Targeted temperature management in critical care: A report and recommendations from five professional societies

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**Objective:** Representatives of five international critical care societies convened topic specialists and a nonexpert jury to review, assess, and report on studies of targeted temperature management and to provide clinical recommendations.

**Data Sources:** Questions were allocated to experts who reviewed their areas, made formal presentations, and responded to questions. Jurors also performed independent searches. Sources used for consensus derived exclusively from peer-reviewed reports of human and animal studies.

**Study Selection:** Question-specific studies were selected from literature searches; jurors independently determined the relevance of each study included in the synthesis.

**Conclusions and Recommendations:**

1. The jury opines that the term “targeted temperature management” replace “therapeutic hypothermia.”

2. The jury opines that descriptors (e.g., “mild”) be replaced with explicit targeted temperature management profiles.

3. The jury opines that each report of a targeted temperature management trial enumerate the physiologic effects anticipated by the investigators and actually observed and/or measured in subjects in each arm of the trial as a strategy for increasing knowledge of the dose/duration/response characteristics of temperature management. This enumeration should be kept separate from the body of the report, be organized by body systems, and be made without assertions about the impact of any specific effect on the clinical outcome.

4. The jury STRONGLY RECOMMENDS targeted temperature management to a target of 32°C–34°C as the preferred treatment (vs. unstructured temperature management) of out-of-hospital adult cardiac arrest victims with a first registered electrocardiography rhythm of ventricular fibrillation or pulseless ventricular tachycardia and still unconscious after restoration of spontaneous circulation (strong recommendation, moderate quality of evidence).

5. The jury WEAKLY RECOMMENDS the use of targeted temperature management to 33°C–35.5°C (vs. less structured management) in the treatment of term newborns who sustained asphyxia and exhibit acidosis and/or encephalopathy (weak recommendation, moderate quality of evidence). (Crit Care Med 2011; 39:000–000)

**KEY WORDS:** temperature; consensus; cardiac arrest; targeted temperature management; hypothermia

EXECUTIVE SUMMARY

Intentional manipulation of body temperature for treatment of disease or mitigation of its symptoms is as old as medicine itself. Although modern clinical practice embraces normothermia as the desired final state (through “active rewarming,” administration of antipyretics, and the like), temporary change to an abnormal temperature has been advocated since antiquity as a therapeutic strategy. Fever therapy was recommended by no less an authority than Parmenides (ca. 500 BC), who stated, “Give me the power to produce fever, and I will cure all disease.” Hippocrates (ca. 460–370 BC), who believed in fever as a treatment for epilepsy, was somewhat more nuanced: he advocated the packing of wounded soldiers in snow and ice.

There has been a recent resurgence of interest in “therapeutic hypothermia.” Current experiment and practice focuses on...
diverse brain, spinal cord, and cardiac pathologies. New technologies facilitating hypothermia have been developed and marketed. Conflicting reports of success, failure, and complications have recently appeared in the professional literature.

Since so many conditions for which therapeutic hypothermia is advocated are in the realm of critical care medicine, five intensive care professional societies jointly sponsored a critical review, expert presentations, and juried evaluation of the evidence. The experts, jurors representing each of the professional societies, and an audience convened in April 2009 to consider the evidence for intentional hypothermia as a treatment for selected critical illnesses.

Using Grading of Recommendations Assessment, Development and Evaluation methodology and informed by published meta-analyses, primary peer-reviewed manuscripts, and expert presentations, the jurors sifted and weighed the evidence to arrive at opinions and recommendations. Opinions represent the consensus of the jury about terminology and future approaches, whereas recommendations that emerged from the Grading of Recommendations Assessment, Development and Evaluation process advise on specific indications for intentional hypothermia.

On the basis of information available in April 2009, the following were offered by the jury:

First, the jury opined that the terminology and descriptions of treatment were inadequate. The term “therapeutic hypothermia” should be discarded in favor of “targeted temperature management” to emphasize the importance of defining a complete temperature profile. Just as with a pharmaceutical, the safety and reproducibility of a therapeutic effect requires careful and complete definition, not just of the drug but also of the dosing schedule and route of administration. Qualitative descriptors (e.g., “mild,” “moderate”) should be entirely replaced by specific temperature values. The jury emphasized the need for accurate reporting of the indication for temperature management, the interval between disease onset and cooling, the management profile, including the rates of decrement and increment as well as the temperatures achieved, and a comprehensive description of the effects on each body system.

Second, the jury strongly recommended the use of targeted temperature management as a treatment for patients who sustain a cardiac arrest with ventricular fibrillation as the first observed rhythm in the prehospital environment. The strong recommendation signifies that this treatment should be administered unless there is a clear extenuating circumstance.

Third, the jury weakly recommended the use of targeted temperature management as a treatment for perinatal asphyxia. The weak recommendation signifies that the benefits, risks, and alternatives should be weighed by caregivers and decision makers, with an expectation that the majority would make an informed choice to accept the treatment.

Given the available evidence, no additional recommendations were made. The absence of a recommendation does not signify the absence of value or benefit. Rather, it signifies only that sufficient evidence was lacking to make an unambiguous recommendation. Generally, “no recommendation” should be interpreted as a need for additional careful study.

Body temperature, which is systematically measured and reported as a vital sign, contributes to maintenance of normal physiology and affects the processes that lead to recovery after illness. Intentional manipulation of body temperature has emerged as a treatment strategy. Thus, anecdotal reports of unexpectedly favorable outcomes following intentional reduction of temperature have contributed to a renaissance in basic laboratory investigations and also to clinical studies of targeted temperature management (TTM).

To evaluate the indications, profiles, and outcomes of TTM in critical care, five intensive care societies sponsored an expert review and juried analysis of existing knowledge. The international conference, which convened April 23–24, 2009 in San Juan, Puerto Rico, aimed to describe current practice, to offer consensus recommendations, and to consider future directions for TTM in critical care.

The conference began with 22 presentations by basic and clinical scientists with expertise in various aspects of TTM (supplemental Appendix). Ten jurors nominated by the five societies and a jury chairperson were provided with lecture summaries in advance and prepared questions for each expert based on the summary, the lecture content, and each juror’s independent review of existing peer-reviewed primary reports and scholarly reviews (including meta-analyses). An audience of 213 also participated in the question-and-response sessions. Following the public presentations and juror questioning, the jury deliberated April 25–26. Each of the five sponsoring societies was asked to endorse the process and/or the work product (this report).

To maintain transparency, provide accountability, and avoid confusing speculation with analysis, the jurors selected a Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to weighing information. In particular, jurors agreed to assess the quality and importance of peer-reviewed studies. Since many of the conference lectures were forward looking and speculative, this report is narrower in scope than the conference itself.

DATA SOURCES, METHODS, AND JURY OBSERVATIONS

1) Experts and jurors were counseled to not only seek relevant meta-analyses and papers cited therein but also to perform additional searches focusing on the specific questions assigned to the experts to identify recent and potentially relevant reports in the peer-reviewed literature.

2) After hearing the presentations of the experts, the jurors reviewed papers cited in the published meta-analyses as well as others recovered from additional searches and performed additional meta-analyses, pooling all relevant data.

3) The jury considered the term “therapeutic hypothermia” inadequate. The adjective “therapeutic” implies a favorable effect that cannot be generally assumed. The noun “hypothermia” does not include interventions intended to maintain temperature near 37°C, a value that is widely considered to be normal. Instead, the jury saw a compelling need for an accurate description of TTM (supplemental Appendix). The jury observed that experimental and clinical studies consistently specify three events in TTM profiles: an intentional change from the current temperature to a lower temperature (“induction”), maintenance of that temperature for a time (“maintenance”), and a change to a new value after which temperature management is either increased at a specific rate to a normothermic target or released to intrinsic physiologic control (“reversion”). Therefore, clinical practice of TTM should specify at least a description of the intended temperature profile (targets as well as rates of temperature change), the thermodulatory interventions used to achieve the target, the actual performance of the
TTM strategy, and the primary and secondary outcomes that the TTM intended to achieve.

4) The jury had the greatest confidence in data obtained from clinical experiments (randomized studies) in which the inclusion/exclusion criteria were tightly defined, the subjects were rigorously screened, the trial arms were explicitly described, the performance in each arm was clearly reported, and the trial end points were clinically important functional outcomes. This generally required an expanded screening strategy to ensure a sufficient number of on-treatment (per protocol) subjects. While an intention-to-treat analysis is essential to predict the utility of an intervention in general practice, assessment of a particular TTM is easily confounded by a failure to isolate and complete the intended on-treatment comparison. Thus, power calculations used to project needed enrollment in future studies should take into account failures to achieve temperature targets and reflect the number of subjects needed to actually compare adequately powered on-treatment arms, a number that is larger (in some cases substantially larger) than the number actually analyzed in those arms.

5) The jury opined that each future report of a TTM experience, whether prospective or retrospective, observational or a trial, discuss the standard care at the time just before the report. It appears that TTM has already become standard care for selected patients and illnesses. As a result, the appropriate reference arm could consist of untargeted management, of targeted management to a “normal” temperature, or of targeted management to a specific low temperature. Understanding the rationale for selection of the reference arm is important to interpretation of the results of TTM studies.

6) The jury was tasked with writing a consensus document. Jurors were selected on the basis of their skill at reviewing and weighing evidence and not on the basis of familiarity with the intricacies of the protocols or methods. The jury was not qualified to specify specific TTM interventions, much less design implementation strategies. Rather, the jury determined whether there was sufficient evidence to make a specific recommendation for implementation of a TTM strategy in particular pathologic settings and, if appropriate, made general recommendations. Where sufficient evidence was lacking, the jury chose not to make a recommendation. There were two general insufficiencies. The first insufficiency related to (in)adequacy of data—too few studies, too few patients, imprecision, end points only marginally related to patient-important outcomes, and so on. In such cases, the jury generally encouraged ongoing exploration of TTM both inside and outside prospective controlled trials to gain additional experience and evidence. Regardless of how that experience is gained, practitioners and investigators have ethical obligations to record outcomes and to evaluate adverse events. The second insufficiency related to conflicting data and conflicts arising from reports of treatment-related harm. While acknowledging that the diseases being studied are devastating to patients and society, the jury perceived a general ethical duty to advise that the use of TTM in frequently encountered conditions (for example, in-hospital cardiac arrest with pulseless electrical activity) be confined to prospective trials supervised by an independent data-safety-monitoring board with the expertise to evaluate favorable and adverse outcomes and the authority to terminate a TTM study on the basis of benefit, harm, or futility.

7) Medical knowledge continues to accumulate. Through the presentations and through comments from the audience, the jury was made aware of additional trials in various stages, including some that have been submitted for peer review. This consensus document focuses on completed studies that have undergone peer review and achieved publication. This document, written in mid-2009, serves as a basis for clinical and scientific decision making only after review and consideration of reports that will appear subsequently.

8) There exists no universally accepted strategy for translation of studies into best practice advice. Deliberation, objectivity, and transparency seem desirable. Once the quality of evidence was established (high, moderate, low, or very low quality), the jury formulated a recommendation and suggested its strength (1). The strength of the recommendation (strong vs. weak) represents the balanced judgment of the jury and reflects previously assessed quality of evidence, the degree of uncertainty about the balance between desirable and undesirable effects, the uncertainty or variability in values and preferences among patients, and the uncertainty about whether the intervention represents a reasonable use of resources. With GRADE, the jurors made strong recommendations on the basis of high confidence that the salutary effects of adherence to a recommendation outweigh the undesirable effects. Weak recommendations indicate the jurors’ judgment that the desirable effects of implementing a given recommendation probably outweigh the undesirable effects, but they are less confident in this judgment. Operationally, one would expect that a strong recommendation corresponds to a situation in which an informed patient would choose the recommended action, and therefore, a strong recommendation could be used as a policy decision. A weak recommendation implies that a substantial proportion of patients would consider and choose an alternative action. Weak recommendations demand that clinicians be much more explicit in discussion of alternatives and furthermore that the weak recommendation should not be operationalized as policy until additional experience is reported.

9) The opinions expressed herein are the collective responsibility of the jury. Neither individual jurors nor the sponsoring societies are responsible for the opinions. Rather, the opinions represent a collective good faith assessment of what can be recommended and what might remain to be learned concerning TTM as a treatment strategy in critical care.

**Question 1: What Is Mild Therapeutic Hypothermia?**

**Executive Summary**

**Recommendation 1.1.** The jury opined that the term “targeted temperature management” replace “therapeutic hypothermia.”

**Recommendation 1.2.** The jury opined that descriptors (e.g., “mild”) be replaced with explicit TTM profiles.

The idea that therapeutic hypothermia could mitigate brain injury was introduced in the 1950s. Recently, TTM has gained popularity as a means to improve neurological outcomes in critical illness and injury.

Hypothermia is often defined as a core temperature of <35°C. The term “therapeutic hypothermia” has been used to connote the intentional lowering of core temperature as a management strategy. However, protocols have used different temperature profiles, and each profile appears to offer a unique balance of favorable and adverse effects. Furthermore,
descriptors (“mild,” “moderate,” “deep”) confound interpretation because they are inconsistently used and imply different levels of TTM complexity (supplemental Appendix).

These definitions are not capricious. Nevertheless, they are inconsistent. Furthermore, they do not reflect possible effects of timing, rates of temperature change, and duration and depth of treatments.

Further confounding the definition of hypothermia has been the use of different terminologies for similar temperature targets (supplemental Appendix).

The jury therefore advises adoption of the expression “targeted temperature management” for the interventions. The jury further advises that terms such as “mild,” “moderate,” and “deep” be abandoned and that subsequent studies of TTM in the critically ill population should describe the intended TTM profile, the method used to achieve that profile, the measurement strategy (vide infra), and the actual profile achieved for each arm of each TTM study.

A TTM profile is divided into three distinct phases (2) (supplemental Appendix).

- Induction: an intentional change from the current temperature to a lower temperature.
- Maintenance: tight control of the target temperature for a period of time.
- Reversion: change to a new value after which temperature management is released to intrinsic physiologic control.

**Question 2: What Are the Definitions and Physiologic Effects of TTM? Executive Summary**

**Recommendation 2.1.** The jury opined that each report of a TTM trial enumerate the physiologic effects anticipated by the investigators and actually observed and/or measured in subjects in each arm of the trial as a strategy for increasing knowledge of the dose/duration/response characteristics of temperature management. This enumeration should be kept separate from the body of the report, be organized by body systems, and be made without assertions about the impact of any specific effect on the clinical outcome. Data elements that might contribute to an enumeration are collected in the supplemental Appendix.

**Commonly Observed Effects of Temperature Reduction below Normal Values**

- **36°C:** Increased activity attempting to warm up, skin pale, numb, and waxy, muscles tense, fatigue, and signs of weakness.
- **34°C–35°C:** Uncontrolled intense shivering, still alert but movements uncoordinated, and pain and discomfort due to coldness.
- **31°C–33°C:** Shivering slows or stops, muscles stiffen, mental confusion, apathy, speech slowed and slurred, breathing slower and shallow, and drowsiness.
- **<31°C:** Skin cold, pupils dilated, extreme weakness, slurred speech, exhausted, denies problems, resists help, gradual loss of consciousness, and progressive respiratory arrest and arrhythmias.

Research in understanding the normal body response to hypothermia has been limited due to the ethical restrictions on systematically inducing hypothermia in volunteers.

The physiologic effects of TTM appear to be temperature-dependent and are further modified by age and comorbidities, especially in patients with cardiovascular disease. The following are often described in peer-reviewed studies:

- Shivering and peripheral vasoconstriction. Common physiologic responses to lowering temperature are shivering and peripheral vasoconstriction. Shivering is predicted when the core temperature decreases below 35.5°C. Shivering increases muscle activity and the total metabolic rate up to four-fold, thereby increasing the production of heat and most importantly oxygen consumption. Prevention of shivering is a component of many TTM strategies. When the core temperature is <30°C, shivering ceases and the metabolic rate decreases.

- General circulatory response. Little is known of the cardiovascular effects of hypothermia in intensive care unit patients. Inferences are made from the perioperative population. Most “mild hypothermia” trials reported no substantive hemodynamic compromise during induced hypothermia (3–7). An exception was the study by Clifton et al (8) in which 10% of hypothermic (vs. 3% of normothermic) patients had critical hypotension. Since critical hypotension required treatment, a larger fraction of hypothermia patients required vasopressors. This might have been an effect of hypovolemia. Bernard et al (3, 9) reported the hemodynamic effects post cardiac arrest of before, during, and after TTM. In a subset of patients, the cardiac index was transiently suppressed while systemic vascular resistance was transiently increased during hypothermia induction.

- Arrhythmias. A substantive effect of temperature reduction on arrhythmias was not observed in TTM where the targeted reduction was “mild” (3–7). This is different from “deeper,” inadvertent hypothermia, where arrhythmias are common.

- Bleeding and coagulation. In the studies of induced “mild” hypothermia in the intensive care unit, hemorrhage was not reported (3–7). Bernard et al (3) did not report problems with platelets or white blood cells. However, hypothermia affects platelet function and prolongs the prothrombin time and partial thromboplastin time (4, 10). These effects are masked when laboratory analysis is performed at 37°C, suggesting that any risk will be mitigated by rewarming. Measuring coagulation tests at actual patient temperature would mirror functional performance of the clotting system better than measurement conventionally performed at 37°C. Neutropenia is observed in TTM patients, and inadvertent hypothermia is a risk factor for infection in perioperative medicine (10).

- a stat/pH stat. There is controversy regarding the measurement and reporting of blood gas data. Temperature affects pH as well as PCO2. Temperature also modulates cerebral blood flow. A strategy that maintains PaCO2 and pH at normothermic physiologic values when actually measured at the treatment temperature (pH stat) produces different data compared to a strategy where blood gases are measured and treated at values closer to 37°C (a stat). A study by Kollmar et al (11) showed that a pH stat management strategy augments cerebral blood flow but also increases intracranial pressure (ICP) in patients with large strokes where treatment includes TTM.

- Renal effects and electrolytes. During temperature reduction, urine flow increases. The increase is attributable to changes in renal blood flow and to failure...
to reabsorb sodium in the distal tubules, leading to obligate water wasting (10). Renal losses of potassium, magnesium, calcium, and phosphate also occur. In aggregate, hypothermia leads to significant derangements in water and electrolyte homeostasis.

Gastrointestinal effects. Bernard and Buist (12) report that hypothermia is associated with ileus and elevation of serum amylase. The ileus includes delayed gastric emptying.

Endocrine/insulin effects. With decreasing temperature, insulin levels are decreased, likely secondary to catecholamine release. This results in decreased insulin secretion and peripheral sensitivity. As a consequence, hyperglycemia is common and insulin must be augmented. Insulin treatment to correct the hyperglycemia can further derange potassium levels and handling (12–14).

Cellular and Molecular Mechanisms of Neurological Injury and Neuroprotection. A complete review of these mechanisms is beyond the charge to the jury. However, selective consideration of the mechanisms sheds some light on design considerations in future TTM trials. The jury cautions that most information comes from animal experiments. The few human studies offer only indirect evidence (usually inference from cerebrospinal fluid and plasma analysis) of injury and of the mechanisms by which TTM improves outcome.

The relative contributions of various mechanisms to the beneficial effects of hypothermia differ among different experimental models. This is at least partly due to the fact that secondary insults to the brain differ between different central nervous system pathologies, reperfusion injury being important after cardiac arrest, stroke, and axonal injury and brain swelling following traumatic brain injury (TBI). It is likely that the salutary effects of hypothermia, when present, are due to additive and potentially synergistic effects on multiple pathways. Nevertheless, a comparison of mechanisms may be useful.

Pathology-Dependent Mechanisms. In the uninjured human brain, hypothermia reduces cerebral blood flow and metabolism (oxygen consumption) in proportion to the depth of the temperature reduction (15). However, the effects of hypothermia in the injured brain depend on the underlying pathology. Thus, global (cardiac arrest) or focal (stroke) brain ischemia make it unlikely that further reduction in blood flow consequent to TTM constitutes the protective mechanism. In contrast, in TBI, hypothermia reduces cerebral blood flow (resulting in cerebral blood volume-mediated reductions in ICP) and cerebral metabolism (16).

Energy “failure” may or may not be the cause of cell death. Two waves of neuronal cell death occur after a central nervous system insult. Immediately after the insult, neurons die by necrosis (caused by membrane disruption, irreversible metabolic disturbances, and/or excitotoxicity). The second wave of neuronal death is delayed and appears apoptotic with features of programmed cell death. Hypothermia attenuates proapoptotic signals such as cytochrome c release (17), caspases and Bax up-regulation, and caspase activation (caspase-dependent apoptosis) (18, 19). Hypothermia activates antiapoptotic mechanisms such as the Erk1/2 pathway (20, 21) (which correlates with up-regulation of brain-derived neurotrophic factor) (22) and the Akt pathway (23). Activated Akt blocks caspase/cytocrome c mediated apoptosis by phosphorylating Akt substrates (19).

Hypothermia blocks ischemic damage by keeping the negative regulator of Akt, phosphatase and tensin homologue, in its inactive phosphorylated form (19, 24). Hypothermia also enhances p53 expression, promoting repair after focal ischemia (25). The survival benefit of hypothermia for neurons is indirectly evidenced in humans by the reduced levels of neuron-specific enolase, a marker of the death of neurons, in patients who sustained ventricular fibrillation cardiac arrest and were treated with hypothermia (26, 27).

Hypothermia attenuates and/or delays axonal depolarization caused by adenosine triphosphate depletion and the consequent increases in the release of glutamate in the extracellular space, thus reducing excitotoxicity (19). Attenuation of spreading depression (15, 28) and hyperglycolosis (29) are also noted after temperature reduction.

Hypothermia attenuates various markers of oxidative and nitrosative stress and preserves antioxidant levels in experimental models of global and focal cerebral ischemia and TBI (30–34). There is also evidence that this is the case in humans, males more than females (35, 36). Lower temperatures also prevent blood-brain barrier breakdown probably by inhibiting matrix metalloproteinases and thus preserving basal lamina proteins (37–39).

Hypothermia attenuates axonal injury in experimental TBI mainly by attenuating calpain-mediated proteolysis (40). Effects on axonal injury in stroke or cardiac arrest models remain inadequately explored.

In experimental stroke, inflammatory gene expression (such as IL-6) and relevant transcription factors (nuclear factor κB) are suppressed by therapeutic hypothermia (41). In contrast, in experimental and clinical TBI and in experimental cardiac arrest, the effects of hypothermia on inflammatory gene expression are minimal or undetectable (42–44). Hypothermia also attenuates neutrophil, macrophage, and microglia accumulation and proliferation and vascular adhesion molecule expression in experimental TBI and stroke (45, 46) yet failed to reduce cerebrospinal fluid markers of macrophage accumulation in clinical TBI (47). Thus, evidence is limited for any benefit of “mild” hypothermia being mediated by attenuation of neuroinflammation, especially in TBI or cardiac arrest.

Rapid rewarming exacerbates neural injury, in part by modulating the cellular and molecular mechanisms discussed (48, 49). Rapid rewarming also leads to macroscopic loss of cerebral blood flow autoregulation in experimental models of TBI and stroke. Slow rewarming protects vascular reactivity (50) and appears to mitigate reactive oxygen species mediated endothelial and smooth muscle cell injury in brain vessels of TBI and stroke models (48, 51).

More experimental studies (including genetically manipulated animals) are needed to unravel the mechanisms of the beneficial effects of TTM. More importantly, human data are needed in situations (cardiac arrest or stroke) where cerebrospinal fluid samples are not usually obtained.

Question 3: What Is the Clinical Evidence in Support of Targeted Temperature Reduction as Treatment After Focal or Global Ischemia Reperfusion Injury? Executive Summary

Recommendation 3.1. Sufficient evidence exists for the jury to RECOMMEND STRONGLY in favor of TTM to a target of 32°C–34°C as the preferred treatment (vs. unstructured temperature management) of out-of-hospital adult cardiac arrest victims with a first registered elec-
tetrocardiographic rhythm of ventricular fibrillation or pulseless ventricular tachycardia and still unconscious after restoration of spontaneous circulation (strong recommendation, moderate quality of evidence).

No Recommendation. The jury makes NO RECOMMENDATION regarding the use of TTM in out-of-hospital cardiac arrest victims with other electrocardiographic rhythms, on the basis of insufficient evidence.

No Recommendation. Insufficient evidence exists for the jury to make a data-driven recommendation regarding the use of TTM in treatment of in-hospital adult cardiac arrest victims. The distinction between in-hospital and out-of-hospital events is a reflection that out-of-hospital patients are generally well or at least physiologically well compensated before cardiac arrest whereas hospitalized patients are heterogeneously ill. Thus, NO RECOMMENDATION can be made regarding the use of TTM for in-hospital adult cardiac arrest. The absence of a recommendation must not preclude clinical judgment, and clinical judgment could well include a TTM strategy.

Recommendation 3.2. Sufficient evidence exists for the jury to WEAKLY RECOMMEND the use of TTM to 32.5°C–35.5°C (vs. less structured management) in the treatment of term newborns who sustained asphyxia and exhibit acidosis and/or encephalopathy (weak recommendation, moderate quality of evidence).

What Is the Clinical Evidence in Support of TTM After Ventricular Fibrillation Cardiac Arrest?

Cerebral ischemia/reperfusion injury is a consequence of cessation and restoration of circulation, either globally (cardiac arrest or perinatal asphyxia) or locally (TBI). Such an ischemia/reperfusion injury starts a cascade of events that further injure neural tissues.

Among the common pathophysiologic processes in these injuries are energy failure, apoptosis, influx of Ca$^{2+}$ into the cell, intra- and extracellular acidosis, accumulation of glutamate and other excitotoxins, neurotransmitters, release of glycine, nitric oxide production, free radical production, glial activation, blood–brain barrier disruption, and inflammation as discussed in the prior section. In some cases there is brain swelling, resulting in intracranial hypertension. TTM may have a protective effect via one or more of these mechanisms. It is therefore important to ascertain the effect on functional outcome of early TTM as a treatment strategy following these (and other) specific injuries.

TTM for Cardiac Arrest: Study Summary and Evaluation. The jury evaluated the expert summary and performed their own literature search using PubMed to search for “hypothermia” and “cardiac arrest,” screening titles and abstracts for relevance. Selected studies were reviewed for results, and attention was paid to the proportion of subjects with ventricular fibrillation or pulseless ventricular tachycardia as their presenting rhythm vs. patients presenting with asystole or pulseless electrical activity. Relevant evidence was assessed using the GRADE method to judge the quality of evidence. Jurors assembled the data in a meta-analysis (labeled “jury analysis”). A recent meta-analysis of hypothermia for neuroprotection after cardiac arrest was compared to these results (52). The number of subjects and events in our analyses was reconciled with the meta-analyses and, where different or missing, was adjudicated by two jurors.

GRADE Jury Analysis: Ventricular Fibrillation/Pulseless Ventricular Tachycardia Out-of-Hospital Cardiac Arrest in Adults. Two multicenter randomized trials (3, 4) and one randomized pilot study (53) were identified and considered to be key studies. Because of the low quality of evidence in the observational studies, only randomized controlled trials were included in the final jury meta-analysis. A favorable neurological outcome (cerebral performance class 2 [moderate disability] or 1 [good recovery] or discharge to home or a rehabilitation facility) and mortality at the last follow-up were selected as the most important clinically relevant outcomes (critical outcomes). The supplemental Appendix presents selected details of individual studies and shows the forest plots for survival and a favorable neurological outcome.

Study Limitations. All included studies were randomized controlled trials. Application of TTM was not blinded due to the complex nature of managing patients with TTM. Managing temperature can be a labor-intensive strategy, and it is difficult to know what role the extra attention paid to patients might have had on other clinically relevant variables, as well as on clinical decisions to withdraw support.

The jury decided not to lower the quality of evidence on this basis nor on the basis of a lack of randomization concealment. Inconsistency. For both outcomes there was little inconsistency of the results indicated by overlapping confidence intervals (CIs) for individual studies, nonsignificant tests for heterogeneity ($p > .05$), and an $I^2$ of 0%. The jury did not lower the quality of evidence for either outcome.

Indirectness. Temperature management in control subjects varied substantially. Temperatures of $>37.5°C$ were suggested in at least a sizable minority ($>15%$, assuming a normal distribution) of patients in the two multicenter studies (3, 4) but not in the pilot study (53). As hyperthermia might worsen outcomes after cardiac arrest, even mild fevers in the control group might bias outcomes in favor of TTM.

All selected studies evaluated critical outcomes in populations of interest. As our question of interest was the use of a TTM strategy that lowers temperature below a normal range of $36.5°C–37.5°C$, indirectness was an issue because of the presence of fever in control subjects. For this reason, the jury lowered the overall quality of evidence by one level when a temperature of $>37.5°C$ was likely among some control subjects at any point during the intervention period.

Imprecision. For mortality and a favorable neurological outcome, the results using the fixed-effects model were significant and the precision was judged satisfactory. The jury did not lower the quality of evidence for either outcome.

Publication bias. The jury did not observe any evidence of publication bias on a funnel plot.

Final summary of jury analysis. The supplemental Appendix includes a GRADE profile of jury-reviewed outcomes. By meta-analysis, the odds ratio for survival with TTM vs. unstructured temperature management is 1.87 (95% CI = 1.25–2.78) and for a favorable neurological outcome it is 2.02 (95% CI = 1.32–3.11).

The overall quality of evidence was judged as moderate because of indirectness (control group temperatures of $>37.5°C$). Although one may dispute this decision about quality, the jury’s judgment did not include considerations of lack of blinding or allocation concealment. Regardless of the interpretation of individual study aspects, the overall quality of evidence is likely moderate.
Taking the available data into account, the jury decided to strongly recommend the use of TTM in ventricular fibrillation/pulseless ventricular tachycardia out-of-hospital cardiac arrest with subsequent coma.

GRADE Jury Analysis: Pulseless Electrical Activity/Asystolic Out-of-Hospital Cardiac Arrest in Adults. One single-center randomized trial (54) and one randomized pilot study (53) comparing patients treated with TTM against controls provided data on these specific patients and were considered as key studies. Because of the very low quality of evidence in observational studies, only randomized controlled trials were included in the final jury meta-analysis. A favorable neurological outcome (cerebral performance class 2 [moderate disability] or 1 [good recovery]) and mortality at the last follow-up were selected as the most important clinically relevant outcomes (critical outcomes). The supplemental Appendix presents selected details of individual studies and shows the forest plots for survival analysis and a favorable neurological outcome.

Study limitations. All included studies were randomized controlled trials. Application of TTM was not blinded due to the complex nature of managing patients with TTM. Managing temperature can be a labor-intensive strategy, and it is difficult to know what role the extra attention paid to patients might have had on other clinically relevant variables, as well as on clinical decisions to withdraw support. The jury decided not to lower the quality of evidence on this basis nor on the basis of a lack of randomization concealment.

Inconsistency. For survival there was moderate inconsistency of the results indicated by opposite directions of CIs for individual studies, borderline tests for heterogeneity (p = .09), and an I² of 65%. As a result, the quality of evidence was lowered by one level for the outcome of survival. In the case of a favorable neurological outcome, there was only one randomized trial, so no action was taken. The jury has not explored the sources of heterogeneity, which might include differences in the methodological quality, cooling technique and duration, and/or duration and rate of rewarming.

Indirectness. All selected studies evaluated critical outcomes in populations of interest. As our question of interest was the use of a TTM strategy that lowers temperature below a normal range of 36.5°C–37.5°C, indirectness could have been an issue because of the presence of fever in control subjects. No data were available regarding control group fever in the study by Hachimi-Idrissi et al (54), and there was no significant hyperthermia in the pilot study (53). As hyperthermia might worsen outcomes after cardiac arrest, even mild fevers in the control group might bias outcomes in favor of TTM. The jury has not lowered the quality of evidence for either outcome.

Imprecision. For survival and favorable neurological outcome, the results using the fixed-effects model were not significant (p = .33 and .31 for survival and a favorable neurological outcome, respectively) on the basis of a total of 14 and 2 outcomes, respectively, and the precision was judged very unsatisfactory. The jury therefore lowered the quality of evidence for both outcomes by two levels.

Publication bias. The jury analyzed only two studies and did not speculate on publication bias. The quality of evidence was not lowered because of possible publication bias.

Final summary of jury analysis. The supplemental Appendix includes a GRADE profile of jury-reviewed outcomes. By meta-analysis, the odds ratio for survival with TTM vs. unstructured temperature management is nonsignificantly worse at 0.56 (95% CI = 0.17–1.79) and for a favorable neurological outcome it is nonsignificantly improved at 5 (95% CI = 0.22–113.5).

The overall quality of evidence was judged as very low for survival and low for a favorable neurological outcome because of inconsistency for survival and major imprecision for both. The jury’s judgment did not include considerations of lack of blinding or allocation concealment. Regardless of the interpretation of individual study aspects, the findings are nonsignificant and, in the case of survival, unfavorable.

Meta-analysis of available studies. A recent meta-analysis (52) incorporated three randomized clinical trials (RCTs) (3, 4, 54). Two included trials addressed mostly ventricular fibrillation/pulseless ventricular tachycardia arrest (3, 4), and one addressed exclusively asystole/pulseless electrical activity arrest (54). All three studies evaluated out-of-hospital cardiac arrest. The supplemental Appendix gives a forest plot for the outcome of survival to hospital discharge with survival and a favorable neurological recovery. In an analysis that pooled all cardiac arrest rhythms, the risk ratio for survival to hospital discharge with a favorable neurological outcome was 1.68 (95% CI = 1.29–2.07), similar to the jury’s odds ratio looking specifically at favorable neurological outcomes in ventricular fibrillation patients (2.02 [95% CI = 1.32–3.11]). Those results reflect, however, mostly data on patients with ventricular fibrillation/pulseless ventricular tachycardia and were considered confirmatory for jury analysis. The applicability of these data to patients with different rhythms is very limited.

Taking the available data into account, the jury concludes that no sufficient evidence exists to make any recommendations regarding the use of TTM in cardiac arrest victims with a first recorded electrocardiographic rhythm other than ventricular fibrillation or pulseless ventricular tachycardia with subsequent coma. Given the heterogeneity of patients and very small number of studies and events, further studies with ongoing monitoring of patients for complications and undesirable side effects seem appropriate.

Jury Analysis: In-Hospital Cardiac Arrest in Adults. No randomized controlled trials studied TTM in in-hospital cardiac arrest. The available data are insufficient to make a recommendation for (or against) the use of TTM following in-hospital cardiac arrest. Unresolved issues include the appropriate temperature profile, the role concomitant acute illness or the exacerbation of chronic illness has on the outcome, and the added value of specific temperature management goals, including unstructured management, “normal” ranges of 36.5°C–37.5°C with aggressive fever control, or lower temperature ranges as different targets in TTM protocols. Further surveillance of outcomes and complications might well be achieved by organizing and reporting patient data to national or international registries of TTM outcomes, and the jury suggests that the creation of such a registry would be a useful collaborative effort among the sponsoring societies.

The jury suggests that those who adopt TTM in asystole/pulseless electrical activity out-of-hospital cardiac arrest or in-hospital cardiac arrest should describe in a systematic fashion the results of their treatment in a way that is accessible to the community. Variables that should be addressed include the outcome differences in asystole, pulseless electrical activity, ventricular tachycardia and ventricular fibrillation, fever control (vs.
targeted temperature lowering), the role of gender, and the time to return of spontaneous circulation.

**Perinatal Asphyxia in Term Newborns: Study Summary and Evaluation.**

The jury evaluated the expert summary and performed their own literature search, screening titles and abstracts for relevance. Selected studies were reviewed and their results assembled in a meta-analysis (labeled “jury analysis”), and the quality of evidence was assessed using the GRADE method. The most recent Cochrane meta-analysis of hypothermia in newborn hypoxic encephalopathy, defined as whole-body or selective head cooling (55), was compared to these results. The number of subjects and events in our analyses was reconciled with the Cochrane meta-analysis and, where different or missing, was adjudicated by two authors. In several cases, judgment was involved. Jurors therefore conducted sensitivity analyses aiming to introduce maximum bias in opposite directions. In all cases, differences in the results were minor and of no consequence to clinical judgments.

**GRADE Jury Analysis: Quality of Evidence.**

Death, severe disability, and the composite of death and severe disability (measured by a neonatal or infant developmental scale) were selected as the most important and patient-relevant outcomes (critical outcomes). The jury analyzed eight randomized controlled trials evaluating mortality and five evaluating death or severe disability. The Supplemental Appendix presents selected details of individual studies and shows the forest plots for the outcomes of mortality, a favorable neurological outcome, and severe disability.

Study limitations. All studies were randomized controlled trials. Application of TTM was not blinded due to the complex nature of managing patients with TTM. Managing temperature can be a labor-intensive strategy, and it is therefore difficult to know what role the extra attention paid to patients might have had on other clinically relevant variables. The jury decided not to lower the quality of evidence on this basis. The jury has not considered the issue of the follow-up interval (see the discussion of Cochrane meta-analysis).

Inconsistency. For death, the composite of death and major disability, and major disability among survivors, there was minimal inconsistency of the results indicated by overlapping CIs of individual studies, nonsignificant tests for heterogeneity ($p = .49, .91$, and .99, respectively), and an $I^2$ of 0% for all outcomes. The jury did not lower the quality of evidence for inconsistency.

Indirectness. Temperature management in control subjects varied substantially. Temperatures of $>37.5^\circ{C}$ were suggested in at least a sizable minority ($>15\%$, assuming a normal distribution) of patients in seven studies (6, 56–61), and in another study no data on temperature increases were available (5). As hyperthermia may worsen outcomes after TBI, even mild fevers in the control group might bias outcomes in favor of TTM.

All selected studies evaluated critical outcomes in populations of interest. As our question of interest was the use of a TTM strategy that lowers temperature below a normal range of $36.5^\circ{C}$–$37.5^\circ{C}$, indirectness was an issue because of the presence of fever in control subjects. For this reason, the jury lowered the overall quality of evidence by one level.

Imprecision. For mortality, the results using the fixed-effects model were non-significant ($p = .09$) and the precision was judged unsatisfactory (odds ratio $0.74$ [95% CI $0.52$–$1.05$]). For the composite outcome of death and major disability and major disability among survivors, the results using the fixed-effects model were significant ($p = .0004$ and .007) and the precision was judged satisfactory (odds ratio $0.53$ [95% CI $0.38$–$0.76$] and $0.55$ [95% CI $0.35$–$0.85$]). We have lowered the quality of evidence for mortality but not the composite outcome of death and severe disability and major disability in survivors.

Publication bias. The supplemental Appendix gives funnel plots of the studies analyzed. No significant asymmetry was noted. The jury does not see evidence of publication bias.

**Final summary of jury analysis.**

The supplemental Appendix includes a GRADE profile of jury-reviewed outcomes. By meta-analysis, the odds ratio for mortality with TTM vs. unstructured temperature management is $0.74$ (95% CI $0.52$–$1.05$), for death and major disability it is $0.53$ (95% CI $0.38$–$0.76$), and for severe disability among survivors it is $0.55$ (95% CI $0.35$–$0.85$).

The overall quality of evidence for the critical outcome was judged as low for death and moderate for death and severe disability and major disability among survivors because of indirectness (control group temperatures of $>37.5^\circ{C}$) for all outcomes and imprecision for mortality. Although one may dispute these decisions about quality, the jury’s judgments did not include considerations of lack of blinding or allocation concealment. Regardless of the interpretation of individual study aspects, the overall quality of evidence is likely moderate to low.

Comparing the jury analysis to the Cochrane analysis, the latter included eight studies, two of which the jury did not evaluate because of the study design focus on surrogate outcomes or the small size as a pilot study. The jury also included three studies not used in the Cochrane meta-analysis. The supplemental Appendix includes the Cochrane results. For mortality, the relative risk (Mantel-Haenzel, fixed-effects model) is $0.74$ (95% CI $0.58$–$0.94$), and for death and major disabilities (Mantel-Haenzel, fixed-effects model), it is $0.76$ (95% CI $0.65$–$0.89$).

In trials considered by those authors as being of greater importance to patients because of a longer length of follow-up (18–22 months vs. 12 months), the relative risk for mortality was $0.76$ (95% CI $0.58$–$0.99$) and for death and major disability it was $0.79$ (95% CI $0.67$–$0.93$). The jury results and Cochrane results appear consistent with each other. The Cochrane authors, for reasons similar to ours, concluded that TTM is beneficial in newborns with hypoxic ischemic encephalopathy.

Considering all of the above, the jury concluded that the available data support the use of TTM to a temperature of $32.5^\circ{C}$–$35.5^\circ{C}$ to treat perinatal asphyxia on the basis of significant findings for a reduced composite of death and major disability or severe disability among survivors with a moderate quality of evidence.

Sufficient evidence exists from studies to WEAKLY RECOMMEND the use of TTM in the treatment of perinatal asphyxia, with TTM to $32.5^\circ{C}$–$35.5^\circ{C}$ (vs. less structured management). Evidence suggests that TTM might reduce mortality in term infants with objective evidence of encephalopathy and signs of perinatal distress. The patient population expected to benefit may be limited to those patients with less severe encephalopathy. The ideal temperature profile for TTM has yet to be determined. For these reasons, the jury believed that detailed discussions with parents were warranted and a uniformly strong recommendation could not yet be made. As a consequence, the recommendation level remains in our
judgment to “weakly recommend” pending additional information, including (but not limited to) data regarding long-term disability after TTM. Future investigations should seek to determine how to best identify infants likely to benefit from intentional TTM and in that population gather additional data on side effects, such as bleeding risk, infection, and skin injury. One may also consider strict avoidance of hyperthermia in the control group. A national or international registry of TTM-treated infants with perinatal asphyxia might help clarify issues of patient selection and duration of therapy. Such a registry could also clarify risks associated with TTM in this population and ideally provide longer term outcome data. Development of such a registry through the five societies could be of great benefit to international critical care.

**Question 4: Should TTM Be Used in TBI? Executive Summary**

*No Recommendation.* The available data do not support a recommendation either for or against the use of TTM to treat TBI.

Future research should compare aggressive fever management aimed at normothermia with TTM, address its utility in different types of TBI, including different anatomical or clinical injury patterns, evaluate patients with and without elevated ICP, and measure both mortality and functional neurological outcome in blinded trials.

Although the data suggest that TTM can reduce elevated ICP in TBI (*vide infra*), the link between reduction of ICP by hypothermia and clinical outcomes is indeterminate.

Brain trauma generates immediate and delayed injuries through physiologic, metabolic, and functional derangements. Disruption of the blood–brain barrier exposes brain tissue to a flux of plasma fluids. Tissue swelling and bleeding increases local and global pressures in the brain. Tissue metabolism outpaces decreases due to decreased perfusion, leading to high-energy phosphate depletion and ischemia. Inflammatory mediators, free radicals, neurotransmitters, and other signaling molecules activate cellular processes that culminate in microglial activation, necrosis, and apoptosis. Intracellular calcium and extracellular potassium increase, triggering processes that lead to further cell damage. Clinicians caring for patients with TBI try to attenuate various components of this delayed damage syndrome. TTM may improve outcomes by several mechanisms. Effective therapies to date, however, are insufficient to prevent substantial morbidity and mortality from TBI. Each proposed therapy has benefits and risks; in a complex syndrome such as TBI, a targeted approach may improve one facet of disease pathophysiology while worsening another. It is therefore necessary to assess TTM for its effects on clinically important outcomes after TBI.

**TTM: Study Summary and Evaluation.** The jury evaluated the expert summary and performed their own literature search using PubMed to search for “hypothermia” and “traumatic brain injury,” screening titles and abstracts for relevance. Selected studies were reviewed for results, the data were assembled in a meta-analysis (labeled “jury analysis”), and the quality of evidence was assessed using the GRADE method. The most recent Cochrane meta-analysis of hypothermia, defined as management to a temperature lower than 35°C, for TBI was compared to these results (62). The number of subjects and events in our analyses was reconciled with the Cochrane meta-analyses and, where different or missing, was adjudicated by two authors. In several cases, judgment was involved. Jurors have therefore conducted sensitivity analyses aiming to introduce maximum bias in opposite directions. In all cases, differences in the results were minor and of no consequence to clinical judgments.

**GRADE Jury Analysis: Quality of Evidence.** A favorable neurological outcome (Glasgow outcome scale 4 [moderate disability] or 5 [good recovery]) and mortality at the last follow-up were selected as the most important clinically relevant outcomes (critical outcomes). The jury decided against using ICP control as an outcome from which to form recommendations due to uncertainty about its direct effect on patient-relevant outcomes. The jury analyzed 16 randomized controlled trials evaluating favorable neurological outcomes and 15 evaluating survival. The supplemental Appendix presents selected details of individual studies and shows the forest plots of mortality analysis and a favorable neurological outcome.

Study limitations. All studies were randomized controlled trials. Application of TTM was not blinded due to the complex nature of managing patients with TTM. Managing temperature can be a labor-intensive strategy, and it is therefore difficult to know what role the extra attention paid to patients might have had on other clinically relevant variables. The jury decided not to lower the quality of evidence on this basis. The jury has not considered the issue of concealment of randomization (see the Cochrane meta-analysis discussion).

Inconsistency. For both outcomes there was moderate inconsistency of the results indicated by nonoverlapping CIs of individual studies, a significant test for heterogeneity (*p* < .05), and an *I*² of 50% for mortality and 66% for a favorable neurological outcome. As a result, the quality of evidence for both outcomes was lowered by one level. The jury has not explored sources of this heterogeneity (see the Cochrane discussion below), which might include differences in methodological quality, cooling technique and duration, and/or duration and rate of rewarming.

Imprecision. For a favorable neurological outcome, the results using the random-effects model were significant and the precision was judged satisfactory. For mortality, the analysis showed borderline but not significant results (*p* = .06). The jury has not lowered the quality of evidence for either outcome.

Publication bias. The supplemental Appendix gives funnel plots of the studies analyzed. No significant asymmetry was noted. The jury does not see evidence of publication bias.

Final summary of jury analysis. The supplemental Appendix includes a
GRADE profile of jury-reviewed outcomes. By meta-analysis, the odds ratio for mortality with TTM vs. unstructured temperature management is 0.70 (95% CI = 0.48–1.01) and for a favorable neurological outcome it is 1.72 (95% CI = 1.16–2.56).

The overall quality of evidence for the critical outcomes was judged as low because of inconsistency of the results and indirectness (control group temperatures of >37.5°C). Although one may dispute these decisions about quality, the jury’s judgments did not include considerations of lack of blinding or allocation concealment. Regardless of the interpretation of individual study aspects, the overall quality of evidence is likely not higher than “low.”

Comparing the jury analysis to the Cochrane analysis, the latter included 20 studies, 9 of which the jury did not evaluate because of non-English publication, inability to retrieve, or emphasis on surrogate factors. The jury also included four studies not used in the Cochrane meta-analysis. The supplemental Appendix includes the Cochrane results. For mortality, the odds ratio (Mantel-Haenzel, fixed-effects model) is 0.84 (95% CI = 0.67–1.05), and for a favorable neurological outcome (Mantel-Haenzel, fixed-effects model), it is 1.32 (95% CI = 1.08–1.64). Most of the observed differences came from lower quality trials. In trials considered by those authors as having higher methodological quality, the odds ratio for mortality was 1.08 (95% CI = 0.79–1.47) and for a favorable neurological outcome the odds ratio was 1.10 (95% CI = 0.83–1.45). In lower quality trials the corresponding odds ratios were 0.62 (95% CI = 0.44–0.86) and 1.67 (95% CI = 1.22–2.27). The jury results and Cochrane results are qualitatively consistent with each other. The Cochrane authors, citing limitations of evidence, including its inconsistency between studies of lower and higher quality, concluded that routine TTM in patients with TBI should be restricted to patients participating in RCTs.

The jury decided to offer no recommendation concerning the use of temperature reduction strategies in TBI on the basis of nonsignificant findings for mortality, nonsignificant or negative findings in the larger and higher quality studies, and a low quality of evidence. The existing studies incompletely considered the responsiveness of different injury patterns, such as the anatomical patterns of diffuse injury, extracerebral hematoma, and focal lesions, neurological or physiologic exam findings after TTM, the comparative benefit of different levels of temperature control, and the effect of other ICP control measures on the effects of TTM. Future investigations should prospectively compare populations with or without elevated ICP and different brain injury patterns, consider elevated temperatures in the control group, describe specific temperature management profiles, and blind all outcome assessments. The correlation between achieving the ICP control and patient-oriented outcomes will be of major interest.

**Question 5: Does TTM Reduce ICP? Executive Summary**

Sufficient evidence exists to conclude that TTM does decrease ICP compared to unstructured temperature management. However, there is no sufficient evidence to make a recommendation regarding the use of targeted hypothermia to control elevated ICP to improve patent-important outcomes in TBI.

**No Recommendation.** The jury makes NO RECOMMENDATION regarding the use of TTM as an ICP control strategy to improve outcomes in brain injuries regardless of cause (trauma, hemorrhage, or ischemic stroke).

**Narrative.** Elevated ICP is a frequent consequence of severe TBI. Disruption of the blood–brain barrier and tissue inflammation result in increased interstitial fluid volume and cellular swelling. Expansion in the closed intracranial space increases pressure in the cranial vault. Pressure injury to brain tissue can occur as a consequence of mechanical forces, decreased cerebral perfusion pressure (cerebral perfusion pressure equals mean arterial pressure minus ICP or central venous pressure, whichever is higher), or capillary stasis when local tissue pressure exceeds capillary perfusion pressure. Elevated ICP may also be a marker for other processes causing delayed brain injury following trauma. Management of ICP is an important component of therapies for TBI. TTM might positively affect several of the processes, leading to elevated ICP. These include impeding inflammation, decreasing cerebral blood flow, and stabilizing the blood–brain barrier. ICP data are frequently measured in TBI studies. Although ICP is an indirect and surrogate outcome for mortality and neurological recovery, the important role of ICP management in TBI makes the investigation of a TTM effect on ICP reasonable.

**TTM and ICP: Study Summary and Evaluation.** ICP reported among different studies (in terms of absolute level as well as of temporal profile) varied. Thus, available data could not easily be aggregated. A total of 13 of the randomized controlled trials evaluated by the jury addressed ICP control with TTM. These studies are shown in the supplemental Appendix. A total of 11 studies demonstrated a statistically significant reduction in ICP at some point during the intervention with TTM (8, 63, 64, 66, 67, 69, 71, 75, 76). One study demonstrated a nonsignificant decrease in ICP with TTM (65), and one study demonstrated a significant decrease in ICP in all patients except a subgroup with extracerebral hematoma and compression (72).

Although TTM likely reduces ICP in TBI patients, the jury believes that there is insufficient evidence to recommend either for or against its use in this clinical setting. This opinion is based on the uncertain correlation between the mechanism of ICP reduction and important clinical outcomes and inconclusive data regarding these outcomes. Future investigations should prospectively analyze the concomitant use of additional ICP control measures, avoid even mild fever in the control group, and explicitly state how rebound elevations in ICP on rewarming are monitored and treated. Complete reporting of ICP profiles, including values at regular frequent intervals and duration of time passed above or below goals, would make published data more easily comparable, as would reporting of mortality and neurological outcomes.

**Further Questions**

Beyond these topics, the jury reviewed data and audited presentations on expanded indications for TTM (“Who else might we cool?”), on techniques for temperature management (“How should we cool?”), and on contraindications and complications of cooling (“Why should we not cool?”). These topics were intrinsically speculative. The topics did not lend themselves to GRADE-based analysis. On the basis of the jury’s commitment to GRADE-driven analysis, no additional recommendations emerged from the deliberations. However, several observations are offered by the jury.
• Regarding acute myocardial infarction, the published literature contains no RCT sufficient to support or refute TTM. The outcome from myocardial infarction has improved so much over the past 20 yrs that any cooling intervention must not delay these proven effective treatments. Furthermore, mortality is now so rare that proof of further reduction would likely require a very large RCT.

• Regarding acute ischemic stroke, the published literature contains no RCT sufficient to support or refute an assertion of TTM benefit. Furthermore, the outcome from acute ischemic stroke has improved with thrombolysis. Whether TTM as adjunctive therapy would further improve the outcome is speculative; however, should induction of cooling increase the need for endotracheal intubation and mechanical ventilation, there is also a risk for harm that should be addressed in any clinical trial.

• Regarding pediatric patients with TBI, head trauma alone does not appear to justify TTM. Cooling appears to reduce ICP in children with severe head injuries, but there is insufficient evidence to assert that the outcome is improved.

• Regarding fever, it is a generic response to so many pathologic processes that no recommendation can currently be made for or against TTM. If an RCT is considered, focus should probably include severe fever unrelated to infection.

• Regarding acute liver failure with severe cerebral edema, there are currently no RCTs. There is a case series suggesting a strongly favorable effect. This is a powerful argument for support of an RCT evaluating TTM alone or in combination with hepatic dialysis strategies.

• Regarding adult trauma patients, spontaneous hypothermia is common. Current practice aims to prevent and reverse hypothermia. No RCTs exist that support deliberate cooling, and there is history to suggest that uncontrolled hypothermia is associated with substantially worse outcomes.

• Regarding acute traumatic spinal cord injury, no RCTs exist to support or refute TTM as effective treatment. Animal studies and anecdotal human success point to the importance of designing and executing an RCT evaluating TTM for this common and devastating condition.

• Regarding cooling strategies, there is insufficient evidence to recommend a specific technique or device.

• Regarding temperature measurement, core temperature (vs. surface temperature) appears important to guiding TTM. However, there was insufficient evidence to recommend a specific core temperature (blood, bladder, rectum) provided the probe is properly and securely positioned.

• Regarding secondary effects of hypothermia, no recommendation was made for or against TTM. However, if TTM is used to induce hypothermia, consideration should be given to evaluating predisposition to infection, to coagulopathy, and to altered drug metabolism.

CONCLUSION

TTM is a new treatment strategy in critical care medicine. The appeals of TTM include relative simplicity and reversibility. There is now sufficient experience to recommend the use of TTM in a few well-defined clinical conditions. The jury cautions that a recommendation for use of TTM is just that, a recommendation. It is not a declaration of standard care. It is not a claim of safety. It is a recommendation for use based on the appearance of benefit in excess of harm offered by a panel of clinicians on behalf of their parent intensive care societies.

The few recommendations (strong and weak) supporting use of TTM that emerged from the GRADE analysis are contrasted with sparse and conflicting information about the indications, methods, performance, and outcomes of TTM in so many other circumstances in which TTM is currently being used. Development of registries would assist by accumulating data on which to base new hypotheses and RCTs. It is ethically appropriate for a physician to select a therapy believed to be in the best interest of the patient, provided that the perceived benefits, the quality of available best evidence (including situations where RCTs are absent or of poor quality), and the values of all involved support the selection. It is equally appropriate to share the outcomes of such treatments with the clinical community. Future TTM RCTs and their subjects will benefit from systematic reporting of individual experiences, including those experiences in which an adverse event or unfavorable outcome occurs.

We believe that this initial consensus document fairly describes what is known, and what is unknown, about TTM in critical illnesses in mid-2009.

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