incl. withdrawal) not blinded, ? other treatment not same [admitted] (eg. paralysis), no control for baseline differences. Positive (discharge destination)
Multicentre study of out-of-hospital cardiac arrest in Melbourne Australia. Patients in VF at arrival of ambulance, ROSC and persistent coma, but not age < 18 (men) or <50 (women, as ? pregnant), hypotension (SBP < 90 despite epinephrine infusion), or other causes of coma. Allocated according to day of month (ie. not randomised, not blinded; but ? authors "not aware of eligible patients who were not included in the outcome analysis"). 84 eligible over 33 months, 7 excluded. Standard management included midazolam and vecuronium, temperature corrected CO2 of 40, MAP 90-100 (with epinephrine or GTN), lignocaine infusion and glucose < 10 mmol/L.
Normothermia passively rewarmed to target of 37°C, sedated and paralysed as needed. Hypothermia group had clothing removed, and ice-packs to head and torso (paramedics), then sedated and paralysed as needed to prevent shivering; target temperature 33°C for 12 hours after hospital arrival then actively rewarmed over 6 hours. Treatment group obvious to treating physicians; 2/3 to 3/4 received PA catheters; most deaths as a result of withdrawal of therapy. Outcome assessment (by specialist "unaware" of treatment group) = death or discharge destination (home/rehab facility vs nursing home/death in hospital). Power analysis based on retrospective data (14% to 50%; p<0.05, power 80%; 31 in each group), but study continued because of trend until positive! More discharged home/rehab with hypothermia (26% vs 49%, OR 2.7 [1.0-7.0]; NNT 4.5 [2.3 - 76]; Chi square P=0.046; FE, P=0.061. Not adjusted from repeat/multiple looks.) Power calculations on 26% and 49% give 70 in each group!!! Adjusted for baseline differences (in age and time collapse to ROSC) OR for good outcome 5.25 [1.5 to 18.8; p=0.011). No adjustment made for differences in bystander CPR (71% in normo vs 49%) and male sex (71% in normo vs 49%). Difference in home discharge not significant. No mortality difference (hypo 22/43 [51%] vs 23/34 [68%], ChiSq P=0.145; NNT=6.1).
Decreased pulse rate and increased SVR, but no effects on white cells, platelets of obvious sepsis.

Bernard S, Buist M, Monteiro O, Smith K. Induced hypothermia using large volume, ice-cold intravenous fluid in comatose survivors of out-of-hospital cardiac arrest: a preliminary report. Resuscitation 2003; 56:9-13.

Level 4, neutral. Fair. Used 30 mL/kg cold fluids (4C) to decrease core temperature.

Borgquist O, Friberg H. Therapeutic hypothermia for comatose survivors after near-hanging-a retrospective analysis. Resuscitation 2009;80:210-2.

Level 3, neutral, poor. Very small retrospective study of cardiac arrests secondary to hanging.

Bro-Jeppesen J, Kjaergaard J, Horsted TI, et al. The impact of therapeutic hypothermia on neurological function and quality of life after cardiac arrest. Resuscitation 2009;80:171-6.

Level 3, supportive, fair. Better neurological function at discharge but no difference when assessed at 30 months. No significant differences were found in long-term survival (57% vs. 56% alive at 30 months), MMSE, or SF-36.

Busch M, Soreide E, Lossius HM, Lexow K, Dickstein K. Rapid implementation of therapeutic hypothermia in comatose out-of-hospital cardiac arrest survivors. Acta Anaesthesiol Scand 2006; 50: 1277-83.

Level 3, supportive (hospital discharge), neutral (neurological outcome), fair. Historical controls. Survival to discharge 11/34 (32%) versus 16/27 (59%) P = 0.036; CPC 1 or 2 = 9/34 (26%) versus 11/27 (41%) P =0.21

Castrejon S, Cortes M, Salto ML, et al. Improved prognosis after using mild hypothermia to treat cardiorespiratory arrest due to a cardiac cause: comparison with a control group. Rev Esp Cardiol 2009;62:733-41.

Level 3, supportive (neurological outcome), neutral (hospital discharge), poor. Retrospective control and study groups. No significant difference in survival to discharge but better neurological outcome at 6 months in cooled group.

Cheung KW, Green RS, Magee KD. Systematic review of randomized controlled trials of therapeutic hypothermia as a neuroprotectant in post cardiac arrest patients. CJEM 2006; 8: 329-37.

Level 1. Poor. Adds nothing further to the Holzer meta-analysis. The only other study that was included (Mori K, Takeyama Y, Itoh Y, et al. Multivariate analysis of prognostic factors in survivors of out-of-hospital cardiac arrest with brain hypothermia therapy. Crit Care Med 2000;28:A168.) was an abstract that has not been published in full.

Cronberg T, Lilja G, Rundgren M, Friberg H, Widner H. Long-term neurological outcome after cardiac arrest and therapeutic hypothermia. Resuscitation 2009;80:1119-23.

Level 4, good, neutral. 36/43 (84%) of survivors that were assessed were CPC 1, but 37/43 had a mild cognitive deficit.

Damian MS, Ellenberg D, Gildemeister R, et al. Coenzyme Q10 combined with mild hypothermia after cardiac arrest: a preliminary study. Circulation 2004; 110: 3011-6.

Level 4, good, neutral. Although this is a level 1 study, both groups were cooled – the CoQ10 was randomly assigned. Therefore included as case series. Hypothermia target range was 35-36^{o}C.

Derwall M, Stoppe C, Brucken D, Rossaint R, Fries M. Changes in S-100 protein serum levels in survivors of out-of-hospital cardiac arrest treated with mild therapeutic hypothermia: a prospective, observational study. Crit Care 2009;13:R58.

Level 2, Neutral (outcome E: S-100), poor. Prospective, observational study. Physicians decided whether or not to cool.

Doherty DR, Parshuram CS, Gaboury I, et al. Hypothermia therapy after pediatric cardiac arrest. Circulation 2009;119:1492-500.

Level 2, fair, neutral. Retrospective study, but concurrent controls. Although unadjusted mortality was higher in the hypothermia group, the outcomes were not significantly different when adjusted for multiple confounders. Relatively rare paediatric data on this topic.

Don CW, Longstreth WT, Jr., Maynard C, et al. 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. Crit Care Med 2009;37:3062-9.

Level 3, fair, supportive (overall for hospital discharge and neurological outcome [all rhythms combined; only univariate analysis reported] Subsequent analysis: VF supportive for neurological outcome (multivariate) but neutral for non-VF.

Felberg RA, Krieger DW, Chuang R, et al. Hypothermia after cardiac arrest: feasibility and safety of an external cooling protocol. Circulation. 2001 Oct 9;104(15):1799-804

Level 4, neutral. Feasibility study.
Safety and feasibility study from Houston, Texas. Out-of-hospital cardiac arrest, with ROSC ≥ 90 within 60 min, 18-85, GCS ≤8, but not cardiac instability, ongoing myocardial ischemia, sepsis, need for vasoactive drugs, coagulopathy or thrombocytopaenia, QTc > 470 msec. 9 patients enrolled in 15 months. Sedated (propofol) and paralysed, cooled to 33°C for 24 hours, then rewarmed at 1°C every 4 hours. Cooled with cooling blankets and ice packs (axillae, groin) and iced saline gastric lavage. ACLS to initiation of hypothermia 78 (40 to 109 min). Time to goal temp 391 min (167 to 770), 301 (90 to 690) min after initiation (goal was 120 minutes!). Rewarmed quicker than expected 645 min (330-990), and all overshot (≥38°C). Survival in 4/9; pneumonia occurred in 5/9, but coagulopathy in only 1/9. Only 28/110 OOH cardiac arrests had ROSC, and only 9/28 ROSC enrolled (13 not eligible, 6 eligible but not enrolled).

Feuchtl A, et al. Endovascular cooling improves neurological short-term outcome after prehospital cardiac arrest. Intensivmed 2007; 44:37–42.

Level 4, fair, neutral. Cooling attempted in all patients. This is actually a study comparing surface cooling with endovascular cooling. The outcome is neutral for the question. However, very few of the historical group reached target temperature (mean core temp = 36.1^{o}C).

Flint AC, Hemphill JC, Bonovich DC. Therapeutic hypothermia after cardiac arrest: performance characteristics and safety of surface cooling with or without endovascular cooling. Neurocrit Care 2007; 7: 109-18.

Level 4, poor, neutral. Neutral for clinical question but another study indicating better temperature control with endovascular cooling.

Fries M, Stoppe C, Brucken D, Rossaint R, Kuhlen R. Influence of mild therapeutic hypothermia on the inflammatory response after successful resuscitation from cardiac arrest. J Crit Care 2009;24:453-7.

Level 2, neutral (survival, neurology), opposing (E = bacterial colonization), poor. Physicians chose whether to cool or not. IL-6 and bacterial colonization higher in cooled group but trend to reduced mortality 74% versus 53% (P = 0.053)

Gal R, Slezak M, Zimova I, Cundrle I, Ondraskova H, Seidlova D. Therapeutic hypothermia after out-of-hospital cardiac arrest with the target temperature 34-35 degrees C. Bratisl Lek Listy 2009;110:222-5.

Level 4, neutral, fair. Full paper not studied.

Gaieski DF, Band RA, Abella BS, et al. Early goal-directed hemodynamic optimization combined with therapeutic hypothermia in comatose survivors of out-of-hospital cardiac arrest. Resuscitation 2009;80:418-24.

Level 3, fair, neutral. Combination of early goal directed therapy and hypothermia, therefore difficult to tease out the impact of TH alone.

Hachimi-Idrissi S, Corne L, Ebinger G, et al. Mild hypothermia induced by a helmet device: a clinical feasibility study. Resuscitation. 2001 Dec;51(3):275-81. Hachimi-Idrissi, 2001 (1)

Level 1 (small study). Poor, neutral (survival), supportive (E =lactate, O2 extraction, CvO2).
"Feasibility" trial from Brussels. Patients who achieved ROSC after asystole or PEA (presumed cardiac origin), > 18 yrs, tympanic T>30°C on admission to ER, GCS < 7, not pregnant, no known coagulopathy, no CNS depressant drugs, haemodynamically stable (MAP>60, SBP>100). All PaCO2 40-45 mmHg, MAP >60, no glucose solutions, 30° head up, paralysed with pancuronium. Blindly randomised. Hypothermic group had refrigerated helmet device (-4°C; Frigicap), replaced hourly until bladder temperature 34°C or 4 hrs reached. 30 consecutive patients included (unable to exclude any significant baseline differences between groups). Able to cool tympanic to 34°C in median 60 min (15-240 min), and bladder in 180 (70-240 min). After 4 hours (presumably not blinded assessor and treating doctor not blinded), hypothermia group had significantly higher CvO2, with a lower O2 extraction ratio, and a lower arterial lactate (P<0.05). 13/16 hypothermia died, vs 13/14 normothermia (P = NS).

Hammer L, Vitrat F, Savary D, et al. Immediate prehospital hypothermia protocol in comatose survivors of out-of-hospital cardiac arrest. Am J Emerg Med 2009;27:570-3.

Level 2 (concurrent controls), fair, neutral (survival, neurology). Trend towards better neurological outcome in control group.

Haugk M, Sterz F, Grassberger M, et al. Feasibility and efficacy of a new non-invasive surface cooling device in post-resuscitation intensive care medicine. Resuscitation 2007; 75: 76-81.

Level 4, fair, neutral. A feasibility study using the Artic Sun system.

HACA Study Group (2002). Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. New England Journal of Medicine 346(8): 549-56.

Level 1 study. Good, supportive. Positive neurological outcome.
Randomised controlled multicentre European study with blinded assessment of outcome. Consecutive cases considered for inclusion if initial VF/pulseless VT with , witnessed, presumed cardiac cause, collapse-EMS resuscitation attempt time 5-15 min, ROSC within 60 min of collapse, no subsequent prolonged hypotension or hypoxia before cooling, temperature not <30°C on admission, or pre-existing malignancy/pregnancy/coma/CNS depression with drugs/known coagulopathy. Family informed about trial, but no withdrawals. Random numbers, blocks of 10, stratified by centre, sealed envelope. Treating personnel not blinded, neurologic assessors "unaware". All sedated and paralysed (midazolam & fentanyl infusions, and pancuronium boluses) for 32 hours. Cooling group used special mattress/blanket delivering cold air to reach 32-34°C (bladder) within 4 hours and maintained for 24 hours then passively rewarming. Control group had "normothermia" maintained.
3551 patients assessed, 275 enrolled (137 hypo, 138 normothermia). No sample size calculation. All included in mortality. One in each group lost to follow up (ie. neurology). Baseline: more in normothermia group with diabetes (26/138 19% vs 11/135 8% Chi2=0.01) and coronary heart disease (59/138 43% vs 43/135 32% Chi2 = 0.05). Cooling achieved in 8 hrs (IQR 4-16); 19 not reached desired temperature, 70% required ice packs; maintained for 24 hours (IQR 12-29). Control group temperature high (37-38°C for 40 hours).

Pittsburgh Cerebral Performance Category assessed at 6 months: more favorable in hypothermia (75/136 55% vs 54/137 39%; RR 1.40 [1.08-1.81], p=0.009). Adjusted for all of table 1 (1.47 [1.09-1.82]), but decreased (not shown) by adjust for diabetes, coronary disease and bystander BLS. NNT = 6 [4-25].
Deaths by 6 months more favorable in hypothermia (56/137 41% vs 76/138 55%; RR 0,74 [0.58-0.95], p=0.02). NNT = 7 [4-33]. Adjusted RR similar.
Complications occurred 22% more in Hypothermia group (NS), with more pneumonia (37 vs 29%, NS, NNH 12), and bleeding (26 vs 19%, NS, NNH 14) and nearly twice as much sepsis (13 vs 7%, p=0.08, NNH 16)

Heard KJ et al. A randomized controlled trial comparing the Arctic Sun to standard cooling for induction of hypothermia after cardiac arrest. Resuscitation 2010;81:9-14.

Level 4, neutral for the question, fair. This is an RCT comparing Arctic Sun with standard external cooling. Essentially, no difference in proportion of patients reaching target temperature by 4 h.

Hay AW, Swann DG, Bell K, Walsh TS, Cook B. Therapeutic hypothermia in comatose patients after out-of-hospital cardiac arrest. Anaesthesia 2008;63:15-9.

Level 4 study, poor, neutral. Case series but because only 100/139 sets of notes were available (typical of the UK) we have no idea how many were cooled overall!!

Hoedemaekers CW, Ezzahti M, Gerritsen A, van der Hoeven JG. Comparison of cooling methods to induce and maintain normo- and hypothermia in intensive care unit patients: a prospective intervention study. Crit Care 2007; 11: R91.

Level 4, poor, neutral. A study comparing cooling techniques – randomly assigned to technique. No survival data. Endovascular cooling enabled tighter temperature control.

Holzer M, Bernard SA, Hachimi-Idrissi S, et al. Hypothermia for neuroprotection after cardiac arrest: systematic review and individual patient data meta-analysis. Crit Care Med 2005; 33: 414-8.

Level 1, fair, supportive. Meta-analysis using individual patient data from HACA, Bernard and Hachimi-Idrissi. NNT for favourable outcome (95% CI) was 4-13.

Holzer M, Mullner M, Sterz F, et al. Efficacy and safety of endovascular cooling after cardiac arrest: cohort study and Bayesian approach. Stroke 2006; 37: 1792-7.

Level 2, fair, supportive. Concurrent controls but strong possibility of selection of bias although statistical methods used in attempt to adjust for baseline differences. Odds ratio for survival 1.96 (1.19 -3.23) after adjustment for baseline differences. No differences in complication between frequency-matched groups except for more bradycardia in cooled group.

Hovdenes J, Laake JH, Aaberge L, Haugaa H, Bugge JF. Therapeutic hypothermia after out-of-hospital cardiac arrest: experiences with patients treated with percutaneous coronary intervention and cardiogenic shock. Acta Anaesthesiol Scand 2007; 51: 137-42.

Level 4, good, supportive. 50 patients cooled after OHCA from VF. 72% had PCI and 46% had IABP. At 6 months 41/50 (82%) survival and 34/50 (78%) = CPC 1 or 2.

Jacobshagen C, Pax A, Unsold BW, et al. Effects of large volume, ice-cold intravenous fluid infusion on respiratory function in cardiac arrest survivors. Resuscitation 2009;80:1223-8.

Level 4, neutral, fair. Retrospective study showing no change in respiratory function after infusion of 3500 ml of ice cold fluid.

Jimmink JJ, Binnekade JM, Paulus F, Mathus-Vliegen EM, Schultz MJ, Vroom MB. The influence of body composition on therapeutic hypothermia: a prospective observational study of patients after cardiac arrest. Crit Care 2008;12:R87.

Level 4, neutral, fair – indicating influence of body composition on ability to cool.

Kamarainen A, Virkkunen I, Tenhunen J, Yli-Hankala A, Silfvast T. Prehospital induction of therapeutic hypothermia during CPR: a pilot study. Resuscitation 2008;76:360-3.

Level 4, neutral, poor. Pilot showing feasibility of prehospital cooling with cold fluid.

Kamarainen A, Virkkunen I, Tenhunen J, Yli-Hankala A, Silfvast T. Induction of therapeutic hypothermia during prehospital CPR using ice-cold intravenous fluid. Resuscitation 2008;79:205-11.

Level 4, neutral, poor. Small study showing feasibility of prehospital cooling with cold fluid – includes 5 patients from the pilot study from the same group.

Kamarainen A, Virkkunen I, Tenhunen J, Yli-Hankala A, Silfvast T. Prehospital therapeutic hypothermia for comatose survivors of cardiac arrest: a randomized controlled trial. Acta Anaesthesiol Scand 2009;53:900-7.

Level 4, neutral (mortality and neurology), fair. Small RCT of prehospital cooling. No control of in-hospital cooling (not all patients cooled in hospital, but outcomes not described for these, so unable to compare cooling with no cooling). Includes subjects from previous study??

Kilgannon JH, Roberts BW, Stauss M, et al. Use of a standardized order set for achieving target temperature in the implementation of therapeutic hypothermia after cardiac arrest: a feasibility study. Acad Emerg Med 2008;15:499-505.

Level 4, neutral, poor. Simply indicating that hypothermia can be implemented.

Kim F, Olsufka M, Carlbom D, et al. Pilot study of rapid infusion of 2 L of 4 degrees C normal saline for induction of mild hypothermia in hospitalized, comatose survivors of out-of-hospital cardiac arrest. Circulation 2005; 112: 715-9.

Level 4, fair, neutral. Efficacy study of hypothermia induced with cold IV saline.

Kim F, Olsufka M, Longstreth WT, Jr., et al. Pilot randomized clinical trial of prehospital induction of mild hypothermia in out-of-hospital cardiac arrest patients with a rapid infusion of 4 degrees C normal saline. Circulation 2007; 115: 3064-70.

Level 4, fair, neutral (survival). RCT of prehospital cooling. No control of in-hospital cooling (not all patients cooled in hospital, but outcomes not described sufficiently, so unable to compare cooling with no cooling). "60 of 97 admitted patients (62%) received hospital cooling regardless of field cooling. Our preliminary analyses did not suggest that the effect of field cooling on outcomes was either confounded or modified by hospital cooling, although these questions need to be addressed in larger studies". "When we adjusted for the effects of hospital cooling, the odds ratio for survival to hospital discharge for the field cooling group increased slightly from 1.25 to 1.38 (95% CI, 0.58 to 3.29)". Prehospital cooling successfully reduced core temperature but survival to discharge was cooled: 21/63 (33%) versus normothermia 18/62 (29%) NS.

Kliegel A, Losert H, Sterz F, et al. Cold simple intravenous infusions preceding special endovascular cooling for faster induction of mild hypothermia after cardiac arrest--a feasibility study. Resuscitation 2005; 64: 347-51.

Level 4, fair, neutral. Feasibility study of IV fluid for cooling.

Kliegel A, Janata A, Wandaller C, et al. Cold infusions alone are effective for induction of therapeutic hypothermia but do not keep patients cool after cardiac arrest. Resuscitation 2007; 73: 46-53.

Level 4, fair, neutral. Case series of cooling technique – ice cold IV fluid to maintain hypothermia. Of all patients, 8 (40%) survived to discharge and 7 (35%) had a favourable neurological outcome (CPC 1 or 2).

Knafelj R, Radsel P, Ploj T, Noc M. Primary percutaneous coronary intervention and mild induced hypothermia in comatose survivors of ventricular fibrillation with ST-elevation acute myocardial infarction. Resuscitation 2007; 74: 227-34.

Level 3, fair, supportive. 40 patients treated with PCI and hypothermia compared with historical control of 32 patients with primary PCI but no hypothermia. 6-month survival 27/40 (68%) versus 12/32 (38%) P=0.021; CPC 1 or 2 = 21/40 (53%) versu 6/32 (19%) P = 0.007.

Koreny M, Sterz F, Uray T, et al. Effect of cooling after human cardiac arrest on myocardial infarct size. Resuscitation 2009;80:56-60.

Level 1, neutral, good. Cooling did not influence infarct size.

Larsson I-M et al. Cold saline infusion and ice packs alone are effective in inducing and maintaining therapeutic hypothermia after cardiac arrest. Resuscitation 2010;81:15-19.

Level 4, neutral, fair. Demonstrates that hypothermia can be achieved with simple techniques.

Merchant RM, Abella BS, Peberdy MA, et al. Therapeutic hypothermia after cardiac arrest: unintentional overcooling is common using ice packs and conventional cooling blankets. Crit Care Med 2006; 34: S490-4.

Level 4, fair, neutral. Shows problems associated with external cooling but neutral for the clinical question.

Nagao K, Hayashi N, Kanmatsuse K, et al. Cardiopulmonary cerebral resuscitation using emergency cardiopulmonary bypass, coronary reperfusion therapy and mild hypothermia in patients with cardiac arrest outside the hospital. J Am Coll Cardiol. 2000 Sep;36(3):776-83.

Level 4, fair, neutral. No real control group (as others were excluded as unstable). Not excluded as not all patients had CPB. Extra-ordinarily aggressive interventions to support circulation and brain preservation after out-of-hospital cardiac arrest in Tokyo. Inclusions age 18-74, witnessed CPR, BLS within 15 min, or VF; no aortic dissection or intracranial haemorrhage, GCS 3-5 on arrival in ED. Resistant VF or after second dose of adrenaline in other rhythms, emergency cardiopulmonary bypass and intra-aortic balloon pump. If ROSC just intra-aortic balloon pump. Then angiography if suspected acute coronary syndrome. When SBP > 90 and GCS 3-5, mild hypothermia induced (direct blood cooling in two stages to 34° [in 6.3±3.4 h], maintained for 2-3 days, and slowly up to 36°C). SBP goal >90 mmHg, sedated and paralysed, mildly anticoagulated. 50 patients treated, 46 had ROSC for more than 1 hour, and hypothermia able to be induced in 23 of these (ie. SBP good enough). Good cerebral performance category in 12/23 (52%) and survival to discharge in 15/23 (65%).
Department of Emergency and Critical Care Medicine, Nihon University School of Medicine, Tokyo, Japan.

Nielsen N, Hovdenes J, Nilsson F, et al. Outcome, timing and adverse events in therapeutic hypothermia after out-of-hospital cardiac arrest. Acta Anaesthesiol Scand 2009;53:926-34.

Level 4, good, supportive. Registry data – no controls. 50% survival and 90% good neurological recovery.

Oddo M, Schaller MD, Feihl F, Ribordy V, Liaudet L. From evidence to clinical practice: effective implementation of therapeutic hypothermia to improve patient outcome after cardiac arrest. Crit Care Med 2006; 34: 1865-73.

Level 3, fair, supportive for neurological outcome (neutral [underpowered] for hospital discharge) . 55 cooled OHCA patients compared with 54 historical controls. Overall survival to discharge = 28/55 (51%) versus 20/54 (37%) (p=0.15). After VF CPC 1 or 2 = 55.8% versus 25.6% (p=0.004)

Oksanen T, Pettila V, Hynynen M, Varpula T. Therapeutic hypothermia after cardiac arrest: implementation and outcome in Finnish intensive care units. Acta Anaesthesiol Scand 2007; 51: 866-71.

Level 4, poor, supportive. Six-month survival data collected by 10 of 19 ICUs: 93/178 (52.5%)

Pichon N, Amiel JB, Francois B, Dugard A, Etchecopar C, Vignon P. Efficacy of and tolerance to mild induced hypothermia after out-of-hospital cardiac arrest using an endovascular cooling system. Crit Care 2007;11:R71.

Level 4. Neutral, fair. Interesting case series of endovascularly cooled patients – defines problem of post-rewarming rebound hyperthermia.

Sagalyn E, Band RA, Gaieski DF, Abella BS. Therapeutic hypothermia after cardiac arrest in clinical practice: review and compilation of recent experiences. Crit Care Med 2009;37:S223-6.

Level 4 and 3 (multiple studies – 6 with retrospective controls), fair, supportive. OR for survival among the 6 LOE 3 studies was 2.5 (1.8 – 3.3).

Scott BD, Hogue T, Fixley MS, Adamson PB. Induced hypothermia following out-of-hospital cardiac arrest; initial experience in a community hospital. Clin Cardiol 2006; 29: 525-9.

Level 4, poor, neutral.

Skulec R, Kovarnik T, Dostalova G, Kolar J, Linhart A. Induction of mild hypothermia in cardiac arrest survivors presenting with cardiogenic shock syndrome. Acta Anaesthesiol Scand 2008;52:188-94.

Level 4, fair, neutral. This study was actually comparing outcomes of those in cardiogenic shock with those were not (retrospectively analysed) – all patients were cooled. Although there is a control group it was not comparing cooled versus not cooled.

Silfvast T, Tiainen M, Poutiainen E, Roine RO. Therapeutic hypothermia after prolonged cardiac arrest due to non-coronary causes. Resuscitation 2003; 57:109-12.

Level 4, fair, neutral.

Simosa HF, Petersen DJ, Agarwal SK, Burke PA, Hirsch EF. Increased risk of deep venous thrombosis with endovascular cooling in patients with traumatic head injury. Am Surg 2007;73:461-4.

Level 5, poor, against. Study indicating risk of DVT with intravascular cooling – in head-injured patients –not cardiac arrest.

Spiel AO, Kliegel A, Janata A, et al. Hemostasis in cardiac arrest patients treated with mild hypothermia initiated by cold fluids. Resuscitation 2009;80:762-5.

Level 4, neutral, fair. 18 post cardiac arrest patients cooled – slightly prolonged clotting time, otherwise no significant change in clotting.

Storm C, Steffen I, Schefold JC, et al. Mild therapeutic hypothermia shortens intensive care unit stay of survivors after out-of-hospital cardiac arrest compared to historical controls. Crit Care 2008;12:R78.

Level 3, fair supportive. Historical control group; reduced ITU LOS and improved 1-year survival.

Sunde K, Pytte M, Jacobsen D, et al. Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. Resuscitation 2007; 73: 29-39.

Level 3, fair, supportive. This study compares a package of care (including hypothermia) with historical controls. 77% of the study group were cooled. Survival to discharge with CPC 1 or 2 = 34/61 (56%) versus 15/58 (26%); (OR 3.61, CI 1.66-7.84, p=0.001).

Tiainen M, Roine RO, Pettila V, Takkunen O. Serum neuron-specific enolase and S-100B protein in cardiac arrest patients treated with hypothermia. Stroke 2003; 34: 2881-6.

Level 1 study, good, supportive – NSE was reduced in the hypothermia group. Neutral for neurologically intact survival.
Patients from the HACA trial. At 6 months, good neurological outcome was achieved in 69% (25/36) of hypothermia-treated patients (CPC 1, 22; CPC 2, 3) and in 47% (16/34) of normothermia-treated patients (CPC 1, 11; CPC 2, 5) (FE = 0.089)

Tiainen M, Poutiainen E, Kovala T, et al. Cognitive and neurophysiological outcome of cardiac arrest survivors treated with therapeutic hypothermia. Stroke 2007; 38: 2303-8.

Level 1, good, neutral. Same cohort as the paper from the same group above. No significant differences reflecting small groups.

Tiainen M, Parikka HJ, Makijarvi MA, Takkunen OS, Sarna SJ, Roine RO. Arrhythmias and heart rate variability during and after therapeutic hypothermia for cardiac arrest. Crit Care Med 2009;37:403-9.

Level 1, neutral (neurology), good. Subset of the HACA study. Only minor arrhythmias in cooled group (not considered clinically significant: ie. not "opposing")..

Uray T, Malzer R. Out-of-hospital surface cooling to induce mild hypothermia in human cardiac arrest: A feasibility trial. Resuscitation 2008.

Level 4, fair, neutral. Feasibilty trial for out-of-hospital use of EMCOOLS external cooling system

Virkkunen I, Yli-Hankala A, Silfvast T. Induction of therapeutic hypothermia after cardiac arrest in prehospital patients using ice-cold Ringer's solution: a pilot study. Resuscitation 2004; 62: 299-302.

Level 4, fair, neutral. Feasibility trial for using ice-cold saline to induce hypothermia in the field.

Werling M, Thoren AB, Axelsson C, Herlitz J. Treatment and outcome in post-resuscitation care after out-of-hospital cardiac arrest when a modern therapeutic approach was introduced. Resuscitation 2007; 73: 40-5.

Level 3, poor, neutral. 85 patients from 2003-2005 compared with 1310 patients from 1980-2000. Survival to discharge was 32% versus 36% (NS). CPC 1 or 2 was 85% for current cohort of survivors (CPC 3 = 15%). Same group reported in 1997 a CPC of 1 in 56% of survivors.

Williams, G. R. and F. C. Spencer (1958). "The clinical use of hypothermia following cardiac arrest." Ann Surg 148: 462-8.

Level 4. Case series. poor, supportive.
Case report of 4 cases of good neurological outcome after in-hospital cardiac arrest. All had open cardiac massage, 3/4 had fixed dilated pupils, all cooled after ROSC to 30-34°C with water cooled mattress for 24-72 hours.
Also level 6 but excluded as great vessel occlusion model(brief report with table). Positive. Mortality.
10 minutes of circulatory arrest in dogs, hypothermia instituted after anoxic injury (18-36 hours of 32-34°C), had better survival 10/12 vs 4/12 controls (FE, P=0.036). "Zimmerman J.McK. and Spencer F.C" to be published. Referred to in Wolfe 1960.

Wolff B, Machill K, Schumacher D, Schulzki I, Werner D. Early achievement of mild therapeutic hypothermia and the neurologic outcome after cardiac arrest. *Int J Cardiol.* 2009; 133: 223-8.

Level 4. Good, supportive. Case series of 49 patients all cooled endovascularly – the first human data to show that time to target temperature is an independent predictor for good outcome.

Wolfrum S, Pierau C, Radke PW, Schunkert H, Kurowski V. Mild therapeutic hypothermia in patients after out-of-hospital cardiac arrest due to acute ST-segment elevation myocardial infarction undergoing immediate percutaneous coronary intervention. Crit Care Med 2008;36:1780-6.

Level 3, neutral, fair. Compared PCI with MTH versus PCI only group (historical).

Yanagawa Y, Ishihara S, Norio H, et al. Preliminary clinical outcome study of mild resuscitative hypothermia after out-of-hospital cardiopulmonary arrest. Resuscitation. 1998 Oct-Nov;39(1-2):61-6.

*Level 3. Fair, neutral (type II error survival/GOS) to **opposing** (worse outcome = pneumonia).*
Prospective study from Tokyo using matched retrospective controls (1995). 13 consecutive patients after cardiopulmonary arrest, not due to trauma/CNS/terminal disease, < 70 and < 0.3 mg(!)/kg/min adrenaline. Core temperature (bladder/PA catheter) maintained at 33-34°C for 48 hrs then slowly rewarmed (1°C/day). Cooled with blankets and topical alcohol(!), and sedated/paralysed throughout (CO2 30-40 mmHg; MAP > 70, SBP 90-170; PaO2 100-150; glucose 100-200 mg/dL). No discussion about control group management. Similar causes of arrest (small numbers) and baseline characteristics except more witnessed collapse in control group. Survival to discharge (7/13 vs 5/15) and Glasgow Outcome score at discharge not significantly different (3/13 good vs 1/15). Primary outcome variable not reported (6 month GOS). Significantly more pneumonia in cooling group (11/13 vs 6/15, FE p = 0.024).

Zeiner A, Holzer M, Sterz F, et al. Mild resuscitative hypothermia to improve neurological outcome after cardiac arrest. A clinical feasibility trial. Hypothermia After Cardiac Arrest (HACA) Study Group. Stroke. 2000 Jan;31(1):86-94.

Level 4, fair, neutral. Safe and feasible.
Case series (pilot study) from Austria of 27 patients (April 95 - Jan 96) with out-of-hospital cardiac arrest. Consecutive cases (with multiplicity of exclusions; only 31 of 153 eligible, and 4 subsequently excluded): initial VF with , witnessed, non-traumatic, no-flow time 5-15 min, ROSC within 60 min, no subsequent prolonged hypotension or hypoxia before cooling, or malignancy/pregnancy/unfavorable CPC/OPC before, additional arrest within 6 months. Managed with standard protocols except for cooling (with blankets and cold air) on arrival in ED to 33±1°C (typanic then PA catheter) for 24 hours (then passive rewarming) with midazolam/fentanyl/pancuronium infusions. No complications (renal failure, sepsis, coagulopathy, neutropenia, thrombocytopaenia, frostbite). 6 month neurologic outcome Cerebral Performance Category of 1/2 (good) in 14/27, poor in 2/27,

and 11/27 died. Demonstrated safe and feasible. Passing reference to historic outcomes (2-fold improvement in outcome) but no true control group (ie. Level 4 not 3).

Zeiner A, Sunder-Plassmann G, Sterz F, et al. The effect of mild therapeutic hypothermia on renal function after cardiopulmonary resuscitation in men. Resuscitation 2004; 60: 253-61.

Level 1 study, fair, neutral, but used the patients from the HACA study.