ILCOR Advisory Statement

Temperature Management After Cardiac Arrest

An Advisory Statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation

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This document was approved by the American Heart Association Science Advisory and Coordinating Committee on May 14, 2015, and the American Heart Association Executive Committee on September 10, 2015.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.00000000000313/-/DC1

The American Heart Association requests that this document be cited as follows: Donnino MW, Andersen LW, Berg KM, Reynolds JC, Nolan JP, Morley PT, Lang E, Cocchi MN, Xanthos T, Callaway CW, Soar J, ILCOR ALS Task Force. Temperature management after cardiac arrest: an advisory statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. *Circulation*. 2015;132:•••-•••

This article has been copublished in *Resuscitation*.

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(Circulation. 2015;132:000-000.)

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Circulation is available at http://circ.ahajournals.org

DOI: 10.1161/CIR.00000000000313

Abstract/Summary

For more than a decade, mild induced hypothermia $(32^{\circ}C-34^{\circ}C)$ has been standard of care for patients remaining comatose after resuscitation from out-of-hospital cardiac arrest with an initial shockable rhythm, and this has been extrapolated to survivors of cardiac arrest with initially nonshockable rhythms and to patients with in-hospital cardiac arrest. Two randomized trials published in 2002 reported a survival and neurologic benefit with mild-induced hypothermia. One recent randomized trial reported similar outcomes in patients treated with targeted temperature management at either 33°C or 36°C. In response to these new data, the International Liaison Committee on Resuscitation (ILCOR) Advanced Life Support (ALS) Task Force performed a systematic review to evaluate 3 key questions: (1) Should mild induced hypothermia (or some form of targeted temperature management) be used in comatose post-cardiac arrest patients? (2) If used, what is the ideal timing of the intervention? (3) If used, what is the ideal duration of the intervention? The Task Force used GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology to assess and summarize the evidence, and to provide a consensus on science statement and treatment recommendations. The Task Force recommends targeted temperature management for adults with out-of-hospital cardiac arrest with an initial shockable rhythm at a constant temperature between 32°C and 36°C for at least 24 hours. Similar suggestions are made for out-of-hospital cardiac arrest with a nonshockable rhythm and in-hospital cardiac arrest. The Task Force recommends against prehospital cooling with rapid infusion of large volumes of cold intravenous fluid. Additional and specific recommendations are provided in the document.

Introduction

Sudden cardiac arrest is one of the leading causes of death in adults around the world. Although incidence varies from country to country, cardiac arrest affects several million people annually, with an average survival rate of <10%.^{1,2} In patients who remain comatose after cardiac arrest, the post-cardiac arrest syndrome is a complex set of pathophysiological processes consisting of brain injury, myocardial depression, and systemic ischemia-reperfusion injury as well as ongoing injury caused by the precipitating etiology of the arrest.³

For more than a decade, mild induced hypothermia (32°C–34°C) has been the cornerstone of post-cardiac arrest care. Mild to moderate hypothermia induced after global brain ischemia or cardiac arrest was initially evaluated in animal models that showed improved neurological function for those receiving induced hypothermia.⁴⁻⁷ After 2 human randomized trials published in 2002,^{8.9} the International Liaison Committee on Resuscitation (ILCOR) recommended in 2003 that "unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest (OHCA) should be cooled to 32°C to 34°C for 12 to 24 hours when the initial rhythm was VF" [ventricular fibrillation] and that "such cooling may also be beneficial for other rhythms or inhospital cardiac arrest."¹⁰ Similar recommendations were provided in the *2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations*.¹¹

Recently, a prospective randomized trial comparing a targeted temperature of 33°C with 36°C for a large group of OHCA patients found that both groups had similar mortality (primary end point) and neurologic outcome at 180 days.¹² As a result of that trial, there has been debate about the optimal target temperature for post-cardiac arrest patients.^{13,14} To address the evolving science of targeted temperature management (defined as an active therapy to achieve and

maintain a specific target temperature for a defined duration), the ILCOR Advanced Life Support (ALS) Task Force conducted an evidence review and created an updated position paper to address 3 key questions about temperature management in the post-cardiac arrest patient:

- 1. For patients who remain comatose after return of spontaneous circulation (ROSC), should targeted temperature management be used?
- 2. If targeted temperature management is used, what is the optimal timing of initiation?
- 3. If targeted temperature management is used, what is the optimal duration of therapy?

To address these questions, the Task Force created formal PICO (Population, Intervention, Comparison, and Outcome) questions and performed a comprehensive literature search. The Task Force evaluated, compiled, and summarized the evidence by using GRADE (Grading of Recommendations Assessment, Development and Evaluation; www.gradeworkinggroup.org) methodology and performed meta-analyses when appropriate. The Task Force then created a consensus statement by considering the available evidence as well as balancing benefits and harms to guide the final recommendations.

Methods

Overview

We conducted a systematic review and, when appropriate, meta-analyses for 3 distinct questions about temperature management (outlined in the section on "Questions Asked"). We completed a bias assessment for all included studies and then used GRADE methodology to evaluate this evidence and develop treatment recommendations. The outcomes of interest were defined and prioritized by the ILCOR ALS Task Force, as part of the evidence review process for the 2015 ILCOR guidelines.

Questions Asked

The literature searches were designed to address the following 3 PICO¹⁵ questions:

- Among patients with ROSC after cardiac arrest in any setting (P), does inducing mild hypothermia (target temperature 32°C-34°C) (I), compared with no targeted temperature management (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year or survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year (O)?
- 2. Among patients with ROSC after cardiac arrest in any setting (P), does induction of hypothermia before some time point (eg, 1 hour after ROSC or before hospital arrival) (I), compared with induction of hypothermia after that time point (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year or survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year (O)?
- 3. Among patients with ROSC after cardiac arrest in any setting (P), does induction and maintenance of hypothermia for any duration other than 24 hours (I), compared with induction and maintenance of hypothermia for a duration of 24 hours (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year or survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year (O)?

Selection of Studies

Information specialists searched PubMed, EMBASE, and the Cochrane Library in December 2013 (questions #2 and #3) and January 2014 (question #1) and again in December 2014 by using the search terms outlined in Appendix A in the <u>online-only Data Supplement</u>.

Data Selection and Extraction

Two reviewers independently screened titles and abstracts that resulted from the search for studies that addressed the question posed by each PICO. Inclusion criteria within each question were chosen on the basis of the amount and type of evidence available. The entire Task Force approved each set of criteria. Disagreement on individual studies was settled via consensus between the reviewers and a facilitator from the Task Force.

- Question #1: For patient populations in which randomized control trials (RCTs) were available (ie, out-of-hospital shockable cardiac arrest), only RCTs were included. Otherwise, observational studies were included for the 2 patient populations in which there were no RCT data: in-hospital cardiac arrest (IHCA) and OHCA with an initial nonshockable rhythm. We did not include studies without a comparator group, studies that did not report separate outcomes for shockable and nonshockable rhythms, or studies that only reported unadjusted outcomes. We chose to exclude studies with a pre-post design because of the significant changes in post-cardiac arrest care over the past several years and the consequent danger of significant confounding based on year of arrest.
- Question #2: Only human RCTs were included. Given the number of human RCTs available for review, observational data was excluded.

• Question #3: Given the lack of human RCT data, all studies with a comparator group were included. Case reports/series were not included.

Studies published only in abstract form were excluded from all 3 questions because of the risk of incomplete reporting. There were no exclusions based on language. Articles were initially included based on title and/or abstract. Subsequently, the manuscript was reviewed to determine whether the article addressed the PICO question and whether all inclusion and no exclusion criteria were met. Inclusion of animal studies were beyond the scope of the current manuscript although we recognize that animal studies have and will continue to provide valuable preliminary and mechanistic data.

Bias Assessment and GRADE Methodology

All included RCTs were assessed for bias based on criteria from the *Cochrane Handbook for Systematic Reviews of Interventions*.¹⁶ Briefly, RCTs were assessed on the adequacy of allocation generation, allocation concealment, blinding of participants, blinding of outcome assessors, completeness of follow-up, selectivity of outcome reporting, and a final category for "other" sources of bias. Observational studies were assessed for the presence of appropriate eligibility criteria, clear exposure and outcome definitions, confounding, and completeness of follow-up.¹⁷ The results of the bias assessments are detailed in the Appendixes in the <u>online-only</u> <u>Data Supplement</u>. The overall quality of evidence was summarized using the GRADE approach and online tools.¹⁸ Briefly, the GRADE approach assesses the combined quality of the evidence, or confidence in the estimates of effect, across individual outcomes by evaluation for risk of bias, indirectness, imprecision and inconsistency, as well as other considerations of the included studies. In each category the evidence for a given outcome can be rated as being free of serious concerns or downgraded by 1 or 2 levels for serious or very serious concerns respectively. The quality of evidence across each outcome is rated as very low, low, moderate or high based on these considerations. RCTs start as high quality and observational studies start as low quality and can then be upgraded or downgraded based on the above criteria. The details of the current GRADE evaluations are provided in the Appendixes in the <u>online-only Data Supplement</u>. The GRADE approach, inclusive of definitions and details of the above, is described in extensive detail at www.gradeworkinggroup.org. In this manuscript, for the sake of consistency we chose to report mortality and poor neurological outcome throughout the manuscript, acknowledging that this differs from the phrasing of the PICO question outcomes in some cases.

Meta-analysis

Meta-analyses were conducted when the included RCTs were judged to be comparable in terms of patients, interventions, comparisons, and outcomes. To be conservative, we assumed a considerable amount of heterogeneity and used random-effects models for all analyses. All plots and estimates were calculated with RevMan version 5.2, and data are summarized as relative risks (RR) or odds ratios (OR) with 95% confidence intervals (95% CI).

Development of the Treatment Recommendations

The GRADE approach was used to grade the strength of recommendations and inform the language of the treatment recommendations.¹⁹ The evidence reviewers drafted a statement of the consensus on science and treatment recommendations, which was then reviewed and revised by the Task Force through an iterative process. The final advisory statement was voted on and

approved by the members of the Task Force. A majority rule was applied, though the vote was close to unanimous for all recommendations.

Results and Recommendations (Consensus on Science)

Question #1: Does Mild Hypothermia Compared With No Targeted Temperature Management Improve Outcome?

Evidence

The search yielded a total of 5,045 studies. Of these, 6 RCTs and 5 observational studies were included for bias assessment (online-only Data Supplement: see Appendix B for study selection flow diagram, Appendix C for study overview, and Appendix D for bias assessment). One small feasibility RCT was not included in the bias assessment because the intervention group received cooling only until the target temperature was reached or for 4 hours, whichever came first.²⁰ After bias assessment, 1 RCT was not considered further because of a high risk of bias as outlined in Appendix D of the <u>online-only Data Supplement</u>.²¹ We used the remaining 5 RCTs to assess the evidence for temperature management in OHCA.^{8,9,12,22,23} Five observational studies addressed the evidence for targeted temperature management for IHCA²⁴ and OHCA with an initial nonshockable rhythm.²⁵⁻²⁸ We organized the available evidence into separate but related categories:

- Evidence to support targeted temperature management versus no targeted temperature management for
 - a. Adult patients with ROSC after OHCA with an initially shockable rhythm
 - b. Adult patients with ROSC after OHCA with an initially nonshockable rhythm
 - c. Adult patients with ROSC after IHCA with any initial rhythm

2. In patients for whom targeted temperature management is performed, what is the ideal target temperature?

OHCA With an Initial Shockable Rhythm

One RCT⁸ and 1 quasi-randomized trial⁹ enrolling a total of 352 patients provided overall lowquality evidence for decreased poor neurologic outcome in patients with OHCA with ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT) as an initial rhythm who were cooled to 32°C to 34°C compared with no cooling. The pooled RR was 0.75 (95% CI, 0.61–0.92) for mortality and 0.73 (95% CI, 0.60–0.88) for poor neurologic/functional outcome at 6 months⁸ or hospital discharge⁹ (online-only Data Supplement: see Appendix F for forest plots). One additional small RCT of 61 patients evaluated hypothermia in the setting of high-volume hemofiltration and found no increase in survival at 6 months.²³ This study was downgraded for potential confounding because patients received concomitant hemofiltration with high volumes of cold fluid, and this trial was therefore not included in the meta-analysis.

OHCA With an Initial Nonshockable Rhythm

Three cohort studies including a total of 1,034 patients provided overall very low-quality evidence for no difference in poor neurologic outcome in patients with nonshockable OHCA (adjusted pooled OR, 0.90 [95% CI, 0.45–1.82]; forest plot in Appendix F of the <u>online-only</u> <u>Data Supplement</u>).²⁵⁻²⁷ One additional retrospective study using a large registry, analyzing 1,830 patients, provided very low-quality evidence for an increase in poor neurologic outcome in patients with nonshockable OHCA (adjusted OR 1.44 [95% CI, 1.04–2.01].²⁸ These data were not pooled with the above studies due to very high risk of bias (inconsistent results with different

analyses reported from the study). One of these studies reported mortality and provided overall very low-quality evidence for decreased mortality at 6 months (adjusted OR, 0.56; 95% CI, 0.34-0.93).²⁵

In-hospital Cardiac Arrest

One retrospective cohort study of 8,316 IHCA patients with any initial rhythm provided overall very low-quality evidence for no difference in mortality at hospital discharge (adjusted OR, 1.11; 95% CI, 0.81–1.54) or poor neurologic outcome (adjusted OR, 1.08; 95% CI, 0.76–1.54).²⁴

Evidence for an Ideal Temperature When Using Targeted Temperature Management?

One RCT of 939 patients compared target temperatures of 33°C and 36°C in adult patients with OHCA of any initial rhythm except unwitnessed asystole.¹² This study provided moderatequality evidence for no decrease in mortality at 180 days (RR, 1.01; 95% CI, 0.88–1.16) or poor neurologic outcome at 6 months (RR, 1.03; 95% CI, 0.91–1.16) in the 33°C compared with the 36°C group. One additional small pilot RCT of 36 patients compared 32°C and 34°C in patients with OHCA and an initial shockable rhythm or asystole. This study provides overall very lowquality evidence for decreased mortality with 32°C compared with 34°C (RR, 0.63; 95% CI, 0.40–0.97) but no decrease in poor neurologic outcome (RR, 0.64; 95% CI, 0.38–1.09) or increase in survival free from severe dependence (RR, 0.32; 95% CI, 0.08–1.37).²² However, given the very small sample size, the findings of this study are very imprecise.

Conclusions

One RCT and 1 quasi-RCT provide overall low-quality evidence to use targeted temperature management after ROSC from OHCA with an initial shockable rhythm. Although there is no direct evidence supporting this therapy in nonshockable OHCA or IHCA, indirect evidence extrapolated from studies of shockable OHCA may support this strategy. There is no good direct evidence that suggests that one target temperature within the 32°C to 36°C range is superior to another.

Recommendations

We *recommend* targeted temperature management as opposed to no targeted temperature management for adults with OHCA with an initial shockable rhythm who remain unresponsive after ROSC (strong recommendation, low-quality evidence).

We *suggest* targeted temperature management as opposed to no targeted temperature management for adults with OHCA with an initial nonshockable rhythm (weak recommendation, very low-quality evidence) who remain unresponsive after ROSC.

We *suggest* targeted temperature management as opposed to no targeted temperature management for adults with IHCA (weak recommendation, very low-quality evidence) with any initial rhythm who remain unresponsive after ROSC.

We *recommend* selecting and maintaining a constant, target temperature between 32°C and 36°C for those patients in whom temperature control is used (strong recommendation, moderate-

quality evidence). Whether certain subpopulations of cardiac arrest patients may benefit from lower (32°C–34°C) or higher (36°C) temperatures remains unknown, and further research may help elucidate this.

Question #2: Does Early (Prehospital) Induction of Targeted Temperature Management Affect Outcome?

Evidence

Seven RCTs were identified for inclusion from 2,286 studies generated from the search (onlineonly Data Supplement: see Appendix B for study selection flow diagram). Five²⁹⁻³³ of the 7 studies used cold intravenous fluids after ROSC to induce hypothermia, 1 study used cold intravenous fluid during resuscitation³⁴ and 1 study³⁵ used intra-arrest intranasal cooling. The volume of cold fluid ranged from 20 to 30 mL/kg and up to 2 L though some patients did not receive the full amount prior to hospital arrival. One small feasibility trial was not included.³⁶ All 7 included studies suffered from the unavoidable lack of blinding of the clinical team, and 3 also failed to blind the outcomes assessors (online-only Data Supplement: see Appendixes C, D, and E for study overview, bias assessments, and GRADE tables).

Five of the studies, enrolling a total of 1,867 patients with OHCA, evaluated the outcome of poor neurologic outcome. Meta-analysis of these studies showed that initiation of induced hypothermia in the prehospital environment did not differ from no initiation of prehospital induced hypothermia for poor neurologic outcome (RR, 1.00; 95% CI, 0.95–1.06). All 7 trials examined the outcome of mortality, and meta-analysis of the total of 2,237 patients provided moderate-quality evidence demonstrating no overall difference in mortality for patients treated with prehospital cooling (RR, 0.98; 95% CI, 0.92–1.04) compared to those who did not receive

prehospital cooling. Forest plots are presented in Appendix F of the <u>online-only Data</u> <u>Supplement</u>. When reviewed individually, none of the trials found an effect on either poor neurologic outcome or mortality.

Meta-analysis of 4 RCTs that examined the outcome of re-arrest demonstrated an increased risk for re-arrest among patients who received prehospital induced hypothermia (RR, 1.22; 95% CI, 1.01–1.46). This result was driven by data from the largest trial.³³ Six trials included pulmonary edema as an outcome. Three of these recorded no pulmonary edema in either group. The remaining three did record patients who had pulmonary edema. Two small pilot trials^{29, 34} found no statistically significant difference between the groups whereas the larger trial by Kim et al found an increase in pulmonary edema in patients who received prehospital cooling (RR, 1.34; 95% CI, 1.15–1.57).³³ Forest plots are presented in Appendix F of the <u>online-only Data</u> Supplement.

Conclusions

In 7 RCTs, providing overall moderate-quality evidence, prehospital induction of mild hypothermia did not reduce poor neurologic outcome or mortality after OHCA. The largest study³³ found an increased risk of pulmonary edema and re-arrest with prehospital induction of mild hypothermia using rapid infusion of cold intravenous fluid.

Recommendation

We recommend against routine use of prehospital cooling with rapid infusion of large volumes of cold intravenous fluid immediately after ROSC (strong recommendation, moderate-quality evidence). Other cooling strategies and cooling during cardiopulmonary resuscitation in the prehospital setting have not been studied adequately, and further research in this area is needed.

Question #3: Does the Duration of Targeted Temperature Management Affect Outcome

Evidence

We found no human interventional studies comparing different durations of targeted temperature management after cardiac arrest with ROSC (online-only Data Supplement: see Appendix B for study flow chart). One observational study provided overall very low-quality evidence for no difference in duration of hypothermia in those with a good versus a poor neurologic outcome³⁷ and 1 observational study provided overall very low-quality evidence for no difference in mortality or poor neurological outcome with 24 hours compared with 72 hours of hypothermia³⁸ (online-only Data Supplement: see Appendixes C and D for study overview and bias assessment). Previous trials for targeted temperature management ranged from 12 to 28 hours depending on the trial. One trial (Nielsen et al¹²) provided strict normothermia (<37.5°C) after rewarming until 72 hours after ROSC. However this intervention was applied to both groups and therefore treatment effect cannot be assessed.

Conclusion

There are no data that can be used to compare different durations of targeted temperature management in humans.

Recommendation

We suggest that if targeted temperature management is used, duration should be at least 24 hours as done in the 2 largest previous RCTs (weak recommendation, very low-quality evidence).^{8,12}

Discussion and Knowledge Gaps

Although some recent reports suggest modest improvements in outcome over the past decade,^{39,40} cardiac arrest continues to be associated with high morbidity and mortality.² The recommendations within this statement should be viewed in light of the very poor prognosis in this patient population and the fact that there are currently very few proven interventions for patients after cardiac arrest. The execution of well-controlled RCTs in post-cardiac arrest patients is challenging due to the complexity, heterogeneity, and high acuity of the patients. Moreover, the inability to blind clinicians to treatments such as temperature management adds an additional layer of difficulty when weighing the evidence.

The most notable difference between the trials by Bernard et al⁹ and the Hypothermia After Cardiac Arrest (HACA) group⁸ (both published in 2002) compared with the trial by Nielsen et al¹² (published in 2013) is that the earlier studies did not adequately control temperature in the control arm. Average temperatures were >37°C in the control groups in both the study by Bernard et al and the HACA group, whereas tight control was maintained in the 36°C group in the trial by Nielsen et al. Although there is no high-quality evidence, some observational studies have found an association between post-cardiac arrest fever and poor outcome.⁴¹⁻⁴⁷

The second notable difference between the Bernard et al and HACA trials compared with the trial by Nielsen et al was the use of a blinded neurologic prognosticator instead of reliance on unblinded clinical teams. For both Bernard et al and the HACA investigators, clinical teams aware of the treatment allocation provided families with the prognostic information that informed decisions regarding withdrawal of care; moreover, the timing of prognosis and decision-making was not controlled for. In contrast, Nielsen et al minimized this bias by having

neurologists blinded to the treatment allocation evaluate the patient at 72 hours and provide prognostic information at that time. Of note, none of the studies provided information on whether the total dosage of preceding sedation was different in the 2 allocation groups at the time of neuroprognostication.

Although the results of the trial by Nielsen et al¹⁵ suggest that controlling temperature at 33°C is not superior to strict temperature control at 36°C, whether this is true for patients who differ from the patient population included in the study is not entirely clear. Patients in the trial by Nielsen et al had higher rates of bystander cardiopulmonary resuscitation than were seen in the HACA trial, for example, (73% compared with 43%–49%). Median no-flow time in patients receiving bystander cardiopulmonary resuscitation was short in the trial by Nielsen et al but this parameter was not reported in other post-cardiac arrest trials and therefore is not comparable. The possibility remains that some unidentified subgroups of patients may benefit from a specific target temperature. We ultimately recommend targeted temperature management at a constant temperature within the range of 32°C to 36°C (the temperature range used in published studies) for comatose post-cardiac arrest patients. Although we recommend that a constant temperature should be maintained during TTM, we also recognize that potential side effects may appropriately lead a clinician to adjust from a lower to higher target temperature despite no direct evidence for this approach. For example, if overt bleeding were to occur at a temperature of 32°C, then one may decide to increase the target temperature to theoretically mitigate this potential side effects. The weaknesses in existing studies illustrate potential knowledge gaps and areas for future research. Of note, the recommendation to control temperature post-cardiac arrest is distinct from mere prevention or treatment of fever which has not been studied in any of the randomized controlled trials.

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With respect to the timing of targeted temperature management, the main confounder for the majority of analyzed RCTs is the rapid uncontrolled infusion of a large volume of cold fluid (as opposed to other cooling methods) immediately after ROSC for OHCA. This method for cooling was used for all of the pooled studies with the exception of 1 relatively small pilot study that provided intranasal cooling.³⁵ The trials using cold fluid specified either amounts up to 2 L or 20 to 30 mL/kg, although not all patients received the full amount prior to hospital arrival. The rapid infusion of large amounts of cold fluid immediately after achieving ROSC and in the prehospital setting could theoretically be harmful, as indicated by increased rates of re-arrest and pulmonary edema in the largest of the included studies, and could therefore negate any potential benefits of early targeted temperature management. Whether similar issues exist with rapid cold fluid infusion in the in-hospital setting is unknown; however, any potential harm from this therapy may relate specifically to the prehospital setting, where there may be less control over the environment, fewer personnel, and reduced monitoring capabilities. We recommend against the use of rapid infusion of large volumes of cold fluid immediately after ROSC for induction of hypothermia in the prehospital setting but recognize that other cooling methods were not adequately evaluated and therefore are not commented on. Thus, further investigation of cooling methods and location may be warranted.

Finally, evidence for a specific duration of targeted temperature management is lacking. In the absence of evidence, we believe that choosing a duration of therapy similar to previous RCTs in targeted temperature management is the most appropriate approach. Human studies specifically focused on different durations have not been performed, and this remains a knowledge gap.

There are many knowledge gaps, and we suggest the following key questions for future research:

- Are there subpopulations in which aggressive prevention of fever instead of targeted temperature management (32°C–36°C) is justified?
- Are there subpopulations in which a temperature of 32°C to 34°C is beneficial compared with 36°C? For example, are patients with more severe neurologic injury more likely to benefit from a lower target temperature?
- Are there subpopulations in which a temperature of 36°C is beneficial compared with 32°C to 34°C, such as patients with hemodynamic instability or bleeding?
- Is there utility in intra-arrest cooling or prehospital cooling (to between 32°C and 36°C) by means other than the rapid infusion of large volumes of cold intravenous fluids immediately after ROSC? Might this be helpful in patients for whom transport time to a hospital is longer than average (ie, patients in rural areas)?
- What is the ideal duration of targeted temperature management and of fever prevention?
- Does use of targeted temperature management, including various temperature targets, have an effect on long term neurocognitive and functional outcomes?
- Does the choice of sedation particularly with respect to different targeted temperatures impact or influence outcome?
- What are the reasons for the discrepancy between experimental/animal data and human clinical trials on the effects of targeted temperature management?

Summary Recommendations

Based on the published evidence to date, the ALS Task Force of ILCOR made the following recommendations in February 2015:

- We recommend targeted temperature management as opposed to no targeted temperature management for adults with OHCA with an initial shockable rhythm who remain unresponsive after ROSC (strong recommendation, low-quality evidence).
- We suggest targeted temperature management for adults with OHCA with an initial nonshockable rhythm who remain unresponsive after ROSC (weak recommendation, low-quality evidence).
- We suggest targeted temperature management for adults with IHCA with any initial rhythm who remain unresponsive after ROSC (weak recommendation, very low-quality evidence).
- We recommend selecting and maintaining a constant target temperature between 32°C and 36°C for those patients in whom targeted temperature management is used (strong recommendation, moderate-quality evidence).
- We recommend against routine use of prehospital cooling with rapid infusion of large volumes of cold intravenous fluid immediately after ROSC (strong recommendation, moderate-quality evidence).
- We suggest that if targeted temperature management is used, duration should be at least 24 hours as done in the 2 largest previous RCTs.

Acknowledgments

Besides the authors (M.W. Donnino, C.W. Callaway, J. Soar, and J.P. Nolan), members of the

ILCOR ALS Task Force include: Mayuki Aibiki, Bernd W. Böttiger, Steven C. Brooks, Charles

D. Deakin, Saul Drajer, Walter Kloeck, Laurie J. Morrison, Robert W. Neumar, Tonia C.

Nicholson, Brian J. O'Neil, Edison F. Paiva, Michael Parr, Tzong-Luen Wang, and Jonathan

Witt.

We would like to acknowledge Christine Neilson and the team at St Michael's Hospital in Toronto for their literature searches.

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Member	Employment	Research Grant	Research Support	Bureau/ Honoraria	Expert	Ownersnip Interest	Advisory Board	Other
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	Center							
Lars W.	Beth Israel	None	None	None	None	None	None	None
Andersen	Deaconess Medical							
Katharina M	Center Both Jarool	Nono	Nono	Nono	Nono	Nono	Nono	Nono
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Xanthos	University of							
	Chicago College of							
	Pharmacy							

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$10,000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$10,000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

Reviewer Disclosures

			Other Research	Speakers'	Expert	Ownership	Consultant/	
Reviewer	Employment	Research Grant	Support	Honoraria	Witness	Interest	Board	Other
Gavin	Warwick Medical	Funding from	None	None	None	None	None	None
Perkins	School and Heart	National Institute for						
	of England NHS	Health Research†						
	Foundation Trust							
	(UNITED							
	KINGDOM)							
Niklas	Helsingborg	Swedish Heart and	None	Bard	None	None	None	None
Nielsen	Hospital	Lung Foundation†;		Medical*				
	(SWEDEN)	AFA Insurance						
		Foundation†;						
		Swedish Research						
		Council†						
Kjetil	University of	None	None	Bard	None	None	None	None
Sunde	Oslo (NORWAY)			Medical*				

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$10,000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$10,000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition. *Modest.

+Significant.

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Appendix A: Search Strategies

Question #1:

PubMed: (Search Completed: January 2015)

("paramedic cooling"[TIAB] OR "field hypothermia"[TIAB] OR "hypothermia, induced"[MeSH] OR "targeted temperature management" [TIAB] OR "therapeutic hypothermia" [TIAB] OR "hypothermia therapy"[TIAB] OR "whole body cooling"[TIAB] OR "whole-body cooling"[TIAB] OR ((cool*[TIAB] OR cold[TIAB] OR "target temperature"[TIAB] OR "body temperature"[MeSH] OR "body temperature" [TIAB]) AND ("brain injuries" [MeSH] OR "brain injury" [TIAB] OR "brain injuries" [TIAB] OR "neurological status" [TIAB] OR "neurological outcome" [TIAB] OR "neurological outcomes" [TIAB] OR "functional outcome" [TIAB] OR "functional outcomes" [TIAB] OR neuroprotect*[TIAB] OR "hypoxia-ischemia, brain"[MeSH] OR "hypoxic-ischemic encephalopathy" [TIAB] OR "cognitive impairment" [TIAB] OR "cognitive impairments" [TIAB] OR "cognitive function" [TIAB] OR "outcome and process assessment (health care)" [MeSH] OR "treatment outcome"[MeSH] OR "Glasgow Outcome Scale"[MeSH]))) AND ("out-of-hospital cardiac arrest"[MeSH] OR "out of hospital cardiac arrest"[TIAB] OR "out-of-hospital cardiac arrest"[TIAB] OR "return of spontaneous circulation"[TIAB] OR ROSC[TIAB] OR "heart arrest"[MeSH] OR "cardiac arrest"[TIAB] OR "cardiac arrests"[TIAB] OR "cardiovascular arrest"[TIAB] OR "cardiovascular arrests"[TIAB] OR "heart arrest"[TIAB] OR "heart arrests"[TIAB] OR "asystole" [TIAB] OR "pulseless electrical activity" [TIAB] OR "cardiopulmonary arrest" [TIAB] OR "cardiopulmonary arrests" [TIAB] OR "advanced cardiac life support" [MeSH] OR "advanced cardiac life support" [TIAB] OR "ACLS" [TIAB] OR "ventricular fibrillation" [MeSH] OR "cardiopulmonary resuscitation" [MeSH] OR "cardiopulmonary resuscitation" [TIAB] OR CPR[TIAB] OR "heart massage"[MeSH]) NOT ((animal[MeSH] NOT humans[MeSH])) NOT ("letter"[publication type] OR "comment"[publication type] OR "editorial"[publication type] or "Case Reports" [publication type])

Embase: (Search Completed: January 2015)

('heart arrest'/exp OR "cardiac arrest":ti,ab OR "cardiac arrests":ti,ab OR "cardiovascular arrest":ti,ab OR "cardiovascular arrests":ti,ab OR "heart arrest":ti,ab OR "heart arrests":ti,ab OR "asystole":ti,ab OR "pulseless electrical activity":ti,ab OR "cardiopulmonary arrest":ti,ab OR "cardiopulmonary arrests":ti,ab OR 'heart ventricle fibrillation'/exp OR "out of hospital cardiac arrest":ti,ab OR "out-of-hospital cardiac arrest":ti,ab OR 'return of spontaneous circulation'/exp OR "return of spontaneous circulation":ti,ab OR ROSC:ti,ab OR 'resuscitation'/exp OR resuscitat*:ti,ab OR "advanced cardiac life support":ti,ab OR "ACLS":ti,ab OR CPR:ti,ab OR 'heart massage'/exp) AND (hypothermia:ti,ab OR "targeted temperature management":ti,ab OR "whole body cooling":ti,ab OR "whole-body cooling":ti,ab OR cool*:ab,ti OR 'induced hypothermia'/exp OR "paramedic cooling":ti,ab OR ((cool*:ti,ab OR cold:ti,ab OR 'cooling'/de OR 'body temperature'/exp OR "body temperature":ti,ab) AND ('brain injury'/de OR "brain injury":ti,ab OR "brain injuries":ti,ab OR "neurological status":ti,ab OR neuroprotect*:ti,ab OR 'hypoxic ischemic encephalopathy'/exp OR "hypoxic-ischemic encephalopathy":ti,ab OR Donnino et al | 2 Temperature Management After Cardiac Arrest Online-Only Data Supplement

"neurological outcome":ti,ab OR "neurological outcomes":ti,ab OR "functional outcome":ti,ab OR "functional outcomes":ti,ab OR 'cognitive defect'/exp OR "cognitive impairment":ti,ab OR "cognitive function":ti,ab OR 'treatment outcome'/exp OR 'Glasgow outcome scale'/exp))) NOT ('animal'/exp NOT 'human'/exp) NOT ([editorial]/lim OR [letter]/lim OR 'case report'/de) AND [Embase]/lim

<u>Cochrane</u>: (Search Completed: January 2015)

("paramedic cooling":ti,ab OR "field hypothermia":ti,ab OR [mh "hypothermia, induced"] OR "targeted temperature management":ti,ab OR "therapeutic hypothermia":ti,ab OR "hypothermia therapy":ti,ab OR "whole body cooling":ti,ab OR "whole-body cooling":ti,ab OR ((cool*:ti,ab OR cold:ti,ab OR "target temperature":ti,ab OR [mh "body temperature"] OR "body temperature":ti,ab) AND ([mh "brain injuries"] OR "brain injury":ti,ab OR "brain injuries":ti,ab OR "neurological status":ti,ab OR "neurological outcome":ti,ab OR "neurological outcomes":ti,ab OR "functional outcome":ti,ab OR "functional outcomes":ti,ab OR neuroprotect*:ti,ab OR [mh "hypoxia-ischemia, brain"] OR "hypoxic-ischemic encephalopathy":ti,ab OR "cognitive impairment":ti,ab OR "cognitive impairments":ti,ab OR "cognitive function":ti,ab OR [mh "outcome and process assessment (health care)"] OR [mh "treatment outcome"] OR [mh "Glasgow Outcome Scale"]))) AND ([mh "out-of-hospital cardiac arrest"] OR "out of hospital cardiac arrest":ti,ab OR "out-of-hospital cardiac arrest":ti,ab OR "return of spontaneous circulation":ti,ab OR ROSC:ti,ab OR [mh "heart arrest"] OR "cardiac arrest":ti,ab OR "cardiac arrests":ti,ab OR "cardiovascular arrest":ti,ab OR "cardiovascular arrests":ti,ab OR "heart arrest":ti,ab OR "heart arrests":ti,ab OR "asystole":ti,ab OR "pulseless electrical activity":ti,ab OR "cardiopulmonary arrest":ti,ab OR "cardiopulmonary arrests":ti,ab OR [mh "advanced cardiac life support"] OR "advanced cardiac life support":ti,ab OR "ACLS":ti,ab OR [mh "ventricular fibrillation"] OR [mh "cardiopulmonary resuscitation"] OR "cardiopulmonary resuscitation":ti,ab OR CPR:ti,ab OR [mh "heart massage"])

Question #2:

PubMed: (Search Completed: January 2015)

("paramedic cooling"[TIAB] OR "field hypothermia"[TIAB] OR "hypothermia, induced"[MeSH] OR "targeted temperature management"[TIAB] OR "therapeutic hypothermia"[TIAB] OR "hypothermia therapy"[TIAB] OR "whole body cooling"[TIAB] OR "whole-body cooling"[TIAB] OR ((cool*[TIAB] OR cold[TIAB]) AND ("brain injuries"[MeSH] OR "brain injury"[TIAB] OR "brain injuries"[TIAB] OR "neurological status"[TIAB] OR neuroprotect*[TIAB] OR "hypoxia-ischemia, brain"[MeSH] OR "hypoxic-ischemic encephalopathy"[TIAB] OR impair*[TIAB] OR impare*[TIAB]))) AND ("heart arrest"[MeSH] OR "cardiac arrest"[TIAB] OR "cardiac arrests"[TIAB] OR "cardiovascular arrest"[MeSH] OR "cardiovascular arrests"[TIAB] OR "heart arrest"[TIAB] OR "heart arrests"[TIAB] OR "asystole"[TIAB] OR "pulseless electrical activity"[TIAB] OR "cardiopulmonary arrest"[TIAB] OR "cardiopulmonary arrests"[TIAB] OR "advanced cardiac life support"[MeSH] OR "advanced cardiac life support"[TIAB] OR "ACLS"[TIAB] OR "ventricular fibrillation"[MeSH] OR "cardiopulmonary resuscitation"[MeSH] OR "cardiopulmonary resuscitation"[TIAB] OR CPR[TIAB] OR "heart massage"[MeSH]) AND (initiat*[TIAB] OR induc*[TIAB] OR early[TIAB] OR earlie*[TIAB] OR late[TIAB] OR later[TIAB] OR length[TIAB] OR prolong*[TIAB] OR hour*[TIAB] OR hrs[TIAB] OR minute*[TIAB] OR rapid*[TIAB] OR fast*[TIAB] OR quick*[TIAB] OR slow*[TIAB] OR time[TIAB] OR timing[TIAB] OR speed[TIAB] OR rate[TIAB] OR "time factors"[MeSH] OR "time-to-treatment"[MeSH] OR delay*[TIAB] OR "emergency medical technicians"[MeSH] OR "emergency medic"[TIAB] OR "emergency medical"[TIAB] OR "EMS"[TIAB] OR "EMTT"[TIAB] OR "pre-hospital"[TIAB] OR prehospital[TIAB] OR paramedic*[TIAB] OR "out-of-hospital"[TIAB] OR "out of hospital"[TIAB]) NOT ((animal[MeSH] NOT humans[MeSH]) OR rabbit*[TIAB] OR mouse[TIAB] OR mice[TIAB] OR swine[TIAB] OR pig[TIAB] OR pigs[TIAB] OR dog[TIAB] OR "animal model"[TIAB] OR "animal models"[TIAB]) NOT ("letter"[pt] OR "comment"[pt] OR "editorial"[pt] or "case reports"[ptyp])

Embase: (Search Completed: January 2015)

(('heart arrest'/exp OR "cardiac arrest":ti,ab OR "cardiac arrests":ti,ab OR "cardiovascular arrest":ti,ab OR "cardiovascular arrests":ti,ab OR "heart arrest":ti,ab OR "heart arrests":ti,ab OR "asystole":ti,ab OR "pulseless electrical activity":ti,ab OR "cardiopulmonary arrest":ti,ab OR "cardiopulmonary arrests":ti,ab OR 'heart ventricle fibrillation'/exp OR 'resuscitation'/exp OR resuscitat*:ti,ab OR "advanced cardiac life support":ti,ab OR "ACLS":ti,ab OR CPR:ti,ab OR 'heart massage'/exp) AND (initiat*;ti,ab OR induc*:ti,ab OR early:ti,ab OR earlie*:ti,ab OR late:ti,ab OR later:ti,ab OR length:ti,ab OR prolong*:ti,ab OR hour*:ti,ab OR hrs:ti,ab OR minute*:ti,ab OR rapid*:ti,ab OR fast*:ti,ab OR quick*:ti,ab OR slow*:ti,ab OR time:ti,ab OR timing:ti,ab OR speed:ti,ab OR rate:ti,ab OR delay*:ti,ab OR 'therapy delay'/exp OR 'time'/exp OR 'time to treatment'/exp OR 'rescue personnel'/exp OR "emergency medic":ti,ab OR "emergency medical":ti,ab OR "EMS":ti,ab OR "EMT":ti,ab OR "pre-hospital":ti,ab OR prehospital:ti,ab OR paramedic*:ti,ab OR "out-of-hospital":ti,ab OR "out of hospital":ti,ab) AND (hypothermia:ti,ab OR "targeted temperature management":ti,ab OR "whole body cooling":ti,ab OR "whole-body cooling":ti,ab OR cool*:ab,ti OR 'induced hypothermia'/exp OR "paramedic cooling":ti,ab OR ((cool*:ti,ab OR cold:ti,ab OR 'cooling'/de) AND ('brain injury'/de OR "brain injury":ti,ab OR "brain injuries":ti,ab OR "neurological status":ti,ab OR neuroprotect*:ti,ab OR 'hypoxic ischemic encephalopathy'/exp OR "hypoxic-ischemic encephalopathy":ti,ab OR impair*:ti,ab OR impare*:ti,ab)))) OR ('heart arrest'/exp OR "cardiac arrest":ti,ab OR "cardiac arrests":ti,ab OR "cardiovascular arrest":ti,ab OR "cardiovascular arrests":ti,ab OR "heart arrest":ti,ab OR "heart arrests":ti,ab OR "asystole":ti,ab OR "pulseless electrical activity":ti,ab OR "cardiopulmonary arrest":ti,ab OR "cardiopulmonary arrests":ti,ab OR 'heart ventricle fibrillation'/exp OR 'resuscitation'/exp OR resuscitat*:ti,ab OR "advanced cardiac life support":ti,ab OR "ACLS":ti,ab OR CPR:ti,ab OR 'heart massage'/exp) AND (('therapy delay'/exp OR 'time'/exp OR 'time to treatment'/exp OR 'rescue personnel'/exp OR "emergency medic":ti,ab OR "emergency medical":ti,ab OR "EMS":ti,ab OR "EMT":ti,ab OR "pre-hospital":ti,ab OR prehospital:ti,ab OR paramedic*:ti,ab OR "out-of-hospital":ti,ab OR "out of hospital":ti,ab) AND ('induced hypothermia'/exp OR "paramedic cooling":ti,ab OR ((cool*:ti,ab OR cold:ti,ab OR 'cooling'/de) AND ('brain injury'/de OR "brain injury":ti,ab OR "brain injuries":ti,ab OR "neurological status":ti,ab OR neuroprotect*:ti,ab OR 'hypoxic ischemic encephalopathy'/exp OR "hypoxicischemic encephalopathy":ti,ab OR impair*:ti,ab OR impare*:ti,ab))) OR ((initiat* OR induc* OR

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early OR earlie^{*} OR late OR later OR length OR prolong^{*} OR hour^{*} OR hrs OR minute^{*} OR rapid^{*} OR fast^{*} OR quick^{*} OR slow^{*} OR time OR timing OR speed OR rate OR delay^{*}) NEAR/5 (hypothermia OR "targeted temperature management" OR "whole body cooling" OR "or "whole-body cooling" OR cool^{*})):ti,ab) NOT ('animal'/exp NOT 'human'/exp) NOT ([editorial]/lim OR [letter]/lim OR 'case report'/de) AND [Embase]/lim

Cochrane: (Search Completed: January 2015)

("paramedic cooling":ti,ab OR "field hypothermia"ti,ab OR [mh "hypothermia, induced"] OR "targeted temperature management":ti,ab OR "therapeutic hypothermia":ti,ab OR "hypothermia therapy":ti,ab OR "whole body cooling":ti,ab OR "whole-body cooling":ti,ab OR ((cool*:ti,ab OR cold:ti,ab) AND ([mh "brain injuries"] OR "brain injury":ti,ab OR "brain injuries":ti,ab OR "neurological status":ti,ab OR neuroprotect*:ti,ab OR [mh "hypoxia-ischemia, brain"] OR "hypoxic-ischemic encephalopathy":ti,ab OR impair*:ti,ab OR impare*:ti,ab))) AND ([mh "heart arrest"] OR "cardiac arrest":ti,ab OR "cardiac arrests":ti,ab OR "cardiovascular arrest":ti,ab OR "cardiovascular arrests":ti,ab OR "heart arrest":ti,ab OR "heart arrests":ti,ab OR "asystole":ti,ab OR "pulseless electrical activity":ti,ab OR "cardiopulmonary arrest":ti,ab OR "cardiopulmonary arrests":ti,ab OR [mh "advanced cardiac life support"] OR "advanced cardiac life support":ti,ab OR "ACLS":ti,ab OR [mh "ventricular fibrillation"] OR [mh "cardiopulmonary resuscitation"] OR "cardiopulmonary resuscitation":ti,ab OR CPR:ti,ab OR [mh "heart massage"]) AND (initiat*;ti,ab OR induc*:ti,ab OR early:ti,ab OR earlie*:ti,ab OR late:ti,ab OR later:ti,ab OR length:ti,ab OR prolong*:ti,ab OR hour*:ti,ab OR hrs:ti,ab OR minute*:ti,ab OR rapid*:ti,ab OR fast*:ti,ab OR quick*:ti,ab OR slow*:ti,ab OR time:ti,ab OR timing:ti,ab OR speed:ti,ab OR rate:ti,ab OR [mh "time factors"] OR [mh "time-to-treatment"] OR delay*:ti,ab OR [mh "emergency medical technicians"] OR "emergency medic":ti,ab OR "emergency medical":ti,ab OR "EMS":ti,ab OR "EMT":ti,ab OR "pre-hospital":ti,ab OR prehospital:ti,ab OR paramedic*:ti,ab OR "out-of-hospital":ti,ab OR "out of hospital":ti,ab)

Question #3:

PubMed: (Search Completed: January 2015)

("hypothermia, induced"[MeSH] OR "targeted temperature management"[TIAB] OR "therapeutic hypothermia"[TIAB] OR "hypothermia therapy"[TIAB] OR "whole body cooling"[TIAB] OR "whole-body cooling"[TIAB] OR ((cool*[TIAB] OR cold[TIAB]) AND ("brain injuries/prevention and control"[MeSH] OR neuroprotection[TIAB] OR "hypoxia-ischemia, brain/prevention and control"[MeSH] OR "hypoxic-ischemic encephalopathy"[TIAB]))) AND ("heart arrest"[MeSH] OR "cardiac arrest"[TIAB] OR "cardiovascular arrest"[ITAB] OR "cardiovascular arrests"[TIAB] OR "cardiac arrests"[TIAB] OR "cardiovascular arrest"[TIAB] OR "cardiovascular arrests"[TIAB] OR "heart arrest"[TIAB] OR "heart arrests"[TIAB] OR "asystole"[TIAB] OR "pulseless electrical activity"[TIAB] OR "cardiopulmonary arrest"[TIAB] OR "cardiopulmonary arrests"[TIAB] OR "advanced cardiac life support"[MeSH] OR "advanced cardiac life support"[TIAB] OR "ACLS"[TIAB] OR "ventricular fibrillation"[MeSH] OR "cardiopulmonary resuscitation"[MeSH] OR "cardiopulmonary resuscitation"[TIAB] OR CPR[TIAB] OR "heart massage"[MeSH]) AND (prolong*[TIAB] OR hour*[TIAB] OR hrs[TIAB] OR Donnino et al | 5 Temperature Management After Cardiac Arrest Online-Only Data Supplement

duration*[TIAB] OR "time factors"[MeSH]) NOT ("letter"[pt] OR "comment"[pt] OR "editorial"[pt] or "case reports"[ptyp])

Embase: (Search Completed: January 2015)

('dose time effect relation'/exp OR 'time'/exp OR "thermal dose":ab,ti OR ((duration* OR hour* OR hr* OR prolong* OR short* OR long*) NEAR/10 (hypotherm* OR cool*)):ab,ti) AND ('induced hypothermia'/exp OR "targeted temperature management":ab,ti OR "therapeutic hypothermia":ab,ti OR "hypothermia therapy":ab,ti OR "whole body cooling":ab,ti OR "wholebody cooling":ab,ti OR ((cool*:ab,ti OR cold:ab,ti) AND ('brain injury'/exp OR 'neuroprotection'/exp OR neuroprotection:ab,ti OR 'hypoxic ischemic encephalopathy'/exp OR "hypoxic-ischemic encephalopathy":ab,ti))) AND ('out of hospital cardiac arrest'/exp OR 'heart arrest'/exp OR "heart arrest":ab,ti OR "heart arrests":ab,ti OR "cardiac arrest":ab,ti OR "cardiac arrests":ab,ti OR "cardiovascular arrest":ab,ti OR "cardiovascular arrests":ab,ti OR "asystole":ab,ti OR "pulseless electrical activity":ab,ti OR "cardiopulmonary arrest":ab,ti OR "cardiopulmonary arrests":ab,ti OR CPR:ab,ti OR 'heart stimulation'/exp NOT ([editorial]/lim OR [letter]/lim OR 'case report'/de) AND [Embase]/lim

<u>Cochrane</u>: (Search Completed: January 2015)

([mh "hypothermia, induced"] OR "targeted temperature management":ab,ti OR "therapeutic hypothermia":ab,ti OR "hypothermia therapy":ab,ti OR "whole body cooling":ab,ti OR "wholebody cooling":ab,ti OR ((cool*:ab,ti OR cold:ab,ti) AND ([mh "brain injuries/prevention and control"] OR neuroprotection:ab,ti OR [mh "hypoxia-ischemia, brain/prevention and control"] OR "hypoxic-ischemic encephalopathy":ab,ti))) AND ([mh "heart arrest"] OR "cardiac arrest":ab,ti OR "cardiac arrests":ab,ti OR "cardiovascular arrest":ab,ti OR "cardiovascular arrests":ab,ti OR "heart arrest":ab,ti OR "heart arrests":ab,ti OR "asystole":ab,ti OR "pulseless electrical activity":ab,ti OR "cardiopulmonary arrest":ab,ti OR "cardiopulmonary arrests":ab,ti OR [mh "advanced cardiac life support"] OR "advanced cardiac life support":ab,ti OR "ACLS":ab,ti OR [mh "ventricular fibrillation"] OR [mh "cardiopulmonary resuscitation"] OR "cardiopulmonary resuscitation":ab,ti OR CPR:ab,ti OR [mh "heart massage"]) AND (prolong*:ab,ti OR hour*:ab,ti OR hrs:ab,ti OR duration*:ab,ti OR [mh "time factors"]) Donnino et al | 6 Temperature Management After Cardiac Arrest Online-Only Data Supplement

Appendix B: Selection of Articles

Question #1:



OHCA indicates out-of-hospital cardiac arrest; RCT: randomized controlled trial.

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Question #2:



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Question #3:



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Appendix C: Overview of Studies

Question #1:

Study	No. of Patients Analyzed	No. of Patients Screened	Inclusion Criteria	Exclusion Criteria	Experimental Intervention	Control Group	Primary Outcome	Main Clinical Results (Intervention vs Control)
Randomized c	ontrolled tria	ıls						
HACA (2002)[11]	275	3551	Age 18–75 y, OHCA, witnessed arrest, initial shockable rhythm, presumed cardiac origin, collapse-to- CPR interval >5 to <15 min, collapse- to-ROSC interval <60 min	Initial temperature <30°C, pre–cardiac arrest coma, pregnancy, following commands, hypotension >30 min, severe hypoxia >15 min, pre–cardiac arrest terminal illness, unlikely to follow up, concomitant enrollment in another study, EMS-witnessed arrest, preexisting coagulopathy	Surface cooling to 32°C to 34°C within 4 h of ROSC, maintenance for 24 h, then passive rewarming	Normothermia (not otherwise defined)	Good neurologic status at 6 mo (CPC 1–2)	55% vs 39% (P=0.009) Adjusted RR 1.47 (95% CI, 1.09– 1.82)
Bernard et al. (2002)[12]	77	84	OHCA, initial shockable rhythm, persistent coma	Female age <50 y and male age <18 y, systolic blood pressure <90 mm Hg despite vasopressor support, other possible causes of coma, unavailable ICU bed at hospital	Prehospital initiation of surface cooling to 33°C after ROSC, maintenance for 12 h, then active rewarming for 6 h	Target core temperature of 37°C, passive rewarming if spontaneously hypothermic	Good functional status at hospital discharge (discharge to home or acute rehabilitation)	49% vs 26% (P=0.046) Adjusted OR 5.25 (95% CI, 1.47–18.76)
Laurent et al. (2005)[13]	61	244	Age 18–75 y, OHCA, initial shockable or asystolic rhythm, collapse-to-CPR <10 min, collapse- to-ROSC <50 min, presumed cardiac origin	Pregnancy, following commands, preexisting terminal illness	Hemofiltration plus active cooling with replacement fluid to 32°C to 33°C for 24 h, then passive rewarming	Hemofiltration with replacement fluid set to 37°C	Mortality at 6 mo	32% vs 45% (P=0.28)
Zhang et al. (2005)[14]	16	Not reported	Received CPR for cardiac arrest	Previous history of cardiac arrest, trauma	Surface cooling to 33°C for 72 h, then rewarming at 1°C/h	No temperature management	Secondary outcome: functional status at 3 mo	Barthel Index score: 86±6 vs 52±12 (P<0.01)

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Lopez-de- Sa et al. (2012)[15]	36	73	Age >18 y, OHCA, witnessed arrest, presumed cardiac cause, initial shockable or asystolic rhythm, collapse-to-ROSC ≤ 60 min	GCS >8, pregnancy, initial PEA rhythm, preceding terminal illness, other possible causes of coma, shock despite 30 min of administration of inotropes	Induction with ice- cold crystalloid and maintenance of 32°C with endovascular device for 24 h, then rewarming at 0.1°C to 0.3°C/h	Induction with ice-cold crystalloid and maintenance of 34°C with endovascular device for 24 h, then rewarming at 0.1°C to	Good functional status at 6 mo (Barthel Index score ≥60)	44% vs 11% (<i>P</i> =0.12)
Nielsen et al. (2013)[16]	939	1431	OHCA, any initial rhythm, GCS <8	Obvious or suspected pregnancy, known bleeding diathesis, suspected or confirmed acute intracranial bleeding or acute stroke, unwitnessed cardiac arrest with initial rhythm asystole, known limitations in therapy and do- not-resuscitate order, known disease that would make 180-d survival unlikely, known prearrest CPC 3 or 4, >4 h from ROSC to screening, systolic blood pressure <80 mm Hg in spite of fluid loading/vasopressor and/or inotropic medication/ intra-aortic balloon pump, temperature on admission <30°C	Cooling via any method as rapidly as possible to 33°C, maintenance for 28 h, then rewarming ata maximum of 0.5°C/h to 37°C, then active fever prevention until 72 h after the cardiac arrest	0.3°C/h Cooling via any method as rapidly as possible to 36°C, maintenance for 28 h, then rewarming at maximum 0.5°C/h to 37°C, then active fever prevention until 72 h after the cardiac arrest	All-cause mortality through the end of the trial	50% vs 48% (<i>P</i> =0.51) Hazard ratio 1.06 (95% CI, 0.89– 1.28)
Observational	studies							
Testori et al. (2011)[17]	374	N/A	Age >18 y, nontraumatic OHCA in a registry, witnessed, initial nonshockable rhythm	Died <24 h after ROSC, GCS >8, prearrest CPC 3–5, CVA cause of arrest, initial temperature <30°C	Cooling via any method to 32°C to 34°C for 24 h	No temperature management	Good functional status at 6 mo (CPC 1–2)	35% vs 23% (P=0.02) Adjusted OR 1.84 (95% CI, 1.08– 3.13)
Dumas et al. (2011)[18]	437	N/A	OHCA patients in a registry, initial nonshockable rhythm	Trauma	Surface cooling to 32°C to 34°C for 24 h, then passive rewarming for additional 24 h	No temperature management	Good functional status at hospital discharge (CPC 1–2)	15% vs 17% (P=0.48) Adjusted OR 0.71 (95% CI, 0.37– 1.36)

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Vaaher-salo	223	N/A	Age >18 y, OHCA,	Noncomatose patients	Cooling to 33°C,	No temperature	Poor functional	77% vs 82%
et al. (2013)[19]			initial nonshockable rhythm, admitted to the ICU		primarily via endovascular devices although not mandated	management	status (CPC 3, 4, or 5, or death) 1 y after discharge	Adjusted OR 1.16 (95%CI, 0.33–4.12)
Nichol et al. (2013)[20]	8316	N/A	IHCA on general inpatient ward in a registry, index event	Trauma, unknown time of arrest	Coded as "induced hypothermia" in registry. Cooling methods not described	Not coded as "induced hypothermia" in registry	Survival to hospital discharge	27% vs 31% (P=0.29) Adjusted OR 0.90 (95% CI, 0.65–1.23)
Mader et al. (2014)[21]	1830	N/A	CARES registry; Age > 18 y, OHCA, initial nonshockable rhythm, presumed cardiac etiology	Missing data on temperature management or outcome, cardiac arrest at long-term care facility, EMS- witnessed	Coded as "therapeutic hypothermia" in CARES	Not coded as "therapeutic hypothermia" in CARES	Poor functional status at hospital discharge (CPC 3-5)	85% vs. 78% (P<0.0001) Adjusted OR1.44 (95% CI, 1.04-2.01)

CARES indicates Cardiac Arrest registry to Enhance Survival; CI, confidence interval; CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; CVA, cerebrovascular accident; EMS, emergency medical service; GCS, Glasgow Coma Scale; ICU, intensive care unit; IHCA, in-hospital cardiac arrest; N/A, not applicable; OHCA, out-of -hospital cardiac arrest; OR, odds ratio; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; RR, risk ratio.

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Question #2:

Study	No. of	No. of	Inclusion	Exclusion	Experimental	Control	Clinical	Main Clinical
	Patients	Patients	Criteria	Criteria	Intervention	Intervention	Outcome	Kesuits
	Analyzed	Screened						(Intervention vs
	10.7					<u> </u>		Control)
Kim et al.	125	559	OHCA with ROSC,	Traumatic arrest, age	Prehospital rapid	Standard of care	Survival to	21/63 (33%) vs
(2007)[22]			intubation, IV access,	<18 y	infusion of up to 2 L	(60/97 admitted	nospital	18/62 (29%)
			temperature probe		of 4 C normal same	combined group	uischarge	
			$(\text{temperature } > 34^{\circ}\text{C})$			received surface		
			unresponsive, any			cooling in the		
			initial rhythm			hospital)		
Kamaraine	37	44	OHCA with ROSC,	Pregnancy, traumatic	Prehospital rapid	13 of 18 received	Hospital	Hospital survival:
n et al			>9 min until ROSC,	arrest, arrest due to	infusion of 4°C	in-hospital TTM	survival and	8/19 (42%) vs
(2009)[23]			age ≥ 18 y, GSC ≤ 5 ,	intoxication,	Ringer's acetate at a		good	8/18 (44%)
(2007)[23]			any initial rhythm	persistent initial	rate of 100 mL/min		neurologic	
				hypotension after	(10 of 19 received in-		outcome at	CPC 1–2: 42% vs 44%
				RUSC	nospital 11M)		(CPC 1 2)	
							(CFC 1-2)	
Castran at	194	Unknown	OHCA > 18 v	Trauma drug	Prehospital intra-	In-hospital	ROSC rate	ROSC: 35/94 (38%) vs
	191	Children	witnessed, CPR	overdose.	arrest transnasal	cooling (modality	survival to	43/101 (43%) (P=0.48)
			initiated by EMS	cerebrovascular	cooling	according to	discharge,	
(2010)[24]			within 20 min, any	accident, known	_	"institutional	good	Survival to discharge in
			initial rhythm	coagulopathy,		standards," not	neurologic	those admitted alive:
				asphyxia or known		otherwise	outcome at	14/32 (44%) vs 13/42
				requirement for		specified)	discharge	(31%) (<i>P</i> =0.26)
				supplemental			(CPC 1–2)	
				oxygen,				CPC 1–2 in those
				by pothermia do not				admitted anve: $11/32$ (34%) vs 0/42
				attempt-resuscitation				(21%)
				order and intranasal				(P=0.21)
				obstruction. ROSC				(1 -0.21)
				before randomization				

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Bernard et	234	6730	OHCA with ROSC,	Not intubated,	Prehospital rapid	In-hospital rapid	Good	56/118 (48%) vs 61/116
91			ventricular fibrillation,	poor prearrest	infusion of up to	infusion of 40	functional	(53%)
(2010)[25]			systolic blood pressure	functional status,	2 L of ice-cold	mL/kg ice-cold	status at	(<i>P</i> =0.43)
(2010)[25]			>90 mm Hg, cardiac	hypothermic, or	lactated Ringer's	lactated Ringer's	hospital	
			arrest time >10 min,	pregnant	solution	solution	discharge	
			age ≥ 15 y, and IV				(discharge to	
			access				home or to	
							rehabilitation)	
Bernard et	163	6730	OHCA with ROSC,	Not intubated,	Prehospital rapid	In-hospital	Good	10/82 (12%) vs 7/81
a1			PEA or asystole,	poor prearrest	infusion of 40 mL/kg	cooling with	functional	(9%)
(2012)[26]			systolic blood pressure	functional status,	(up to 2 L) ice-cold	rapid infusion of	status at	(P=0.50)
(2012)[20]			>90 mm Hg, cardiac	hypothermic,	Hartmann's solution	40 mL/kg ice-	hospital	
			arrest time >10 min,	pregnant, or		cold Hartmann's	discharge	
			age ≥ 15 y, and IV	traumatic arrest		solution, and	(discharge to	
			access available			surface cooling	home or to	
							rehabilitation)	
Kim et al.	1359	5696	OHCA with ROSC,	Traumatic arrest, age	Prehospital rapid	Standard of care	Hospital	Survival to discharge:
(2014)[27]			intubation, IV access,	<18 y,	infusion of up to 2 L		mortality and	VF: 63% vs 64%
(2011)[27]			esophageal		of 4°C normal saline	(224 of 291	good	(<i>P</i> =0.69)
			temperature probe		(224 of 292 patients	patients with VF	neurologic	Non-VF: 19% vs 16%
			(temperature \geq 34°C),		with VF received in-	received in-	outcome at	(P=0.30)
			unresponsive, any		hospital cooling; no	hospital cooling;	discharge	Good neurologic
			initial rhythm		information provided	no information		outcome:
					for non-VF patients)	provided for non-		VF: 58% vs 62%
						VF patients)		(<i>P</i> =0.59)
								Non-VF: 14% vs 13%
								(P=0.74)
Debaty et	245	1559	OHCA, > 18 y,	Trauma, hemorrhage,	Intra-arrest up to 2 L	In-hospital TTM	Survival at 30	5.7% vs 4.1%
al.			eligible for	asphyxia,	< 8°C saline at	with cold saline	days	(P=0.58)
(2014)[28]			resuscitation	hypothermia,	100mL/min with	infusion, cooling		
(2014)[20]				pregnant, ROSC	pressure bag and gel	mattress, cold air		
				before randomization	pads surface cooling.	circulation or		
					Aim for 32-34°C. In-	extra corporeal		
					hospital TTM	life support		

CPC indicates cerebral performance category; EMS, emergency medical service; GCS, Glasgow Coma Scale; IV, intravenous; OHCA, out-of -hospital cardiac arrest; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; TTM, targeted temperature management; VF, ventricular fibrillation.

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Question 3:

Study	No. of Patients Analyzed	Inclusion Criteria	Exclusion Criteria	Intervention	Clinical Outcomes	Results Related to Duration
Yokoyama et al. (2011)[29]	452	OHCA, receiving temperature management, age >18 y, stable hemodynamics, comatose, presumed cardiac cause of arrest	Pregnancy, aortic dissection, pulmonary embolism, drug addiction, poor daily activity before onset	Various durations of targeted temperature management	Neurologic outcome at 30 d	Duration of cooling in CPC 1–2: 24 (24–42) h vs CPC 3–5: 26 (24–45) h (Nonsignificant <i>P</i> value, exact <i>P</i> value not reported)
Lee et al. (2014)[30]	79	OHCA, unconscious asphyxia (i.e. preceding respiratory failure)	< 18 y, preexisting terminal illness, trauma, exsanguination, toxin other than tetrodotoxin	24 h at 33°C ± 1°C compared to 72 h at 32°C ± 1°C	Survival and good neurologic outcome (CPC 1-2) at 30 days	Survival: 49% vs. 47% (P=0.61) Good neurological outcome: 3% vs. 3% (P=1.00)

CPC indicates cerebral performance category; OHCA, out-of-hospital cardiac arrest.

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Appendix D: Bias Assessment

Question #1:

a. Bias Assessment: RCTs

Study	Allocation: Generation	Allocation: Concealment	Blinding: Participants	Blinding: Assessors	Outcome: Complete	Outcome: Selective	Other Bias
HACA (2002)[11]	Low	Low	High*	Low	Low	Low	Unclear†
Bernard et al. (2002)[12]	High‡	High‡	High*	Low	Low	Low	Unclear†
Laurent et al. (2005)[13]	Low	Low	High*	High§	Low	Low	Unclear†∥
Zhang et al. (2005)[14]	High§	High§	High*	High§	Low	High¶	High†#
Lopez-de-Sa et al. (2012)[15]	Low	Low	High*	Low	Low	Low	Unclear ^{†**}
Nielsen et al. (2013)[16]	Low	Low	High*	Low	Low	Low	Low

*Study participants and clinical teams not blinded.

†Clinician performing neurologic prognostication not blinded.

‡Allocation by day of week.

[§]Not described in manuscript. |All subjects received 8 hours of hemofiltration.

Did not report survival.

#Very limited patient information/baseline data provided.

**Some baseline imbalance between groups.

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b. Bias Assessment: Observational Studies

Study	Eligibility Criteria	Exposure/Outcome	Confounding	Follow-Up
Testori et al. (2011)[17]	Low	Low	High*	Low
Dumas et al. (2011)[18]	Unclear†	Low	Low	Low
Nichol et al. (2013)[20]	High†	High‡	High§	Low
Vaahersalo et al. (2013)[19]	Unclear†	Low	High*	Low
Mader et al. (2014)[21]	Unclear ^{**†}	High [#]	High*	Low

*High risk of residual confounding.

†Patients with traditional targeted temperature management exclusion criteria not excluded before analysis.

‡Less than 3% of subjects received hypothermia, and inclusion criteria rely solely on coding in the registry.

§Independent documentation of therapeutic temperature was available for only 40% of patients cooled and was not always consistent with reaching target temperature for those reportedly cooled. Less than 3% of patients received the intervention, which causes high concern for confounding by indication.

**Limited data on how decision to use hypothermia was made

*No actual temperature data; exclusion criteria rely solely on coding in the registry

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Question #2:

a. Bias Assessment: RCTs

Study	Allocation: Generation	Allocation: Concealment	Blinding: Participants	Blinding: Assessors	Outcome: Complete	Outcome: Selective	Other Bias
Kim et al. (2007)[22]	Low	Low	High*	Low	Low	Low	Low
Kamarainen et al. (2009)[23]	Low	Low	High*	High†	Low	Low	Low
Castren et al. (2010)[24]	Low	Low	High*	High‡	Low	Low	Low
Bernard et al. (2010)[25]	Low	Low	High*	Low	Low	Low	Low
Bernard et al. (2012)[26]	Low	Low	High*	Low	Low	Low	Low
Kim et al. (2014)[27]	Low	Low	High*	Low	Low	Low	Low
Debaty et al. (2014)[28]	Low	Low	High*	High†	Low	Low	Low

*Study participants and clinical teams not blinded.

[†]Outcome assessors not blinded.

‡According to the study, "assessment may not always have been performed by an individual blinded to the treatment group."

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Question #3:

a. Bias Assessment: Observational Studies

Study	Eligibility Criteria	Exposure/Outcome	Confounding	Follow-Up
Yokoyama et al. (2011)[29]	Low	Low	High*	Low
Lee et al. (2014)[30]	Low	Low	High†	Low

*No adjustment for any potential confounders.

†High risk of residual confounding, pre/post study, different temperature target

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Appendix E: GRADE Tables

Question #1:

TTM compared with no TTM in adults with OHCA with an initial shockable rhythm who remain unresponsive after ROSC												
No. of Patients,			Quality Asse	ssment				Summ	ary of Finding	gs		
No. of Studies,							No. of Patients Effect					
Follow-Up Period	Risk of	Inconsistency	Indirectness	Imprecision	Other*	Overall	TTM	No	Relative [†]	Absolute‡		
	Bias					Quality of		TTM	(95% CI)	(95% CI)		
						Evidence						
Mortality												
352 patients	Serious§	Not serious	Not serious	Serious	None	Low	78/180	99/172	RR 0.75	144 fewer per		
2 RCTs[11, 12]							(43%)	(58%)	(0.61–0.92)	1000		
6 mo/hospital										(-224 to -46)		
discharge												
42 patients	Serious§	Not serious	Serious#	Serious	None	Very low	15/22	11/20	RR 1.24	132 more per		
1 RCT[13]							(68%)	(55%)	(0.76–2.02)	1000		
6 mo										(-132 to 561)		
Poor neurologic/functional outcome**												
350 patients	Serious§	Not serious	Not serious	Serious	None	Low	83/179	108/	RR 0.73	171 fewer		
2 RCTs[11, 12]							(46%)	171	(0.60 - 0.88)	per 1000		
6 mo/hospital								(63%)		(-253 to -76)		
discharge												

CI indicates confidence interval; OHCA, out-of-hospital cardiac arrest; RCT, randomized controlled trial; ROSC, return of spontaneous circulation; RR, risk ratio; TTM, targeted temperature management.

*Includes assessment of publication bias, magnitude of the effect, dose-response gradient, and plausible residual confounding leading to spurious effect when no effect was observed or reduction of a demonstrated effect.

[†]The risk ratios represent the risk of the outcome in the treatment group (targeted temperature management) compared to the control group (no targeted temperature management) such that a risk ratio <1 indicates the outcome being less common in the intervention group. When more than 1 trial is included the pooled risk ratio is reported. See appendix F for forest plots.

‡Absolute effect is calculated as the absolute difference in the outcome between the treatment group (targeted temperature management) and the control group (no targeted temperature management) expressed as number of patients per 1000 patients treated. For the confidence interval, positive numbers reflect more patients and negative numbers fewer patients with the outcome.

\$Neurological prognosticators and clinical team not blinded.

[One of the included trials used quasi-randomization (alternating days).[12] We did not consider this to introduce enough additional concern to increase the overall risk of bias to "very serious".

¹Optimal information size not achieved. Based on a conservative alpha of 0.01, beta of 0.2, a control outcome rate of 55% and a relative risk reduction of 10% the optimal information size was calculated at 3,922 total patients.

#Simultaneous hemofiltration.

**Poor neurological/functional outcome defined as a cerebral performance category score of 3,4 or 5 or dead[11] or not being discharged home or to rehabilitation.[12]

TTM compared with no TTM in adults with OHCA with an initial nonshockable rhythm who remain unresponsive after ROSC											
			Quality Accor	remont			Summary of Findings				
No. of Patients,			Quality Asses	sillent			No. of 1	Patients	Effect		
No. of Studies, Follow-Up Period	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other*	Overall Quality of Evidence	TTM	No TTM	Relative† (95% CI)	Absolute‡ (95% CI)	
Mortality											
374 patients 1 observational[17] 6 mo	Serious§	Not serious	Not serious	Serious ^I	None	Very low	82/135 (61%)	180/239 (75%)	OR 0.56 (0.34–0.93)	122 fewer per 1000 (-244 to -14)	
Poor neurologic outcom	e¶										
1034 patients 3 observational[17-19] 6 mo/1 y	Serious§	Not serious	Not serious	Serious#	None	Very low	365/466 (78%)	456/568 (80%)	OR 0.90 (0.45–1.82)	17 fewer per 1000 (-156 to 78)	
Poor neurologic outcome											
1830 patients 1 observational[21] Hospital discharge	Very serious**	Not serious	Not serious	Serious#	None	Very low	NA††	NA††	NE††	NE††	

CI, confidence interval; NA, not available; NE, not estimable; OHCA, out-of-hospital cardiac arrest; OR, odds ratio; ROSC, return of spontaneous circulation; TTM, targeted temperature management.

*Include assessment of publication bias, magnitude of the effect, dose-response gradient, and plausible residual confounding leading to spurious effect when no effect was observed or reduction of a demonstrated effect.

†Adjusted ORs are reported for mortality. For the outcome of poor neurologic outcome the pooled OR was used (see Appendix F for forest plot). The ORs represent the risk of the outcome in the treatment group (TTM) compared with the control group (no TTM) adjusted for various confounders.

‡Absolute effect is calculated as the absolute difference in the outcome between the treatment group (TTM) and the control group (no TTM) calculated based on the control group risk and the adjusted OR, expressed as number of patients per 1000 patients treated. For the CI, positive numbers reflect more patients and negative numbers fewer patients with the outcome.

\$High risk of residual confounding.

lOptimal information size not achieved. Based on a conservative α of 0.01, a β of 0.2, a control outcome rate of 75%, and a relative risk reduction of 10%, the optimal information size was calculated at 1748 total patients.

Poor neurologic outcome defined as a cerebral performance category score of 3, 4, or 5 or dead.

#CI cannot exclude clinically relevant benefit or harm.

**Very high risk of residual confounding

†† Study reported multiple analyses with inconsistent results

	\TTM compared with no TTM in adults with IHCA with any initial rhythm who remain unresponsive after ROSC											
			Quality Acco	semont			Summary of Findings					
No. of Patients			Quanty Asse	ssment			No. of H	Patients	Effect			
No. of Studies Follow-Up Period	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other*	Overall quality of evidence	TTM	No TTM	Relative† (95% CI)	Absolute‡ (95% CI)		
Mortality												
8316 patients 1 observational[20] Hospital discharge	Very serious§	Not serious	Not serious	Serious	None	Very low	156/ 214 (73%)	5648/ 8102 (70%)	OR 1.11 (0.81–1.54)	22 more per 1000 (-45 to 83)		
Poor neurologic outcome¶												
8316 patients 1 observational[20] Hospital discharge	Very serious§	Not serious	Not serious	Serious	None	Very low	174/ 214 (81%)	6511/ 8102 (80%)	OR 1.08 (0.76–1.54)	11 more per 1000 (-48 to 59)		

CI, confidence interval; IHCA, in-hospital cardiac arrest; OR, odds ratio; ROSC, return of spontaneous circulation; TTM, targeted temperature management.

*Includes assessment of publication bias, magnitude of the effect, dose-response gradient, and plausible residual confounding leading to spurious effect when no effect was observed or reduction of a demonstrated effect.

†Adjusted ORs are reported for all relative effect measures. The ORs represent the risk of the outcome in the treatment group (TTM) compared with the control group (no TTM) adjusted for various confounders.

‡Absolute effect is calculated as the absolute difference in the outcome between the treatment group (TTM) and the control group (no TTM) calculated based on the control group risk and the adjusted OR, expressed as number of patients per 1000 patients treated. For the CI, positive numbers reflect more patients and negative numbers fewer patients with the outcome.

\$High risk of residual confounding, high risk of selection bias, and unclear exposure.

CI cannot exclude clinically relevant benefit or harm.

Poor neurologic outcome defined as a cerebral performance category score of 3, 4, or 5 or dead.

33°C compared with 36°C for adults with OHCA who remain unresponsive after ROSC and receive TTM											
			Quality Acc	acmont				Summary of Findings			
No. of Patients,			Quanty Asse	essment			No. of I	Patients	Effect		
No. of Studies, Follow-Up Period	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other*	Overall Quality of Evidence	33°C	36°C	Relative† (95% CI)	Absolute‡ (95% CI)	
Mortality§											
939 patients 1 RCT[16] 180 d	Not serious	Not serious	Not serious	Serious¶	None	Moderate	226/473 (48%)	220/466 (47%)	RR 1.01 (0.88–1.16)	6 more per 1000 (-54 to 74)	
Poor neurologic outcome#											
933 patients 1 RCT[16] 180 d	Not serious	Not serious	Not serious	Serious¶	None	Moderate	251/469 (54%)	242/464 (52%)	RR 1.03 (0.91–1.16)	14 more per 1000 (-48 to 83)	

CI indicates confidence interval; OHCA, out-of-hospital cardiac arrest; RCT, randomized controlled trial; ROSC, return of spontaneous circulation; RR, risk ratio; TTM, targeted temperature management.

*Includes assessment of publication bias, magnitude of the effect, dose-response gradient, and plausible residual confounding leading to spurious effect when no effect was observed or reduction of a demonstrated effect.

†The RRs represent the risk of the outcome in the 33°C group compared with the 36°C group.

‡Absolute effect is calculated as the absolute difference in the outcome between the treatment group (TTM) and the control group (no TTM) calculated based on the control group risk and the risk ratio, expressed as number of patients per 1000 patients treated. For the CI, positive numbers reflect more patients and negative numbers fewer patients with the outcome.

The authors also reported the results of a time-to-event analysis (hazard ratio, 1.06 [95% CI, 0.89–1.28]).

Although clinicians and patients were not blinded, we do not consider this to introduce enough bias to downgrade the evidence, because the neurologic prognosticators were blinded.

¶CI cannot exclude clinically relevant benefit or harm.

#Poor neurologic outcome defined as a cerebral performance category score of 3, 4, or 5 or dead. The authors also reported poor neurologic outcome, defined as a modified Rankin scale score of 4 to 6 (RR 1.01 [95% CI, 0.89–1.14]).

32°C compared with 34°C for adults with OHCA who remain unresponsive after ROSC and receive targeted temperature management											
			Quality Acc	acmont				Summary of Findings			
No. of Patients			Quality Asso	essment			No. of I	Patients	Effect		
No. of Studies Follow-Up Period	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other*	Overall Quality of Evidence	32°C	34°C	Relative† (95% CI)	Absolute‡ (95% CI)	
Mortality											
36 patients 1 RCT[15] 180 days	Very serious§	Not serious	Not serious	Seriousl	None	Very low	10/18 (56%)	16/18 (89%)	RR 0.63 (0.40–0.97)	233 fewer per 1000 (-533 to -23)	
Poor neurologic outcome¶											
36 patients 1 RCT[15] 180 days	Very serious§	Not serious	Not serious	Serious#	None	Very low	9/18 (50%)	14/18 (78%)	RR 0.64 (0.38–1.09)	278 fewer per 1000 (-482 to 66)	

CI, confidence interval; OHCA, out-of-hospital cardiac arrest; RCT, randomized controlled trial; ROSC, return of spontaneous circulation; RR, risk ratio.

*Includes assessment of publication bias, magnitude of the effect, dose-response gradient, and plausible residual confounding leading to spurious effect when no effect was observed or reduction of a demonstrated effect.

†The RRs represent the risk of the outcome in the $32^{\circ}C$ group compared with the $34^{\circ}C$ group .

‡Absolute effect is calculated as the absolute difference in the outcome between the treatment group (targeted temperature management) and the control group (no targeted temperature management) calculated based on the control group risk and the adjusted odds ratio, expressed as number of patients per 1000 patients treated. For the CI, positive numbers reflect more patients and negative numbers fewer patients with the outcome.

§Neurologic prognosticators not blinded, and risk of confounding caused by unbalanced groups.

Optimal information size not achieved. See calculations above.

Poor neurologic outcome, defined as the best cerebral performance category score being 3, 4, or 5. The authors also reported death or severe dependence, defined as a Barthel score <60 (RR 0.32 [95% CI, 0.08–1.37]).

#CI cannot exclude clinically relevant benefit or harm.

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Question #2:

Prehospital targeted temperature management compared with no prehospital targeted temperature management in adults with OHCA who remain unresponsive after ROSC											
			Quality Acc	ocemont			Summary of Findings				
No. of Patients			Quality Ass	essment			No. of Patients		Eff	ect	
No. of Studies Follow-Up Period	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other*	Overall Quality of Evidence	Prehos pital	No Prehos pital	Relative† (95% CI)	Absolute‡ (95% CI)	
Mortality											
2237 patients 7 RCTs[22-28] Hospital discharge	Serious§	Not serious	Not serious	Not serious	None	Moderate	640/ 1125 (57%)	638/ 1112 (57%)	RR 0.98 (0.92–1.04)	13 fewer per 1000 (-51 to 26)	
Poor neurologic/functional outcomel											
1867 patients 5 RCTs[23-27] Hospital discharge	Serious§	Not serious	Not serious	Not serious	None	Moderate	629/939 (67%)	612/928 (66%)	RR 1.00 (0.95–1.06)	0 more per 1000 (-33 to 33)	
Rearrest											
1719 patients 5 RCTs[22, 23, 25- 27] Prehospital	Serious¶	Serious#	Not serious	Not serious	None	Low	200/968 (21%)	161/948 (17%)	RR 1.27 (1.10–1.47)	65 more per 1000 (24 to 114)	
Pulmonary edema**											
1860 patients 6 RCTs[22, 23, 25- 28] Prebospital/arrival	Serious¶	Serious#	Not serious	Not serious	None	Low	287/952 (30%)	219/909 (24%)	††	††	

CI indicates confidence interval; OHCA, out-of-hospital cardiac arrest, RCTs, randomized controlled trials; ROSC, return of spontaneous circulation; RR, risk ratio. *Includes assessment of publication bias, magnitude of the effect, dose-response gradient, and plausible residual confounding leading to spurious effect when no effect was observed or reduction of a demonstrated effect.

[†]Pooled RRs are reported for all relative effect measures. The RRs represent the risk of the outcome in the treatment group (prehospital targeted temperature management) compared with the control group (no prehospital targeted temperature management). The corresponding forest plots are presented in Appendix F. [‡]Absolute effect is calculated as the absolute difference in the outcome between the treatment group (prehospital targeted temperature management) and the control group (no prehospital targeted temperature management) calculated based on the control group risk and the pooled RR, expressed as number of patients per 1000 patients treated. For the CI, positive numbers reflect more patients and negative numbers fewer patients with the outcome.

§Neurologic prognosticators and clinical team not blinded.

Poor neurologic outcome defined as a cerebral performance category score of 3, 4, or 5 or not being discharged home or to rehabilitation

 $\car{Clinical}$ team and outcome assessors not blinded.

#Very large variability in reported incidences.

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**Pulmonary edema was assessed with initial radiography[22, 27] or "oxygen desaturation <90% with froth visible in the endotracheal tube" prehospital.[25, 26] Two studies did not report details related to assessment of pulmonary edema.[23, 28] †† No pooled estimate was calculated. See Appendix F. Donnino et al | 26 Temperature Management After Cardiac Arrest Online-Only Data Supplement

Appendix F: Forest Plots (meta-analyses)

Question #1:

A. Forest Plot – Outcome: Mortality

	TTN	1	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Bernard, 2002	22	43	23	34	31.2%	0.76 [0.52, 1.10]	
HACA, 2002	56	137	76	138	68.8%	0.74 [0.58, 0.95]	
Total (95% CI)		180		172	100.0%	0.75 [0.61, 0.92]	•
Total events	78		99				
Heterogeneity: Tau² =	: 0.00; Ch	i ^z = 0.01	6				
Test for overall effect:	Z= 2.75	(P = 0.0		Favours TTM Favours Control			

B. Forest Plot – Outcome: Poor Neurologic/Functional Outcome

	TTN	1	Contr	ol		Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl			
Bernard, 2002	22	43	25	34	29.6%	0.70 [0.49, 0.99]				
HACA, 2002	61	136	83	137	70.4%	0.74 [0.59, 0.93]				
Total (95% CI)		179		171	100.0%	0.73 [0.60, 0.88]	•			
Total events	83		108							
Heterogeneity: Tau² =	: 0.00; Ch	i = 0.08	8, df = 1 (P = 0.7	7); I² = 09	6		<u> </u>		
Test for overall effect:	Z = 3.24	Eavours TTM Eavours Cont	trol							

C. Forest Plot – Nonshockable rhythm. Outcome: Poor Neurologic Outcome*



*Adjusted odds ratios and inverse variance weighting were used to calculate the pooled odds ratio. The study by Mader et al.[21] was not included in the meta-

analysis given the very high risk of bias.

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Question #2:

For the study by Castren et al. [24] only patients who had return of spontaneous circulation were included in the meta-analysis. The exclusion of the studies that

initiated temperature management during cardiopulmonary resuscitation (Castren et al.[24] and Debaty et al.[28]) did not meaningfully change the pooled risk ratios

for any of the outcomes (data not shown).

A. Forest Plot – Outcome: Poor Neurologic Outcome

	Pre-hospita	I TTM	No Pre-hospita	I TTM		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
Kamarainen, 2009	11	19	10	18	1.1%	1.04 [0.59, 1.83]	2009	
Castren, 2010	21	32	33	42	3.9%	0.84 [0.62, 1.12]	2010	
Bernard, 2010	62	118	55	116	5.1%	1.11 [0.86, 1.43]	2010	
Bernard, 2012	72	82	74	81	30.8%	0.96 [0.87, 1.07]	2012	
Kim, 2014	463	688	440	671	59.2%	1.03 [0.95, 1.11]	2014	—
Total (95% CI)		939		928	100.0%	1.00 [0.95, 1.06]		•
Total events	629		612					
Heterogeneity: Tau² =	0.00; Chi ² = 3	3.31, df=	: 4 (P = 0.51); l ² =	0%				
Test for overall effect:	Z = 0.06 (P =	0.95)						Favours pre-hospital Favours no pre-hospital

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B. Forest Plot – Outcome: Mortality



C. Forest Plot – Outcome: Rearrest

	Pre-hospita	I TTM	No Pre-hospita	al TTM		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
Kim, 2007	15	63	13	62	7.8%	1.14 [0.59, 2.19]	2007	-
Kamarainen, 2009	2	19	3	18	1.2%	0.63 [0.12, 3.35]	2009	
Bernard, 2010	0	118	0	116		Not estimable	2010	
Bernard, 2012	7	82	7	81	3.3%	0.99 [0.36, 2.69]	2012	_
Kim, 2014	176	686	138	671	87.6%	1.25 [1.03, 1.52]	2014	
Total (95% CI)		968		948	100.0%	1.22 [1.01, 1.46]		◆
Total events	200		161					
Heterogeneity: Tau² =	0.00; Chi ² = 0).86, df=	3 (P = 0.83); I ² =	= 0%				
Test for overall effect:	Z = 2.11 (P =	0.03)						Eavours pre-hospital Eavours no pre-hospital

D. Forest Plot – Outcome: Pulmonary Edema*



* Given that only three studies with high heterogeneity had pulmonary edema events reported no pooled analysis was performed. For the Debaty et al.[28] study only patients who survived to hospital admission were included.

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Temperature Management After Cardiac Arrest: An Advisory Statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation Michael W. Donnino, Lars W. Andersen, Katherine M. Berg, Joshua C. Reynolds, Jerry P. Nolan, Peter T. Morley, Eddy Lang, Michael N. Cocchi, Theodoros Xanthos, Clifton W. Callaway and Jasmeet Soar

Circulation. published online October 4, 2015; *Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231 Copyright © 2015 American Heart Association, Inc. All rights reserved. Print ISSN: 0009-7322. Online ISSN: 1524-4539

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