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SPECIAL ARTICLE

Practice guideline summary: Reducing brain injury following cardiopulmonary resuscitation

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

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ABSTRACT

Objective: To assess the evidence and make evidence-based recommendations for acute interventions to reduce brain injury in adult patients who are comatose after successful cardiopulmonary resuscitation.

Methods: Published literature from 1966 to August 29, 2016, was reviewed with evidence-based classification of relevant articles.

Results and recommendations: For patients who are comatose in whom the initial cardiac rhythm is either pulseless ventricular tachycardia (VT) or ventricular fibrillation (VF) after out-of-hospital cardiac arrest (OHCA), therapeutic hypothermia (TH; 32–34°C for 24 hours) is highly likely to be effective in improving functional neurologic outcome and survival compared with non-TH and should be offered (Level A). For patients who are comatose in whom the initial cardiac rhythm is either VT/VF or asystole/pulseless electrical activity (PEA) after OHCA, targeted temperature management (36°C for 24 hours, followed by 8 hours of rewarming to 37°C, and temperature maintenance below 37.5°C until 72 hours) is likely as effective as TH and is an acceptable alternative (Level B). For patients who are comatose with an initial rhythm of PEA/asystole, TH possibly improves survival and functional neurologic outcome at discharge vs standard care and may be offered (Level C). Prehospital cooling as an adjunct to TH is highly likely to be ineffective in further improving neurologic outcome and survival and should not be offered (Level A). Other pharmacologic and nonpharmacologic strategies (applied with or without concomitant TH) are also reviewed. *Neurology*® 2017;88:1–9

GLOSSARY

AAN = American Academy of Neurology; **AE** = adverse event; **CI** = confidence interval; **CPC** = Cerebral Performance Category; **CPR** = cardiopulmonary resuscitation; **ECMO** = extracorporeal membrane oxygenation; **HF** = hemofiltration; **IHCA** = in-hospital cardiac arrest; **OHCA** = out-of-hospital cardiac arrest; **PEA** = pulseless electrical activity; **RD** = risk difference; **ROSC** = return of spontaneous circulation; **TH** = therapeutic hypothermia; **TTM** = targeted temperature management; **VT** = ventricular tachycardia; **VF** = ventricular fibrillation.

Outcomes for patients after nontraumatic cardiac arrest are dismal. Only 6%–9.6% of all patients with out-of-hospital cardiac arrest (OHCA) survive to hospital discharge,[1,2] and an estimated 22.3% of patients with in-hospital cardiac arrest (IHCA) survive to hospital discharge.[3] Brain injury related to cardiac arrest is a major determinant of mortality and disability.[3] Until recently, the postresuscitation acute management of survivors of cardiac arrest was directed mainly toward systemic injuries, and acute neurologic care focused mainly on prognostication, with supportive care of neurologic complications. Recently, interest in providing acute neuroprotective interventions has surged, intent on improving survival and independence of survivors.[4]

This summary highlights the findings, conclusions, and recommendations of a practice guideline reviewing available evidence regarding neuroprotective

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interventions in adults who are comatose after successful cardiopulmonary resuscitation (CPR), with particular attention on the outcomes of good neurologic recovery, disability, and death. The full text of the guideline is available as a data supplement at Neurology.org. Appendices e-1 and e-2 and references e1–e3, cited in this summary, are available in the complete guideline.

The guideline addresses 3 questions:

1. In patients with nontraumatic cardiac arrest, does induced mild therapeutic hypothermia (TH) or targeted temperature management (TTM) improve outcome after CPR in adults who are initially comatose?
2. In patients with nontraumatic cardiac arrest, do putative neuroprotective drugs improve outcome after CPR in adults who are initially comatose?
3. In patients with nontraumatic cardiac arrest, do other medical interventions or combinations of interventions improve outcome after CPR in adults who are initially comatose?

DESCRIPTION OF THE ANALYTIC PROCESS The American Academy of Neurology (AAN) convened a panel of experts to develop this practice guideline (appendices e-1 and e-2 of the full-length guideline) according to the process outlined in the 2004 AAN guideline development process manual.[5] A description of the exact literature search strategy and the process for reviewing evidence is available in the full-length guideline. The recommendations are based on Class I, II, and III studies (table e-1).

ANALYSIS OF EVIDENCE **In patients with nontraumatic cardiac arrest, does induced mild TH or TTM improve outcome after CPR in adults who are initially comatose?** TH is defined as core body temperature of 32–34°C and is achieved via various methods. Studies are distinguished by patients' type of initial cardiac rhythm upon return of spontaneous circulation (ROSC). Ventricular tachycardia (VT) or ventricular fibrillation (VF) is an indication for immediate cardiac defibrillation (shockable rhythm), whereas asystole and pulseless electrical activity (PEA) do not require electrical intervention (nonshockable rhythm). Because these groups differ significantly with respect to cause (PEA/asystole has numerous noncardiac causes), outcomes (mortality rates are higher in patients with PEA/asystole),[4] and potential response to TH, studies reporting outcomes separately for patients presenting with VT/VF and PEA/asystole are described preferentially for question 1.

Initial cardiac rhythm: VT/VF. Four Class I studies provided TH (32–34°C) to patients who were comatose with VT/VF as the initial cardiac rhythm after ROSC. The first study[6] used the 5-point Cerebral Performance Category (CPC)[7] as the primary outcome, wherein 1 = good recovery, 2 = moderate disability, 3 = severe disability, 4 = vegetative state, and 5 = death; this scale was also frequently used in other identified studies in the guideline, though the other studies in this section[8–10] defined good outcome differently. Results are summarized in table 1. No differences in adverse events (AEs) between groups were reported.

Conclusions and recommendations. For patients who are comatose after an initial cardiac rhythm of VT/VF, TH (32–34°C for 24 hours) is highly likely to be effective in improving neurologic outcome and survival compared with non-TH (2 Class I studies) and should be offered (Level A).

For patients who are comatose with an initial cardiac rhythm of either VT/VF or PEA/asystole, TTM (36°C for 24 hours followed by 8 hours of

Table 1 Response to TH in patients with ventricular tachycardia/ventricular fibrillation as the initial cardiac rhythm after return of spontaneous circulation

Study/class	Intervention	Favorable neurologic outcome	Death
Hypothermia after Cardiac Arrest Study Group 2002[6] (Class I)	TH (32–34°C for 24 hours followed by passive rewarming over 8 hours) or non-TH	RD 16% favoring TH (95% CI 4%–27%) at 6 months	RD 14% (95% CI 3%–26%) with fewer deaths in TH group at 6 months
Bernard et al.[8] (Class I)	TH (33°C for 12 hours followed by active rewarming over 6 hours) or non-TH	RD 22% favoring TH (95% CI 1%–43%) at discharge	NA
Nielsen et al.[9] (Class I)	TH (33°C for 24 hours) or TTM (core temperature target 36°C for 24 hours), each followed by 8 hours of rewarming to 37°C and then maintenance of core body temperature below 37.5°C until 72 hours post cardiac arrest	NA	HR 1.06 for TH (95% CI 0.84–1.34) at end of trial
Lopez-de-Sa et al.[10] (Class I)	TH at either 34°C or 32°C for 24 hours using an intravascular cooling technique	RD 46% favoring 32°C (95% CI 13%–79%) at 6 months; not significant after correcting for multiple comparisons	NA

Abbreviations: CI = confidence interval; HR = hazard ratio; NA = not applicable; RD = risk difference; TH = therapeutic hypothermia; TTM = target temperature management.

rewarming to 37°C and temperature maintenance below 37.5°C until 72 hours) is likely as effective as TH in improving neurologic outcome and survival (1 Class I study) and is an acceptable alternative to TH (Level B).

For patients who are comatose with an initial rhythm of VF, there is insufficient evidence to support or refute the use of 32°C vs 34°C TH because of lack of statistical precision (Class III studies; Level U).

Clinical context. In the study investigating TTM,[9] patients in both groups were cooled to achieve a target temperature of either 33°C or 36°C. This study compared 2 levels of cooling and should not be interpreted as comparing cooling with no cooling. Also notable is that 72 hours of TTM is longer than the TH periods in the other 2 studies (24 hours TH + 8 hours rewarming[6] and 12 hours TH + 6 hours rewarming[8]). Although the outcomes are considered equivalent, differences in trial designs may have contributed importantly to the outcomes. Previous studies[6,8] focused on maintaining non-TH without controlling for fever and allowed managing clinicians to decide the manner and timing of prognostication and withdrawal of life-sustaining therapies, whereas the TTM study[9] focused on fever control and provided a defined prognostication protocol resulting in a longer observation period after active intervention. Although the studies have emphasized temperature and medical interventions, the timing of decisions regarding withdrawal of life-sustaining therapies may also affect outcomes. Despite the methodologic differences between the TH and TTM trials, available data strongly support the use of temperature control.

Initial cardiac rhythm: PEA/asystole. One Class I study and 12 Class III studies examined induced mild hypothermia (32–34°C) in patients who were comatose with asystole/PEA after ROSC. In the Class I TTM study mentioned previously,[9] for those with asystole/PEA, death occurred in 82/98 (84%) patients in the TH group and in 74/88 (84%) patients in the TTM group (hazard ratio 1.08, 95% confidence interval [CI] 0.79–1.48).

Class III study results are described in the full-length guideline. Because many of these studies lacked the statistical precision to drive conclusions individually, 2 meta-analyses were performed. Seven studies[11–17] provided data on good neurologic outcome. With use of a random-effects model, the proportion of patients with a good neurologic outcome was significantly higher when TH vs non-TH was used (risk difference [RD] 6%, 95% CI 3%–9%, $I^2 = 41$). Five studies provided data on survival to hospital discharge,[11,13,14,17,18] 3 of which showed a benefit of TH on survival.[11,14,17] With use of a random-effects model, a significant benefit was seen in the proportion of patients who survived to hospital discharge for patients treated with TH vs non-TH (RD 12%, 95% CI 8%–16%, $I^2 = 49$).

Conclusions and recommendations. For patients who are comatose in whom the initial rhythm is PEA/asystole, treatment with TH vs non-TH possibly improves functional neurologic outcome (RD 6%, 95% CI 3%–9%, $I^2 = 41$; meta-analysis of 7 Class III studies) and survival (RD 12%, 95% CI 8%–16%, $I^2 = 49$; meta-analysis of 5 Class III studies) at hospital discharge and may be offered (Level C).

Prehospital cooling. The progression of neurologic injury after the initial brain insult is time-dependent. Laboratory studies suggest that neurologic injury is significantly decreased if cooling is initiated as soon as possible after resuscitation.[19–22] Five Class I studies and 1 Class II study investigated optimal timing of TH induction after resuscitation, full details of which are available in the complete guideline.

One Class I study[23] treated adults with any initial cardiac rhythm after ROSC following OHCA with prehospital administration of 2 L of 4°C normal saline or no prehospital cooling. In patients subsequently receiving in-hospital cooling (77% of VF cohort and 57% of non-VF cohort), prehospital cooling reduced the time to reach target temperature. However, it did not improve survival or neurologic status at hospital discharge in the VF group (RD for survival to hospital discharge 2% favoring prehospital cooling, 95% CI −10% to 6%; RD for minimal neurologic impairment at discharge −4% favoring no prehospital cooling, 95% CI −12% to 4%) or the non-VF group (RD for survival to hospital discharge 3% favoring prehospital cooling, 95% CI −2% to 8%; RD for minimal neurologic impairment at discharge 1% favoring prehospital cooling, 95% CI −4% to 6%). The prehospital cooling group had significantly higher rates of rearrest, lower oxygenation, increased pulmonary edema on first chest x-ray, and greater use of diuretics during the first 12 hours of hospitalization.

Another Class I study[24] included 200 patients with no specified initial cardiac rhythm after witnessed OHCA. Of the 37 patients presenting with VF who survived to hospital admission, more patients receiving prehospital cooling (using an intranasal cooling device) survived (RD 15% favoring cooling, 95% CI −17% to 47%) and had a favorable outcome at discharge (RD 21% favoring prehospital cooling, 95% CI −10% to 53%), but results were not statistically significant. Similar results were observed in the 37 patients with PEA/asystole surviving to hospital admission (RD for survival: 11% favoring prehospital cooling, 95% CI −15% to 37%; RD for favorable outcome at discharge: 5% favoring prehospital cooling, 95%

CI −20% to 29%). Small sample sizes limited statistical precision. Epistaxis (serious in one patient) and nasal whitening were reported AEs of the intranasal cooling device.

Another Class I study[25] included 234 patients with VF after OHCA treated with prehospital cooling using 2 L of ice-cold Ringer lactate or no prehospital cooling. All patients surviving to admission received in-hospital cooling. A concurrent study[26] used the same protocol in 163 patients with PEA/asystole. In patients with VF, RDs favored the nontreated (control) group with regard to favorable outcome (RD −5%, 95% CI −18% to 8%) and survival to hospital discharge (RD −6%, 95% CI −19% to 7%). In patients with PEA/asystole, RDs favored prehospital cooling (RD for favorable outcome 4% favoring prehospital cooling, 95% CI −6% to 13%; RD for survival to discharge 5% favoring prehospital cooling, 95% CI −5% to 14%). No significant differences in AEs were found between the groups in the VF study. AEs were not reported in the PEA/asystole study.

Another Class I study[27] (for the primary endpoint of nasopharyngeal temperature at hospital admission) randomized 43 patients to a prehospital cooling group that received +4°C Ringer solution with a target temperature of 33°C or conventional fluid therapy, regardless of initial rhythm, and with postadmission hypothermia administered at the discretion of the treating physician. The primary endpoint was nasopharyngeal temperature on arrival to the emergency department. Nasopharyngeal temperature was lower at the time of admission in the cooling group (34.1 ± 0.9°C vs 35.2 ± 0.8°C, $p < 0.001$), but there was no benefit of prehospital cooling on survival to discharge or favorable outcome at discharge (all surviving patients had a favorable outcome; 42% in prehospital cooling group vs 44% of controls, RD 2.3%, 95% CI −27.0% to 31.3%).

The final Class I study[28] included 245 patients with any rhythm after OHCA. Patients were randomized to receive either intra-arrest TH with external cooling and an infusion of cold saline or no prehospital cooling. All patients surviving to hospital admission received in-hospital TH. There was no benefit of intra-arrest TH on survival to discharge (5.7% in intra-arrest TH group vs 4.1% of controls, RD 1.6%, 95% CI −4.3% to 7.7%) or favorable outcome at discharge (5.7% vs 3.3%, RD 2.4%, 95% CI −3.2% to 8.4%).

Conclusion and recommendation. For patients who are comatose after cardiac arrest, prehospital cooling as an adjunct to in-hospital cooling is highly likely to be ineffective in further improving neurologic outcome and survival (multiple Class I studies) and should not be offered (level A).

Clinical context. Several clinical studies with varying methodologies showed that prehospital cooling, whether post-ROSC or intra-arrest, did not provide additional neurologic benefit when added to in-hospital cooling. The absence of a clear understanding of the mechanisms by which hypothermia exerts its neuroprotective effects limits the ability to identify the most opportune time to initiate the intervention.

Studies comparing different cooling methods and protocol use. Two Class III studies compared different invasive vs superficial cooling methods.[29,30] An additional Class III study[31] investigated the effect of a standardized treatment protocol. Because single Class III studies cannot drive recommendations, details of these studies are discussed only in the complete guideline.

Induced mild hypothermia in combination with pharmacologic options. A Class II study[32] randomized 49 adults with OHCA and various initial rhythms to receive 24 hours of either hypothermia (35°C) plus liquid coenzyme Q_{10} 250 mg once, followed by 150 mg TID for 5 days, or hypothermia alone. Significantly more patients receiving coenzyme Q_{10} survived to 3 months (RD 39%, 95% CI 13%–65%). Survival to hospital discharge and good neurologic status at 3 months were not significantly different between groups. No significant AEs were reported.

A Class III study[33] compared hypothermia plus epoetin-α 40,000 U every 12 hours for 2 days with hypothermia alone; this single Class III study cannot drive recommendations and is discussed in the complete guideline.

Conclusions and recommendations. In patients who are comatose after OHCA, the addition of coenzyme Q_{10} to TH possibly improves survival but not neurologic status at 3 months (1 Class II study) and may be offered (Level C).

Clinical context. The success of TH in post–cardiac arrest brain injury is defined by improvement not only in survival but also in survivors' neurologic status, leading to hope that agents or combinations of agents will improve neurologic outcomes. When added to TH, coenzyme Q_{10} showed survival benefit but not improvement in neurologic status at 3 months. More data are needed to define the role of coenzyme Q_{10}.

In patients with nontraumatic cardiac arrest, do putative neuroprotective drugs improve outcome after CPR in adults who are initially comatose? Studies were identified investigating xenon gas,[34] nimodipine,[35] lidoflazine,[36] selenium,[37] thiopental,[38] magnesium,[39] diazepam,[39] and corticosteroids[40,e1] as putative neuroprotective agents (table 2).

Conclusions and recommendations. In patients with witnessed OHCA and VT/VF, there is insufficient evidence to support or refute the routine clinical use of xenon gas in addition to TH (Level U), as it

probably results in less white matter damage as measured by fractional anisotropy, but the clinical importance of this is unknown and it probably does not improve 6-month neurologic outcome as measured by the CPC. In patients with OHCA, there is insufficient evidence to support or refute the use of nimodipine because of insufficient statistical precision (Level U). Lidoflazine is likely ineffective in improving survival and neurologic outcome in this population (1 Class I study) and should not be offered (Level B). A single loading dose of thiopental is also likely to be ineffective in improving survival or neurologic outcome (1 Class I study) and should not be offered (Level B). There is insufficient evidence to support or refute the effectiveness of selenium (single Class III study; Level U) or a single loading dose of magnesium sulfate (1 Class I study with insufficient statistical precision to exclude a meaningful benefit; Level U). A single loading dose of diazepam is likely ineffective in improving survival or awakening (Level B). There is insufficient evidence to support or refute corticosteroid use for improving survival or neurologic outcome (1 Class II and 1 Class III study with insufficient statistical precision to exclude a moderate or large benefit; Level U).

Clinical context. To date, no neuroprotective drug has been shown to be effective in improving survival or neurologic outcome in patients who are comatose after cardiac arrest. Furthermore, these agents may have serious AEs. Currently none of these agents is used routinely in clinical practice.

In patients with nontraumatic cardiac arrest, do other medical interventions or combinations of interventions improve outcome after CPR in adults who are initially comatose? ***Oxygen therapy.*** One Class I study[e2]

Table 2 Studies of putative neuroprotective drugs after nontraumatic cardiac arrest

Drug	Study/class	Initial rhythm	Outcomes
Xenon gas	Laitio et al.[34] (Class I)	VF/VT	Mean global fractional anisotropy value: 3.8% higher (95% CI 1.1% to 6.4%) in the xenon group when adjusting for age, sex, and study site
			6-month mortality: 27.3% xenon group vs 34.5% controls (RD −7.3%, 95% CI −24.0% to 9.8%)
			Good neurologic outcome at 6 months: Median scores of 1 (IQR 1–5) in both groups (median difference 0, 95% CI 0–0, $p = 0.93$)
Nimodipine	Roine et al.[35] (Class I)	VF	Survival at 1 year: 40% nimodipine vs 36% controls (RD 4%, 95% CI −12% to 19%)
			Good neurologic outcome at 1 year: 29% nimodipine vs 24% placebo (RD 6%, 95% CI −8% to 20%)
Lidoflazine	Brain Resuscitation Clinical Trial II Study Group[36] (Class I)	Mixed	Survival at 6 months: 18.5% lidoflazine vs 17% controls (RD 1%, 95% CI −5% to 8%)
			Good neurologic outcome during study: 24% lidoflazine vs 23% controls (RD 1%, 95% CI −6% to 8%)
Selenium	Reisinger et al.[37] (Class III)	Mixed	Survival at 6 months: 46% selenium vs 35% controls (RD 11%, 95% CI −2% to 23%)
			Good neurologic outcome at 6 months: 67% selenium vs 48% controls (RD 19%, 95% CI 6% to 32%)
Thiopental	Brain Resuscitation Clinical Trial I Group[38] (Class I)	Mixed	Survival at 1 year: 23% thiopental, 20% controls (RD 3%, 95% CI −7% to 13%)
			Good neurologic outcome at 1 year: 20% thiopental, 15% controls (RD 5%, 95% CI −5% to 14%)
Magnesium	Longstreth et al.[39] (Class I)	Mixed	Awakening at 3 months: 38% magnesium vs 34% no magnesium (RD 4%, 95% CI −7% to 15%)
			Survival at 3 months: 30% magnesium vs 28% no magnesium (RD 2%, 95% CI −8% to 12%)
Diazepam	Longstreth et al.[39] (Class I)	Mixed	Awakening at 3 months: Adjusted RD −3% (95% CI −13.5% to 7.4%) (adjusted because of differences in baseline characteristics between groups)
Steroids	Jastremski et al.[40] (Class II)	Mixed	Survival at 1 year: RD 10% favoring steroids (95% CI −4% to 20%)
			Good neurologic outcome: RD 0% (95% CI −13% to 13%)
	Grafton and Longstreth 1988[e1] (Class III)	Mixed	Survival to discharge: 55% steroids, 55% no steroids (RD 0%, 95% CI −8% to 10%)
			Ever awakening: 60% steroids, 61% no steroids (RD 1%, 95% CI −10% to 8%)

Abbreviations: CI = confidence interval; IQR = interquartile range; RD = risk difference; VF = ventricular fibrillation; VT = ventricular tachycardia.

randomized 28 patients with ROSC after witnessed OHCA (initial rhythm VF) to receive either 30% or 100% oxygen for 60 minutes followed by standard care. There was no difference in survival (RD 0%, 95% CI −34% to 34%) or good neurologic outcome (RD 14%, 95% CI −51% to 22%) at hospital discharge, although the study lacked the statistical precision to exclude a potentially important effect.

High-volume hemofiltration. One Class I study[e3] randomized 61 patients with OHCA and any initial rhythm to isovolumic high-volume hemofiltration (HF) alone, HF combined with TH, or routine care. There was no statistical difference in 6-month survival between groups (RD for HF vs controls 24.0%, 95% CI −5.5% to 48.2%, RD for HF plus hypothermia vs controls 10.8%, 95% CI −16.4% to 35.1%). After adjustment for baseline characteristics, including initial rhythm, a multivariate logistic regression model showed an improved odds of survival using pooled HF data (OR for 6-month survival 4.4, 95% CI 1.1–16.6), but the CI included a lower bound of uncertain clinical relevance.

Conclusions and recommendations. There is insufficient evidence to support or refute the use of 100% oxygen immediately postresuscitation (1 Class I study with insufficient statistical precision to exclude a potentially important clinical effect; Level U). There is also insufficient evidence to support or refute the use of isovolumic high-volume HF (1 Class I study with insufficient statistical precision for the primary analysis of 6-month survival and with a secondary logistic regression model including a lower CI of uncertain clinical relevance; Level U).

CLINICAL CONTEXT FOR ALL EVIDENCE Patients who are comatose after successful resuscitation from cardiac arrest require complex neurologic and medical care in the critical care unit. Induced mild hypothermia has emerged as an effective therapy to improve outcomes in patients with VT/VF as their initial cardiac rhythm, but its role in patients with PEA/asystole remains uncertain. Other aspects of TH requiring further study include the optimal method for inducing and maintaining TH, the ideal rate of cooling, the optimal target temperature range, and protocols for rewarming, many of which varied between studies and which could explain some variation in results. No method has established superiority, and clinicians need to understand existing methods and technologies so they are better informed when acquiring equipment and developing protocols.

Multiple brain-related complications such as seizures, status epilepticus, myoclonus, and cerebral edema can occur in patients post arrest. Although these conditions are believed to have a large effect on prognostication and survivors' quality of life, studies are too limited to offer evidence-based treatment recommendations at this time. In the absence of adequate evidence to provide a treatment recommendation, it is best to consider prevailing local standards in the management of these complications.

The guideline panel also notes that most of the studies did not specifically address the effect of withdrawal of life-sustaining therapies in their analyses (table e-1). The effect of this practice on the outcome of trials needs careful study. Finally, there is a great need for further studies on methods of supplementing TH protocols, such as extracorporeal membrane oxygenation (ECMO) and pharmacologic agents (e.g., xenon gas, where the most recent study had mixed results).

RECOMMENDATIONS FOR FUTURE RESEARCH The complexity of patient characteristics and the clinical course after resuscitation from cardiac arrest need to be addressed carefully in future research. Future research questions may include the following:

1. What are the best assessment methods and outcome measures to use? When is the best time to use these methods and measures?
2. What is the beneficial effect of TH and TTM on patients resuscitated from IHCA with all types of initial cardiac rhythm?
3. What are optimal temperature settings (time initiating and reaching target temperature, rate of rewarming, depth of target temperature [e.g., 32°C, 34°C, 36°C], duration of temperature management [e.g., 12 hours, 24 hours, 48 hours]) to provide the best outcome?
4. What is the treatment window (time lapse after ROSC) in which TTM will be most effective and ineffective?
5. What is the role of fever control over days after active TTM?
6. What strategies (e.g., ECMO, pharmacologic agents) may provide benefit in addition to hypothermia, and what is the effect of hypothermia on the action of other putative neuroprotective agents or interventions?
7. What is the best method of delivering hypothermia (external vs internal, global vs regional cooling)?
8. What is the effect of aggressive management of post–cardiac arrest neurologic complications (e.g., brain edema, seizures or seizure prophylaxis, intracranial pressure elevation, and intensive care unit–related complications) on outcomes?
9. What is the effect of aggressive management of the etiology of cardiac arrest (e.g., myocardial infarction) and aggressive management of other systemic complications?

10. How does the use of TH affect the ability to prognosticate outcome in patients who are comatose after cardiac arrest?
11. What is the role of TTM induced and maintained by pharmacologic means in patients who are comatose after ROSC?
12. What is the role of biomarkers in the delivery and maintenance of TTM and the effect of biomarkers on prognostication?
13. What is the role of withdrawal of life-sustaining therapies in the outcomes of studies related to cardiac arrest resuscitation?

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AUTHOR CONTRIBUTIONS

Dr. Geocadin: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision. Dr. Wijdicks: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Armstrong: analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Damian: acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Mayer: acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Ornato: acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Rabinstein: acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Suarez: acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Torbey: acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Dubinsky: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision. Dr. Lazarou: acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision.

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