Resuscitation 98 (2016) 97–104

Contents lists available at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

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[1], Jasmeet Soar[1], the ILCOR ALS Task Force

ARTICLE INFO

Keywords:
AHA Scientific Statements
Cardiac arrest
Duration
Heart arrest
Hypothermia
Resuscitation
Temperature management
Timing

ABSTRACT

For more than a decade, mild induced hypothermia (32 °C–34 °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 neurological 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 Advanced Life Support 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 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.

Sudden cardiac arrest is one of the leading causes of death in adults around the world. Although the 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 cause 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

☆ This article has been copublished in *Circulation*.
[1] ALS Task Force co-chairs and equal senior co-authors.

http://dx.doi.org/10.1016/j.resuscitation.2015.09.396

cardiac arrest (OHCA) should be cooled to 32 °C to 34 °C for 12 to 24 hours when the initial rhythm was [ventricular fibrillation] VF" and that "such cooling may also be beneficial for other rhythms or in-hospital cardiac arrest" (IHCA).[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 patients with OHCA found that both groups had similar mortality (primary end point) and neurological 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 ALS Task Force created formal Population, Intervention, Comparison, and Outcome (PICO) questions and performed a comprehensive literature search.[15] The task force evaluated, compiled, and summarized the evidence by using Grading of Recommendations Assessment, Development and Evaluation (GRADE; www.gradeworkinggroup.org) methodology and performed meta-analyses when appropriate. The task force then created a consensus statement by considering the available evidence and 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 Questions Asked section). We completed a bias assessment for all included studies and then used GRADE methodology to evaluate this evidence and to 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 PICO questions:

1. 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 neurological/functional outcome at discharge, 30 days, 60 days, 180 days, or 1 year or survival only at discharge, 30 days, 60 days, 180 days, 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 neurological/functional outcome at discharge, 30 days, 60 days, 180 days, or 1 year or survival only at discharge, 30 days, 60 days, 180 days, 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 neurological/functional outcome at discharge, 30 days, 60 days, 180 days, or 1 year or survival only at discharge, 30 days, 60 days, 180 days, 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 online-only Data Supplement.

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, controlled trials (RCTs) were available (ie, shockable OHCA), only RCTs were included. Otherwise, observational studies were included for the 2 patient populations in which there were no RCT data: 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 were 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 on the basis of title or abstract. Subsequently, the text 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 was beyond the scope of the present document, 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 on the basis of 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 online-only Data Supplement. The overall quality of evidence was summarized by use of 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 on the basis of these considerations. RCTs start as high quality and observational studies start as low quality and can then be upgraded or downgraded on the basis of the above criteria. Details of the current GRADE evaluations are provided in the appendixes in the online-only Data Supplement. The GRADE approach, inclusive of definitions and details of the above, is described in extensive detail at www.gradeworkinggroup.org. In this document, for the sake of consistency, we chose to report mortality and poor neurological outcome throughout the article, 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 (RRs) or odds ratios (ORs) with 95% confidence intervals (CIs).

Development of the Treatment Recommendations

The GRADE approach was used to grade the strength of recommendations and to 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 members of the task force voted on and approved the final advisory statement. A majority rule was applied, although 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 5045 studies. Of these, 6 RCTs and 5 observational studies were included for bias assessment (in the online-only Data Supplement, Appendix B shows the study selection flow diagram, Appendix C provides the study overview, and Appendix D describes 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 online-only Data Supplement.[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 IHCA[24] and OHCA with an initial nonshockable rhythm.[25–28] We organized the available evidence into separate but related categories:

1. Evidence to support targeted temperature management versus no targeted temperature management for the following:
   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 RCT[8] and 1 quasi-randomized trial[9] enrolling a total of 352 patients provided overall low-quality evidence for decreased poor neurological outcome in patients with OHCA with ventricular fibrillation or pulseless ventricular tachycardia 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 neurological/functional outcome at 6 months[8] or hospital discharge[9] (see Appendix F in the online-only Data Supplement 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 1034 patients provided overall very low-quality evidence for no difference in poor neurological outcome in patients with nonshockable OHCA (adjusted pooled OR, 0.90; 95% CI, 0.45–1.82; forest plot in Appendix F of the online-only Data Supplement).[25–27] One additional retrospective study using a large registry, analyzing 1830 patients, provided very low-quality evidence for an increase in poor neurological 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 because of a 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 8316 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 neurological 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 moderate-quality evidence for no decrease in mortality at 180 days (RR, 1.01; 95% CI, 0.88–1.16) or poor neurological 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 low-quality 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 neurological 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 1 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 2286 studies generated from the search (Appendix B in the online-only Data Supplement gives the study selection flow diagram). Five[29–33] of the 7 studies used cold intravenous fluids after ROSC to induce hypothermia; 1 study[34] used cold intravenous fluid during resuscitation; and 1 study[35] used intra-arrest intranasal cooling. The volume of cold fluid ranged from 20 to 30 mL/kg and up to 2 L, although some patients did not receive the full amount before 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 (Appendixes C, D, and E in the online-only Data Supplement give the study overview, bias assessments, and GRADE tables).

Five of the studies, enrolling a total of 1867 patients with OHCA, evaluated the outcome of poor neurological 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 neurological 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 2237 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 with those who did not receive prehospital cooling. Forest plots are presented in Appendix F of the online-only Data Supplement. When reviewed individually, none of the trials found an effect on either poor neurological outcome or mortality.

Meta-analysis of 4 RCTs that examined the outcome of rearrest demonstrated an increased risk for rearrest 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 3 trials 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[33] found an increase in pulmonary edema in patients who received prehospital cooling (RR, 1.34; 95% CI, 1.15–1.57). Forest plots are presented in Appendix F of the online-only Data Supplement.

Conclusions

In 7 RCTs providing overall moderate-quality evidence, prehospital induction of mild hypothermia did not reduce poor neurological outcome or mortality after OHCA. The largest study[33] found an increased risk of pulmonary edema and rearrest 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 (Appendix B in the online-only Data Supplement gives the study flowchart). One observational study provided overall very low-quality evidence for no difference in duration of hypothermia in those with a good versus a poor neurological outcome,[37] and 1 observational study provided overall very low-quality evidence for no difference in mortality or poor neurological outcome with 24 compared with 72 hours of hypothermia[38] (Appendixes C and D in the online-only Data Supplement give the study overview and bias assessment). Previous trials for targeted temperature management ranged from 12 to 28 hours. One trial (Nielsen et al[12]) provided strict normothermia (<37.5 °C) after rewarming until 72 hours after ROSC. However, this intervention was applied to both groups; 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 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 because of the complexity, heterogeneity, and high acuity of the patients. Moreover, the inability to blind clinicians to treatments such as temperature management adds another layer of difficulty when weighing the evidence.

The most notable difference between the trials by Bernard et al[9] and the Hypothermia After Cardiac Arrest (HACA) group[8] (both published in 2002) and the trial by Nielsen et al[12] (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 the studies by both 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 and the trial by Nielsen et al. was the use of a blinded neurological prognosticator instead of reliance on unblinded clinical teams. For both the Bernard et al. and the HACA investigations, clinical teams aware of the treatment allocation provided families with the prognostic information that informed decisions about 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 who were 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 dose of preceding sedation was different in the 2 allocation groups at the time of neuroprognostication.

Although the results of the trial by Nielsen et al[15] 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 Nielsen et al. trial had higher rates of bystander cardiopulmonary resuscitation than were seen in the HACA trial (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 targeted temperature management, we also recognize that potential side effects may appropriately lead a clinician to adjust from a lower to a higher target temperature despite no direct evidence for this approach. For example, if overt bleeding occurs at a temperature of 32 °C, then one may decide to increase the target temperature to theoretically mitigate this potential side effect. The weaknesses in existing studies illustrate potential knowledge gaps and areas for future research. Of note, the recommendation to control temperature after cardiac arrest is distinct from mere prevention or treatment of fever, which has not been studied in any of the RCTs.

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 except for 1 relatively small pilot study that provided intranasal cooling.[35] The trials using cold fluid specified amounts up to either 2 L or 20 to 30 mL/kg, although not all patients received the full amount before 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 rearrest 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 the induction of hypothermia in the prehospital setting but recognize that other cooling methods were not adequately evaluated and therefore are not discussed. 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 those in previous RCTs of 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.

Many knowledge gaps remain, 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 neurological 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 the use of targeted temperature management, including various temperature targets, affect long-term neurocognitive and functional outcomes?
- Does the choice of sedation, particularly with respect to different targeted temperatures, affect or influence outcome?
- What are the reasons for the discrepancy between experimental/animal data and human clinical trials of the effects of targeted temperature management?

Summary Recommendations

On the basis of 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 in the 2 largest previous RCTs.

Conflict of interest statement

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

Acknowledgments

Besides the authors (Drs Donnino, Callaway, Soar, and 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.

Disclosures.

Writing Group Disclosures.

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Lars W. Andersen	Beth Israel Deaconess Medical Center	None	None	None	None	None	None	None
Katherine M. Berg	Beth Israel Deaconess Medical Center	None	None	None	None	None	None	None
Clifton W. Callaway	University of Pittsburgh	None	None	None	None	None	None	None
Michael N. Cocchi	Beth Israel Deaconess Medical Center	None	None	None	None	None	None	None
Michael W. Donnino	Beth Israel Deaconess Medical Center	None	None	None	None	None	AHA†	None
Eddy Lang	University of Calgary Emergency Medicine	None	None	None	None	None	AHA†	University of Calgary†
Peter T. Morley	University of Melbourne Clinical School	None	None	None	None	None	AHA†	None
Jerry P. Nolan	Royal United Hospital, Bath	NIHR*	None	None	None	None	None	None
Joshua C. Reynolds	Michigan State University College of Human Medicine	None	None	None	None	None	None	None
Jasmeet Soar	Southmead Hospital Department of Anesthesia and Intensive Care	None	None	None	None	None	None	None
Theodoros Xanthos	Midwestern University of Chicago College of Pharmacy	None	None	None	None	None	None	None

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.

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

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.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.resuscitation.2015.09.396.

References

1. Berdowski J, Berg RA, Tijssen JG, Koster RW. Global incidences of out-of-hospital cardiac arrest and survival rates: systematic review of 67 prospective studies. Resuscitation 2010;81:1479–87, http://dx.doi.org/10.1016/j.resuscitation.2010.08.006.
2. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics—2015 update: a report from the American Heart Association [published correction appears in *Circulation*. 2015;131:e535]. Circulation 2015;131:e29–322, http://dx.doi.org/10.1161/CIR.0000000000000152.
3. Neumar RW, Nolan JP, Adrie C, Aibiki M, Berg RA, Bottiger BW, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication: a consensus statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; and the Stroke Council. Circulation 2008;118:2452–83, http://dx.doi.org/10.1161/CIRCULATIONAHA.108.190652.
4. Ginsberg MD, Sternau LL, Globus MY, Dietrich WD, Busto R. Therapeutic modulation of brain temperature: relevance to ischemic brain injury. Cerebrovasc Brain Metab Rev 1992;4:189–225.
5. Colbourne F, Sutherland G, Corbett D. Postischemic hypothermia: a critical appraisal with implications for clinical treatment. Mol Neurobiol 1997;14:171–201, http://dx.doi.org/10.1007/BF02740655.
6. Coimbra C, Wieloch T. Moderate hypothermia mitigates neuronal damage in the rat brain when initiated several hours following transient cerebral ischemia. Acta Neuropathol 1994;87:325–31.
7. Hicks SD, DeFranco DB, Callaway CW. Hypothermia during reperfusion after asphyxial cardiac arrest improves functional recovery and selectively alters stress-induced protein expression. J Cereb Blood Flow Metab 2000;20:520–30, http://dx.doi.org/10.1097/00004647-200003000-00011.
8. Hypothermia After Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest [published correction appears in *N Engl J Med.* 2002;30:1756]. N Engl J Med 2002;346:549–56.
9. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346:557–63, http://dx.doi.org/10.1056/NEJMoa003289.
10. Nolan JP, Morley PT, Vanden Hoek TL, Hickey RW, Kloeck WG, Billi J, et al. Therapeutic hypothermia after cardiac arrest: an advisory statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation. Circulation 2003;108:118–21, http://dx.doi.org/10.1161/01.CIR.0000079019.02601.90.
11. Morrison LJ, Deakin CD, Morley PT, Callaway CW, Kerber RE, Kronick SL, et al. Part 8: advanced life support: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Circulation 2010;122(Suppl. 2):S345–421, http://dx.doi.org/10.1161/CIRCULATIONAHA.110.971051.
12. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, et al. Targeted temperature management at 33 °C versus 36 °C after cardiac arrest. N Engl J Med 2013;369:2197–206, http://dx.doi.org/10.1056/NEJMoa1310519.
13. Bernard S. Inducing hypothermia after out of hospital cardiac arrest. BMJ 2014;348:g2735.
14. Wise MP, Horn J, Åneman A, Nielsen N. Targeted temperature management after out-of-hospital cardiac arrest: certainties and uncertainties. Crit Care 2014;18:459, http://dx.doi.org/10.1186/s13054-014-0459-3.
15. Counsell C. Formulating questions and locating primary studies for inclusion in systematic reviews. Ann Intern Med 1997;127:380–7.
16. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. [Updated March 2011]. The Cochrane Collaboration. http://handbook.cochrane.org/ [accessed 2.1.15].
17. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4: rating the quality of evidence: study limitations (risk of bias). J Clin Epidemiol 2011;64:407–15, http://dx.doi.org/10.1016/j.jclinepi.2010.07.017.
18. GRADEpro [online computer program]. McMaster University. 2012. http://www.guidelinedevelopment.org/ [accessed 2.1.15].
19. Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15: going from evidence to recommendation: determinants of a recommendation's direction and strength. J Clin Epidemiol 2013;66:726–35, http://dx.doi.org/10.1016/j.jclinepi.2013.02.003.
20. Hachimi-Idrissi S, Corne L, Ebinger G, Michotte Y, Huyghens L. Mild hypothermia induced by a helmet device: a clinical feasibility study. Resuscitation 2001;51:275–81.
21. Zhang J. Comparison and evaluation of brain-functional protection with mild hypothermia technique and normal temperature technique. Chin J Clin Rehab 2005;9:136–8.
22. Lopez-de-Sa E, Rey JR, Armada E, Salinas P, Viana-Tejedor A, Espinosa-Garcia S, et al. Hypothermia in comatose survivors from out-of-hospital cardiac arrest: pilot trial comparing 2 levels of target temperature. Circulation 2012;126:2826–33.
23. Laurent I, Adrie C, Vinsonneau C, Cariou A, Chiche JD, Ohanessian A, et al. High-volume hemofiltration after out-of-hospital cardiac arrest: a randomized study. J Am Coll Cardiol 2005;46:432–7, http://dx.doi.org/10.1016/j.jacc.2005.04.039.
24. Nichol G, Huszti E, Kim F, Fly D, Parnia S, Donnino M, et al. Does induction of hypothermia improve outcomes after in-hospital cardiac arrest? Resuscitation 2013;84:620–5, http://dx.doi.org/10.1016/j.resuscitation.2012.12.009.
25. Testori C, Sterz F, Behringer W, Haugk M, Uray T, Zeiner A, et al. Mild therapeutic hypothermia is associated with favourable outcome in patients after cardiac arrest with non-shockable rhythms. Resuscitation 2011;82:1162–7, http://dx.doi.org/10.1016/j.resuscitation.2011.05.022.
26. Dumas F, Grimaldi D, Zuber B, Fichet J, Charpentier J, Pene F, et al. Is hypothermia after cardiac arrest effective in both shockable and nonshockable patients? Insights from a large registry. Circulation 2011;123:877–86, http://dx.doi.org/10.1161/CIRCULATIONAHA.110.987347.
27. Vaahersalo J, Hiltunen P, Tiainen M, Oksanen T, Kaukonen KM, Kurola J, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest in Finnish intensive care units: the FINNRESUSCI study. Intensive Care Med 2013;39:826–37, http://dx.doi.org/10.1007/s00134-013-2868-1.

28. Mader TJ, Nathanson BH, Soares 3rd WE, Coute RA, McNally BF. Comparative effectiveness of therapeutic hypothermia after out-of-hospital cardiac arrest: insight from a large data registry. Ther Hypothermia Temp Manag 2014;4:21–31, http://dx.doi.org/10.1089/ther.2013.0018.
29. Kim F, Olsufka M, Longstreth Jr WT, Maynard C, Carlbom D, Deem S, 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, http://dx.doi.org/10.1161/CIRCULATIONAHA.106.655480.
30. Kämäräinen 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, http://dx.doi.org/10.1111/j.1399-6576.2009.02015.x.
31. Bernard SA, Smith K, Cameron P, Masci K, Taylor DM, Cooper DJ, et al. Induction of therapeutic hypothermia by paramedics after resuscitation from out-of-hospital ventricular fibrillation cardiac arrest: a randomized controlled trial. Circulation 2010;122:737–42, http://dx.doi.org/10.1161/CIRCULATIONAHA.109.906859.
32. Bernard SA, Smith K, Cameron P, Masci K, Taylor DM, Cooper DJ, et al. Induction of prehospital therapeutic hypothermia after resuscitation from nonventricular fibrillation cardiac arrest. Crit Care Med 2012;40:747–53, http://dx.doi.org/10.1097/CCM.0b013e3182377038.
33. Kim F, Nichol G, Maynard C, Hallstrom A, Kudenchuk PJ, Rea T, et al. Effect of prehospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest: a randomized clinical trial. JAMA 2014;311:45–52, http://dx.doi.org/10.1001/jama.2013.282173.
34. Debaty G, Maignan M, Savary D, Koch FX, Ruckly S, Durand M, et al. Impact of intra-arrest therapeutic hypothermia in outcomes of prehospital cardiac arrest: a randomized controlled trial. Intensive Care Med 2014;40:1832–42, http://dx.doi.org/10.1007/s00134-014-3519-x.
35. Castren M, Nordberg P, Svensson L, Taccone F, Vincent JL, Desruelles D, et al. Intra-arrest transnasal evaporative cooling: a randomized, prehospital, multicenter study (PRINCE: Pre-ROSC IntraNasal Cooling Effectiveness). Circulation 2010;122:729–36, http://dx.doi.org/10.1161/CIRCULATIONAHA.109.931691.
36. Callaway CW, Tadler SC, Katz LM, Lipinski CL, Brader E. Feasibility of external cranial cooling during out-of-hospital cardiac arrest. Resuscitation 2002;52:159–65.
37. Yokoyama H, Nagao K, Hase M, Tahara Y, Hazui H, Arimoto H, et al. Impact of therapeutic hypothermia in the treatment of patients with out-of-hospital cardiac arrest from the J-PULSE-HYPO study registry. Circ J 2011;75:1063–70.
38. Lee BK, Lee SJ, Jeung KW, Lee HY, Heo T, Min YI. Outcome and adverse events with 72-hour cooling at 32 °C as compared to 24-hour cooling at 33 °C in comatose asphyxial arrest survivors. Am J Emerg Med 2014;32:297–301, http://dx.doi.org/10.1016/j.ajem.2013.11.046.
39. Girotra S, Nallamothu BK, Spertus JA, Li Y, Krumholz HM, Chan PS. Trends in survival after in-hospital cardiac arrest. N Engl J Med 2012;367:1912–20, http://dx.doi.org/10.1056/NEJMoa1109148.
40. Wissenberg M, Lippert FK, Folke F, Weeke P, Hansen CM, Christensen EF, et al. Association of national initiatives to improve cardiac arrest management with rates of bystander intervention and patient survival after out-of-hospital cardiac arrest. JAMA 2013;310:1377–84, http://dx.doi.org/10.1001/jama.2013.278483.
41. Takino M, Okada Y. Hyperthermia following cardiopulmonary resuscitation. Intensive Care Med 1991;17:419–20.
42. Zeiner A, Holzer M, Sterz F, Schorkhuber W, Eisenburger P, Havel C, et al. Hyperthermia after cardiac arrest is associated with an unfavorable neurologic outcome. Arch Intern Med 2001;161:2007–12.
43. Takasu A, Saitoh D, Kaneko N, Sakamoto T, Okada Y. Hyperthermia: is it an ominous sign after cardiac arrest? Resuscitation 2001;49:273–7.
44. Suffoletto B, Peberdy MA, van der Hoek T, Callaway C. Body temperature changes are associated with outcomes following in-hospital cardiac arrest and return of spontaneous circulation. Resuscitation 2009;80:1365–70, http://dx.doi.org/10.1016/j.resuscitation.2009.08.020.
45. Gebhardt K, Guyette FX, Doshi AA, Callaway CW, Rittenberger JC, Post Cardiac Arrest Service. Prevalence and effect of fever on outcome following resuscitation from cardiac arrest. Resuscitation 2013;84:1062–7, http://dx.doi.org/10.1016/j.resuscitation.2013.03.038.
46. Nolan JP, Laver SR, Welch CA, Harrison DA, Gupta V, Rowan K. Outcome following admission to UK intensive care units after cardiac arrest: a secondary analysis of the ICNARC Case Mix Programme Database. Anaesthesia 2007;62:1207–16, http://dx.doi.org/10.1111/j.1365-2044.2007.05232.x.
47. Langhelle A, Tyvold SS, Lexow K, Hapnes SA, Sunde K, Steen PA. In-hospital factors associated with improved outcome after out-of-hospital cardiac arrest: a comparison between four regions in Norway. Resuscitation 2003;56:247–63.