Resuscitation Guidelines

Guidelines Development Process Manual

February 2012

Submitted by

Dr Jerry Nolan
Guidelines Project Group, Chairman

Approved February 2012 by

The Resuscitation Council (UK) Executive Committee

Table of contents

Document authors and reviewers

Process manual editors:

Dr Claire Lemer, Paediatric Registrar, Barnet and Chase Farm Hospitals NHS Trust, Enfield EN2 8JL

Sarah Mitchell, Director Resuscitation Council (UK), 5th Floor Tavistock House North, Tavistock Sq, London WC1H 9HR

Dr Jerry Nolan, Consultant in Anaesthesia and Intensive Care Medicine, Royal United Hospital Bath, Combe Park, Bath BA1 3NG

Dr Jasmeet Soar, Consultant in Anaesthesia and Intensive Care Medicine, Southmead Hospital, North Bristol NHS Trust, Bristol BS10 5NB

Members of Guidelines Project Group (GPG):

- Dr Robert Bingham, Consultant Paediatric Anaesthetist, Great Ormond St Hospital for Children NHS Trust, London WC1 3JH

- Dr Ian Bullock, Chief Operating Officer, National Clinical Guideline Centre, Royal College of Physicians, St Andrews place, Regents Park, London NW1 4LE

- Mr Robin Davies, Senior Resuscitation Officer, Heart of England NHS Foundation Trust, Birmingham B9 5SS

- Dr Anthony Handley, Honorary Consultant Physician, c/o Resuscitation Council (UK), Tavistock House North, Tavistock Sq, London WC1H 9HR

- Bob Harris, Data and Information Manager, Resuscitation Council (UK), Tavistock House North, Tavistock Sq, London WC1H 9HR

- Sara Harris, Assistant Director, Resuscitation Council (UK), Tavistock House North, Tavistock Sq, London WC1H 9HR

- Dr Andrew Lockey, Consultant Emergency Medicine, Calderdale and Huddersfield NHS Trust, Halifax, HX3 0PW

- Dr Ian Maconochie, Consultant Paediatric Emergency Medicine, St Mary's Hospital, London W2 1NY

- Ms Sarah Mitchell, Director Resuscitation Council (UK), Tavistock House North, Tavistock Sq, London WC1H 9HR

- Dr Jerry Nolan, (GPG Chairman), Consultant in Anaesthesia and Intensive Care Medicine, Royal United Hospital Bath, Combe Park, Bath BA1 3NG

- Professor Gavin Perkins, Critical Care and Resuscitation, University of Warwick, Warwick Medical School, CV4 7AL

- Dr Sam Richmond, Consultant Neonatologist, Sunderland District General Hospital, Sunderland, SR4 7TP

- Dr Jasmeet Soar, Consultant in Anaesthesia and Intensive Care Medicine, Southmead Hospital, North Bristol NHS Trust, Bristol BS10 5NB

Authors of RC(UK) guidelines:

- Dr Robert Bingham, Consultant Paediatric Anaesthetist, Great Ormond St Hospital for Children NHS Trust, London WC1 3JH

- Dr Michael Colquhoun, General Practitioner (retired), c/o Resuscitation Council (UK), Tavistock House North, Tavistock Sq, London WC1H 9HR

- Mr Robin Davies, Senior Resuscitation Officer, Heart of England NHS Foundation Trust, Birmingham B9 5SS

- Dr Charles Deakin, Consultant Anaesthetist, Southampton General Hospital, SO16 6YD

- Dr Anthony Handley, Honorary Consultant Physician, c/o Resuscitation Council (UK), Tavistock House North, Tavistock Sq, London WC1H 9HR

- Dr Fiona Jewkes, Clinical Author, NHS Pathways, RBDT Connecting for Health, Vantage House, 40 Aire Street, Leeds, LS1 4HT

- Dr Andrew Lockey, Consultant Emergency Medicine, Calderdale and Huddersfield NHS Trust, Halifax, HX3 0PW

- Dr Ian Maconochie, Consultant Paediatric Emergency Medicine, St Mary's Hospital, London W2 1NY

- Dr Jerry Nolan, (Editor), Consultant in Anaesthesia and Intensive Care Medicine, Royal United Hospital Bath, Combe Park, Bath BA1 3NG

- Professor Gavin Perkins, Critical Care and Resuscitation, University of Warwick, Warwick Medical School, CV4 7AL

- Dr Sam Richmond, Consultant Neonatologist, Sunderland District General Hospital, Sunderland, SR4 7TP

- Dr Jasmeet Soar, Consultant in Anaesthesia and Intensive Care Medicine, Southmead Hospital, North Bristol NHS Trust, Bristol BS10 5NB

- Dr David Pitcher, Consultant Cardiologist, Worcester Royal Hospital, Charles Hastings Way, Worcester,

- Sheila Simpson, Senior Resuscitation Officer, Great Ormond St Hospital for Children NHS Trust, London WC1 3JH

- Professor Gary Smith, Consultant in Anaesthesia and Intensive Care Medicine, c/o Resuscitation Council (UK), Tavistock House North, Tavistock Sq, London WC1H 9HR

- Dr Jonathan Wyllie, Neonatal Unit, James Cook University Hospital, Marton Road, Middlesbrough, TS4 3BW

Executive summary

This guidelines development process manual is written under the auspices of the Guidelines Project Group (GPG) set up by the Resuscitation Council (UK) (RC(UK)). It is intended to clarify and delineate the methods, principles, and processes used by the RC(UK) in the development of resuscitation guidelines 'Guidelines 2010' for use in the UK.[1] It outlines the technical work underpinning guideline development processes.

The GPG is a subgroup of the Executive Committee of the RC(UK).

Introduction

The RC(UK) has a long history in developing national guidelines in cardiopulmonary resuscitation (CPR), including basic life support (BLS), advanced life support (ALS), paediatric life support (PLS) and neonatal life support (NLS). The principle aim of these guidelines is to improve the quality of patient care and outcomes from cardiac arrest. The RC(UK) guidelines provide healthcare professionals and laypeople with evidencebased clinical pathways for all patient groups (adults, children, newborn) and all settings.

The scientific evidence supporting the RC(UK) guidelines is reviewed every 5 years (most recently in 2010). Interim updates may be considered if there is significant new scientific evidence supporting a change in practice (e.g., guidance on the use of therapeutic hypothermia in comatose survivors of cardiac arrest in 2002). The 5yearly consensus on CPR science comprises systematicreview and grading of all published resuscitation science by a large international group of experts that is coordinated by the International Liaison Committee on Resuscitation (ILCOR). This international systematic review comprises multiple evidence reviews of all topics relating to resuscitation, following QUOROM[2] principles and Cochrane methods. This leads to the production and publication of the ILCOR Consensus on Science with Treatment Recommendations (CoSTR), which is then translated into country specific recommendations.

The derivation of resuscitation guidelines from CoSTR follows a standard process. This manual specifies the methods used in the development of resuscitation guidelines for the UK.

Guidelines development

1. ILCOR establishes the scientific evidence base that underpins the guidance and creates treatment recommendations. The detailed process used by ILCOR is published in peer reviewed literature.[3]

   Approximately 3 years before the publication date of CoSTR, ILCOR convenes its science task forces (ALS, BLS, PLS, NLS, Acute Coronary Syndromes (ACS)), and Education, Implementation and Teams (EIT). Membership of these task forces is determined by identification of expertise in the related area. The task forces are responsible for generating the clinical questions for all the systematic reviews. They are helped in this process by national Resuscitation Councils from around the world, and other stakeholder groups. An example of a clinical question is "*In adult patients with ROSC* after cardiac arrest (prehospital or in-hospital) (P), does treatment with corticosteroids (I) as opposed to standard care (C), improve outcome (O) (e.g. survival)?*"

   Each question is formatted into a population, intervention, comparator and outcome (PICO) format and categorised as a therapeutic, diagnostic or prognostic question. The questions are allocated to worksheet (systematic review) authors by the relevant task forces, with two authors initially allocated to independently complete each systematic review. All potential reviewers complete a detailed conf ict of interest disclosure form and systematic review authors are screened and selected to avoid significant conflicts. Authors also list specific potential conf icts of interest on the individual systematic reviews, thus ensuring transparency of the review process.

   Worksheet authors submit the initial evidence search strategy electronically using a knowledge and content management webbased portal for initial review by one of the ILCOR task force chairs and one of four systematic review evidence evaluation experts (these individuals are experts in evidencebased medicine and are appointed by open competitive process). The evidence evaluation experts are payed by ILCOR for this work. The task force chairs and worksheet authors are not salaried. The search strategy is subsequently returned to the author with comments. The authors search multiple databases including the Cochrane database for systematic reviews and the Central Register of Controlled Trials[4], MEDLINE[5], EMBASE[6], CINAHL[7]and a master EndNote reference library collated by the American Heart Association (AHA). The search strategy used is included in each systematic review and freely available on the ILCOR website (www.ILCOR.org).

   Authors are asked to review the titles and abstracts of all articles identified by preliminary searches and quality assure and assess the relevance of the articles to the question being asked. Once this process is completed, the included original studies are retrieved for critical appraisal. Studies are included or excluded based on their relevance to the PICO question being addressed in the systematic review. If the worksheet author completing the review is unsure, he or she can ask the task force chair and/or evidence evaluation expert for advice. This results in a definitive evidence base that is then included for systematic review. Inclusion of all relevant evidence will ensure that animal and manikin/model studies as well as human studies are reviewed, unless substantive human data are available.

---

* Return of spontaneous circulation

A simplified list of five levels of evidence (LOE) is used to classify the studies. The LOEs reflect the likely absence of bias in clinical evidence. Systematic review authors are educated about the LOEs and instruction material is available on the Internet (www.ILCOR.org). **See Appendix 1 for a detailed description of the LOEs.**

Systematic review authors are also asked to comment on the sources of funding for the individual studies, identifying if there is potential for publication bias (e.g. industry sponsored studies).

All of the evidence identified and evaluated is displayed in standardised evidence tables. In each of three tables (supporting evidence, neutral evidence and opposing evidence) studies are displayed according to level of evidence, methodological quality and outcomes identified. The systematic review authors consider the internal and external validity of each included study, and then summarise the information reviewed. To facilitate interpretation of the results of the studies identified, the authors are asked to include the magnitude of any differences in the outcomes with an expression of their precision (i.e. 95% confidence interval) whenever possible.

After the two systematic review authors have independently assessed and graded the evidence they present their work to the relevant task force either facetoface or by webinar (webbased presentation). This enables the two authors to compare their searches and evidence grading and the authors and task force to reach consensus on a single systematic review of the science. Interpretation of this scientific evidence review allows the authors and task force to formulate draft CoSTR statements using standard formats. Within the treatment recommendations, authors are asked to consider the magnitude of the effect, the outcome affected, the generalisability from the specific population studied, and the potential barriers to implementation (including cost, education, logistics etc).

The recommended generic format for the science statement is:
"Evidence from X type of study in adults [insert study design and highest quality design] and Y additional studies [insert range of LOE] document consistent improvement in [insert relevant clinical outcome] when [insert treatment] is administered by [insert provider] to patients with [insert clinical condition] in the [insert prehospital, hospital, etc] setting. For example: *"There was little evidence to suggest a survival-to-discharge advantage with any antiarrhythmic drug used during resuscitation from out-of-hospital or in-hospital cardiac arrest. Two randomized trials demonstrated the benefit of amiodarone over standard of care, which included lidocaine in 80% of cases, or routine use of lidocaine for shock refractory or recurrent VT/VF for the endpoint of survival to hospital admission, but not to survival to hospital discharge. A retrospective review demonstrated improved survival to admission with lidocaine (compared with standard treatment) for patients in VF out of hospital (LOE 4)."*

The generic format for the treatment recommendation statement is: "therefore, administration of [therapy] for patients with [condition, setting by personnel] is recommended/should be considered." For example: *"Amiodarone may be considered for those who have refractory VT/VF, defined as VT/VF not terminated by defibrillation, or VT/VF recurrence in out-of-hospital cardiac arrest or in-hospital cardiac arrest. There is inadequate evidence to support or refute the use of lidocaine in the same settings."*

Each systematic review is submitted electronically and undergoes a rigorous iterative evaluation process. The layers of review before final acceptance of the systematic

review include the task force chair and task force, and the nominated evidence evaluation expert.

2. When the systematic review (the worksheet) is finalized, it is posted on the Internet for public comment[8] and stakeholder consultation – this includes industry and healthcare professionals. The RC(UK) ensures this information is widely disseminated to its members, instructors and stakeholders to maximise active engagement at every development stage. The science statements and treatment recommendations drafted by the systematic review authors are also iteratively reviewed by the relevant task force(s) and writing groups in facetoface meetings or by web conferences ('webinars'). This text is used to create the draft of the CoSTR document, which includes any relevant public and stakeholder comments. The text is then reviewed by the international councils and the editorial board that then creates the final manuscript. The final manuscript undergoes full peer review by 23 reviewers for each section. This peer review process is handled by the editorial staff of the journal Circulation.

3. Once CoSTR is created, it is disseminated to the five continents for context specific translation by a collaborative of National Resuscitation Councils. The European Resuscitation Council (ERC) uses these recommendations to develop the ERC guidelines. **See Appendix 2 for guidelines development process flowchart**. The ERC Guidelines are written by members of the ERC ALS, BLS, PLS and ACS Working Parties.

4. Some members of the RC(UK) Executive, Guidelines Project Group (GPG) and the RC(UK) guideline authors sit on the ILCOR and ERC processes to ensure a smooth evidence translation process and to ensure that the knowledge and experience of the RC(UK) plays an active role in these processes. **See Appendix 3 for RC(UK) members involved with ILCOR or ERC processes.**

5. Thus, the RC(UK) derives its guidelines by taking the ILCOR source statements that inform ERC guidelines and then translates this evidence base into treatment and practice recommendations that are relevant for UK clinical practice. Reasons for differences in guidelines between countries are mainly due to differing availability of certain drugs and also differences in how healthcare is delivered (e.g. doctor versus paramedic staffed ambulance services). Where there is lack of consensus the RC(UK) GPG uses a nominal group method for decisionmaking, i.e. the available treatment options are discussed and then ranked by the group. Conflicts between ILCOR and ERC guidance and that from UK bodies (e.g. NICE, NPSA) are avoided by ensuring any relevant UK guidance and the supporting evidence for it is included in the ILCOR guidelines process. The RC(UK) ensures its guidance is in accordance with NICE guidelines; furthermore the RC(UK) ensures it is a stakeholder for relevant NICE guidance so that its views are taken into account.

6. Simultaneously with the ILCOR and ERC processes the RC(UK) convenes the GPG. The RC(UK) GPG is a subgroup of the Executive and will convene at least 18 months before new guidelines are published. The Chairman will be chosen from the Executive Committee and should be involved in the ILCOR process. Members of the GPG are multidisciplinary and include:
   a. Chairmen of the subcommittees, (e.g. ALS, immediate life support (ILS), paediatric life support (EPLS and PILS), NLS, BLS)
   b. Executive members who contribute to the activities of ILCOR
   c. An educator
   d. A resuscitation officer
   e. Director of the Resuscitation Council and administrative staff
   f. Additional members, including lay representation, will be invited.

7. Patients' views are represented by the RC(UK) Patient Advisory Group. ILCOR processes actively encourage patient groups through stakeholder engagement, with opportunity to comment on systematic reviews and their clinical interpretation once posted on the Internet. For RC(UK) guidelines, patient/carer representation is achieved through lay representation on the GPG and RC(UK) Executive Committee. A subgroup of the Executive is responsible for supporting patient participation and reviewing the terms of reference supporting their involvement to ensure they have equity and a voice within RC(UK). UK Patient Groups will be alerted to the publication of the ILCOR consultation period to allow them the opportunity to feed into the process at an early stage, and the RC(UK) has established audit trails in addressing and responding to comments provided.

8. The purpose of the guidelines is to provide evidencebased interventions that are most likely to prevent cardiac arrest or increase the chances of successful resuscitation (with full neurological recovery). The guidelines cover major areas of relevance to resuscitation and prevention of the need for resuscitation. The guidelines are linked to supporting evidence and list relevant references. Integral to the interpretation of evidence and translation of this into national clinical guidelines is consideration of equality issues. **See Appendix 4 for the Equality Impact Assessment Tool used.**

9. The guidelines identify the strategy used to develop them in a transparent and open manner. Clear criteria for variation from the CoSTR are identified and the reasoning stated.

10. Where there is disagreement, the evidence is reviewed and discussed by the GPG until consensus is achieved. The RC(UK) GPG uses a nominal group method for decisionmaking, i.e. the available treatment options are discussed and then ranked by the group. This allows the views of all the members of the GPG to be taken into account. Where necessary external opinions are also sought. As existing guidelines are already in place, often the main issue for disagreement is whether there is a good enough reason to change guidance, especially where there are important implementation issues (e.g. additional cost of equipment, training needs etc).

11. As the guidelines will be used in emergencies, where efficient, timely action is critical, they should include clear, succinct recommendations with easily understood algorithms. Considerable care is taken to ensure that the guidelines are written plainly and unambiguously; this includes review by nonmedical individuals prior to publication. The implementation of the guidelines in support of new evidence benefits from multiple approaches. This can include updating training course curricula, manuals and other materials by RC(UK).

12. The final RC(UK) guidelines are peer reviewed by the Executive Committee, which comprises 24 individuals including lay individuals and representatives of key stakeholder groups.

13. The guidelines are freely accessible and disseminated widely. The cost and ease of implementation are considered in the guidelines process. For example, atropine, for which there is no supporting evidence, was removed from the guidelines in 2010.

14. The final RC(UK) Guidelines are published at the same time as the ILCOR Consensus on Science with Treatment Recommendations (CoSTR) and the ERC guidelines. The ILCOR CoSTR and ERC guidelines are published in the journal Resuscitation. The date of publication of the RC(UK) guidelines is recommended by the GPG and

approved by the Executive Committee. Instructors, members, and stakeholder organisations are then advised of the date.

15. ILCOR convenes to generate CoSTR on a fiveyearly cycle, and RC(UK) guidance runs in parallel with updates very 5 years. Unscheduled updates occur only if there is new evidence for an interim statement. This is usually when a study shows a significant treatment benefit or harm (e.g. the beneficial effects of therapeutic hypothermia were published in 2002 and ILCOR made an advisory statement in early 2003). This is assessed by the ILCOR task forces[9], and follows the same evidence evaluation and guideline process as for the 5yearly updates.

16. The final guidelines are posted on the RC(UK) website with free access. Within the document, where applicable, live links to relevant evidence, references or documents are provided. All RC(UK) instructors and members, and stakeholder organisations are notified by email, free iPhone app (iResus), and other means. The American and European guidelines are published in the journals Circulation and Resuscitation respectively and are also available free of charge.

17. Release of the guidelines also includes planned press releases to both the medical and lay press to ensure wide dissemination. Stakeholders are also provided with advance copies of the guidance to enable implementation on the release date.

Guidelines – content and structure

1. The format and example of how RC(UK) guidelines are presented is given in **Appendix 5**.

2. Content and structure:

   - Each guideline section is listed together with the authors from the GPG and lead editor(s).

   - The methodology and process used is described in detail. This includes the background, search strategy, systematic reviews and literature reviewed.

   - A description of how stakeholders, the public and others are able to view and comment on the ILCOR systematic reviews. An example of an ILCOR systematic review is given in **Appendix 6** (Hypothermia Worksheet).

   - The objectives of the guidelines including scope and purpose, target audience and target population are described.

   - Live links to supporting evidence or literature are provided where available.

   - Auditable outcome measures. The role of the National Cardiac Arrest Audit (NCAA) in measuring the effect of implementing the recommendations is delineated.

   - Statement of editorial independence **Appendix 7**.

   - Declaration of Conflict of Interest. All members of the RC(UK) committees and Project Groups are required to complete RC(UK) Conflict of Interest forms. The form is shown in **Appendix 8**.

- GPG members' affiliation and background is stated.

- Acknowledgements to those who have supported the GPG.

3. Clear and unambiguousness guidelines:

- Each section clearly identifies the clinical question being answered by the guideline, with the key recommendations highlighted.

- The certainty of the underlying evidence is clearly identified.

- Guideline recommendations demonstrate analysis and discussion of the health benefits, side effects and risks e.g. to survival or quality of life.

- The recommendations pertinent to prevention and treatment are clearly demarcated, with the most important recommendations easy to find and implement, including the use of algorithms.

4. Supporting materials. These tools are developed to support effective implementation of the guidelines and include:

- Posters

- Applications on iPhones and Androids

- Animations and DVDs – available on the website and on YouTube

- Course manuals and course teaching material, e.g. ALS, ILS, EPLS, NLS and PILS

- PowerPoint presentation of guideline changes on the website.

Summary

The GPG has developed this process manual to ensure that there is a high level of quality assurance, stakeholder engagement, and transparency on methods and processes used. Its purpose is to support and direct those who in the future are tasked with developing or updating resuscitation guidelines.

References

1   http://www.resus.org.uk/pages/guide.htm

2   Improving the quality of reports of metaanalyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Metaanalyses. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF.Lancet. 1999 Nov 27;354(9193):1896900 (http://www.ncbi.nlm.nih.gov/pubmed/10584742)

3   Morley PT, Atkins DL, Billi JE, et al. Part 3: Evidence evaluation process: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Resuscitation* 2010; 81 Suppl 1: e3240

4   http://www.cochrane.org/

5   http://www.ncbi.nlm.nih.gov/PubMed/

6   http://www.embase.com

7   http://www.cinahl.com

8   http://www.ilcor.org

9   http://www.ilcor.org/en/aboutilcor/taskforces/

Appendix 1

Levels of Evidence (LOE)

There are specific LOEs based on the likelihood for bias for therapeutic interventions, diagnostic questions and prognosis (see **Table 1** Levels of Evidence). The principles of allocation for studies related to therapeutic interventions are based on the likelihood of eliminating bias in the control group: true randomization (LOE 1), concurrent (LOE 2) versus historic (LOE 3) controls, absence of controls (LOE 4), or studies that are related to the systematic review question but that do not directly answer it (LOE 5). LOE 5 studies include studies in related populations (e.g. noncardiac arrest), animal studies, and bench and mathematical models. Systematic reviews and metaanalyses are considered in addition to the original studies. If they add information beyond that of the studies they include, they are allocated the same LOE as that of the studies included in the review (http://www.cebm.net/index.aspx?o=1025), otherwise they are allocated LOE 5. A list of quality factors is provided for each level of evidence (1 through 5, including systematic reviews) and for the different types of LOEs (intervention, diagnostic and prognostic). Three quality terms are defined on the basis of these lists: good, fair and poor. Studies are allocated 'good' if they have most or all of the relevant quality items, 'fair' if they have some of the relevant quality items, and 'poor' if they have only a few of the relevant quality items, but sufficient quality to include for further review (See **Table 2**: Quality factors for LOE 1, LOE P1 and LOE D1).

Table 1: Levels of Evidence

A. C2010 Levels of Evidence for Studies of Therapeutic Interventions
LOE 1: Randomised Controlled Trials (or metaanalyses of RCTs)
LOE 2: Studies using concurrent controls without true randomisation (e.g. "pseudo"randomised)
LOE 3: Studies using retrospective controls
LOE 4: Studies without a control group (e.g. case series)
LOE 5: Studies not directly related to the specific patient/population (e.g. different patient/population, animal models, mechanical models etc.)

B. C2010 Levels of Evidence for Prognostic Studies
LOE P1: Inception (prospective) cohort studies (or metaanalyses of inception cohort studies), or validation of Clinical Decision Rule (CDR)
LOE P2: Followup of untreated control groups in RCTs (or metaanalyses of followup studies), or derivation of CDR, or validated on splitsample only
LOE P3: Retrospective cohort studies
LOE P4: Case series
LOE P5: Studies not directly related to the specific patient/population (e.g. different patient/population, animal models, mechanical models etc.)

C. C2010 Levels of Evidence for Diagnostic Studies
LOE D1: Validating cohort studies (or metaanalyses of validating cohort studies), or validation of Clinical Decision Rule (CDR)
LOE D2: Exploratory cohort study (or metaanalyses of followup studies), or derivation of CDR, or a CDR validated on a splitsample only
LOE D3: Diagnostic case control study
LOE D4: Study of diagnostic yield (no reference standard)
LOE D5: Studies not directly related to the specific patient/population (e.g. different patient/population, animal models, mechanical models etc.)

Table 2: Quality factors for LOE 1, LOE P1, LOE D1

The seven factors that were included as the relevant quality items for RCTs (LOE 1) are:

- Was the assignment of patients to treatment randomized?

- Was the randomization list concealed?

- Were all patients who entered the trial accounted for at its conclusion?

- Were the patients analysed in the groups to which they were randomized?

- Were patients and clinicians "blinded" to which treatment was being received?

- Aside from the experimental treatment, were the groups treated equally?

- Were the groups similar at the start of the trial?

Good studies = have most/all of the relevant quality items. Fair studies = have some of the relevant quality items. Poor studies = have few of the relevant quality items (but sufficient value to include for further review).

The four factors that we have included as the relevant quality items for studies of LOE P1 (as well as P2, and P3) are:
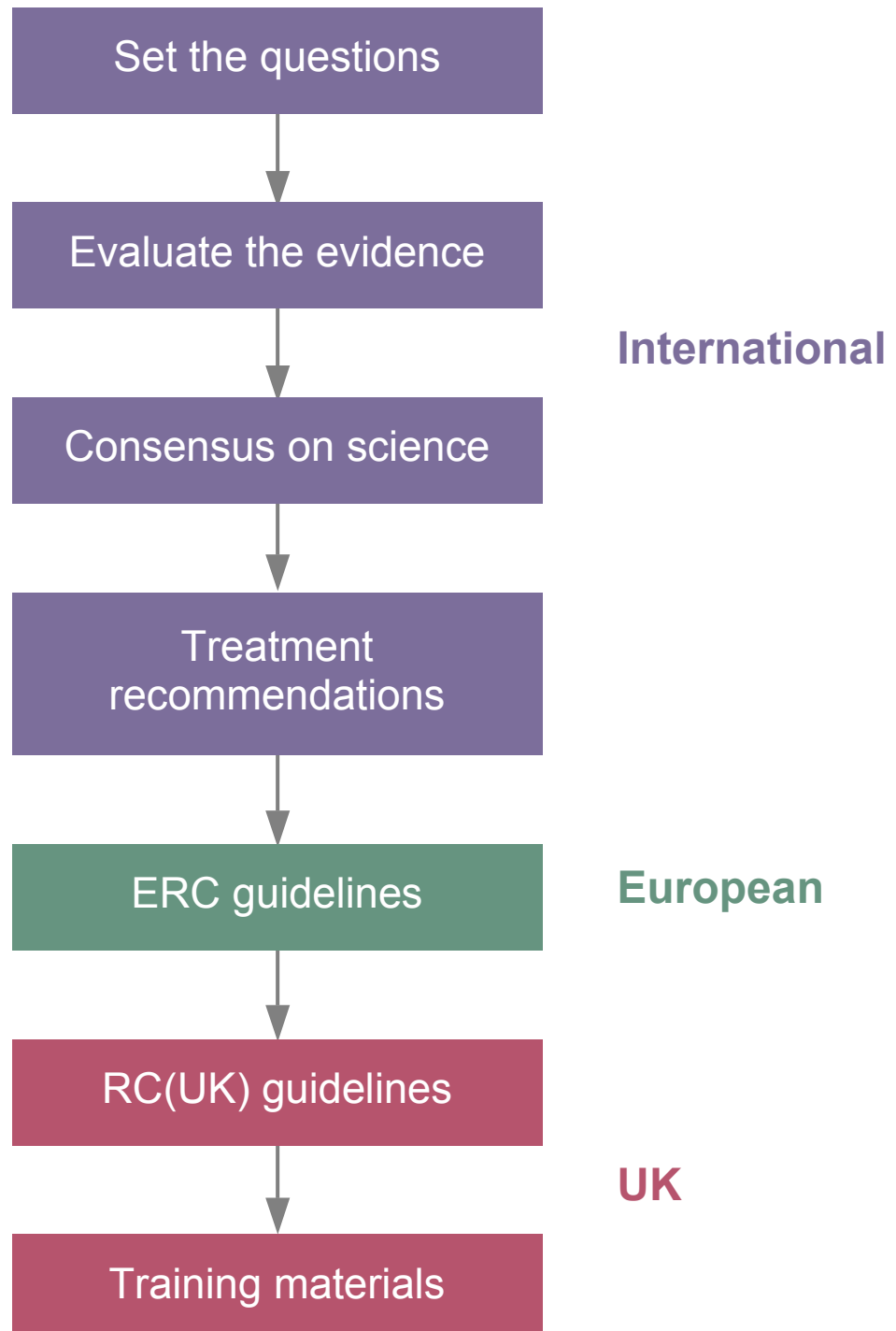
- Were comparison groups clearly defined?

- Were outcomes measured in the same (preferably blinded), objective way in both groups?

- Were known confounders identified and appropriately controlled for?

- Was followup of patients sufficiently long and complete (eg. >80%)?

For these studies it would be reasonable to consider the presence of all 4 factors = Good, only 3 factors = Fair, and only 2 factors = Poor. A study with only one would be considered of insufficient quality to include in the next step of the review.

The three factors that we have included as the relevant quality items for studies of LOE D1 (as well as D2, and D3) are:

- Was the diagnostic test evaluated in an appropriate spectrum of patients (eg. in those in whom it would be used in practice)? (Minimizing "spectrum bias")?

- Was there an independent, blind comparison with a reference ("gold") standard of diagnosis? (Minimizing "review bias")

- Was the reference standard applied regardless of the test result? (Minimizing "verification bias")

For these studies it would be reasonable to consider the presence of all 3 factors = Good, only 2 factors = Fair, and only 1 factor = either Poor or of insufficient quality to include in the next step of the review.

Appendix 2

Guideline development process

```
┌─────────────────────────────┐
│      Set the questions      │
└─────────────────────────────┘
                │
                ▼
┌─────────────────────────────┐
│     Evaluate the evidence   │          International
└─────────────────────────────┘
                │
                ▼
┌─────────────────────────────┐
│     Consensus on science    │
└─────────────────────────────┘
                │
                ▼
┌─────────────────────────────┐
│          Treatment          │
│       recommendations       │
└─────────────────────────────┘
                │
                ▼
┌─────────────────────────────┐
│        ERC guidelines       │          European
└─────────────────────────────┘
                │
                ▼
┌─────────────────────────────┐
│      RC(UK) guidelines      │
└─────────────────────────────┘          UK
                │
                ▼
┌─────────────────────────────┐
│      Training materials     │
└─────────────────────────────┘
```

Appendix 3

RC(UK) members involved with ILCOR or ERC processes

- Dr Robert Bingham, Consultant Paediatric Anaesthetist, Great Ormond St Hospital for Children NHS Trust, London WC1 3JH

- Dr Ian Bullock, Chief Operating Officer, National Clinical Guideline Centre, Royal College of Physicians, St Andrews place, Regents Park, London NW1 4LE

- Mr Robin Davies, Senior Resuscitation Officer, Heart of England NHS Foundation Trust, Birmingham B9 5SS

- Dr Charles Deakin, Consultant Anaesthetist, Southampton General Hospital, SO16 6YD

- Dr Anthony Handley, Honorary Consultant Physician, c/o Resuscitation Council (UK), Tavistock House North, Tavistock Sq, London WC1H 9HR

- Dr Andrew Lockey, Consultant Emergency Medicine, Calderdale and Huddersfield NHS Trust, Halifax, HX3 0PW

- Dr Ian Maconochie, Consultant Paediatric Emergency Medicine, St Mary's Hospital, London W2 1NY

- Dr Jerry Nolan, Consultant in Anaesthesia and Intensive Care Medicine, Royal United Hospital Bath, Combe Park, Bath BA1 3NG

- Professor Gavin Perkins, Critical Care and Resuscitation, University of Warwick, Warwick Medical School, CV4 7AL

- Dr Sam Richmond, Consultant Neonatologist, Sunderland District General Hospital, Sunderland, SR4 7TP

- Dr Rani Robson, Specialist Registrar in Cardiology, Bristol Heart Institute, Bristol

- Sheila Simpson, Senior Resuscitation Officer, Great Ormond St Hospital for Children NHS Trust, London WC1 3JH

- Dr Jasmeet Soar, Consultant in Anaesthesia and Intensive Care Medicine, Southmead Hospital, North Bristol NHS Trust, Bristol BS10 5NB

- Professor Gary Smith, Consultant in Anaesthesia and Intensive Care Medicine, c/o Resuscitation Council (UK), Tavistock House North, Tavistock Sq, London WC1H 9HR

- Dr Joyce Yeung, Specialist Registrar in Anaesthesia, Heart of England NHS Foundation Trust, Birmingham B9 5SS

- Dr Jonathan Wyllie, Neonatal Unit, James Cook University Hospital, Marton Road, Middlesbrough, TS4 3BW

Appendix 4

RC(UK) equality impact assessment tool

		Yes/No	Comments
1.	**Does the guidance affect one group less or more favourably than another on the basis of:**		
	• Race		
	• Ethnic origins (including gypsies and travellers)		
	• Nationality		
	• Gender		
	• Culture		
	• Religion or belief		
	• Sexual orientation including lesbian, gay and bisexual people		
	• Age		
	• Disability – learning disabilities, physical disability, sensory impairment and mental health problems		
2.	**Is there any evidence that some groups are affected differently?**		
3.	**If you have identified potential discrimination, are any exceptions valid, legal and/or justifiable?**		
4.	**Is the impact of the policy/guidance likely to be negative?**		
5.	**If so can the impact be avoided?**		
6.	**What alternatives are there to achieving the policy/guidance without the impact?**		
7.	**Can we reduce the impact by taking different action?**		

Appendix 5

Format of guidelines publication

Resuscitation Council (UK) guidelines

Title	Resuscitation Guidelines 2010
Date of publication	October 2010
Edited by	Jerry Nolan
ISBN	9781903812211
Foreword	The objectives of the Charity
Contents page and authors	Guidelines Project Group
Links to other websites / documents / references	
Introduction	An overview of the methodology
Summary of changes	A summary of the main changes for each section of the guidelines
Content for each section comprises: • **Introduction** • **Guideline changes** • **Algorithm** • **Sequence of actions** • **Background and additional information**	
References	
Conflict of interest declaration	

Appendix 6

Example of worksheet for ILCOR systematic review

The following is an example of a worksheet used during the systematic review of evidence relating to a clinical question. This particular example concerns the possible benefits of therapeutic hypotheremia following cardiac arrest. The length of this document (31 pages) reflects the amount of detail collected during the assembly and analysis of evidence.

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

Worksheet author(s)

Jerry Nolan, Peter Morley	Date Submitted for review: 10 Jan 2010

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

	1	2	3	4	5
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   C = Survival to hospital discharge   E = Other endpoint

B = Survival of event   D = Intact neurological survival   # = meta-analysis

* = overlapping patients

20

Evidence Neutral to Clinical question

	1	2	3	4	5
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   C = Survival to hospital discharge   E = Other endpoint

B = Survival of event   D = Intact neurological survival   (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   C = Survival to hospital discharge   E = Other endpoint
B = Survival of event   D = Intact neurological survival

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°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°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°C for 24 hours, and rewarming should be passive over at about $0.25°C \ h^{-1}$.

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).

Conclusion

CONSENSUS ON SCIENCE:
Who to cool?
Evidence from one good randomized trial (LOE 1) (HACA, 2002, 549) and a pseudo-randomised trial (LOE 2) (Bernard, 2002, 557) demonstrate improvement in neurological outcome after discharge from hospital in patients who had an out-of-hospital VF cardiac arrest, who were still comatose, and who were cooled within minutes to hours after return of spontaneous circulation to 32-34ºC for 12-24 hours. Two studies with historical control groups (LOE 3) showed improvement in neurological outcome after therapeutic hypothermia for comatose survivors of VF cardiac arrest (Belliard, 2007, 252; Castrejon, 2009, 733)

One small (n = 30) randomized trial (LOE 1) showed reduced plasma lactate values and oxygen extraction ratios in a group (n =16) of comatose survivors after cardiac arrest with asystole or PEA who were cooled with a cooling cap (Hachimi-Idrissi, 2001, 275).
Six studies with historical control groups (LOE 3) showed benefit after therapeutic hypothermia in comatose survivors of OHCA after all rhythm arrests (Bernard, 2007, 146; Oddo, 2006, 1865; Busch, 2006, 1277; Sunde, 2007, 29; Storm, 2008, R78; Don, 2009 3062). 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, 171). Two non-randomised studies with concurrent controls (Arrich, 2007, 1041; Holzer, 2006, 1792) indicate possible benefit of hypothermia following cardiac arrest from other initial rhythms in- and out-of-hospital.

How to cool?
Nine case series (LOE 4) indicate that cooling can be initiated safely with intravenous ice-cold fluids (30 ml/kg of saline 0.9% or Ringer's lactate) (Kliegel, 2005, 347; Kliegel 2007, 56; Bernard, 2003, 9; Virkkunen, 2004, 299; Kim, 2005, 715 ; Jacobshagen, 2009; Kilgannon, 2008; Spiel, 2009; Larsson, 2010;). Two randomised controlled trials (Kim, 2007, 3064; Kamarainen, 2009, 900), one study with concurrent controls (LOE 2: Hammer, 2009, 570) and three cases series (LOE 3) (Kamarainen, 2008, 360; Kamarainen, 2008, 205) indicate that cooling with IV cold saline can be initiated in the pre-hospital phase.

When to cool?
One case series (Level 4) (Wolff, 2009, 223) of comatose patients intravascularly cooled after out-of-hospital cardiac arrest indicates that the time to coldest temperature (TCT) is an independent predictor of good neurological outcome (OR for every hour TCT: 0.72 [95% CI 0.56 – 0.94])

Safe with PCI?

Three studies with historic controls (LOE 3) (Sunde, 2007, 29; Knafelj, 2007, 227; Wolfrum, 2008, 1780) and two case series (LOE 4) (Hovdenes, 2007, 137; Nielsen, 2009, 926) indicate that the combination of therapeutic hypothermia and primary percutaneous intervention is feasible and safe after cardiac arrest caused by acute myocardial infarction.

TREATMENT RECOMMENDATION:
Unconscious adult patients with spontaneous circulation after out-of-hospital VF cardiac arrest should be cooled to 32–34°C for at least 24 hours. Although the data support cooling to 32-34ºC, the optimal temperature has not been determined. Induced hypothermia might also benefit unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest from a non-shockable rhythm, or cardiac arrest in hospital. Although the optimal timing of initiation has not been defined clinically, it is reasonable to start cooling as soon as possible. The therapeutic window, or time after ROSC at which therapeutic hypothermia is no longer beneficial, has also not been clinically defined. Rapid infusion of ice-cold fluid 30 ml kg^{-1} is a very effective, simple method for initiating cooling.

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.
Background: Recent studies have proven the positive effect of mild hypothermia (32-34°C) on neurologic outcome in patients after cardiopulmonary resuscitation (CPR) due to ventricular fibrillation. Nevertheless, this method is generally not utilized. Here we report our initial experiences with the technical procedures, physiologic effects and complications involved with hypothermia through conduction and convection. Patients and Methods: The data of 20 hospitalized patients who received mild hypothermic therapy following cardiopulmonary resuscitation were retrospectively evaluated. Results: The target temperature of 33°C was attained in 19 of 20 patients within 2 to maximally 5.4 hours. Relevant fluctuation of the body temperature was observed. In two patients significant hyperkalemia (>6.0 mmol/l) occurred during the rewarming period and in one case the patient developed bradycardia, requiring acute therapeutic treatment. Conclusions: Controlled mild hypothermia is a method that can be performed well on a medical intensive care unit. However, intensive monitoring of patients, in particular with regard to potassium levels, is necessary. Based on our experience there is no reason why mild hypothermic therapy should not be used in patients with a proper medical indication, even in intensive care stations without any special cooling technique.
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.
Background: Cardiac arrest causes devastating neurological morbidity and mortality. Mild/moderate hypothermia is neuroprotective after global cerebral ischemia. More rapid controlled attainment of the target temperature may increase efficacy. Methods: We assessed the safety and feasibility of endovascular cooling in a single arm study of comatose patients who had been successfully resuscitated after cardiac arrest. Core temperature was reduced to a target of 33 degrees C for 24h using a closed loop endovascular system placed in the inferior vena cava, followed by controlled rewarming. Primary outcomes were speed and accuracy of cooling, survival and GOS after 30 days. Results: Thirteen patients were enrolled, six male, age [Formula: see text] years. Time from cardiac arrest to return of spontaneous circulation was 14.3min (range 5-32.5). It took 3h and 39min (median 210min, IQ 80-315) to reach 33 degrees C; cooling averaged [Formula: see text] degrees C/h (range 0.22-1.12 degrees C/h). Temperature was tightly maintained for all patients averaging [Formula: see text] degrees C. Rewarming lasted [Formula: see text] h. Five patients (38%) had 30-day Glasgow Outcome Scores of 1-2. Four patients died, none related to the hypothermia procedure. No unanticipated or procedure-related adverse events occurred. Conclusion: In comatose survivors of cardiac arrest, hypothermia via endovascular methods is safe and feasible, and target temperatures can be achieved and controlled rapidly and precisely. More studies are needed to assess the efficacy of rapid endovascular hypothermia after cardiac arrest.
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.
OBJECTIVE: Postresuscitative mild hypothermia lowers mortality, reduces neurologic impairment after cardiac arrest, and is recommended by the International Liaison Committee on Resuscitation. The European Resuscitation Council Hypothermia After Cardiac Arrest Registry was founded to monitor implementation of therapeutic hypothermia, to observe feasibility of adherence to the guidelines, and to document the effects of hypothermic treatment in terms of complications and outcome. DESIGN: Cardiac arrest protocols, according to Utstein style, with additional protocols on cooling and rewarming procedures and possible adverse events are documented. SETTING: Between March 2003 and June 2005, data on 650 patients from 19 sites within Europe were entered. PATIENTS: Patients who had cardiac arrest with successful restoration of spontaneous circulation were studied. MEASUREMENTS AND MAIN RESULTS: Of all patients, 462 (79%) received therapeutic hypothermia, 347 (59%) were cooled with an endovascular device, and 114 (19%) received other cooling methods such as ice packs, cooling blankets, and cold fluids. The median cooling rate was 1.1 degrees C per hour. Of all hypothermia patients, 15 (3%) had an episode of hemorrhage and 28 patients (6%) had at least one episode of arrhythmia within 7 days after cooling. There were no fatalities as a result of cooling. CONCLUSIONS: Therapeutic hypothermia is feasible and can be used safely and effectively outside a randomized clinical trial. The rate of adverse events was lower and the cooling rate was faster than in clinical trials published.
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.
Background

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

Objectives

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

Search strategy

We searched the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, 2007 Issue 1); MEDLINE (1971 to January 2007); EMBASE (1987 to January 2007); CINAHL (1988 to January 2007); PASCAL (2000 to January 2007); and BIOSIS (1989 to January 2007).

Selection criteria

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

Data collection and analysis

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

Main results

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

Authors' conclusions

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

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.

AIM OF THE STUDY: We investigated implementation and efficacy of mild therapeutic hypothermia in the treatment of out-of-hospital cardiac arrest due to ventricular fibrillation. MATERIALS AND METHODS: Two periods were compared, an historical one (36 patients) between 2000 and 2002 where therapeutic hypothermia was never used, and a recent period (32 patients) between 2003 and 2005 where therapeutic hypothermia (32-34 degrees C) was implemented prospectively in our unit. Cooling was obtained by simply using wet cloths and ice packs. Survival in the two groups and factors associated with survival were analysed, together with the neurological prognosis in discharged patients. RESULTS: Survival was significantly higher in the hypothermia group (56% versus 36%), whereas no significant difference was observed in severity between the two periods. Only age, time from return to spontaneous circulation <20min, and therapeutic hypothermia were independently associated with survival. Therapeutic hypothermia was well tolerated and was associated with a significant improvement in neurological outcome. Whereas only 23% of patients actually reached the target temperature in 2003, 100% did in 2005. CONCLUSION: Therapeutic hypothermia is efficient in significantly improving survival and neurological outcome of out-of-hospital cardiac arrest with ventricular fibrillation. By using a simple method, it can be implemented easily and quickly, without side effects.

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.
Study objective: To examine the effects of moderate hypothermia (33° C), induced by surface cooling in the ED and maintained for 12 hours in the ICU, on patients with anoxic brain injury after out-of-hospital cardiac arrest. **Methods:** We conducted the study in a teaching hospital in Melbourne, Victoria, Australia. Participants were 22 adults who remained unconscious after return of spontaneous circulation following out-of-hospital cardiac arrest. This treatment group was studied prospectively, and a control group of 22 similar patients was studied by retrospective chart review. Moderate hypothermia (33° C) was induced in the ED by means of surface cooling and maintained for 12 hours in the ICU with rewarming to normothermia over 6 hours; control patients were maintained at normothermia. **Results:** There were no significant adverse effects of induced hypothermia. Cardiovascular changes included decreased pulse rate, but there were no significant differences in mean arterial blood pressure between the two groups. Small increases in serum potassium and decreases in pH at 18 hours in the hypothermic patients compared with normothermic controls were of no clinical significance. There were no septic complications. There was a significant increase in the number of patients with good outcome (Glasgow Outcome Coma Scale category 1 or 2) with induced hypothermia (11 of 22, versus 3 of 22 for normothermic controls; *P*<.05), and the mortality rate was significantly lower (10 of 22 versus 17 of 22; *P*<.05). **Conclusion:** Compared with historical normothermic controls, outcome was significantly improved and there was no increase in complications when moderate hypothermia was induced in comatose survivors of out-of-hospital cardiac arrest and maintained for 12 hours. Larger, prospective, randomized, controlled studies of induced moderate hypothermia in comatose survivors of out-of-hospital cardiac arrest are warranted.
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.
BACKGROUND: Cardiac arrest outside the hospital is common and has a poor outcome. Studies in laboratory animals suggest that hypothermia induced shortly after the restoration of spontaneous circulation may improve neurologic outcome, but there have been no conclusive studies in humans. In a randomized, controlled trial, we compared the effects of moderate hypothermia and normothermia in patients who remained unconscious after resuscitation from out-of-hospital cardiac arrest. METHODS: The study subjects were 77 patients who were randomly assigned to treatment with hypothermia (with the core body temperature reduced to 33 degrees C within 2 hours after the return of spontaneous circulation and maintained at that temperature for 12 hours) or normothermia. The primary outcome measure was survival to hospital discharge with sufficiently good neurologic function to be discharged to home or to a rehabilitation facility. RESULTS: The demographic characteristics of the patients were similar in the hypothermia and normothermia groups. Twenty-one of the 43 patients treated with hypothermia (49 percent) survived and had a good outcome--that is, they were discharged home or to a rehabilitation facility--as compared with 9 of the 34 treated with normothermia (26 percent, P=0.046). After adjustment for base-line differences in age and time from collapse to the return of spontaneous circulation, the odds ratio for a good outcome with hypothermia as compared with normothermia was 5.25 (95 percent confidence interval, 1.47 to 18.76; P=0.011). Hypothermia was associated with a lower cardiac index, higher systemic vascular resistance, and hyperglycemia. There was no difference in the frequency of adverse events. CONCLUSIONS: Our preliminary observations suggest that treatment with moderate hypothermia appears to improve outcomes in patients with coma after resuscitation from out-of-hospital cardiac arrest.
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.
STUDY HYPOTHESIS: Recent studies have shown that induced hypothermia for twelve to twenty four hours improves outcome in patients who are resuscitated from out-of-hospital cardiac arrest. These studies used surface cooling, but this technique provided for relatively slow decreases in core temperature. Results from animal models suggest that further improvements in outcome may be possible if hypothermia is induced earlier after resuscitation from cardiac arrest. We hypothesized that a rapid infusion of large volume (30 ml/kg), ice-cold (4 degrees C) intravenous fluid would be a safe, rapid and inexpensive technique to induce mild hypothermia in comatose survivors of out-of-hospital cardiac arrest. METHODS: We enrolled 22 patients who were comatose following resuscitation from out-of-hospital cardiac arrest. After initial evaluation in the Emergency Department (ED), a large volume (30 ml/kg) of ice-cold (4 degrees C) lactated Ringers solution was infused intravenously over 30 min. Data on vital signs, arterial blood gas, electrolyte and hematological was collected immediately before and after the infusion. RESULTS: The rapid infusion of large volume, ice-cold crystalloid fluid resulted in a significant decrease in median core temperature from 35.5 to 33.8 degrees C. There were also significant improvements in mean arterial blood pressure, renal function and acid-base analysis. No patient developed pulmonary odema. CONCLUSION: A rapid infusion of large volume, ice-cold crystalloid fluid is an inexpensive and effective method of inducing mild hypothermia in comatose survivors of out-of-hospital cardiac arrest, and is associated with beneficial haemodynamic, renal and acid-base effects. Further studies of this technique are warranted.
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.
BACKGROUND: Patients who survive after suicidal hanging attempts suffer from transient brain ischaemia. Morbidity and mortality is high, and no specific therapy is available. Hypothermia attenuates ischaemic brain damage and has become standard care in comatose survivors of cardiac arrest; therapeutic hypothermia may thus be useful for near-hanging victims as well. OBJECTIVES: To perform a literature review on outcome and outcome predictors after near-hanging. To make a retrospective chart review on treatment and outcome of near-hanging victims in two Swedish intensive care units during a 4-year period (2003-2006). METHODS: The literature review was conducted as a Medline search. Study patients were identified and data retrieved from the intensive care units' medical records. The primary outcome measure was neurological function at discharge. RESULTS: No randomised, controlled trials were found in the Medline search. Thirteen patients could be identified and were included in the study, all were in coma and three had suffered cardiac arrest. Outcome was good in six of eight patients treated with hypothermia, as compared to three of five patients who were not. All three patients with cardiac arrest received hypothermia treatment and outcome was good in one. CONCLUSION: No randomised, controlled trial for treatment of near-hanging victims has been published. No conclusions could be drawn regarding treatment effects of hypothermia in this survey, but in the absence of better evidence, it seems reasonable to consider hypothermia treatment in all comatose near-hanging victims.
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.
AIMS: To assess the impact of therapeutic hypothermia on cognitive function and quality of life in comatose survivors of out of Hospital Cardiac arrest (OHCA). METHODS: We prospectively studied comatose survivors of OHCA consecutively admitted in a 4-year period. Therapeutic hypothermia was implemented in the last 2-year period, intervention period (n=79), and this group was compared to patients admitted the 2 previous years, control period (n=77). We assessed Cerebral Performance Category (CPC), survival, Mini Mental State Examination (MMSE) and self-rated quality of life (SF-36) 6 months after OHCA in the subgroup with VF/VT as initial rhythm. RESULTS: CPC in patients alive at hospital discharge was significantly better in the intervention period with a CPC of 1-2 in 97% vs. 71% in the control period, p=0.003, corresponding to an adjusted odds ratio of a favourable cerebral outcome of 17, p=0.01. No significant differences were found in long-term survival (57% vs. 56%

alive at 30 months), MMSE, or SF-36. Therapeutic hypothermia (hazard ratio: 0.15, p=0.007) and bystander CPR (hazard ratio 0.19, p=0.002) were significantly related to survival in the intervention period. CONCLUSION: CPC at discharge from hospital was significantly improved following implementation of therapeutic hypothermia in comatose patients resuscitated from OCHA with VF/VT. However, significant improvement in survival, cognitive status or quality of life could not be detected at long-term follow-up.

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.
BACKGROUND: The implementation of therapeutic hypothermia (TH) into daily clinical practice appears to be slow. We present our experiences with rapid implementation of a simple protocol for TH in comatose out-of-hospital cardiac arrest (OHCA) survivors. METHODS: From June 2002, we started cooling pre-hospitally with sport ice packs in the groin and over the neck. In the intensive care unit (ICU), we used ice-water soaked towels over the torso. All patients were endotracheally intubated, on mechanical ventilation and sedated and paralysed. The target temperature was 33 +/- 1 degrees C to be maintained for 12-24 h. We used simple inclusion criteria: (i) no response to verbal command during the ambulance transport independent of initial rhythm and cause of CA; (ii) age 18-80 years; and (iii) absence of cardiogenic shock (SBP < 90 mmHg despite vasopressors). We compared the first 27 comatose survivors with a presumed cardiac origin of their OHCA with 34 historic controls treated just before implementation. RESULTS: TH was initiated in all 27 eligible patients. The target temperature was reached in 24 patients (89% success rate). ICU- and hospital- length of stay did not differ significantly before and after implementation of TH. Hypokalemia (P= 0.001) and insulin resistance (P= 0.025) were more common and seizures (P= 0.01) less frequently reported with the use of TH. The implementation of TH was associated with a higher hospital survival rate (16/27; 59% vs. 11/34; 32%, respectively; P< or = 0.05). Our results indicate a population-based need of approximately seven cooling patients per 100,000 person-years served. CONCLUSION: Our simple, external cooling protocol can be implemented overnight in any system already treating post-resuscitation patients. It was well accepted, feasible and safe, but not optimal in terms of cooling rate. Neither safety concerns nor costs should be a barrier for implementation of TH.

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.
INTRODUCTION AND OBJECTIVES: Patients who survive a cardiac arrest have a poor short-term prognosis in terms of mortality and neurological function. The use of mild hypothermia has been investigated in only a few randomized studies, but appears to be effective for treating these patients. The aim of this study was to investigate the effect of this treatment on survival and neurological outcomes. METHODS: We compared mild hypothermia and usual treatment in patients who had experienced a prolonged cardiac arrest due to ventricular fibrillation or tachycardia and who showed signs of neurological damage. Patient were divided into two groups: a control group of 28 patients and a group of 41 patients who were treated with hypothermia. Patients were assessed at discharge and at 6 months. RESULTS: There was no significant difference between the two groups in baseline characteristics, including those of the cardiac arrest, or in the time to treatment. At discharge, neurological status was good in 18 patients (43.9%) in the hypothermia group but in only five (17.9%) in the control group (risk ratio=2.46; 95% confidence interval, 1.11-3.98; P=.029). At 6 months after discharge, neurological status was found to be good in 19 patients (46.3%) in the treatment group and six (21.4%) in the control group (risk ratio=2.16; 95% confidence interval, 1.05-3.36; P=.038). The effect of hypothermia may have been affected by various confounding factors. CONCLUSIONS: Our findings demonstrate that hypothermic treatment after cardiac arrest prolonged by ventricular fibrillation or tachycardia helps improve the prognosis of anoxic encephalopathy.

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.
OBJECTIVE: Several randomized controlled trials have suggested that mild induced hypothermia may improve neurologic outcome in comatose cardiac arrest survivors. This systematic review of randomized controlled trials was designed to determine if mild induced hypothermia improves neurologic outcome, decreases mortality, or is associated with an increased incidence of adverse events. DATA SOURCES: The following databases were reviewed: Cochrane Controlled Trials Register (Issue 4, 2005), MEDLINE (January 1966 to November 2005), EMBASE (1980 to November 2005), CINAHL (1982 to November 2005) and Web of Science (1989 to November 2005). For each included study, references were reviewed and the primary author contacted to identify any additional studies. STUDY SELECTION: Studies that met inclusion criteria were randomized controlled trials of adult patients (>18 years of age) with primary cardiac arrest who remained comatose after return of spontaneous circulation. Patients had to be randomized to mild induced hypothermia (32 degrees C-34 degrees

C) or normothermia within 24 hours of presentation. Only studies reporting pre-determined outcomes including discharge neurologic outcome, mortality or significant treatment-related adverse events were included. There were no language or publication restrictions. DATA SYNTHESIS: Four studies involving 436 patients, with 232 cooled to a core temperature of 32 degrees C-34 degrees C met inclusion criteria. Pooled data demonstrated that mild hypothermia decreased in-hospital mortality (relative ratio [RR] 0.75; 95% confidence interval [CI], 0.62-0.92) and reduced the incidence of poor neurologic outcome (RR 0.74; 95% CI, 0.62-0.84). Numbers needed to treat were 7 patients to save 1 life, and 5 patients to improve neurologic outcome. There was no evidence of treatment-limiting side effects. CONCLUSIONS: Therapeutically induced mild hypothermia decreases in-hospital mortality and improves neurologic outcome in comatose cardiac arrest survivors. The possibility of treatment-limiting side effects cannot be excluded.

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.

AIM OF THE STUDY: To analyse the neurological status of survivors after cardiac arrest (CA) treated with hypothermia. METHODS:
We prospectively included all patients with CA treated with hypothermia at intensive care units (ICU) in two university hospitals and one regional hospital. All adult survivors at 6 months after CA, n=48, were invited for neurological follow-up and 43 accepted. History, clinical status, ability testing and questionnaires were administered to screen for difficulties, including Assessment of Motor and Process Skills, Neurobehavioral Cognitive Status Examination, Frontal Lobe Assessment Battery, EQ-VAS quality of life scale, Skane Sleep Index, Hospital Anxiety and Depression Rating Scale, Self-reported Montgomery and Astrand Depression Rating Scale, Global Deterioration Scale, Rivermead Behavioural Memory Test, and the Cerebral Performance Categories (CPC). RESULTS: No patient was found to be in a chronic vegetative state and all patients were living at home, one with extensive help. Thirty-six patients were in CPC1 at follow-up, and some degree of neurological sequelae was found in 40 patients, but was mild in all but 3. Three patients had no subjective complaints, nor could any deficits be detected. Initial defects improved over-time. Short-term memory loss, executive frontal lobe dysfunction along with mild depression and sleep rhythm disturbances were the most common findings. CONCLUSIONS: Mild cognitive impairment is common following hypothermia-treated cardiac arrest but has little effect on activities of daily living or quality of life.

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.

BACKGROUND: Therapeutic hypothermia can improve survival after cardiopulmonary resuscitation (CPR). Coenzyme Q10 (CoQ10) has shown a protective effect in neurodegenerative disorders. We investigated whether combining mild hypothermia with CoQ10 after out-of-hospital cardiac arrest provides additional benefit. METHODS AND RESULTS: Forty-nine patients were randomly assigned to either hypothermia plus CoQ10 or hypothermia plus placebo after CPR. Hypothermia with a core temperature of 35 degrees C was instituted for 24 hours. Liquid CoQ10 250 mg followed by 150 mg TID for 5 days or placebo was administered through nasogastric tube. Age, sex, premorbidity, cause of arrest, conditions of CPR, and degree of hypoxia were similar in both groups; no side effects of CoQ10 were identified. Three-month survival in the CoQ10 group was 68% (17 of 25) and 29% (7 of 24) in the placebo group (P=0.0413). Nine CoQ10 patients versus 5 placebo patients survived with a Glasgow Outcome Scale of 4 or 5. Mean serum S100 protein 24 hours after CPR was significantly lower in the CoQ10 group (0.47 versus 3.5 ng/mL). CONCLUSIONS: Combining CoQ10 with mild hypothermia immediately after CPR appears to improve survival and may improve neurological outcome in survivors.

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°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.

INTRODUCTION: Knowledge about the influence of current neuroprotective interventions on prognostic markers after survival from cardiac arrest is lacking. This study aimed to investigate the effects of mild therapeutic hypothermia on the release of the astroglial protein S-100 after cardiopulmonary resuscitation (CPR) in survivors of out-of-hospital cardiac arrest. METHODS: This was a prospective, observational study performed during a two-year period, involving medical emergency services and five collaborating hospitals at the city of Aachen, Germany. Sixty-eight subjects were enrolled by the emergency physician on duty by taking blood samples after successful attempts at resuscitation with return of spontaneous circulation (ROSC), followed by samples at 6, 12, 24, 72 and 120 hours post ROSC by the appropriate intensive care unit staff. Depending on the decision of the attending physician, subjects were cooled down to 33 degrees C (n = 37) for 24 hours or were held at 37 degrees C (n = 31). Patients were tracked for estimating mortality and gross neurological outcome for 14 days. RESULTS: S-100 levels in patients not receiving mild therapeutic hypothermia (normothermia (NT)) showed equivalent numbers as compared with cooled patients (mild therapeutic hypothermia (MTH)) on baseline (NT = 1.38 mug/l versus MTH = 1.30 microg/l; P = 0.886). S-100 levels on baseline were significantly lower in patients with a good neurological outcome at 14 days after the event in comparison to their peers with adverse outcome (P = 0.014). Although the difference in S-100 levels of MTH

patients with adverse or favourable neurological outcome reached statistical significance, it did not in NT patients.
CONCLUSIONS: Although the predictive power of S-100 levels were best on admission but not at later time points, MTH had no influence on S-100 serum levels in survivors of non-traumatic out-of-hospital cardiac arrest in the particular setting of this investigation.
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.
BACKGROUND: Hypothermia therapy improves mortality and functional outcome after cardiac arrest and birth asphyxia in adults and newborns. The effect of hypothermia therapy in infants and children with cardiac arrest is unknown. METHODS AND RESULTS: A 2-year, retrospective, 5-center study was conducted, and 222 patients with cardiac arrest were identified. Seventy-nine (35.6%) of these patients met eligibility criteria for the study (age >40 weeks postconception and <18 years, cardiac arrest >3 minutes in duration, survival for > or = 12 hours after return of circulation, and no birth asphyxia). Twenty-nine (36.7%) of these 79 patients received hypothermia therapy and were cooled to 33.7+/-1.3 degrees C for 20.8+/-11.9 hours. Hypothermia therapy was associated with higher mortality (P=0.009), greater duration of cardiac arrest (P=0.005), more resuscitative interventions (P<0.001), higher postresuscitation lactate levels (P<0.001), and use of extracorporeal membrane oxygenation (P<0.001). When adjustment was made for duration of cardiac arrest, use of extracorporeal membrane oxygenation, and propensity scores by use of a logistic regression model, no statistically significant differences in mortality were found (P=0.502) between patients treated with hypothermia therapy and those treated with normothermia. Also, no differences in hypothermia-related adverse events were found between groups. CONCLUSIONS: Hypothermia therapy was used in resuscitation scenarios that are associated with greater risk of poor outcome. In an adjusted analysis, the effectiveness of hypothermia therapy was neither supported nor refuted. A randomized controlled trial is needed to rigorously evaluate the benefits and harms of hypothermia therapy after pediatric cardiac arrest.
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.
OBJECTIVE: To evaluate whether implementation of a therapeutic hypothermia protocol on arrival in a community hospital improved survival and neurologic outcomes in patients initially found to have ventricular fibrillation, pulseless electrical activity, or asystole, and then successfully resuscitated from out-of-hospital cardiac arrest. DESIGN: A retrospective study of patients who presented after implementation of a therapeutic hypothermia protocol compared with those who presented before the protocol was implemented. SETTING: Harborview Medical Center, Seattle, WA. PATIENTS: A total of 491 consecutive adults with out-of-hospital, nontraumatic cardiac arrest who presented between January 1, 2000 and December 31, 2004. INTERVENTIONS: An active cooling therapeutic hypothermia protocol, using ice packs, cooling blankets, or cooling pads to achieve a temperature of 32 degrees C to 34 degrees C was initiated on November 18, 2002 for unconscious patients resuscitated from cardiac arrest. MEASUREMENTS AND MAIN RESULTS: Demographics and outcomes were obtained from medical records and an emergency medical database. The primary outcomes were survival and favorable neurologic outcome at discharge associated with the therapeutic hypothermia protocol. An adjusted analysis was performed, using a multivariate regression. During the therapeutic hypothermia period, 204 patients were brought to the emergency department; of these 204 patients, 132 (65%) ultimately achieved temperatures of <34 degrees C. Of the 72 patients who did not achieve goal temperatures: 40 (20%) died in the emergency department or shortly after being admitted to the hospital, 15 (7%) regained consciousness, four (2%) had contraindications, 13 (6%) had temperature increase or did not have documented use of the therapeutic hypothermia protocol. In the prior period, none of the 287 patients received active cooling. Patients admitted in the therapeutic hypothermia period had a mean esophageal temperature of 34.1 degrees C during the first 12 hrs compared with 35.2 degrees C in the pretherapeutic hypothermia period (p < .01). Survival to hospital discharge improved in the therapeutic hypothermia period in patients with an initial rhythm of ventricular fibrillation (odds ratio, 1.88, 95% confidence interval, 1.03-3.45), however not in patients with nonventricular fibrillation (odds ratio, 1.17, 95% confidence interval, 0.66-2.05). In adjusted analysis, ventricular fibrillation patients during the therapeutic hypothermia period trended toward improved survival (odds ratio, 1.71, 95% confidence interval, 0.85-3.46) and had favorable neurologic outcome (odds ratio, 2.62, 95% confidence interval, 1.1-6.27) compared with the earlier period. This benefit was not observed in patients whose initial rhythm was pulseless electrical activity or asystole. CONCLUSIONS: The therapeutic hypothermia period was associated with a significant improvement in neurologic outcomes in patients whose initial rhythm was ventricular fibrillation, but not in patients with other rhythms.
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
BACKGROUND: No proven neuroprotective treatment exists for ischemic brain injury after cardiac arrest. Mild-to-moderate induced hypothermia (MIH) is effective in animal models. METHODS AND RESULTS: A safety and feasibility trial was designed to evaluate mild-to-moderate induced hypothermia by use of external cooling blankets after cardiac arrest. Inclusion

criteria were return of spontaneous circulation within 60 minutes of advanced cardiac life support, hypothermia initiated within 90 minutes, persistent coma, and lack of acute myocardial infarction or unstable dysrhythmia. Hypothermia to 33 degrees C was maintained for 24 hours followed by passive rewarming. Nine patients were prospectively enrolled. Mean time from advanced cardiac life support to return of spontaneous circulation was 11 minutes (range 3 to 30); advanced cardiac life support to initiation of hypothermia was 78 minutes (range 40 to 109); achieving 33 degrees C took 301 minutes (range 90 to 690). Three patients completely recovered, and 1 had partial neurological recovery. One patient developed unstable cardiac dysrhythmia. No other unexpected complications occurred. CONCLUSIONS: Mild-to-moderate induced hypothermia after cardiac arrest is feasible and safe. However, external cooling is slow and imprecise. Efforts to speed the start of cooling and to improve the cooling process are needed.

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.

Mild hypothermia following successful resuscitation from prehospital cardiac arrest has shown to improve patient's short-term neurological outcome. Usually, external methods are performed to achieve a core temperature of 32–34 °C. Recently, an endovascular cooling device has proven to be safe and feasible to induce mild hypothermia. Because of precise target temperature control in daily clinical routine, the endovascular method might lead to more favourable neurological outcomes than external cooling using cold packs. We retrospectively studied 39 patients after prehospital cardiac arrest from various causes, who were treated with mild hypothermia for 24 h either by an endovascular cooling device (group 1; n=19) or by an external method (group 2; n=20) using cold packs. Target temperature was 33°C in group 1 and 32-34 °C in group 2. The efficacy of the cooling procedure and patient's neurological outcome (classified by cerebral performance category CPC) at the time of hospital discharge were compared between both groups. Patient's baseline characteristics were comparable between both groups. During hypothermia, the target temperature was reached in all cases in group 1 but only in two cases in group 2(p<0.001). Mean core temperature was 32.9±0.1°C in group 1and 36.1±1.3°C in group 2 (p<0.001). At the time of hospital discharge, more patients in group1 had a good neurological outcome (group 1 vs group 2, 47.4% CPC 1/2 vs 20.0% CPC 1/2; p=0.08). In the subgroup of nondiabetic patients, this difference was even more pronounced (group 1 vs group 2, 63.6% CPC1/2 vs 23.1% CPC 1/2; p=0.007). Compared to an external method using cold packs, endovascular cooling can improve neurological short-term outcome after prehospital cardiac arrest, especially in non-diabetics. This effect results from better target temperature control in daily clinical routine.

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°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.

INTRODUCTION: Various methods are available to induce and maintain therapeutic hypothermia after cardiac arrest, but little data is available comparing device-mediated cooling to simple surface methods in this setting. METHODS: To assess the performance characteristics of simple surface cooling with or without an endovascular cooling catheter system, we retrospectively reviewed all cases of hypothermia for comatose survivors of cardiac arrest treated at a single academically affiliated urban hospital. Forty two comatose survivors of cardiac arrest were treated over a 3.5-year period. Hypothermia was induced and maintained by simple surface methods (ice packs, cooling blankets) with or without placement of an endovascular cooling catheter system with automated temperature feedback regulation. RESULTS: Overall, the rate of active cooling was not different between patients treated with endovascular catheter-assisted hypothermia and patients treated with surface cooling alone. However, use of a larger (14 F) catheter was associated with faster cooling rates. Maintenance of goal temperature (33 degrees C) was far better controlled with the use of a cooling catheter. Use of surface cooling alone was associated with significant temperature overshoot. Patients treated with surface cooling alone spent more time bradycardic. CONCLUSION: Use of an endovascular cooling catheter as part of a treatment protocol for hypothermia after cardiac arrest provides better control during maintenance of hypothermia, preventing temperature overshoot. Active cooling rates may be enhanced by the use of a larger cooling catheter.

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.

PURPOSE: Although animal studies document conflicting data on the influence of hypothermia on cytokine release in various settings, no data exist if hypothermia affects the inflammatory response after successful cardiopulmonary resuscitation.

33

MATERIALS AND METHODS: Arrest- and treatment-related variables of 71 patients were documented, and serum samples were analyzed for levels of interleukin 6, tumor necrosis factor-alpha, C-reactive protein, and procalcitonin immediately after hospital admission and after 6, 24, and 120 hours. At day 14, patients were dichotomized in those with good and bad neurological outcome. RESULTS: Regardless of outcomes, interleukin 6 levels were significantly elevated by the use of hypothermia (n = 39). The rate of bacterial colonization was significantly higher in hypothermic patients (64.1 vs 12.5 %; P < .001). On the contrary, procalcitonin levels were, independent of the use of hypothermia, only significantly elevated in patients with bad neurological outcome. Hypothermic patients showed a strong trend to reduced mortality. However, there was no influence on neurological recovery. CONCLUSIONS: In this observational study, hypothermia influenced the inflammatory response after cardiopulmonary resuscitation and lead to a higher rate of bacterial colonization without altering ultimate neurologic recovery.

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.
BACKGROUND: The objective of this study was to evaluate the impact of mild hypothermia (34-35 degrees C) on the final neurological outcome in patients after resuscitation from out-of-hospital cardiac arrest. METHODS: Forty three patients, admitted at University Hospital Brno after the out-of-hospital cardiac arrest, were included in the cohort study. The inclusion criteria were out-of-hospital cardiac arrest resulting from ventricular fibrillation or non-perfusing ventricular tachycardia as well as recovery of spontaneous circulation within 60 minutes after first symptoms. Blanketrol II (Cinncinnatti Sub Zero, USA) water mattresses were used for cooling the patients. The temperature was maintained at 34-35 degrees C for 24 hours. Favorable neurological outcome was defined as a Pittsburgh cerebral-performance category 1 (good recovery) or 2 (moderate disability) on five-category scale. RESULTS: The required temperature was reached in all patients; the cooling rate was 0.8 +/- 0.3 degrees C/hour. The time between the restoration of circulation and reaching the temperature of 35 degrees C was 119 +/- 32 minutes. The time induce the hypothermia (with the core body temperature below 35 degrees C) was 26 +/- 2 hours. Good outcome at hospital discharge was achieved in 21 out of 43 (49%) patients. Ten patients died in the hospital and two patients died after the discharge from the hospital, with the overall 6 months mortality being 28%. CONCLUSION: The study confirmed feasibility, safety and possible efficacy of the mild hypothermia (34-35 degrees C) patients after the cardiac arrest. To evaluate whether the target temperature 34-35 degrees C is as beneficial as 32-34 degrees C; a randomised controlled trial design should be used.
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.
BACKGROUND: Comatose survivors of out-of-hospital cardiac arrest (OHCA) have high in-hospital mortality due to a complex pathophysiology that includes cardiovascular dysfunction, inflammation, coagulopathy, brain injury and persistence of the precipitating pathology. Therapeutic hypothermia (TH) is the only intervention that has been shown to improve outcomes in this patient population. Due to the similarities between the post-cardiac arrest state and severe sepsis, it has been postulated that early goal-directed hemodyamic optimization (EGDHO) combined with TH would improve outcome of comatose cardiac arrest survivors. OBJECTIVE: We examined the feasibility of establishing an integrated post-cardiac arrest resuscitation (PCAR) algorithm combining TH and EGDHO within 6h of emergency department (ED) presentation. METHODS: In May, 2005 we began prospectively identifying comatose (Glasgow Motor Score<6) survivors of OHCA treated with our PCAR protocol. The PCAR patients were compared to matched historic controls from a cardiac arrest database maintained at our institution. RESULTS: Between May, 2005 and January, 2008, 18/20 (90%) eligible patients were enrolled in the PCAR protocol. They were compared to historic controls from 2001 to 2005, during which time 18 patients met inclusion criteria for the PCAR protocol. Mean time from initiation of TH to target temperature (33 degrees C) was 2.8h (range 0.8-23.2; SD=h); 78% (14/18) had interventions based upon EGDHO parameters; 72% (13/18) of patients achieved their EGDHO goals within 6h of return of spontaneous circulation (ROSC). Mortality for historic controls who qualified for the PCAR protocol was 78% (14/18); mortality for those treated with the PCAR protocol was 50% (9/18) (p=0.15). CONCLUSIONS: In patients with ROSC after OHCA, EGDHO and TH can be implemented simultaneously.
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)
Abstract: STUDY OBJECTIVE: To test the feasibility and the speed of a helmet device to achieve the target temperature of 34 degrees C in unconscious after out of hospital cardiac arrest (CA). METHODS: Patients with cardiac arrest due to asystole or pulseless electrical activity (PEA) who remained unconscious after restoration of spontaneous circulation (ROSC) were enrolled in the study and randomised into two groups: a normothermic group (NG) and a hypothermic group (HG). Bladder and tympanic temperature were monitored every 15 min. A helmet device was used to induce mild hypothermia in the HG. Later on, the effect of mild hypothermia on the haemodynamics, electrolytes, lactate, arterial pH, CaO2, CvO2 and O2 extraction ratio were analysed and compared to the values obtained from the NG. RESULTS: Thirty patients were eligible for the study, 16 were randomised into the HG and 14 were randomised into the NG. The median tympanic temperature at admission in both groups was 35.5 degrees C (range: 33.3-38.5 degrees C) and the median tympanic temperature after

34

haemodynamic stabilisation was 35.7 degrees C (range: 33.6-38.2 degrees C). In the HG, the core and the central target temperature of 34 degrees C were achieved after a median time of 180 and 60 min, respectively after ROSC. At the start of the study, no significant differences between the NG and HG were seen. At the end of the study, lactate concentration and O2 extraction ratio were significantly lower in the HG; however the CvO2 was significantly lower in the NG. CONCLUSIONS: Mild hypothermia induced by a helmet device was feasible, easy to perform, inexpensive and effective, with no increase in complications.

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.

Therapeutic hypothermia (TH) improves the outcomes of cardiac arrest (CA) survivors. The aim of this study was to evaluate retrospectively the efficacy and safety of an immediate prehospital cooling procedure implemented just after the return of spontaneous circulation with a prehospital setting. During 30 months, the case records of comatose survivors of out-of-hospital CA presumably due to a cardiac disease were studied. A routine protocol of immediate postresuscitation cooling had been tested by an emergency team, which consisted of an infusion of large-volume, ice-cold intravenous saline. We decided to assess the efficacy and tolerance of this procedure. A total of 99 patients were studied; 22 were treated with prehospital TH, and 77 consecutive patients treated with prehospital standard resuscitation served as controls. For all patients, TH was maintained for 12 to 24 hours. The demographic, clinical, and biological characteristics of the patients were similar in the 2 groups. The rate of patients with a body temperature of less than 35 degrees C upon admission was 41% in the cooling group and 18% in the control group. Rapid infusion of fluid was not associated with pulmonary edema. After 1 year of follow-up, 6 (27%) of 22 patients in the cooling group and 30 (39%) of 77 patients in the control group had a good outcome. Our preliminary observation suggests that in comatose survivors of CA, prehospital TH with infusion of large-volume, ice-cold intravenous saline is feasible and can be used safely by mobile emergency and intensive care units.

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.

AIM OF THE STUDY: There is sufficient evidence that therapeutic hypothermia after non-traumatic cardiac arrest improves neurological outcome and reduces mortality. Many different invasive and non-invasive cooling devices are currently available. Our purpose was to show the efficacy, safety and feasibility using a non-invasive cooling device to control patient temperature within a range of 33-37 degrees C. MATERIALS AND METHODS: A convenience sample of patients who have been resuscitated successfully from cardiac arrest and were intended for mild hypothermia therapy according to the guidelines and inclusion criteria were studied in a prospective observational case series at an emergency department of a tertiary care university hospital. The Medivance Arctic Sun System provides a new, non-invasive approach to reach a target temperature of 33 degrees C quickly, to maintain the target temperature for 24h, and then to actively re-warm at 0.4 degrees C/h to normothermia. Cooling was applied using the Arctic Sun in 27 patients. Data are presented as median and the interquartile range (25, 75%). RESULTS: Median age was 58 (49.5, 70) years. Time from cooling start to target temperature was 137 (96, 168)min, cooling rate was 1.2 degrees C/h (0.8, 1.5), stability of target temperature during hypothermia maintenance phase was satisfactory at 33.0 degrees C (32.9, 33.1), and duration of re-warming was 428 (394, 452)min. CONCLUSION: Using the Arctic Sun System in post-resuscitation care medicine for cooling cardiac arrest survivors is feasible and has proven to be highly effective in lowering patients' temperature rapidly without inducing skin irritations.

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.

Abstract: BACKGROUND: Cardiac arrest with widespread cerebral ischemia frequently leads to severe neurologic impairment. We studied whether mild systemic hypothermia increases the rate of neurologic recovery after resuscitation from cardiac arrest due to ventricular fibrillation. METHODS: In this multicenter trial with blinded assessment of the outcome, patients who had been resuscitated after cardiac arrest due to ventricular fibrillation were randomly assigned to undergo therapeutic hypothermia (target temperature, 32 degrees C to 34 degrees C, measured in the bladder) over a period of 24 hours or to receive standard treatment with normothermia. The primary end point was a favorable neurologic outcome within six months after cardiac arrest; secondary end points were mortality within six months and the rate of complications within seven days. RESULTS: Seventy-five of the 136 patients in the hypothermia group for whom data were available (55 percent) had a favorable neurologic outcome (cerebral-performance category, 1 [good recovery] or 2 [moderate disability]), as compared with 54 of 137 (39 percent) in the normothermia group (risk ratio, 1.40; 95 percent confidence interval, 1.08 to

1.81). Mortality at six months was 41 percent in the hypothermia group (56 of 137 patients died), as compared with 55 percent in the normothermia group (76 of 138 patients; risk ratio, 0.74; 95 percent confidence interval, 0.58 to 0.95). The complication rate did not differ significantly between the two groups. CONCLUSIONS: In patients who have been successfully resuscitated after cardiac arrest due to ventricular fibrillation, therapeutic mild hypothermia increased the rate of a favorable neurologic outcome and reduced mortality.

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.

CONTEXT: Hypothermia improves neurological outcome for comatose survivors of out-of-hospital cardiac arrest. Use of computer controlled high surface area devices for cooling may lead to faster cooling rates and potentially improve patient outcome. OBJECTIVE: To compare the effectiveness of surface cooling with the standard blankets and ice packs to the Arctic Sun, a mechanical device used for temperature management. DESIGN, SETTING, AND PATIENTS: Multi-center randomized trial of hemodynamically stable comatose survivors of out-of-hospital cardiac arrest. INTERVENTION: Standard post-resuscitative care inducing hypothermia using cooling blankets and ice (n=30) or the Arctic Sun (n=34). MAIN OUTCOME MEASURES: The primary end point was the proportion of subjects who reached a target temperature within 4h of beginning cooling. The secondary end points were time interval to achieve target temperature (34 degrees C) and survival to 3 months. RESULTS: The proportion of subjects cooled below the 34 degrees C target at 4h was 71% for the Arctic Sun group and 50% for the standard cooling group (p=0.12). The median time to target was 54min faster for cooled patients in the Arctic Sun group than the standard cooling group (p<0.01). Survival rates with good neurological outcome were similar; 46% of Arctic Sun patients and 38% of standard patients had a cerebral performance category of 1 or 2 at 30 days (p=0.6). CONCLUSIONS: While the proportion of subjects reaching target temperature within 4h was not significantly different, the Arctic Sun cooled patients to a temperature of 34 degrees C more rapidly than standard cooling blankets. TRIAL REGISTRATION: ClinicalTrials.gov NCT00282373, registered January 24, 2006.

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.

Our intensive care unit has been treating comatose patients, following an out-of-hospital cardiac arrest, with therapeutic hypothermia since 2002. In all, 139 out-of-hospital cardiac arrest patients were admitted in the 4-year period 2002-5. Of these, 27% had a favourable outcome (discharged home or to rehabilitation). Forty-one per cent of patients presenting with ventricular fibrillation (VF) and 7% of non-VF patients had a favourable outcome. No patient with an estimated time from collapse to first attempt at cardiopulmonary resuscitation over 12 min survived to hospital discharge. Twenty-two per cent of patients over 70 years were discharged home, suggesting age was not a barrier to surviving out-of-hospital cardiac arrest. The introduction of a therapeutic hypothermia clinical pathway, at the end of 2003 improved the efficiency of cooling. The percentage of patients cooled to below 34 degrees C within 4 h increased from 15 to 51% and those cooled for more than 12 h increased from 30 to 83%.

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.
ABSTRACT: BACKGROUND: Temperature management is used with increased frequency as a tool to mitigate neurological injury. Although frequently used, little is known about the optimal cooling methods for inducing and maintaining controlled normo- and hypothermia in the intensive care unit (ICU). In this study we compared the efficacy of several commercially available cooling devices for temperature management in ICU patients with various types of neurological injury. METHODS: Fifty adult ICU patients with an indication for controlled mild hypothermia or strict normothermia were prospectively enrolled. Ten patients in each group were assigned in consecutive order to conventional cooling (that is, rapid infusion of 30 ml/kg cold fluids, ice and/or coldpacks), cooling with water circulating blankets, air circulating blankets, water circulating gel-coated pads and an intravascular heat exchange system. In all patients the speed of cooling (expressed as degrees C/h) was measured. After the target temperature was reached, we measured the percentage of time the patient's temperature was 0.2 degrees C below or above the target range. Rates of temperature decline over time were analyzed with one-way analysis of variance. Differences between groups were analyzed with one-way analysis of variance, with Bonferroni correction for multiple comparisons. A $p < 0.05$ was considered statistically significant. RESULTS: Temperature decline was significantly higher with the water-circulating blankets (1.33 +/- 0.63 degrees C/h), gel-pads (1.04 +/- 0.14 degrees C/h) and intravascular cooling (1.46 +/- 0.42 degrees C/h) compared to conventional cooling (0.31 +/- 0.23 degrees C/h) and the air-circulating blankets (0.18 +/- 0.2 degrees C/h) ($p < 0.01$). After the target temperature was reached, the intravascular cooling device was 11.2 +/- 18.7% of the time out of range, which was significantly less compared to all other methods. CONCLUSION: Cooling with water-circulating blankets, gel-pads and intravascular cooling is more efficient compared to conventional cooling and air-circulating blankets. The intravascular cooling system is most reliable to maintain a stable temperature.
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.
OBJECTIVE: Only a few patients survive cardiac arrest with favorable neurologic recovery. Our objective was to assess whether induced hypothermia improves neurologic recovery in survivors of primary cardiac arrest. DATA SOURCE: Studies were identified by a computerized search of MEDLINE, EMBASE, CINAHL, PASCAL, the Cochrane Controlled Trial Register, and BIOSIS. STUDY SELECTION: We included randomized and quasi-randomized, controlled trials of adults who were successfully resuscitated, where therapeutic hypothermia was applied within 6 hrs after arrival at the emergency department and where the neurologic outcome was compared. We excluded studies without a control group and studies with historical controls. DATA EXTRACTION: All authors of the identified trials supplied individual patient data with a predefined set of variables. DATA SYNTHESIS: We identified three randomized trials. The analyses were conducted according to the intention-to-treat principle. Summary odds ratios were calculated using a random effects model and translated into risk ratios. More patients in the hypothermia group were discharged with favorable neurologic recovery (risk ratio, 1.68; 95% confidence interval, 1.29-2.07). The 95% confidence interval of the number-needed-to-treat to allow one additional patient to leave the hospital with favorable neurologic recovery was 4-13. One study followed patients to 6 months or death. Being alive at 6 months with favorable functional neurologic recovery was more likely in the hypothermia group (risk ratio, 1.44; 95% confidence interval, 1.11-1.76). CONCLUSIONS: Mild therapeutic hypothermia improves short-term neurologic recovery and survival in patients resuscitated from cardiac arrest of presumed cardiac origin. Its long-term effectiveness and feasibility at an organizational level need further research.
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.
BACKGROUND AND PURPOSE: Recently 2 randomized trials in comatose survivors of cardiac arrest documented that therapeutic hypothermia improved neurological recovery. The narrow inclusion criteria resulted in an international recommendation to cool only a restricted group of primary cardiac arrest survivors. In this retrospective cohort study we investigated the efficacy and safety of endovascular cooling in unselected survivors of cardiac arrest. METHODS: Consecutive comatose survivors of cardiac arrest, who were either cooled for 24 hours to 33 degrees C with endovascular cooling or treated with standard postresuscitation therapy, were analyzed. Complication data were obtained by retrospective chart review. RESULTS: Patients in the endovascular cooling group had 2-fold increased odds of survival (67/97 patients versus 466/941 patients; odds ratio 2.28, 95% CI, 1.45 to 3.57; P<0.001). After adjustment for baseline imbalances the odds ratio was 1.96 (95% CI, 1.19 to 3.23; P=0.008). When discounting the observational data in a Bayesian analysis by using a sceptical prior the posterior odds ratio was 1.61 (95% confidence interval, 1.06 to 2.44). In the endovascular cooling group, 51/97 patients (53%) survived with favorable neurology as compared with 320/941 (34%) in the control group (odds ratio 2.15, 95% CI, 1.38 to 3.35; P=0.0003; adjusted odds ratio 2.56, 1.57 to 4.17). There was no difference in the rate of complications except for bradycardia. CONCLUSIONS: Endovascular cooling improved survival and short-term neurological recovery compared with standard treatment in comatose adult survivors of cardiac arrest. Temperature control was effective and safe with this device.

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.
BACKGROUND: Therapeutic hypothermia has been shown to increase survival after out-of-hospital cardiac arrest (OHCA). The trials documenting such benefit excluded patients with cardiogenic shock and only a few patients were treated with percutaneous coronary intervention prior to admission to an intensive care unit (ICU). We use therapeutic hypothermia whenever cardiac arrest patients do not wake up immediately after return of spontaneous circulation. METHODS: This paper reports the outcome of 50 OHCA patients with ventricular fibrillation admitted to a tertiary referral hospital for immediate coronary angiography and percutaneous coronary intervention when indicated. Patients were treated with intra-aortic balloon counterpulsation (IABP) (23 of 50 patients) if indicated. All patients who were still comatose were treated with therapeutic hypothermia at 32-34 degrees C for 24 h before rewarming. The end-points were survival and cerebral performance category (CPC: 1, best; 5, dead) after 6 months. RESULTS: Forty-one patients (82%) survived until 6 months. Thirty-four patients (68%) were in CPC 1 or 2, and seven (14%) were in CPC 3. Of the 23 patients treated with IABP, 14 (61%) survived with CPC 1 or 2. In patients not treated with IABP, 20 patients (74%) survived with CPC 1 or 2. Forty patients (80%) developed myocardial infarction. Percutaneous coronary intervention was performed in 36 patients (72%). CONCLUSION: In OHCA survivors who reached our hospital, the survival rate was high and the neurological outcome acceptable. Our results indicate that the use of therapeutic hypothermia is justified even in haemodynamically unstable patients and those treated with percutaneous coronary intervention.
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.
International guidelines for cardiopulmonary resuscitation recommend mild hypothermia (32-34 degrees C) for 12-24h in comatose survivors of cardiac arrest. To induce therapeutic hypothermia a variety of external and intravascular cooling devices are available. A cheap and effective method for inducing hypothermia is the infusion of large volume, ice-cold intravenous fluid. There are concerns regarding the effects of rapid infusion of large volumes of fluid on respiratory function in cardiac arrest survivors. We have retrospectively studied the effects of high volume cold fluid infusion on respiratory function in 52 resuscitated cardiac arrest patients. The target temperature of 32-34 degrees C was achieved after 4.1+/-0.5h (cooling rate 0.48 degrees C/h). During this period 3427+/-210 mL ice-cold fluid was infused. Despite significantly reduced LV-function (EF 35.8+/-2.2%) the respiratory status of these patients did not deteriorate significantly. On intensive care unit admission the mean PaO_2 was 231.4+/-20.6 mmHg at a F_iO_2 of 0.82+/-0.03 (PaO_2/F_iO_2=290.0+/-24.1) and a PEEP level of 7.14+/-0.31 mbar. Until reaching the target temperature of <or=34 degrees C the F_iO_2 could be significantly reduced to 0.63+/-0.03 with unchanged PEEP level (7.23+/-0.36 mbar). Under these conditions the PaO_2/F_iO_2 ratio slightly decreased to 247.5+/-18.5 (P=0.0893). Continuing the saline infusion to achieve a body temperature of 33 degrees C, the F_iO_2 could be further reduced with unchanged PEEP. The infusion of large volume, ice-cold fluid is an effective and inexpensive method for inducing therapeutic hypothermia. Resuscitation from cardiac arrest is associated with a deterioration in respiratory function. The infusion of large volumes of cold fluid does not cause a statistically significant further deterioration in respiratory function. A larger, randomized and prospective study is required to assess the efficacy and safety of ice-cold fluid infusion for the induction of therapeutic hypothermia.
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.
INTRODUCTION: Patients after out-of-hospital cardiac arrest (OHCA) benefit from therapeutic hypothermia for 24 hours. The time needed to reach hypothermia (target temperature of 32 degrees C to 34 degrees C) varies widely. In this study, we explore the relation between measures of body composition and the time needed to reach target temperature with hypothermia. METHOD: We conducted a prospective observational study in patients treated with hypothermia after OHCA. Data collected included weight and height, body composition by anthropometric measures and by single-frequency body impedance, and waist-to-hip ratio. Analysis of concordance between impedance and anthropometric measures and hazard ratios of achieving target temperature (event) corrected for different body composition measures. RESULTS: Twenty-seven patients were included. The median (interquartile range) time to reach target temperature after admission to the intensive care unit was 191 (105 to 382) minutes. Intraclass correlation for total body fat (TBF) measures was 0.94 (95% confidence interval [CI] 0.89 to 0.97). Only TBF percentage (anthropometrics by the Durnin's table) appeared to be associated with time to reach target temperature: 0.93 (95% CI 0.87 to 0.99; P = 0.03). CONCLUSION: The body composition measures from single-frequency impedance and anthropometrics appear to be very concordant. Only TBF percentage (anthropometrics) showed a significant but clinically irrelevant influence on time needed to achieve target temperature with hypothermia. We conclude that there are no indications to adjust current cooling practice toward the body composition of patients.
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.
AIM OF THE STUDY: We studied induction of therapeutic hypothermia during prehospital resuscitation from cardiac arrest using an infusion of ice-cold Ringer's solution in five adult patients. MATERIAL AND METHODS: Paramedics infused +4 degrees C Ringer's solution into the antecubital vein of the patients with a maximum rate of 33 ml/min to a target temperature of 33.0 degrees C. RESULTS: The mean infused volume of cold fluid was 14.0 ml/kg, which resulted in a mean decrease of 2.5 degrees C in nasopharyngeal temperature. The decrease in temperature continued after the cessation of infusion in two patients, causing suboptimal temperatures below 32 degrees C. CONCLUSION: We conclude that the infusion of small volumes of ice-cold Ringer's solution during resuscitation results in an effective decrease in nasopharyngeal temperature. Caution should be taken to avoid temperatures below the range of mild therapeutic hypothermia.
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.
AIM OF THE STUDY: Primarily, to investigate induction of therapeutic hypothermia during prehospital cardiopulmonary resuscitation (CPR) using ice-cold intravenous fluids. Effects on return of spontaneous circulation (ROSC), rate of rearrest, temperature and haemodynamics were assessed. Additionally, the outcome was followed until discharge from hospital. MATERIALS AND METHODS: Seventeen adult prehospital patients without obvious external causes for cardiac arrest were included. During CPR and after ROSC, paramedics infused +4 degrees C Ringer's acetate aiming at a target temperature of 33 degrees C. RESULTS: ROSC was achieved in 13 patients, 11 of whom were admitted to hospital. Their mean initial nasopharyngeal temperature was 35.17+/-0.57 degrees C (95% CI), and their temperature on hospital admission was 33.83+/-0.77 degrees C (-1.34 degrees C, p<0.001). The mean infused volume of cold fluid was 1571+/-517 ml. The rate of rearrest after ROSC was not increased compared to previous reports. Hypotension was observed in five patients. Of the 17 patients, 1 survived to hospital discharge. CONCLUSION: Induction of therapeutic hypothermia during prehospital CPR and after ROSC using ice-cold Ringer's solution effectively decreased nasopharyngeal temperature. The treatment was easily carried out and well tolerated.
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.
BACKGROUND: Intravenous infusion of ice-cold fluid is considered a feasible method to induce mild therapeutic hypothermia in cardiac arrest survivors. However, only one randomized controlled trial evaluating this treatment exists. Furthermore, the implementation rate of prehospital cooling is low. The aim of this study was to evaluate the efficacy and safety of this method in comparison with conventional therapy with spontaneous cooling often observed in prehospital patients. METHODS: A randomized controlled trial was conducted in a physician-staffed helicopter emergency medical service. After successful initial resuscitation, patients were randomized to receive either +4 degrees C Ringer's solution with a target temperature of 33 degrees C or conventional fluid therapy. As an endpoint, nasopharyngeal temperature was recorded at the time of hospital admission. RESULTS: Out of 44 screened patients, 19 were analysed in the treatment group and 18 in the control group. The two groups were comparable in terms of baseline characteristics. The core temperature was markedly lower in the hypothermia group at the time of hospital admission (34.1+/-0.9 degrees C vs. 35.2+/-0.8 degrees C, P<0.001) after a comparable duration of transportation. Otherwise, there were no significant differences between the groups regarding safety or secondary outcome measures such as neurological outcome and mortality. CONCLUSION: Spontaneous cooling alone is insufficient to induce therapeutic hypothermia before hospital admission. Infusion of ice-cold fluid after return of spontaneous circulation was found to be well tolerated and effective. This method of cooling should be considered as an important first link in the 'cold chain' of prehospital comatose cardiac arrest survivors.
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.
OBJECTIVES: Induced hypothermia (HT) after cardiac arrest improved outcomes in randomized trials. Current post-cardiac arrest treatment guidelines advocate HT; however, utilization in practice remains low. One reported barrier to adoption is clinician concern over potential technical difficulty of HT. We hypothesized that using a standardized order set, clinicians could achieve HT target temperature in routine practice with equal or better efficiency than that observed in randomized trials. METHODS: After a multidisciplinary HT education program, we implemented a standardized order set for HT induction and maintenance including sedation and paralysis, intravenous cold saline infusion, and an external cooling apparatus, with a target temperature range of 33-34 degrees C. We performed a retrospective analysis of a prospectively compiled and maintained registry of cardiac arrest patients with HT attempted (intent-to-treat) over the first year of implementation. The primary outcome measures were defined a priori by extrapolating treatment arm data from the largest and most efficacious randomized trial: 1) successful achievement of target temperature for >or=85% of patients in the cohort and 2) median time from return of spontaneous circulation (ROSC) to achieving target temperature <8 hours. RESULTS: Clinicians attempted HT on 23 post-cardiac arrest patients (arrest location: 78% out-of-hospital, 22% in-hospital; initial

39

rhythm: 26% ventricular fibrillation/tachycardia, 70% pulseless electrical activity or asystole) and achieved the target temperature in 22/23 (96%) cases. Median time from ROSC to target temperature was 4.4 (interquartile range 2.8-7.2) hours. Complication rates were low. CONCLUSIONS: Using a standardized order set, clinicians can achieve HT target temperature in routine practice.

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.
BACKGROUND: Recent clinical studies have demonstrated that mild hypothermia (32 degrees C to 34 degrees C) induced by surface cooling improves neurological outcome after resuscitation from out-of-hospital cardiac arrest. Results from animal models suggest that the effectiveness of mild hypothermia could be improved if initiated as soon as possible after return of spontaneous circulation. Infusion of cold, intravenous fluid has been proposed as a safe, effective, and inexpensive technique to induce mild hypothermia after cardiac arrest. METHODS AND RESULTS: In 17 hospitalized survivors of out-of-hospital cardiac arrest, we determined the effect on temperature and hemodynamics of infusing 2 L of 4 degrees C cold, normal saline during 20 to 30 minutes into a peripheral vein with a high-pressure bag. Data on vital signs, electrolytes, arterial blood gases, and coagulation were collected before and after fluid infusion. Cardiac function was assessed by transthoracic echocardiography before fluid administration and 1 hour after infusion. Passive (fans, leaving patient uncovered) or active (cooling blankets, neuromuscular blockade) cooling measures were used to maintain mild hypothermia for 24 hours. Infusion of 2 L of 4 degrees C cold, normal saline resulted in a mean temperature drop of 1.4 degrees C 30 minutes after the initiation of infusion. Rapid infusion of fluid was not associated with clinically important changes in vital signs, electrolytes, arterial blood gases, or coagulation parameters. The initial mean ejection fraction was 34%, and fluid infusion did not affect ejection fraction or increase central venous pressure, pulmonary pressures, or left atrial filling pressures as assessed by echocardiography. Passive measures were ineffective in maintaining hypothermia compared with active measures. CONCLUSIONS: Infusion of 2 L of 4 degrees C cold, normal saline is safe and effective in rapidly lowering body temperature in survivors of out-of-hospital cardiac arrest.

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.
BACKGROUND: Although delayed hospital cooling has been demonstrated to improve outcome after cardiac arrest, in-field cooling started immediately after the return of spontaneous circulation may be more beneficial. The aims of the present pilot study were to assess the feasibility, safety, and effectiveness of in-field cooling. METHODS AND RESULTS: We determined the effect on esophageal temperature, before hospital arrival, of infusing up to 2 L of 4 degrees C normal saline as soon as possible after resuscitation from out-of-hospital cardiac arrest. A total of 125 such patients were randomized to receive standard care with or without intravenous cooling. Of the 63 patients randomized to cooling, 49 (78%) received an infusion of 500 to 2000 mL of 4 degrees C normal saline before hospital arrival. These 63 patients experienced a mean temperature decrease of 1.24+/-1 degrees C with a hospital arrival temperature of 34.7 degrees C, whereas the 62 patients not randomized to cooling experienced a mean temperature increase of 0.10+/-0.94 degrees C (P<0.0001) with a hospital arrival temperature of 35.7 degrees C. In-field cooling was not associated with adverse consequences in terms of blood pressure, heart rate, arterial oxygenation, evidence for pulmonary edema on initial chest x-ray, or rearrest. Secondary end points of awakening and discharged alive from hospital trended toward improvement in ventricular fibrillation patients randomized to in-field cooling. CONCLUSIONS: These pilot data suggest that infusion of up to 2 L of 4 degrees C normal saline in the field is feasible, safe, and effective in lowering temperature. We propose that the effect of this cooling method on neurological outcome after cardiac arrest be studied in larger numbers of patients, especially those whose initial rhythm is ventricular fibrillation.

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.
OBJECTIVE: Mild therapeutic hypothermia has shown to improve neurological outcome after cardiac arrest. Our study investigated the efficacy and safety of cold simple intravenous infusions for induction of hypothermia after cardiac arrest preceding further cooling and maintenance of hypothermia by specialised endovascular cooling. METHODS: All patients admitted after cardiac arrest of presumed cardiac aetiology were screened. Patients enrolled received 2000 ml of ice-cold (4 degrees C) fluids via peripheral venous catheters. As soon as possible endovascular cooling was applied even if the cold infusions were not completed. The target temperature was defined as 33 +/- 1 degrees C. All temperatures recorded were measured via bladder-temperature probes. The primary endpoint was the time from return of spontaneous circulation to reaching the target temperature. Secondary endpoints were changes in haemodynamic variables, oxygenation, haemoglobin,

clotting variables and neurological outcome. RESULTS: Out of 167 screened patients 26 (15%) were included. With a total amount of 24 +/- 7 ml/kg cold fluid at 4 degrees C the temperature could be lowered from 35.6 +/- 1.3 degrees C on admission to 33.8 +/- 1.1 degrees C. The target temperature was reached 185 +/- 119 min after return of spontaneous circulation, 135 +/- 112 min after start of infusion, and 83 +/- 85 min after start of endovascular cooling. Except for two patients showing radiographic signs of mild pulmonary edema no complications attributable to the infusions could be observed. Thirteen patients (50%) survived with favourable neurological outcome. CONCLUSION: Our results indicate that induction of mild hypothermia with infusion of cold fluids preceding endovascular cooling is safe and effective.
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.
AIM OF THE STUDY: Cold infusions have proved to be effective for induction of therapeutic hypothermia after cardiac arrest but so far have not been used for hypothermia maintenance. This study investigates if hypothermia can be induced and maintained by repetitive infusions of cold fluids and muscle relaxants. MATERIAL AND METHODS: Patients were eligible, if they had a cardiac arrest of presumed cardiac origin and no clinical signs of pulmonary oedema or severely reduced left ventricular function. Rocuronium (0.5 mg/kg bolus, 0.5 mg/kg/h for maintenance) and crystalloids (30 ml/kg/30 min for induction, 10 ml/kg every 6h for 24h maintenance) were administered via large bore peripheral venous cannulae. If patients failed to reach 33+/-1 degrees C bladder temperature within 60 min, endovascular cooling was applied. RESULTS: Twenty patients with a mean age of 57 (+/-15) years and mean body mass index of 27 (+/-4)kg/m(2) were included (14 males). Mean temperature at initiation of cooling (median 27 (IQR 16; 87) min after admission) was 35.4 (+/-0.9) degrees C. In 13 patients (65%) the target temperature was reached within 60 min, 7 patients (35%) failed to reach the target temperature. Maintaining the target temperature was possible in three (15%) patients and no adverse events were observed. CONCLUSION: Cold infusions are effective for induction of hypothermia after cardiac arrest, but for maintenance additional cooling techniques are necessary in most cases.
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.
Primary percutaneous coronary intervention (PCI) is the preferred reperfusion strategy for ST-elevation acute myocardial infarction (STEMI). In comatose survivors of cardiac arrest, mild induced hypothermia (MIH) improves neurological recovery. In the present study, we investigated feasibility and safety of combining primary PCI and MIH in comatose survivors of ventricular fibrillation with signs of STEMI after reestablishment of spontaneous circulation. Forty consecutive patients undergoing primary PCI and MIH from November 1, 2003 to December 31, 2005 were compared to 32 consecutive patients who underwent primary PCI but no MIH between January 1, 2000 and November 1, 2003. There were no significant differences between the MIH and no MIH groups in general characteristics, cardiac arrest circumstances and angiographic features. Except for decreases in heart rate during hypothermia interval, there was no difference between the MIH and no MIH groups in arterial pressure, peak arterial lactate (5.1mmol/l versus 5.7mmol/l; p=.56), need for vasopressors (65% versus 53%; p=.44), inotropes (48% versus 59%; p=.44), aortic balloon counterpulsation (20% versus 22%; p=.92), repeat cardioversion/defibrillation (30% versus 34%; p=.89) and use of antiarrhythmics (33% versus 53%; p=.13). There was also no difference in inspired oxygen requirements during mechanical ventilation and in renal function. Hospital survival with cerebral performance category 1 and 2 was significantly better in MIH group (55% versus 16%; p=.001). Our preliminary experience indicates that primary PCI and MIH are feasible and may be combined safely in comatose survivors of ventricular fibrillation with signs of STEMI. Such a strategy may improve survival with good neurological recovery.
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.
AIMS: The Hypothermia after Cardiac Arrest (HACA) trial assessed whether mild therapeutic hypothermia improved the rate of good neurological recovery in patients after ventricular fibrillation cardiac arrest of presumed cardiac origin. We evaluated the impact of hypothermia on myocardial injury. METHODS: Re-analysis of a HACA trial subset for our department (cooling, n=55; controls, n=56). Plasma levels of CK, CKMB and ST-scores were used as a measure of infarct size. RESULTS: Area under the curve (AUC) for CK was 28,786U/l x 24 h (IQR 5646-44,998) in the cooling group and 20,373U/l x 24 h (IQR 8211-30,801) for controls (p=0.40), for CKMB AUC was 1691U/l x 24 h (IQR 724-3330) and 1187U/l x 24 h (IQR 490-2469), respectively (p=0.18). The ST score was -40% (IQR [-55]-[+16]) in the cooling group (n=23) and -22% (IQR [-84]-[+33]) for controls (n=24) (p=0.76). When the cooling group was stratified into early (< or =8h) and longer (>8h) time to target temperature, the early group displayed a significantly lower CK 7340U/l x 24 h (IQR 3921-33,753) vs. 38,986U/l x 24 h (IQR 23,945-57,514, p=0.007) and a lower CKMB. CONCLUSION: Cooling after successful resuscitation for ventricular fibrillation cardiac arrest did not influence infarct size. Cautious interpretation of the subgroup analysis may indicate a favourable trend for early cooling.
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.
AIM OF THE STUDY: Hypothermia treatment with cold intravenous infusion and ice packs after cardiac arrest has been described and used in clinical practice. We hypothesised that with this method a target temperature of 32-34 degrees C could be achieved and maintained during treatment and that rewarming could be controlled. MATERIALS AND METHODS: Thirty-eight patients treated with hypothermia after cardiac arrest were included in this prospective observational study. The patients were cooled with 4 degrees C intravenous saline infusion combined with ice packs applied in the groins, axillae, and along the neck. Hypothermia treatment was maintained for 26h after cardiac arrest. It was estimated that passive rewarming would occur over a period of 8h. Body temperature was monitored continuously and recorded every 15min up to 44h after cardiac arrest. RESULTS: All patients reached the target temperature interval of 32-34 degrees C within 279+/-185min from cardiac arrest and 216+/-177min from induction of cooling. In nine patients the temperature dropped to below 32 degrees C during a period of 15min up to 2.5h, with the lowest (nadir) temperature of 31.3 degrees C in one of the patients. The target temperature was maintained by periodically applying ice packs on the patients. Passive rewarming started 26h after cardiac arrest and continued for 8+/-3h. Rebound hyperthermia (>38 degrees C) occurred in eight patients 44h after cardiac arrest. CONCLUSIONS: Intravenous cold saline infusion combined with ice packs is effective in inducing and maintaining therapeutic hypothermia, with good temperature control even during rewarming.
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.
OBJECTIVES: Although therapeutic hypothermia for cardiac arrest survivors has been shown to improve neurologically intact survival, optimal methods to ensure controlled induction and maintenance of cooling are not clearly established. Precise temperature control is important to evaluate because unintentional overcooling below the consensus target range of 32-34 degrees C may place the patient at risk for serious complications. We sought to measure the prevalence of overcooling (<32 degrees C) in postarrest survivors receiving primarily noninvasive cooling. DESIGN: Retrospective chart review of postarrest patients. SETTING: Three large teaching hospitals. PATIENTS: Cardiac arrest survivors receiving therapeutic hypothermia. INTERVENTIONS: Charts were reviewed if primarily surface cooling was used with a target temperature goal between 32 degrees C and 34 degrees C. MEASUREMENTS AND MAIN RESULTS: Of the 32 cases reviewed, overcooling lasting for >1 hr was identified as follows: 20 of 32 patients (63%) reached temperatures of <32 degrees C, 9 of 32 (28%) reached temperatures of <31 degrees C, and 4 of 32 (13%) reached temperatures of <30 degrees C. Of those with overcooling of <32 degrees C, 6 of 20 (30%) survived to hospital discharge, whereas of those without overcooling, 7 of 12 (58%) survived to hospital discharge (p = not significant). CONCLUSIONS: The majority of the cases reviewed demonstrated unintentional overcooling below target temperature. Improved mechanisms for temperature control are required to prevent potentially deleterious complications of more profound hypothermia.
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.
Abstract: OBJECTIVES: The purpose of this study was to evaluate the efficacy of an alternative cardiopulmonary cerebral resuscitation (CPCR) using emergency cardiopulmonary bypass (CPB), coronary reperfusion therapy and mild hypothermia. BACKGROUND: Good recovery of patients with out-of-hospital cardiac arrest is still inadequate. An alternative therapeutic method for patients who do not respond to conventional CPCR is required. METHODS: A prospective preliminary study was performed in 50 patients with out-of-hospital cardiac arrest meeting the inclusion criteria. Patients were treated with standard CPCR and, if there was no response, by emergency CPB plus intra-aortic balloon pumping. Immediate coronary angiography for coronary reperfusion therapy was performed in patients with suspected acute coronary syndrome. Subsequently, in patients with systolic blood pressure above 90 mm Hg and Glasgow coma scale score of 3 to 5, mild hypothermia (34 C for at least two days) was induced by coil cooling. Neurologic outcome was assessed by cerebral performance categories at hospital discharge. RESULTS: Thirty-six of the 50 patients were treated with emergency CPB, and 30 of 39 patients who underwent angiography suffered acute coronary artery occlusion. Return of spontaneous circulation and successful coronary reperfusion were achieved in 92% and 87%, respectively. Mild hypothermia could be induced in 23 patients, and 12 (52%) of them showed good recovery. Factors related to a good recovery were cardiac index in hypothermia and the presence of serious complications with hypothermia or CPB. CONCLUSIONS: The alternative CPCR demonstrated an improvement in the incidence of good recovery. Based upon these findings, randomized studies of this hypothermia are needed.
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.
BACKGROUND: Therapeutic hypothermia (TH) after cardiac arrest protects from neurological sequels and death and is recommended in guidelines. The Hypothermia Registry was founded to the monitor outcome, performance and complications of TH. METHODS: Data on out-of-hospital cardiac arrest (OHCA) patients admitted to intensive care for TH were registered. Hospital survival and long-term outcome (6-12 months) were documented using the Cerebral Performance Category (CPC) scale, CPC 1-2 representing a good outcome and 3-5 a bad outcome. RESULTS: From October 2004 to October 2008, 986 TH-treated OHCA patients of all causes were included in the registry. Long-term outcome was reported in 975 patients. The median time from arrest to initiation of TH was 90 min (interquartile range, 60-165 min) and time to achieving the target temperature (< or =34 degrees C) was 260 min (178-400 min). Half of the patients underwent coronary angiography and one-third underwent percutaneous coronary intervention (PCI). Higher age, longer time to return of spontaneous circulation, lower Glasgow Coma Scale at admission, unwitnessed arrest and initial rhythm asystole were all predictors of bad outcome, whereas time to initiation of TH and time to reach the goal temperature had no significant association. Bleeding requiring transfusion occurred in 4% of patients, with a significantly higher risk if angiography/PCI was performed (2.8% vs. 6.2%P=0.02). CONCLUSIONS: Half of the patients survived, with >90% having a good neurological function at long-term follow-up. Factors related to the timing of TH had no apparent association to outcome. The incidence of adverse events was acceptable but the risk of bleeding was increased if angiography/PCI was performed.
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.
OBJECTIVES: Therapeutic hypothermia has been recommended for postcardiac arrest coma due to ventricular fibrillation. However, no studies have evaluated whether therapeutic hypothermia could be effectively implemented in intensive care practice and whether it would improve the outcome of all comatose patients with cardiac arrest, including those with shock or with cardiac arrest due to nonventricular fibrillation rhythms. DESIGN: Retrospective study. SETTING: Fourteen-bed medical intensive care unit in a university hospital. PATIENTS: Patients were 109 comatose patients with out-of-hospital cardiac arrest due to ventricular fibrillation and nonventricular fibrillation rhythms (asystole/pulseless electrical activity). INTERVENTIONS: We analyzed 55 consecutive patients (June 2002 to December 2004) treated with therapeutic hypothermia (to a central target temperature of 33 degrees C, using external cooling). Fifty-four consecutive patients (June 1999 to May 2002) treated with standard resuscitation served as controls. Efficacy, safety, and outcome at hospital discharge were assessed. Good outcome was defined as Glasgow-Pittsburgh Cerebral Performance category 1 or 2. MEASUREMENTS AND MAIN RESULTS: In patients treated with therapeutic hypothermia, the median time to reach the target temperature was 5 hrs, with a progressive reduction over the 18 months of data collection. Therapeutic hypothermia had a major positive impact on the outcome of patients with cardiac arrest due to ventricular fibrillation (good outcome in 24 of 43 patients [55.8%] of the therapeutic hypothermia group vs. 11 of 43 patients [25.6%] of the standard resuscitation group, p = .004). The benefit of therapeutic hypothermia was also maintained in patients with shock (good outcome in five of 17 patients of the therapeutic hypothermia group vs. zero of 14 of the standard resuscitation group, p = .027). The outcome after cardiac arrest due to nonventricular fibrillation rhythms was poor and did not differ significantly between the two groups. Therapeutic hypothermia was of particular benefit in patients with short duration of cardiac arrest (<30 mins). CONCLUSIONS: Therapeutic hypothermia for the treatment of postcardiac arrest coma can be successfully implemented in intensive care practice with a major benefit on patient outcome, which appeared to be related to the type and the duration of initial cardiac arrest and seemed maintained in patients with shock.
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.
BACKGROUND: Therapeutic hypothermia (TH) has been shown to increase survival after out-of-hospital resuscitation. The aim of our study was to find out nationwide implementation and the actual utilization of TH after cardiac arrest in Finnish intensive care units (ICUs). We also determined the outcomes and describe demographic variables of the patients treated with TH. METHODS: We analyzed a nationwide prospective database and included all adult patients (1,555) treated in ICUs after cardiac arrest during 2004 and 2005. RESULTS: During 2004 and 2005, 407 patients were treated with TH and TH was used in 19 out of the 20 ICUs. The proportion of cardiac arrest patients treated with TH had increased from 4% in 2002 to 28% in 2005. The incidence of cardiac arrest patients admitted to ICUs was 15/100,000 inhabitants/year. The use of TH varied in different areas of the country from 3.4 to 5.0/100,000 inhabitants/year. In-hospital mortality of TH patients was 32.7% and increased from 13.2% in age group <45 years to 46.0% in age group >75 years (P = 0.0002). Six-month survival was 55.3%. Median (interquartile range) length of stay in the ICU was 3.7 (2.7-5.3) days. CONCLUSION: In Finland, TH is implemented in almost all ICUs but it is applied only to a selected group of patients. Six months after cardiac arrest, more than half of the patients treated with TH were alive. Among patients treated with TH, younger patients had lower in-hospital mortality.
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.
INTRODUCTION: We evaluated the efficacy of and tolerance to mild therapeutic hypothermia achieved using an endovascular cooling system, and its ability to reach and maintain a target temperature of 33 degrees C after cardiac arrest. METHODS: This study was conducted in the medical-surgical intensive care unit of an urban university hospital. Forty patients admitted to the intensive care unit following out-of-hospital cardiac arrest underwent mild induced hypothermia (MIH). Core temperature was monitored continuously for five days using a Foley catheter equipped with a temperature sensor. Any equipment malfunction was noted and all adverse events attributable to MIH were recorded. Neurological status was evaluated daily using the Pittsburgh Cerebral Performance Category (CPC). We also recorded the mechanism of cardiac arrest, the Simplified Acute Physiologic Score II on admission, standard biological variables, and the estimated time of anoxia. Nosocomial infections during and after MIH until day 28 were recorded. RESULTS: Six patients (15%) died during hypothermia. Among the 34 patients who completed the period of MIH, hypothermia was steadily maintained in 31 patients (91%). Post-rewarming 'rebound hyperthermia', defined as a temperature of 38.5 degrees C or greater, was observed in 25 patients (74%) during the first 24 hours after cessation of MIH. Infectious complications were observed in 18 patients (45%), but no patient developed severe sepsis or septic shock. The biological changes that occurred during MIH manifested principally as hypokalaemia (< 3.5 mmol/l; in 75% of patients). CONCLUSION: The intravascular cooling system is effective, safe and allows a target temperature to be reached fairly rapidly and steadily over a period of 36 hours.
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.
OBJECTIVES: We sought to review findings from recent literature on the postresuscitation care of cardiac arrest patients using therapeutic hypothermia as part of nontrial treatment. DESIGN: Literature review. SETTING: Hospital-based environment. SUBJECTS: Patients initially resuscitated from cardiac arrest who underwent hypothermia induction as a treatment regimen or historical control patients who did not receive hypothermia therapy. MEASUREMENT:: We compiled protocol methodology from the various studies, as well as survival-to-hospital discharge and neurological outcomes. MAIN RESULTS: Although varied in their protocols and outcome reporting, results from published investigations confirmed the findings from landmark randomized controlled trials, in that the use of therapeutic hypothermia increased survival with an odds ratio of 2.5 (95% confidence interval, 1.8-3.3) and favorable outcome with an odds ratio of 2.5 (95% confidence interval, 1.9-3.4). CONCLUSIONS: The survival and neurological outcomes benefit from therapeutic hypothermia are robust when compared over a wide range of studies of actual implementation.
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.
BACKGROUND: Successful resuscitation from sudden cardiac death is frequently accompanied by severe and often fatal neurologic injury. Induced hypothermia (IH) may attenuate the neurologic damage observed in patients after cardiac arrest. HYPOTHESIS: This study examined a population of nonselected patients presenting to a community hospital following successful resuscitation of sudden cardiac death. We sought to determine whether a program of induced hypothermia would improve the clinical outcome of these critically ill patients. METHODS: We initiated a protocol of IH at the Oklahoma Heart Hospital in August of 2003. Study patients were consecutive adults admitted following successful resuscitation of out-of-hospital cardiac arrest. Moderate hypothermia was induced by surface cooling and maintained for 24 to 36 h in the Intensive Care Unit with passive rewarming over 8 h. RESULTS: Forty-nine patients who were resuscitated and had the return of spontaneous circulation completed the hypothermia protocol. The cause of cardiac arrest was acute myocardial infarction in 24 patients and cardiac arrhythmias in 19 patients. Nineteen patients (39%) survived and were discharged. Sixteen of the patients discharged had no or minimal residual neurologic dysfunction and 3 patients had clinically significant residual neurologic injury. CONCLUSION: A program of induced hypothermia based in a community hospital is feasible, practical, and requires limited additional financial and nursing resources. Survival and neurologic recovery compare favorably with clinical trial outcomes.
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.
BACKGROUND: Induction of mild hypothermia (MH) in patients resuscitated from cardiac arrest improves their outcome. However, benefits and risks of MH in patients who remain in cardiogenic shock after the return of spontaneous circulation (ROSC) are unclear. We analysed all cardiac arrest survivors who were treated with MH in our intensive coronary care unit (CCU) and compared the outcome of patients with cardiogenic shock syndrome (CSS) with those who were circulatory stable. METHODS: We performed retrospective analysis of all consecutive cardiac arrest survivors treated by MH in our CCU from November 2002 to August 2006. They were classified into two groups, according to whether they met the criteria for cardiogenic shock or not before MH initiation. RESULTS: Out of 56 consecutive patients, 28 fulfilled criteria of cardiogenic shock before MH initiation (group A) and 28 were relatively stable (group B). In-hospital mortality was 57.1% in

group A and 21.4% in group B patients (P=0.013). Favourable neurological outcome anytime during hospitalization was found in 67.9% of group A patients and in 82.1% of group B subjects (P=0.355). Favourable discharge neurological outcome was reached in 39.3% in group A and in 71.4% in group B (P=0.031). The complication rate in both groups did not differ. CONCLUSION: While in-hospital mortality in cardiac arrest survivors treated by MH was expectably higher in those with cardiogenic shock than in stable patients, the favourable neurological outcome during hospitalization was comparable in both groups. Therefore, induction of MH should be considered in cardiac arrest survivors with CSS after ROSC.
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.
Mild resuscitative hypothermia has been shown to improve neurological outcome after cardiac arrest presenting with ventricular fibrillation (VF) due to cardiac causes. We describe the experience of inducing mild hypothermia in three patients with non-cardiac causes of arrest and long delays before a return of spontaneous circulation (ROSC). In one patient, extreme metabolic acidosis due to inadvertent oesophageal intubation complicated therapy, and the role of point-of-care diagnostics in the prehospital setting is briefly discussed. All patients survived to discharge from hospital, and neuropsychological examinations revealed good recovery. It is concluded that mild resuscitative hypothermia may be beneficial also in patients with obvious non-coronary causes for cardiac arrest.
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.
Endovascular therapeutic hypothermia has been shown to preserve neurological function and improve outcomes; however, its use and potential complications have not been fully described in patients with traumatic head injuries. We believe that the use of endovascular cooling leads to deep venous thrombosis (DVT) in this high-risk population. We performed a retrospective review of 11 patients with severe head injuries admitted to our Level I trauma center surgical intensive care unit who underwent intravascular cooling. Duplex sonograms were obtained after 4 days at catheter removal or with clinical symptoms that were suspicious for DVT. Patients had a mean age of 23.2 (range, 16-42) years and an Injury Severity Score of 31.9 (range, 25-43). The overall incidence of DVT was 50 per cent. The DVT rate was 33 per cent if catheters were removed in 4 days or less and 75 per cent if removed after 4 days (risk ratio = 2.25; odds ratio = 6; P = ns). An elevated international normalized ratio upon admission was protective against DVT (no DVT = 1.26 vs DVT = 1.09; P = 0.02). Inferior vena cava filters were placed in most patients with DVT. The use of endovascular cooling catheters is associated with increased risk of DVT in patients with traumatic head injuries. Therefore, we discourage the use of endovascular cooling devices in this patient population.
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.
AIM OF THE STUDY: Application of mild hypothermia (32-33 degrees C) has been shown to improve neurological outcome in patients with cardiac arrest. However, hypothermia affects hemostasis, and even mild hypothermia is associated with bleeding and increased transfusion requirements in surgery patients. On the other hand, crystalloid hemodilution has been shown to induce a hypercoagulable state. The study aim was to elucidate in which way the induction of mild therapeutic hypothermia by a bolus infusion of cold crystalloids affects the coagulation system of patients with cardiac arrest. METHODS: This was a prospective pilot study in 18 patients with cardiac arrest and return of spontaneous circulation (ROSC). Mild hypothermia was initiated by a bolus infusion of cold 0.9% saline fluid (4 degrees C; 30ml/kg/30min) and maintained for 24h. At 0h (before hypothermia), 1, 6 and 24h we assessed coagulation parameters (PT, APPT), platelet count and performed thrombelastography (ROTEM) after in vitro addition of heparinase. RESULTS: A total amount of 2528 (+/-528)ml of 0.9% saline fluid was given. Hematocrit (p<0.01) and platelet count (-27%; p<0.05) declined, whereas APTT increased (2.7-fold; p<0.01) during the observation period. All ROTEM parameters besides clotting time (CT) after 1h (-20%; p<0.05) did not significantly change. CONCLUSION: Mild hypothermia only slightly prolonged clotting time as measured by rotation thrombelastography. Therefore, therapeutic hypothermia initiated by cold crystalloid fluids has only minor overall effects on coagulation in patients with cardiac arrest.
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.
INTRODUCTION: Persistent coma is a common finding after cardiac arrest and has profound ethical and economic implications. Evidence suggests that therapeutic hypothermia improves neurological outcome in these patients. In this analysis, we investigate whether therapeutic hypothermia influences the length of intensive care unit (ICU) stay and ventilator time in patients surviving out-of-hospital cardiac arrest. METHODS: A prospective observational study with historical controls was conducted at our medical ICU. Fifty-two consecutive patients (median age 62.6 years, 43 males, 34 ventricular fibrillation) submitted to therapeutic hypothermia after out-of-hospital cardiac arrest were included. They were compared with a historical cohort (n = 74, median age 63.8 years, 53 males, 43 ventricular fibrillation) treated in the era prior to hypothermia treatment.

All patients received the same standard of care. Neurological outcome was assessed using the Pittsburgh cerebral performance category (CPC) score. Univariate analyses and multiple regression models were used. RESULTS: In survivors, therapeutic hypothermia and baseline disease severity (Acute Physiology and Chronic Health Evaluation II [APACHE II] score) were both found to significantly influence ICU stay and ventilator time (all P < 0.01). ICU stay was shorter in survivors receiving therapeutic hypothermia (median 14 days [interquartile range (IQR) 8 to 26] versus 21 days [IQR 15 to 30] in the control group; P = 0.017). ICU length of stay and time on ventilator were prolonged in patients with CPC 3 or 4 compared with patients with CPC 1 or 2 (P = 0.003 and P = 0.034, respectively). Kaplan-Meier analysis showed improved probability for 1-year survival in the hypothermia group compared with the controls (log-rank test P = 0.013). CONCLUSION: Therapeutic hypothermia was found to significantly shorten ICU stay and time of mechanical ventilation in survivors after out-of-hospital cardiac arrest. Moreover, profound improvements in both neurological outcome and 1-year survival were observed.
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.
BACKGROUND: Mortality among patients admitted to hospital after out-of-hospital cardiac arrest (OHCA) is high. Based on recent scientific evidence with a main goal of improving survival, we introduced and implemented a standardised post resuscitation protocol focusing on vital organ function including therapeutic hypothermia, percutaneous coronary intervention (PCI), control of haemodynamics, blood glucose, ventilation and seizures. METHODS: All patients with OHCA of cardiac aetiology admitted to the ICU from September 2003 to May 2005 (intervention period) were included in a prospective, observational study and compared to controls from February 1996 to February 1998. RESULTS: In the control period 15/58 (26%) survived to hospital discharge with a favourable neurological outcome versus 34 of 61 (56%) in the intervention period (OR 3.61, CI 1.66-7.84, p=0.001). All survivors with a favourable neurological outcome in both groups were still alive 1 year after discharge. Two patients from the control period were revascularised with thrombolytics versus 30 (49%) receiving PCI treatment in the intervention period (47 patients (77%) underwent cardiac angiography). Therapeutic hypothermia was not used in the control period, but 40 of 52 (77%) comatose patients received this treatment in the intervention period. CONCLUSIONS: Discharge rate from hospital, neurological outcome and 1-year survival improved after standardisation of post resuscitation care. Based on a multivariate logistic analysis, hospital treatment in the intervention period was the most important independent predictor of survival.
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.
BACKGROUND AND PURPOSE: High serum levels of neuron-specific enolase (NSE) and S-100B protein are known to be associated with ischemic brain injury and poor outcome after cardiac arrest. Therapeutic hypothermia has been shown to improve neurological outcome after cardiac arrest. The aim of this study was to evaluate the effect of therapeutic hypothermia on levels of serum NSE and S-100B protein, their time course, and their prognostic value in predicting unfavorable outcome after out-of-hospital cardiac arrest. METHODS: Seventy patients resuscitated from ventricular fibrillation were randomly assigned to hypothermia of 33+/-1 degrees C for 24 hours or to normothermia. Serum NSE and S-100B were sampled at 24, 36, and 48 hours after cardiac arrest. Neurological outcome was dichotomized into good or poor at 6 months after cardiac arrest. RESULTS: The levels of NSE (P=0.007 by analysis of variance for repeated measurements) but not S-100B were lower in hypothermia- than normothermia-treated patients. A decrease in NSE values between 24 and 48 hours was observed in 30 of 34 patients (88%) in the hypothermia group and in 16 of 32 patients (50%) in the normothermia group (P<0.001). The decrease in NSE values was associated with good outcome at 6 months after cardiac arrest (P=0.005), recovery of consciousness (P<0.001), and survival for at least 6 months after cardiac arrest (P=0.012). CONCLUSIONS: Decreasing levels of serum NSE but not S-100B over time may indicate selective attenuation of delayed neuronal death by therapeutic hypothermia in victims of cardiac arrest.
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.
BACKGROUND AND PURPOSE: Cognitive deficits are common in survivors of cardiac arrest (CA). The aim of this study was to examine the effect of therapeutic hypothermia after CA on cognitive functioning and neurophysiological outcome. METHODS: A cohort of 70 consecutive adult patients resuscitated from out-of-hospital ventricular fibrillation CA were randomly assigned to therapeutic hypothermia of 33 degrees C for 24 hours accomplished by external cooling or normothermia. Neuropsychological examination was performed to 45 of the 47 conscious survivors of CA (27 in hypothermia and 18 in normothermia group) 3 months after the incident. Quantitative electroencephalography (Q-EEG) and auditory P300 event-related potentials were studied on 42 patients at the same time point. RESULTS: There were no differences between the 2 treatment groups in demographic variables, depression, or delays related to the resuscitation. No differences were found in any of the cognitive functions between the 2 groups. 67% of patients in hypothermia and 44% patients in normothermia group were cognitively intact or had only very mild impairment. Severe cognitive deficits were

found in 15% and 28% of patients, respectively. All Q-EEG parameters were better in the hypothermia-treated group, but the differences did not reach statistical significance. The amplitude of P300 potential was significantly higher in hypothermia-treated group. CONCLUSIONS: The use of therapeutic hypothermia was not associated with cognitive decline or neurophysiological deficits after out-of-hospital CA.

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.
OBJECTIVE: To evaluate the effects of therapeutic hypothermia (HT) of 33 degrees C after cardiac arrest (CA) on cardiac arrhythmias, heart rate variability (HRV), and their prognostic value. DESIGN: Prospective, comparative substudy of a randomized controlled trial of mild HT after out-of-hospital CA, the European Hypothermia After Cardiac Arrest study. SETTING: Intensive care unit of a tertiary referral hospital (Helsinki University Hospital). PATIENTS: Seventy consecutive adult patients resuscitated from out-of-hospital ventricular fibrillation were randomly assigned either to therapeutic HT of 33 degrees C or normothermia. INTERVENTIONS: Patients randomized to HT were cooled with an external cooling device for 24 hours and then allowed to rewarm slowly during 12 hours. In the normothermia group, the core temperature was kept <38 degrees C by antipyretics and physical means. All patients received standard intensive care for at least 2 days. MEASUREMENTS AND MAIN RESULTS: Twenty-four hour ambulatory electrocardiography recordings were performed at 0-24 hours, at 24-48 hours, and at 14 days. The clinical outcome was assessed at 6 months after CA. The occurrence of premature ventricular beats was increased in the HT-treated group during the first two recordings, with no difference in the number of ventricular tachycardia or ventricular fibrillation episodes. All HRV values were significantly higher during the HT (p < 0.01), but no differences were observed 2 weeks later. In multivariate analysis, only shorter delay to restoration of spontaneous circulation (p = 0.009) and the sd of individual normal-to-normal intervals >100 msec of the 24-48-hour recording in the HT group (p = 0.018) predicted good outcome. CONCLUSIONS: The use of therapeutic HT of 33 degrees C for 24 hours after CA was not associated with an increase in clinically significant arrhythmias. Preserved 24 to 48-hour HRV may be a predictor of favorable outcome in patients with CA treated with HT.

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.
AIM: The earliest initiation of mild hypothermia after resuscitation from cardiac arrest is crucial. This study aimed to evaluate the feasibility and safety of out-of-hospital surface cooling in such cases. METHODS: Cooling pads stored below 0 degrees C in the ambulance were applied as soon as possible after restoration of spontaneous circulation in the out-of-hospital setting. This continued in the emergency department until an oesophageal temperature of 34 degrees C was reached, when the pads were removed. A target temperature of 33 degrees C was maintained for 24h. Results are given as Median and interquartile range. RESULTS: From September 2006 to January 2007, 15 victims of cardiac arrest were included. Cooling was initiated at 12 (8.5-15)min after restoration of spontaneous circulation. Oesophageal temperatures decreased from 36.6 (36.2-36.6) degrees C to 33 degrees C within 70 (55-106)min. Hospital admission was at 45 (34-52)min, with oesophageal temperatures of 35.4 (34.6-35.9) degrees C; the target 33 degrees C was achieved 50 (29-82)min after admission. No skin lesions were observed. CONCLUSION: Non-invasive surface cooling immediately after resuscitation from cardiac arrest, in the out-of-hospital setting, proved to be feasible, fast and safe. Whether early cooling will improve neurological outcome needs to be determined in future studies.

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.
The cooling and haemodynamic effects of prehospital infusion of ice-cold Ringer's solution were studied in 13 adult patients after successful resuscitation from non-traumatic cardiac arrest. After haemodynamics stabilisation, 30 ml/kg of Ringer's solution was infused at a rate of 100ml/min into the antecubital vein. Arterial blood pressure and blood gases, pulse rate, end-tidal CO_2 and oesophageal temperature were monitored closely. The mean core temperature decreased from 35.8 +/- 0.9 degrees C at the start of infusion to 34.0 +/- 1.2 degrees C on arrival at hospital (P < 0.0001). No serious adverse haemodynamic effects occurred. It is concluded that the induction of therapeutic hypothermia using this technique in the prehospital setting is feasible.

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.
BACKGROUND: The outcome among patients who are hospitalised alive after out-of-hospital cardiac arrest is still relatively poor. At present, there are no clear guidelines specifying how they should be treated. The aim of this survey was to describe the outcome for initial survivors of out-of-hospital cardiac arrest when a more aggressive approach was applied. PATIENTS:

All patients hospitalised alive after out-of-hospital cardiac arrest in the Municipality of Goteborg, Sweden, during a period of 20 months. RESULTS: Of all the patients in the municipality suffering an out-of-hospital cardiac arrest in whom cardiopulmonary resuscitation (CPR) was attempted (n=375), 85 patients (23%) were hospitalised alive and admitted to a hospital ward. Of them, 65% had a cardiac aetiology and 50% were found in ventricular fibrillation. In 32% of the patients, hypothermia was attempted, 28% underwent a coronary angiography and 21% had a mechanical revascularisation. In overall terms, 27 of the 85 patients who were brought alive to a hospital ward (32%) survived to 30 days after cardiac arrest. Survival was only moderately higher among patients treated with hypothermia versus not (37% versus 29%; NS), and it was markedly higher among those who had early coronary angiography versus not (67% versus 18%; p<0.0001). CONCLUSION: In an era in which a more aggressive attitude was applied in post-resuscitation care, we found that the survival (32%) was similar to that in previous surveys. However, early coronary angiography was associated with a marked increase in survival and might be of benefit to many of these patients. Larger registries are important to further confirm the value of hypothermia in representative patient populations.

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.
No abstract available.
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.**
BACKGROUND: Mild therapeutic hypothermia (MTH) achieved by endovascular cooling has emerged as a new treatment strategy to reduce hypoxic brain injury after cardiac arrest (CA). It remains to be established how the time interval between CA and MTH impacts the neurologic outcome. We hypothesized that a more rapid achievement of MTH (time to target temperature [TTT], time to coldest temperature [TCT]) improves the outcome after CA. METHODS: Forty-nine consecutive patients successfully resuscitated from CA were enrolled. MTH with a body core temperature between 32.0 and 34.0 degrees C (target temperature: 33.0 degrees C) over 24 h was achieved using a closed-loop endovascular system. Based on the neurologic outcome at discharge, the patient group was dichotomized into good (no/mild cerebral disability) and poor (severe disability, coma/vegetative state, brain death) outcomes. Serum neurone specific enolase (NSE) as biochemical marker of brain damage was sampled at 24, 48, and 72 h after CA. RESULTS: Twenty-eight patients were discharged with a good outcome. Multivariate stepwise regression showed TTT (odds ratio for every h TTT: 0.69 [95% confidence interval: 0.51-0.98]) or, if entered into the model, TCT (odds ratio for every h TCT: 0.72 [95% confidence interval: 0.56-0.94]) to be independent predictors for good outcome. Further independent determinants were age, BMI, asystole as presenting rhythm, and thrombolysis during resuscitation. However, TCT was the only variable to correlate with maximum NSE values after CA (r=0.32, P<0.05). CONCLUSIONS: Early achievement of MTH by endovascular cooling appears to reduce hypoxic brain injury and to favour a good neurologic outcome after CA.
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.
OBJECTIVE: Mild therapeutic hypothermia (MTH) has been integrated into international resuscitation guidelines. In the majority of patients, sudden cardiac arrest is caused by myocardial infarction. This study investigated whether a combination of MTH with primary percutaneous coronary intervention (PCI) is feasible, safe, and potentially beneficial in patients after cardiac arrest due to acute myocardial infarction. DESIGN: Single-center observational study with a historical control group. SETTING: University clinic. PATIENTS: Thirty-three patients after cardiac arrest with ventricular fibrillation as initial rhythm and restoration of spontaneous circulation who remained unconscious at admission and presented with acute ST elevation myocardial infarction (STEMI). INTERVENTIONS: In 16 consecutive patients (2005-2006), MTH was initiated immediately after admission and continued during primary PCI. Seventeen consecutive patients who were treated in a similar 2-yr observation interval before implementation of MTH (2003-2004) served as a control group. Feasibility, safety, mortality, and neurologic outcome were documented. MEASUREMENTS AND MAIN RESULTS: Initiation of MTH did not result in longer door-to-balloon times compared with the control group (82 vs. 85 mins), indicating that implementation of MTH did not delay

the onset of primary PCI. Target temperature (32-34 degrees C) in the MTH group was reached within 4 hrs, consistent with previous trials and suggesting that primary PCI did not affect the velocity of cooling. Despite a tendency to increased bleeding complications and infections, patients treated with MTH tended to have a lower mortality after 6 months (25% vs. 35%, p = .71) and an improved neurologic outcome as determined by a Glasgow-Pittsburgh Cerebral Performance Scale score of 1 or 2 (69% vs. 47% in the control group, p = .30). CONCLUSIONS: MTH in combination with primary PCI is feasible and safe in patients resuscitated after cardiac arrest due to acute myocardial infarction. A combination of these therapeutic procedures should be strongly considered as standard therapy in patients after out-of-hospital cardiac arrest due to STEMI.
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.
Abstract: The effects of mild hypothermia (MH) were investigated. From 1995 to 1996, 28 adult patients with out-of-hospital cardiopulmonary arrest (CPA) had return of spontaneous circulation and survived for more than two days. Thirteen patients were in the MH group. In the MH group, core temperature was maintained between 33 and 34 degrees C for 48 h, and then re-warmed to a temperature of 37 degrees C, at a rate of no greater than 1 degrees C per day. Fifteen patients, admitted before the MH protocol was instituted, were in the control group. Despite the fact that the number of witnessed arrests in the control group were greater than in the MH group, there were both more survivors (7/13 vs. 5/15) and more fully recovered patients (3/13 vs. 1/15) in the MH vs Control groups. Eleven of 13 MH patients, as compared to 6/15 controls developed pneumonia. Our study, although preliminary, suggests that MH might confer improved outcome, as has been shown in animal models, after CPA. This treatment is associated with an increase in pneumonic complications.
*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.
Abstract: BACKGROUND AND PURPOSE: Recent animal studies showed that mild resuscitative hypothermia improves neurological outcome when applied after cardiac arrest. In a 3-year randomized, prospective, multicenter clinical trial, we hypothesized that mild resuscitative cerebral hypothermia (32 degrees C to 34 degrees C core temperature) would improve neurological outcome after cardiac arrest. METHODS: We lowered patients' temperature after admission to the emergency department and continued cooling for at least 24 hours after arrest in conjunction with advanced cardiac life support. The cooling technique chosen was external head and total body cooling with a cooling device in conjunction with a blanket and a mattress. Infrared tympanic thermometry was monitored before a central pulmonary artery thermistor probe was inserted. RESULTS: In 27 patients (age 58 [interquartile range [IQR] 52 to 64] years; 7 women; estimated "no-flow" duration 6 [IQR 1 to 11] minutes and "low-flow" duration 15 [IQR 9 to 23] minutes; admitted to the emergency department 36 [IQR 24 to 43] minutes after return of spontaneous circulation), we could initiate cooling within 62 (IQR 41 to 75) minutes and achieve a pulmonary artery temperature of 33+/-1 degrees C 287 (IQR 42 to 401) minutes after cardiac arrest. During 24 hours of mild resuscitative hypothermia, no major complications occurred. Passive rewarming >35 degrees C was accomplished within 7 hours. CONCLUSIONS: Mild resuscitative hypothermia in patients is feasible and safe. A clinical multicenter trial might prove that mild hypothermia is a useful method of cerebral resuscitation after global ischemic states.
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.

BACKGROUND: Mild therapeutic hypothermia (MTH) improves neurological outcome in patients after cardiac arrest. From animal and human studies it appears that hypothermia impairs renal function. The aim of this study was to examine the effects of MTH on renal function in humans. METHODS: Patients were participants recruited in one of the centres of the hypothermia after cardiac arrest-multicenter trial. We measured serum creatinine and creatinine clearance (C(Cr)) within 24 h of MTH, at 4 hourly intervals. Patients were followed for acute renal failure and need for renal supportive therapy for 28 days. RESULTS: We included 60 patients (32 hypothermic, 28 normothermic). Median serum creatinine on admission was [[119 micromol/l (IQR 108-133)] [1.35 mg/dl (IQR 1.22-1.50)]] in hypothermic and [[114 micromol/l (IQR 99-131)] [1.29 mg/dl (IQR 1.12-1.48)]] in normothermic patients, and decreased to [[69 micromol/l (IQR 62-84)] [0.78 mg/dl (IQR 0.70-0.95)]] in the hypothermic group and to [[88 micromol/l (IQR 71-123)] [1.00 mg/dl (IQR 0.80-1.39)]] in the normothermic group within 24h. C(Cr) was decreased on admission. Within 24 h C(Cr) improved to normal values in normothermic patients [1.53 ml/s (IQR 1.15-2.35) [92 ml/min (IQR 69-141)]] and remained low in hypothermic patients [0.88 ml/s (IQR 0.63-1.38) [53 ml/min (IQR 38-83)]] ($P = 0.0006$). No difference was found between the groups in the development of acute renal failure or the need for renal supportive therapy. CONCLUSION: Twenty four hours of MTH was associated with a delayed improvement in renal function. This was not reflected in the serum creatinine values, which were low in the hypothermic group. This transient impaired renal function appeared to be completely reversible within 4 weeks.

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

Appendix   7

Statement of editorial independence

The Resuscitation Council (UK) is a charity. Its income is derived mainly from life support courses. It has no financial relationships with the industry. The Guideline Project Group is completely independent from any commercial organisation and is solely responsible for the content of the RC(UK) guidelines.

Appendix 8

Guidance on conflict of interest (COI)

Scope
This guidance is for the Officers, Trading Company Secretary, members of the Resuscitation Council (UK) Executive Committee, members of the Subcommittees, members of Working Groups set up by the Resuscitation Council (UK), and other individuals appointed to represent the Resuscitation Council (UK).

What constitutes conflict of interest?
The following provides examples of conditions in which a member should declare an interest that might conflict, or be perceived to conflict, with their responsibilities to the Council:

- **Boards or consultancies (paid or not), honoraria, payment for lectures:** if directly related to the areas under discussion, these must be declared.

- **Equity, ownership:** if directly related to the areas under discussion, these must be declared. If you have an investment fund (e.g., pension, ISA) over which you have no control in how the fund is managed, this does not need to be declared.

- **Business relationship with a company:** if the company's business can be affected by outcome in areas under consideration, this must be declared.

- **Industry funding of research grant:** this must be declared unless all of the following criteria are met: there is no salary support, data are controlled by the investigator, and there are no restrictions on publication.

- **Charitable funding of research grants**: this must be declared unless all of the following criteria are met: there is no salary support, data are controlled by the investigator, and there are no restrictions on publication.

- **Anything else** that a member believes their participation in discussions and decisions may be perceived by the public or colleagues to be a COI.

A total income of more than £1,000 from a single source is a COI and must be declared. Only the source of the income and the nature of the interest are required; the amount of any payment or grant etc does not need to be disclosed. Having declared a potential COI, at the discretion of the Chairman of the relevant committee, a member may still participate in discussions that relate to this topic, but should not be involved in decisions. In some circumstances, and at the discretion of the Chairman of the relevant committee, if there is a major COI for a given topic, it may be appropriate to exclude that individual from the whole discussion. A COI will expire after one year after the COI no longer exists. If the Council discovers that an individual has a COI that has not been declared, this will be reviewed by the COI panel (i.e., the Officers). Failure to declare an interest may result in expulsion of the individual from his or her role(s) in the Council.

When should interests be declared?

A COI form should be made on appointment and then annually. All of the individuals listed at the beginning of this document will complete a COI each year. If the individual has no potential conflicts this must be declared on the form. At each meeting throughout the rest of the year the Chairman of a Committee/Subcommittee will ask if there have been any change of circumstance and this will be recorded in the minutes.

Record of interests and their publication

The Resuscitation Council will keep a COI record for all these individuals. Information about any interests declared will be made publicly available in the form of a statement of annual declarations, through the minutes of meetings or in guidance publications.

June 2008
Amended March 2011

Declaration of Conflict of Interest

Name	
Committee / Subcommittee	
Relevant conflict of interest **(Consulting fees, honoraria, grants, positions)** **If none –** **please state 'NONE'**	
Signature	
Date	