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Canadian Guidelines for the use of targeted temperature management (therapeutic hypothermia) after cardiac arrest: A joint statement from The Canadian Critical Care Society (CCCS), Canadian Neurocritical Care Society (CNCCS), and the Canadian Critical Care Trials Group (CCCTG)

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Introduction

Since the publication of two landmark articles in 2002,[1,2] the practice of controlling a patient's core temperature after resuscitation from cardiac arrest has been an important therapeutic option. Targeted Temperature Management (TTM), previously known as therapeutic hypothermia or protective hypothermia,[3] is well recognized and accepted as part of post-resuscitative care.[4,5] It involves active treatment that tries to achieve and maintain a specific body temperature for a specific duration in an effort to improve neurologic outcomes.

Since the publication of these articles there has been extensive research published with the goal of better elucidating the target population and refinement of the technique. Much has

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been published since the previous Canadian Guidelines in 2006,[6] which predated the use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group recommendations.[7] The 2010 International Liaison Committee on Resuscitation (ILCOR) guidelines[5] recommend TTM as a component of post-resuscitation care, but do not address some of the specific implementation issues faced by clinicians. The publication of a large randomized trial[8] in 2013 has stimulated further discussion, debate, and clinical uncertainty.

Given the advancing literature base, we revised the Canadian guidelines to ensure that they reflect the current evidence. The guidelines that follow were developed as a practical guide for clinicians. They are meant to address the treatment decisions physicians face when deciding whether to use TTM, when caring for the cooled patient, and when prognosticating after TTM. Although TTM has been studied for other pathologies and in pediatric age groups, we addressed only the use of TTM after cardiac arrest in adult patients.

The care of post-resuscitation patients can involve a number of clinical environments and provider groups. It is important that these groups share a similar approach. Hence, these guidelines were developed by a committee, with representation from the Canadian Association of Emergency Physicians (CAEP), the Canadian Critical Care Society (CCCS), the Canadian Neurocritical Care Society (CNCCS), and the Canadian Critical Care Trials Group (CCCTG). The purpose of these guidelines is to advise clinicians with evidence based recommendations from informed experts with consideration of current research, Canadian values, our health care system, and the range of clinical environments where TTM may be used.

Methods

We used the GRADE[9–13] and the AGREEII[14] (Appraisal of Guidelines for Research & Evaluation II) recommendations to inform the TTM guideline development process. The methodology was approved by representatives of the four contributing organizations. Each Society had representation on the guideline committee from the beginning of the process.

The Chair and all 13 members of the guideline committee were required to declare potential conflicts at the beginning of the project and again before each stage of the Delphi process. Potential conflicts were shared with all members of the committee. None of the members were from industry; there was no industry funding or presence during any portion of the guideline development process. Support for the project came from an unrestricted grant from the Kingston Resuscitation Institute.

A working group created a draft set of clinical questions. Clinicians representing community, tertiary, and academic centers from across Canada were asked for additional clinical questions using online surveys. The complete set of questions was organized into categories and assigned to a section lead. The guideline committee was comprised of the Chair and eight section leads. Section leads were responsible for coordinating the work of their team in the literature search, extraction and grading of the literature, and formulation of the draft recommendations.

Individual literature searches addressed each clinical question. The variable nature of the clinical questions precluded the use of a single search strategy, but a sample search strategy was provided to section leads to promote consistency and uniform rigor. Section leads developed the literature searches with the assistance of a medical librarian or other individual trained in medical search strategy development. Searches were performed using EMBASE, Medline, Cochrane database of Systematic Reviews, Cochrane Central Register of Controlled Trials and the Cochrane Methodology Register databases from inception to December 31, 2013. Titles and abstracts of the search results were scanned by two independent reviewers for each section. Articles identified for inclusion by at least one reviewer underwent detailed review by both reviewers. Additional references were sought from personal libraries of the section authors, and by scanning the references of systematic reviews, meta-analyses, and included articles.

Articles were summarized on a standardized extraction form that included the abstract, identification of industry funding, level of evidence, and reviewer comments. A level of evidence was assigned to individual articles using a standardized assessment tool[15] (Fig. 1).

Section leads then drafted recommendations for each clinical question based on their review of the literature. Draft recommendations, the extracted literature review results and the lead authors' conflict of interest statements were circulated to the guideline committee. To achieve our goal of developing clinically helpful guidelines, equivocal recommendations were avoided where possible. When the quality of evidence was low we considered physiologic rationale and clinical expertise.

The committee used a combination of Delphi methodology and nominal group technique modified from Jaeschke[16] and Hsu[17] to develop the final recommendations. Early rounds were conducted electronically and by teleconference. The final round was conducted as an in-person meeting of all section leads during a two-day period in September 2014.

The guideline committee considered the body of literature to assign a 'Quality of Evidence' designation for each recommendation. Committee members were asked to consider the likelihood that future evidence might change the recommendation. The level of evidence for each article, the directness of the evidence, consistency and quantity of evidence were considered when making a designation of high, moderate, low or very low (Fig. 2). The committee consolidated the "low" and "very low" designations in to a single "low" category for clarity.[18]

Recommendations were identified as strong or conditional based on consideration of the quality of the evidence, balance between desirable and undesirable outcomes, Canadian societal values of potential outcomes, feasibility and cost. Fig. 3 provides further details on how the committee considered these factors.

The voting process conducted by members of the guideline committee was anonymous during the electronic Delphi process and transparent during the in-person meeting. The final wording of each recommendation was achieved through consensus. For clarity, the phrase "We recommend. . ." was reserved for strong recommendations and "We suggest. . ." for conditional recommendations. A priori, it was decided that assignment of the quality of evidence would require a simple majority, but that the strength of a recommendation would require an 80% majority for a strong recommendation. Members were required to be present and to participate in the discussion of a recommendation to be entitled to vote at the in-person meeting.

The draft manuscript was circulated to all members of the committee for final editorial suggestions. An independent reviewer who was not involved in the development of the guidelines reviewed the document using the AGREE II assessment tool. The final manuscript was submitted to the sponsoring Societies for endorsement. The Canadian Association of Emergency Physicians (CAEP) initially reviewed a draft of the guidelines but we were unable to complete their internal review process before publication.

Recommendations

The clinical questions and recommendations of the committee are summarized in Table 1.

First, assign level according to methodology:

A: Randomized Controlled Trial
B: (for downgraded A or upgraded C or D; see below)
C: Well-done observational studies
D: Case series or expert opinion

Then upgrade or downgrade based on other factors.

Examples of factors that may decrease the evaluation:

1. Poor quality planning and implementation, suggesting high likelihood of bias
2. Inconsistency of results (including problems with subgroup analysis)
3. Indirectness of evidence (different population, intervention, control, outcomes, comparison)
4. Imprecision of results
5. High likelihood of reporting bias
6. Single centre or small populations

Examples of factors that may increase the evaluation:

1. Large magnitude of effect (direct evidence, RR>2 with no plausible confounders)
2. Very large magnitude of effect with RR>5 and no threats to validity (elevate by 2 levels)
3. Dose-response gradient

Fig. 1. Determination of level of evidence for each individual publication. Adapted from Dellinger.[15]

Quality of Evidence for a Recommendation:

High: Further research is very unlikely to change our confidence in the estimate of effect

Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Fig. 2. Definitions for Quality of Evidence used for a Recommendation. Adapted from Guyatt.[9]

The strength of a recommendation:

The **definitions** of strong and conditional recommendations are:

- **Strong recommendation** — the panel is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects; and
- **Conditional recommendation** — the panel concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but is not confident.

The panel considered the following **factors** in determining the strength of a recommendation:

- **Balance between desirable and undesirable effects:** The larger the difference between the desirable and undesirable effects, the more likely a strong recommendation is warranted. The narrower the gradient, the more likely a conditional recommendation is warranted.
- **Quality of evidence:** The higher the quality of evidence, the more likely a strong recommendation is warranted.
- **Values and preferences:** The more variability or uncertainly in the values and preferences of the population around an aspect of the recommendation, the more likely a conditional recommendation is warranted
- **Resource allocation:** The higher the costs of a recommendation, the less likely that a strong recommendation is warranted.

Implications:

The implications of a strong recommendation are:

- for patients — most people in your situation would want the recommended course of action and only a small proportion would not; request discussion if the intervention is not offered;
- for clinicians — most patients should receive the recommended course of action; and
- for policy makers — the recommendation can be adopted as a policy in most situations.

The implications of a conditional recommendation are:

- for patients — most people in your situation would want the recommended course of action, but many would not;
- for clinicians — you should recognize that different choices will be appropriate for different patients and that you must help each patient to arrive at a management decision consistent with his or her values and preferences; and
- for policy makers — policy making will require substantial debate and involvement of many stakeholders.

Fig. 3. Definitions used by the committee to assign the strength of a recommendation. Adapted from Jaeschke[16] and Guyatt.[10]

Table 1
Summary of recommendations CT—computed tomography, ECG—electrocardiogram, EEG—electroencephalogram, MAP—mean arterial pressure, N/A—not applicable, PEA—pulseless electrical activity, ROSC—return of spontaneous circulation, TTM—Targeted Temperature Management, VF—ventricular fibrillation, VT—ventricular tachycardia.

Clinical question	Recommendation	Strength of recommendation	Quality of evidence
Should I use TTM in my clinical practice?	We recommend that TTM be used for neuro-protection in eligible adult patients after resuscitation from cardiac arrest	Strong	High
Which presenting rhythms are eligible for TTM?	We recommend that patients with a presenting rhythm of VF or pulseless VT are eligible for TTM	Strong	High
	We suggest that patients with a presenting rhythm of PEA or asystole are eligible for TTM	Conditional	Low
Are in-hospital and out-of-hospital patients eligible for TTM?	We recommend that patients who suffer out-of-hospital cardiac arrest are eligible for TTM	Strong	High
	We recommend that patients who suffer in-hospital cardiac arrest are eligible for TTM	Strong	Low
Can TTM be used after cardiac arrest from non-cardiac causes?	We recommend that patients who suffer a cardiac arrest of known cardiac cause or of an unknown cause are eligible for TTM	Strong	High
	We suggest that patients who suffer a cardiac arrest from a non-cardiac cause are eligible for TTM	Conditional	Low
Can TTM be used in pregnant women?	We suggest that pregnant patients are eligible for TTM	Conditional	Low
Should I obtain a CT scan prior to instituting TTM?	We recommend that imaging of the brain is not routinely required before the initiation of TTM	Strong	Low
What constitutes unresponsiveness for eligibility for TTM?	We recommend that patients who are comatose and do not respond to verbal commands after cardiac arrest be considered for TTM	Strong	Low
How long should I wait after ROSC before assessing responsiveness?	We recommend that assessment of a patient's level of consciousness for the purpose of determining eligibility for TTM should be completed without delay after ROSC	Strong	Low
What are the contraindications for the use of TTM?	We recommend that uncontrolled bleeding and refractory shock be considered contraindications for TTM	Strong	Low
	We suggest that hypotension (MAP < 60 mmHg) is not an absolute contraindication to TTM. We suggest aggressive resuscitation of the patient with the aim of improving MAP and perfusion	Conditional	Low
	We suggest that patients with severe infection do not undergo TTM	Conditional	Low
	We recommend that advanced age is not a contraindication for TTM	Strong	Low
	We recommend that the need for urgent coronary angiography or percutaneous coronary intervention should not be considered a contraindication for TTM	Strong	Low
Can TTM be used in patients in 'electrical storm'?	We suggest that recurrent ventricular fibrillation or ventricular tachycardia not be considered a contraindication to TTM	Conditional	Low
What consultations are required prior to instituting TTM?	We recommend that TTM be initiated by the first provider knowledgeable and trained in the process, and that consultation with any particular specialty provider prior to the initiation of TTM is not required	Strong	Low
What settings are reasonable for initiating TTM? Should patients be transferred to specialized centers before receiving TTM?	We recommend that TTM can be initiated in any medical environment with the necessary supports, including prehospital, emergency department, and critical care unit	Strong	Moderate
How soon should TTM be initiated?	We recommend that clinicians attempt to achieve target temperature as rapidly as possible	Strong	Low
How late can TTM be started with a reasonable expectation of an effect?	We suggest that in situations where there has been an unavoidable delay, there may be benefit from TTM eight or more hours after ROSC	Conditional	Low
What temperature should patients be cooled to?	We suggest that patients undergoing TTM be cooled to a target temperature between 32 °C and 34 °C	Conditional	High
How should core temperature be monitored?	We recommend that core temperature be continuously monitored during the cooling and rewarming phases of TTM	Strong	Low
	We recommend that esophageal, nasopharyngeal, bladder, endotracheal cuff and pulmonary artery temperature sensors are acceptable options for monitoring core temperature	Strong	Moderate
What is the best method to use to cool patients?	We do not recommend a specific cooling method for TTM	N/A	Low
Should TTM patients receive seizure prophylaxis?	We suggest against the routine use of anticonvulsant medications for seizure prophylaxis in patients undergoing TTM	Conditional	Low
Should TTM patients have an EEG?	We suggest that patients who undergo TTM receive continuous EEG monitoring where it is available	Conditional	Low
Do all TTM patients require sedation and analgesia?	We recommend that patients undergoing TTM should receive sedation and analgesia	Strong	Low
Do all TTM patients require paralytic agents?	We suggest that paralytics be used during induction and rewarming phases of TTM, to facilitate tight temperature control and to prevent shivering	Conditional	Low
What ECG abnormalities can be expected from TTM and how should they be treated?	We suggest monitoring of the QTc interval in patients undergoing TTM	Conditional	Low
	We suggest cautious use of medications that may prolong the QTc interval in patients undergoing TTM	Conditional	Low
	We suggest that anti-arrhythmic agents be used only for the treatment of malignant or hemodynamically significant arrhythmias	Conditional	Low

Table 1 (*Continued*)

Clinical question	Recommendation	Strength of recommendation	Quality of evidence
What should be done when patients undergoing TTM develop hemodynamic instability?	We suggest that hemodynamic instability developing during TTM that is refractory to aggressive resuscitation be considered a cause for discontinuing therapy	Conditional	Low
How should I treat bradycardia in the patient undergoing TTM?	We suggest that bradycardia during TTM not be treated routinely unless it is causing hemodynamic instability	Conditional	Low
How should I deal with hypokalemia in the patient undergoing TTM?	We suggest that potassium levels be kept above 3.0 mmol l^{-1} during the hypothermic phase of TTM	Conditional	Low
Should patients undergoing TTM receive prophylactic antibiotics?	We suggest against the routine use of prophylactic antibiotics in patients treated with TTM	Conditional	Low
Can Procalcitonin be used to monitor for infection in patients undergoing TTM?	We recommend against the use of Procalcitonin for the diagnosis of infection in patients treated with TTM	Strong	Low
Should be have a care bundle for our TTM patients?	We suggest that standard order sets and care bundles be utilized for the initiation and care of patients undergoing TTM	Conditional	Low
Should patients undergoing TTM be fed?	We recommend that patients undergoing TTM receive enteral nutrition	Strong	Moderate
	We suggest that caloric intake targets be calculated as 75% of normothermic targets during the hypothermic phase of TTM if calorimetry is not being used	Conditional	Low
When should rewarming be initiated?	We suggest that rewarming should begin 24 h after the patient reaches the target temperature	Conditional	Low
How rapidly should TTM patients be rewarmed	We suggest that patients should be rewarmed at a rate of 0.25–0.5 °C per hour	Conditional	Low
How should fever be managed after rewarming from TTM?	We suggest that hyperthermia should be prevented for at least 72 h post arrest	Conditional	Low
How long after ROSC should I wait before prognosticating in patients who have received TTM?	We recommend that a clinical neurologic examination for the purpose of prognostication not be performed earlier than 72 h after return of spontaneous circulation	Strong	Moderate
	We suggest that when there is a concern of residual medication effect, clinical neurologic examination for prognostication should be deferred until the clinician is confident that the confounding effects are no longer present	Conditional	Low
What adjunctive testing is required to make a prognosis after the use of TTM?	We suggest that adjunctive testing is not routinely required to identify poor neurological outcome in patients after TTM	Conditional	Low
	We suggest that somatosensory evoked potentials and continuous EEG can facilitate prognostication in specific circumstances	Conditional	Low
Is consultation with a neurologist required for prognostication after the use of TTM?	We recommend that a neurologic consultation is not routinely required for prognostication after the use of TTM	Strong	Low

Indications and Contraindications

We recommend that Targeted Temperature Management (TTM) be used for neuro-protection in eligible adult patients after resuscitation from cardiac arrest.

Quality of evidence: **High**

Strength of recommendation: **Strong**

We recommend that patients with a presenting rhythm of ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT) are eligible for TTM.

Quality of evidence: **High**

Strength of recommendation: **Strong**

We suggest that patients with a presenting rhythm of pulseless electrical activity (PEA) or asystole are eligible for TTM.

Quality of evidence: **Low**

Strength of recommendation: **Conditional**

The highest level of evidence we identified that addressed whether or not to use TTM was from two randomized controlled trials (RCTs).[1,2] These trials demonstrated a decrease in mortality and improvement in neurologic outcome in patients with a presenting rhythm of VF or pulseless VT who were treated with TTM. The Hypothermia After Cardiac Arrest (HACA) trial[2] found favorable neurologic outcome at six-months increased from 39% in the control group to 55% in TTM group (risk ratio 1.40, 95% CI 1.08–1.81). Bernard et al.[1] found that survival with good neurologic function was 26% in the control and 49% in the TTM group ($p = 0.046$). The literature review also identified a significant volume of lower level evidence supporting the use of TTM after cardiac arrest.

The committee discussed the HACA and Bernard trials extensively. There were a number of potential flaws in the methodology identified, which have been identified previously in the literature,[19,20] leading some committee members to downgrade one or both of the studies to level B. After consideration of these trials together with the large volume of observational evidence, the committee found the quality of evidence to be high for the use of TTM when the presenting rhythm is VF of pulseless VT.

On the basis of the quality of the evidence, treatment effect, the value society places on neurologic function and relative cost-effectiveness the committee arrived at a strong recommendation for the use of TTM after cardiac arrest for patients who present in VF or pulseless VT. Particular note was made that 'presenting rhythm' may not be the best method of stratifying cardiac arrests. It is used as a surrogate-marker for cardiac arrest severity, pathogenesis, or prognosis; however the basis for this is not well established.

The committee found the quality of evidence comparing TTM to normothermia for patients presenting with PEA and asystole to be low. Although some evidence has reported reasonable survival[8,21] the committee assigned a conditional recommendation for patients presenting in asystole and PEA. Discussion focused on the inappropriate use of presenting rhythm as determinant of therapy, and low risk of harm from TTM. The committee discussed the possibility of reduced mortality but an increase in the number of patients with a poor neurologic outcome. The uncertainty of this possibility and low quality of evidence in this patient group resulted in the conditional recommendation.

We recommend that patients who suffer out-of-hospital cardiac arrest are eligible for TTM.

Quality of evidence: **High**

Strength of recommendation: **Strong**

We recommend that patients who suffer in-hospital cardiac arrest are eligible for TTM.

Quality of evidence: **Low**

Strength of recommendation: **Strong**

The best evidence demonstrating the beneficial effects of TTM enrolled patients who had suffered cardiac arrest out-of-hospital.[1,2] On the basis of this evidence, the committee assigned a high quality of evidence and a strong recommendation for the eligibility of these patients.

The evidence for the use of TTM for in-hospital cardiac arrest is considerably weaker. One investigation of in-hospital cardiac arrests found an increase in mortality from 40% to 61% (not statistically significant) when patients were treated with TTM.[22] Other studies have not demonstrated a difference in mortality with the use of TTM.[21,23,24] Although the quality of evidence was low, the committee felt that location of the cardiac arrest lacked sufficient discriminative ability as an outcome predictor to be used to establish eligibility, and recommends that all patients who have a cardiac arrest, including those occurring in-hospital, be considered eligible for TTM.

We recommend that patients who suffer a cardiac arrest of known cardiac cause or of an unknown cause are eligible for TTM.

Quality of evidence: **High**

Strength of recommendation: **Strong**

We suggest that patients who suffer a cardiac arrest from a non-cardiac cause are eligible for TTM.

Quality of evidence: **Low**

Strength of recommendation: **Conditional**

The HACA[2] and Bernard[1] trials included patients whose arrest was known to be cardiac in origin, or of unknown cause. This is also the inclusion practice for much of the observational research. On the basis of this evidence, the committee arrived at a strong recommendation for the treatment of these patients with TTM.

We did not find the same level of evidence for arrests known to be from a non-cardiac cause. There are small case series and case reports describing variable neurological outcomes when TTM was used after cardiac arrest associated with various etiologies.[25–38] A case series of 14 consecutive comatose survivors of asphyxia that were treated with TTM observed a survival rate of 65%.[25] In another retrospective cohort study of 16 unconscious patients after near hanging, 13 patients received TTM and 12 of them had poor neurological outcomes.[38]

The committee found the quality of the evidence to be low. We made a conditional recommendation that these patients be considered eligible for TTM based on the opinion that in the absence of other contraindications, the anoxic brain injury suffered from the cardiac arrest may realize benefit from TTM in the same way as patients whose arrest was cardiac in origin. There was significant concern among committee members that this patient population might be more likely to have relative contraindications to TTM, but considered this issue separately.

We suggest that pregnant patients are eligible for TTM.

Quality of evidence: **Low**

Strength of recommendation: **Conditional**

Pregnant patients were excluded from trials demonstrating benefit from the use of TTM.[1] The quality of evidence supporting TTM in pregnant patients was found to be low. Cases of pregnant patients who were cooled after cardiac arrest have been reported.[39–41] Two resulted in normal fetal delivery, the third in fetal demise.

The committee found that the lack of evidence and lack of good physiologic information made addressing this clinical question challenging. Ultimately, when faced with a pregnant patient otherwise eligible for TTM, the majority of committee members would cool the patient. The paucity of evidence for effect and safety in this population and concerns for potential harm resulted in a conditional recommendation.

We recommend that imaging of the brain is not routinely required before the initiation of TTM.

Quality of evidence: **Low**

Strength of recommendation: **Strong**

There was no high-level literature that evaluated this issue directly. One prospective study[42] failed to demonstrate a difference in door to cooling time when computer tomography (CT)scan of the head was performed prior to ICU admission, compared to after admission or not at all. The committee found the quality of evidence for this recommendation to be low.

The consensus of the committee was that although brain imaging may play an important role in the management of these patients at some point during their care, it is not routinely required prior to the initiation of TTM. Routine CT scanning prior to TTM could significantly delay its initiation, particularly in settings that require transport to another centre. It is a reasonable option to cool simultaneously with CT scanning. In cases where there is a strong suspicion of intracranial bleeding, it is reasonable to delay TTM initiation until a CT scan is obtained.

We recommend that patients who are comatose and do not respond to verbal commands after cardiac arrest be considered for TTM.

Quality of evidence: **Low**

Strength of recommendation: **Strong**

We recommend that assessment of a patient's level of consciousness (LOC) for the purpose of determining eligibility for TTM should be completed without delay after return of spontaneous circulation (ROSC).

Quality of evidence: **Low**

Strength of recommendation: **Strong**

The purpose of determining level of consciousness is to identify patients without significant neurologic injury so that TTM may be withheld accordingly. The timing of this assessment as a component of TTM eligibility was not directly addressed in the literature. The reviewers looked to the HACA[2] and Bernard[1] studies and found that the timing was not well defined in either study. Neither of these trials imposed an intentional delay period before the assessment.

The reviewers looked to studies demonstrating a clinical benefit from TTM for their definition of neurologic dysfunction and found significant variation. In the Bernard trial,[1] patients were included if they had "persistent coma" but the term was not further defined in the paper. In the HACA trial,[2] patients were excluded if they were able to "respond to verbal commands after ROSC and before randomization". In the RCT by Laurent et al.,[43] patients were not randomized if they were found to respond to verbal commands after ROSC.

The committee gave this as a strong recommendation despite the low level of evidence. This was based on the perceived importance of avoiding delay and the very low risk of harm in early initiation of TTM. The committee recognized it is not uncommon for some patients to have early and rapid improvements in LOC during the immediate period following ROSC. If such an improvement occurs TTM could reasonably be aborted. The committee was particularly cognizant of the value that members of society place on avoiding even small neurologic insults, and the low level of risk associated with TTM.

We recommend that uncontrolled bleeding and refractory shock be considered contraindications for TTM.

Quality of evidence: **Low**

Strength of recommendation: **Strong**

We suggest that hypotension (MAP < 60 mmHg) is not an absolute contraindication to TTM. We suggest aggressive resuscitation of the patient with the aim of improving MAP and perfusion.

Quality of evidence: **Low**

Strength of recommendation: **Conditional**

We suggest that patients with severe infection should not undergo TTM.

Quality of evidence: **Low**

Strength of recommendation: **Conditional**

We recommend that advanced age is not a contraindication for TTM.

Quality of evidence: **Low**

Strength of recommendation: **Strong**

We recommend that the need for urgent coronary angiography or percutaneous coronary intervention should not be considered a contraindication for TTM.

Quality of evidence: **Low**

Strength of recommendation: **Strong**

For the purpose of identifying contraindications, the reviewers sought reports of adverse effects and reviewed the exclusion criteria of the articles that demonstrated benefit from TTM.

Bleeding

Patients were excluded from the HACA study[2] if they had a "known pre-existing coagulopathy". They found that 19% in the normothermia group and 26% in the treatment group experienced bleeding of any kind. The difference was not statistically significant. In the Bernard study,[1] patients were not excluded on the basis of bleeding or pre-existing coagulopathy. There were no reported bleeding complications in either arm of the study. In the Nielsen trial,[44] there was no difference in bleeding detected between the group cooled to 36 °C and the group cooled to 33 °C.

Hypothermia induces a mild bleeding diathesis with effects on platelet count and function, effects on clotting factors and other components of the clotting cascade.[45,46] The risk of bleeding must be weighed against the potential neurologic benefits on a case by case basis based on the severity and location of the bleeding. The committee felt that it is prudent to withhold TTM in patients who are having active significant bleeding (e.g. severe GI bleed, intracranial hemorrhage) until that bleeding is controlled.

Shock

There is no data from RCTs to support the use of TTM in post cardiac arrest patients with persistent hypotension (SBP < 90 mmHg or MAP < 60). There is evidence from a non-randomized study evaluating TTM to 33 °C for patients in cardiogenic shock who were not post-arrest. They found TTM resulted in reduced heart-rate, increased MAP, increased ejection fraction, increased inotropy and reduced vasopressor and inotrope requirements.[47] Several other non-randomized studies provide weak evidence demonstrating reduced or similar catecholamine requirements to maintain blood pressure in patients treated with TTM to a goal of 32–34 °C compared with normothermic patients after cardiac arrest.[48,49] Sub-group analysis of one observational study found benefit for patients with shock who received TTM.[50]

The committee considered that in some clinical situations the benefits of TTM could be outweighed by further neurologic damage due to hypoperfusion, but found little to support this occurring. There was agreement that patients should not be cooled if they are persistently hypotensive despite full resuscitative efforts (e.g. fluids, inotropes, vasopressors and mechanical support as indicated). Bradycardia without hypotension or hypoperfusion was not considered a contraindication, and is expected with induced hypothermia. The committee agreed that the need for volume resuscitation, vasopressor or inotropic medications, or mechanical support to treat shock should not be contra-indications to TTM if reasonable blood pressure and perfusion goals can be achieved (SBP > 90 mmHg or MAP > 60 mmHg).

Infection

Hypothermia impairs immune function.[51–53] The effect of therapeutic hypothermia for patients who suffer cardiac arrest as a result of severe sepsis or septic shock is not known. It is conceivable that the immune suppression caused by therapeutic hypothermia may be beneficial for patients with overwhelming sepsis by attenuating a destructive, mal-adaptive inflammatory response. It is also possible that hypothermia mediated immune suppression could be detrimental if it impairs the ability to clear infection.

The committee members felt that sepsis and septic shock should be considered relative contra-indications to TTM because of a lack of demonstrated benefit and concern for potential harm.

Age

There is a paucity of evidence for the use of TTM in the elderly (>75 years). Elderly patients were excluded from the HACA trial.[2] Patients in the Bernard study[1] were as old as 89, but the number of included patients >75 is not clear. At least one case series[54] has reported outcomes in an elderly group of patients. In 30 patients >75, half of them had "good neurologic outcome".

It was the opinion of the committee that without evidence or biologic rationale for increased harm from TTM in the elderly, age alone should not be considered a contraindication to TTM. Co-morbidities, baseline quality of life and previously expressed wishes must be considered carefully when determining suitability for all aggressive critical care, including TTM.

Percutaneous coronary interventions

Several reports have demonstrated the feasibility and potential benefit of performing urgent angiography and percutaneous coronary intervention in conjunction with TTM for patients with suspected ACS causing cardiac arrest.[55–57] These small, non-randomized reports provide low level evidence to suggest that TTM can be induced prior to and during PCI without delaying door-to-balloon time.

Although there has been concern expressed that hypothermia may result in increased myocardial irritability, this has not been demonstrated at temperatures above 30 °C. There is some suggestion that core temperatures in the target range may, in fact, result in membrane stabilization.

The committee members were of the opinion that TTM should be initiated as soon as possible for eligible patients, including those requiring urgent coronary angiography. There is no need to delay TTM for PCI.

We suggest that recurrent ventricular fibrillation or ventricular tachycardia not be considered a contraindication to TTM.

Quality of evidence: **Low**

Strength of recommendation: **Conditional**

Despite being a high risk population, clinically significant cardiac arrhythmias are rare in patients treated with TTM.[1,2,58,59] Animal and human studies have demonstrated both a reduction in the electrical threshold required for successful defibrillation,

as well as improved defibrillation success during hypothermic resuscitation.[60–62]

The committee felt that given the lack of evidence to suggest harm and the potential for neurologic benefit from TTM, it would be reasonable to initiate or maintain TTM in patients with recurrent VF/VT. Based on the low level of evidence the committee assigned a conditional strength of recommendation.

We recommend that TTM be initiated by the first provider knowledgeable and trained in the process, and that consultation with any particular specialty provider prior to the initiation of TTM is not required.

Quality of evidence: **Low**

Strength of recommendation: **Strong**

There is no data from controlled studies examining the effect of one type of care provider over another with respect to the induction of TTM for post cardiac arrest syndrome. Feasibility of TTM induction for post cardiac arrest patients has been demonstrated by studies set in the prehospital, emergency department, catheterization laboratory and intensive care settings. Paramedics, emergency physicians, cardiologists and critical care specialists have all demonstrated the ability to initiate TTM.

Despite the low quality of evidence supporting this recommendation, the committee felt that a strong recommendation was important to emphasize that routine delay in initiating TTM in order to defer the care to another group of care givers creates an unnecessary barrier and may not be in the patient's best interest. In complex or confounded situations, consultation with a specialist may be very helpful and is appropriate.

We recommend that TTM can be initiated in any medical environment with the necessary supports, including prehospital, emergency department, and critical care unit.

Quality of evidence: **Moderate**

Strength of recommendation: **Strong**

The reviewers found nine articles[63–71] that addressed TTM use outside of the intensive care unit. Most were in the prehospital setting, and most suggested both safety and feasibility.

The committee discussed the implications of the study by Kim[67] that compared a treatment group that received two liters of 4 °C saline in the prehospital setting compared to a control group cooled in hospital using surface or intravascular cooling. There was no difference in survival or neurologic outcome; however there were suggestions of harm with the treatment group experiencing a higher rate of re-arrest and early pulmonary edema. The committee attributed the signal of potential harm to the use of cold saline rather than the initiation of cooling in the prehospital setting.

It was the opinion of the committee that with appropriate training and support, TTM can be safely provided in a variety of medical environments. The strength of the recommendation was based on the potential benefit to patients from the therapy and the importance of removing setting as a barrier to quality care.

Timing

We recommend that clinicians attempt to achieve target temperature as rapidly as possible.

Quality of evidence: **Low**

Strength of recommendation: **Strong**

The reviewers were unable to identify any high quality studies that directly compared one time target to another time target. Nine studies involved time to target TH/TTM temperature.[1,2,70,72–77] One retrospective study[73] found a worse outcome with quicker time to target temperature. There was no evidence incorporating an intentional delay in the initiation of hypothermia.

When considering the evidence, the committee chose not to give significant weight to the findings of retrospective and observational studies due to the confounding issue of injury severity. There was concern that patients with more severe neurologic injury at ROSC may have disordered autonomic function, including impaired thermoregulation. These patients would be expected to have a lower temperature at presentation and cool more quickly, resulting in a shorter time to target temperature.

When making the recommendation the committee spent considerable time discussing the timing of therapy in trials that showed benefit from TTM, as well as the impact of time delay on the mechanisms proposed for TTM benefit. The strong recommendation was delivered despite the low quality of evidence based on the concern that any delay may result in progressive decrease in benefit, while the risk of harm probably remains constant.

We suggest that in situations where there has been an unavoidable delay, there may be benefit from TTM eight or more hours after ROSC.

Quality of evidence: **Low**

Strength of recommendation: **Conditional**

There are clinical situations when there is a significant delay between ROSC and the opportunity to induce TTM. These could include transport from a site that did not provide TTM or delays for procedures. The reviewers did not find any literature involving an intentional time delay after ROSC before initiating cooling. The HACA trial,[2] which demonstrated a survival and neurologic benefit, had a median time to target of 8 h (interquartile range 4–16 h).

The committee did not set a time period after which patients should not be cooled, but found it likely that the benefits of TTM decrease with time.

Cooling process

We suggest that patients undergoing TTM be cooled to a target temperature between 32 °C and 34 °C.

Quality of evidence: **High**

Strength of recommendation: **Conditional**

The target temperature of 32–34 °C became the standard of care based primarily on the two studies published in 2002[1,2] and further supported by three other studies that showed benefit of cooling to this range compared to no cooling.[78–80] The choice of temperature target in these studies was extrapolated from animal data, and demonstrated benefit when compared to no temperature control. Three studies have specifically assessed the target temperature for therapeutic hypothermia after cardiac arrest.[8,81,82] None of these studies demonstrated that a different target temperature leads to improved survival or neurologic outcomes. This issue generated extensive discussion. The primary issue debated by the committee was whether to extend the range from 32–34 °C to 32–36 °C based on the results of the trial published by Nielsen et al. in 2013.[8] This was a large multicenter randomized controlled trial comparing a target of 36 °C to 33 °C, with a primary endpoint of all-cause mortality to the end of the trial. It was the largest RCT on TTM to date, enrolling 950 patients from 36 intensive care units. They found a hazard ratio with a target temperature of 33 °C of 1.06 (CI 0.89–1.28; $p = 0.51$).

The trial was designed and analyzed as a superiority trial. It is generally not appropriate to use a superiority trial to conclude equivalence or non-inferiority,[83] but the trial's close point estimates and large size has led some to conclude effective demonstration of non-inferiority.[84,85] There are design and analysis requirements for a trial to demonstrate non-inferiority, well described by the Consolidated Standards of Reporting Trials (CONSORT) group[83,86] and others.[87–89] Ultimately, the committee found the study inappropriate for a finding of non-inferiority because of the absence of a defined margin of inferiority, inappropriate inclusion criteria, and a study design lacking assay sensitivity.

In noninferiority and equivalence trials, a prestated margin of noninferiority for the treatment effect in each outcome is defined.[83] It is in relation to this margin that the analysis is expressed. It is usually based on a proportion of the benefit that the standard group previously demonstrated over placebo, but also requires some judgement as to what would be considered clinically meaningful. The confidence intervals in the Nielsen trial include results that some might consider clinically important.

Enrollment of patients in a noninferiority trial should match as closely as possible the enrollment of the trials when the reference treatment demonstrated superiority over controls.[83] A broader enrollment increases the likelihood of incorrectly concluding noninferiority. The Nielsen trial included patients that would not have been included in the Bernard or HACA trials, resulting in a study that more closely matches clinical practice but more likely to incorrectly conclude noninferiority.

Assay sensitivity refers to the ability of a specific clinical trial to demonstrate a difference if such a difference truly exists, and is perhaps the greatest challenge for noninferiority trials.[88] When a superiority trial demonstrates an effect it also proves assay sensitivity, but this is not true for a noninferiority trial. The Nielsen trial had design elements appropriate in a superiority trial but inappropriate when analyzing for noninferiority. The committee made specific note that the intervention (cooling) was not standardized in its method or the rate achieved; there was a significant delay after ROSC before initiation of temperature control; and rewarming was rapid compared to previous trials.

The significance of each of these issues is unclear, but when considered together the committee found it inappropriate to conclude noninferiority of a target temperature of 36 °C.

The committee also looked for a compelling reason to extend the target. We did not find a reduction in cost or resources by targeting 36 °C. We found no evidence of harm reduction to patients by targeting 36 °C. There was no reduction in adverse events by targeting 36 °C (specifically there was no significant differences found in adverse events including bleeding, infection and arrhythmias from the Nielsen data). The committee also discussed the greater risk of potential hyperthermia due to drift when selecting a higher target temperature. For these reasons, the committee found insufficient cause to extend the recommended targeted temperature range. When considering the overall quality of the evidence for this recommendation, the committee discussed and considered the methodological shortcomings of the HACA and Bernard trials. The potential for bias in these studies has been well discussed elsewhere,[19,20] and the committee was particularly concerned about the potential role that unblinded palliation decisions might have had. These limitations were recognized, but when considered in combination with the volume of lower quality supporting research the committee voted to assign a “high” quality for the evidence for the 32–34 °C target range. It does not refer to the evidence for what the precise target temperature should be. In assigning strength to the recommendation, 63% of the voting members were in favor of a strong recommendation. This was below our a priori requirement of an 80% majority for a strong recommendation, and so the recommendation was assigned a ‘conditional’ strength. Those in favor of the strong recommendation did so based on the quality of evidence, lack of harm, the societal value placed on survival and improved neurologic outcome, the size of the treatment effect, as well as the feasibility and low cost of the recommendation. The dissenting opinion was based primarily on acceptance of the Nielsen trial, uncertainty whether future research might demonstrate that a higher target temperature is safer for patients, or easier for physicians to achieve and maintain.

Our understanding of target temperature is still immature. We might expect that there is a dose effect with a therapeutic range for temperature management. There may be a subset of patients who become hemodynamically unstable at the usual target who may tolerate and benefit from a target of 36 °C, but the committee concluded that there is currently not sufficient evidence to change the standard ‘dose’ of 32–34 °C.

We recommend that core temperature should be continuously monitored during the cooling and rewarming phases of TTM.

Quality of evidence: **Low**

Strength of recommendation: **Strong**

We recommend that esophageal, nasopharyngeal, bladder, endotracheal cuff and pulmonary artery temperature sensors are acceptable options for monitoring core temperature.

Quality of evidence: **Moderate**

Strength of recommendation: **Strong**

No studies have attempted to induce TTM without continuous measurement of core temperature. Continuous monitoring is important to avoid significant time spent outside the target temperature range.

One observational study of cardiac arrest patients found that esophageal, pulmonary artery and endotracheal tube cuff sensor measurements were similar,[90] while a second found that pulmonary artery, bladder and nasopharyngeal temperature measurements were well correlated.[91]

Two studies were performed in cardiopulmonary bypass patients. One found that esophageal, nasopharyngeal and pulmonary artery assessments had the closest correlation to cerebral temperature.[92] The second paper found that nasopharyngeal temperatures did not correspond well to arterial temperature measurements.[93]

A case report examined various temperature measurements in a conscious subject undergoing induced hypothermia,[94] and found that esophageal monitoring most closely approximated pulmonary artery temperatures during cooling and rewarming.

Rectal probes have been reported to correlate poorly with esophageal temperature probes[95] and to be less accurate during rewarming phases.[94] Tympanic measurements have been found to not be accurate when ice packs are applied to the head and neck,[96] and may also be inaccurate during rewarming.[94]

We do not recommend a specific cooling method for TTM.

Quality of evidence: **low**

Strength of recommendation: **no recommendation**

The literature review found a number of feasible cooling methods,[1,32,43,69,97–117] however no specific method of cooling has been shown to improve patient outcomes.

Methods vary significantly in terms of ease of use, time to target temperature, temperature variability, cost and availability. It is common to use multiple cooling methods to achieve TTM. Clinicians should consider having a protocol individualized for their institution based on patient factors, ease of use, cost and local resources.

The committee was unable to make a specific recommendation on cooling method due to the range of clinical settings in which this therapy will be used. Surface cooling with ice-packs continues to be an acceptable method of inducing TTM, and is feasible in almost all clinical settings. Centers with resources and sufficient frequency might achieve shorter time to target temperature, tighter temperature control and improved convenience using commercially available cooling devices.

As discussed previously, the trial by Kim[67] suggests potential harm from using 4 °C saline as a component of a cooling strategy. The trial compared a treatment group that received two liters of 4 °C saline in the prehospital setting compared to a control group cooled in-hospital using surface or intravascular cooling. There was no difference in survival or neurologic outcome, however the treatment

group experienced a higher rate of re-arrest and early pulmonary edema.

Care of TTM patient

We suggest against the routine use of anticonvulsant medications for seizure prophylaxis in patients undergoing TTM.

Quality of evidence: **Low**

Strength of recommendation: **Conditional**

There were no high level studies found in the review directly addressing the question. Nine observational studies were reviewed reporting on 1199 patients that addressed the occurrence of seizure during TTM. On meta-analysis the cumulative incidence of seizures was 20.2% (95% CI 15.4–25.4%, $I^2 = 63\%$).[118–126] There was significant heterogeneity in the incidence of seizures likely reflecting different patient populations and sedative regimens.

The committee considered that the use of sedative regimens with anticonvulsant activity is common in patients undergoing TTM and that there were no studies in which prophylaxis with anticonvulsant medications for seizures was administered. Moreover, the administration of enteral anticonvulsant medications may be problematic in patients undergoing TTM as they require enteral access, a functional gastrointestinal tract for absorption and the drugs may have a significant side effect profile. Anticonvulsant medications available in parenteral formulations may have significant side effects and can be costly.

The low quality of evidence resulted in a conditional recommendation.

We suggest that patients who undergo TTM receive continuous electroencephalography (cEEG) monitoring where it is available.

Quality of evidence: **Low**

Strength of recommendation: **Conditional**

Most of the observational studies reporting on the incidence of seizures utilized cEEG, although the largest one did not.[123] The occurrence of seizures, status epilepticus, generalized suppression, burst suppression, or an isoelectric/unreactive pattern were associated with worse outcomes in severalstudies,[122,125] although the treatment of the seizures was not reported as influencing the outcomes.

The committee considered that TTM patients may receive paralytic agents, masking the occurrence of seizures. The incidence of seizures in this patient population is high, and there is significant potential harm of unrecognized and untreated seizures. The committee recognized the lack of widespread availability of cEEG and significant resources required for routine implementation, but identified potential benefit to patients where already available.

We recommend that patients undergoing TTM should receive sedation and analgesia.

Quality of evidence: **Low**

Strength of recommendation: Strong

We suggest that paralytics be used during induction and rewarming phases of TTM, to facilitate tight temperature control and to prevent shivering.

Quality of evidence: **Low**

Strength of recommendation: Conditional

Two observational trials[127,128] and one RCT[129] addressed sedation regimens in patients undergoing TTM. Bjelland et al. randomized 59 patients to propofol/remifentanyl vs. midazolam/fentanyl,[129] and found the time to extubation was significantly shorter in the remifentanyl/propofol group. The small number of patients, as well as the fact that it was not blinded and used subjective endpoints was noted by the committee. Both the HACA and Bernard trials used sedation and paralysis for all patients enrolled.[1,2] The recent TTM trial[8] used sedation and analgesia in all patients during the initiation, maintenance and rewarming phases of temperature management.

The committee reasoned that despite the low quality of evidence, the use of sedation and analgesia warranted a strong recommendation based on the low risk of harm and as a reflection of patient and societal values around symptom control.

The distribution, metabolism, and clinical effect of drugs used for sedation and analgesia are affected by hypothermia.[130,131] It is not known which agent or combination is optimal for use in this setting.[129,132] Given the low quality of evidence, the committee chose not to make a recommendation for a specific medication combination in favor of physician familiarity with commonly used medications.

The conditional recommendation regarding the use of paralytics reflects the low quality of evidence and the perception of greater potential harm from the overuse of neuromuscular blocking agents. The members of the committee uniformly use paralytics during the induction and rewarming phases, but there is significant variation in practice. Most members use paralytics routinely but a few only in response to shivering. Some continue the agents during the entire therapy. Others discontinue the agents when the core temperature is less than 34 °C, a time when patients generally are unable to mount a shivering response. There was agreement that the duration of neuromuscular blocking agents should be minimized, however paralysis may eliminate shivering and permit tight temperature control.

We suggest monitoring of the QTc interval in patients undergoing TTM.

Quality of evidence: **Low**

Strength of recommendation: **Conditional**

We suggest cautious use of medications that may prolong the QTc in patients undergoing TTM.

Quality of evidence: **Low**

Strength of recommendation: **Conditional**

We suggest that anti-arrhythmic agents be used only for the treatment of malignant or hemodynamically significant arrhythmias.

Quality of evidence: **Low**

Strength of recommendation: **Conditional**

A variety of EKG changes are observed during TTM. Osborne waves are seen in up to 30% of patients.[133,134] Prolonged QTc intervals are common but have not been associated with malignant arrhythmias.[59] Additionally, no increases in other arrhythmias have been associated with TTM.[58,135] No studies of the treatment of arrhythmias during TTM were found. The committee recognizes that a large proportion of patients undergoing TTM will have indications for anti-arrhythmic agents based on rhythms present during their cardiac arrest, but did not find TTM alone to be an indication for these medications.

We suggest that hemodynamic instability developing during TTM that is refractory to aggressive resuscitation be considered a cause for discontinuing therapy.

Quality of evidence: **Low**

Strength of recommendation: **Conditional**

We suggest that bradycardia during TTM not be treated routinely unless it is causing hemodynamic instability.

Quality of evidence: **Low**

Strength of recommendation: **Conditional**

There were no randomized trials and only observational trials regarding these issues were reviewed. Hemodynamic instability is common in post cardiac arrest patients, including those undergoing TTM, and is associated with worse outcomes.[136] Similarly, higher doses of vasopressors are associated with worsened outcomes.[137] There are numerous causes for post cardiac hemodynamic instability including vasodilation, systemic inflammatory response, myocardial stunning, myocardial damage and

hypovolemia. However, data from observational studies suggest some of these derangements can be improved by TTM.

In a propensity matched analysis, Zobel et al. found that hypothermia in patients with cardiogenic shock was associated with bradycardia but maintenance of cardiac output with a reduced systemic vascular resistance.[47] In a non-randomized design of patients undergoing TTM, the initiation of TTM was not associated with increased vasopressor requirements or changes in blood pressure.[138] Similarly, Huynh et al. and Jacobshagen et al. did not find that vasopressor requirements were increased in patients undergoing TTM.[48,49] In a small study with historically matched controls, the initiation of TTM hypothermia did not impair resuscitation.[139] There were no studies that compared or studied the treatment of bradycardia during TTM and there were no studies that compared different vasopressor or inotropic regimens during TTM.

The committee's recommendations are based on underlying physiological principles and clinical experience. The members concluded that the value of TTM is sufficient that the therapy be abandoned only in cases where hemodynamic instability cannot be controlled by other means. It is the experience of committee members that for the majority of these patients rewarming does not result in stabilization. The treatment of hemodynamic instability during TTM, including fluid therapy, vasopressors and inotropes should be based on the underlying physiological derangements, as there is significant variation between patients.

We suggest that potassium levels be kept above 3.0 mmol l^{-1} during the hypothermic phase of TTM.

Quality of evidence: **Low**

Strength of recommendation: **Conditional**

Patients treated with TTM have an increased risk of hypokalemia during the cooling phase of TTM.[140] Mirzoyev et al. studied the risk of hypokalemia in a retrospective study of 94 patients undergoing TTM post cardiac arrest. Hypokalemia was associated with QTc prolongation and polymorphic ventricular tachycardia. Rebound hyperkalemia on warming did not occur. Soeholm et al. prospectively studied 54 patients and found that potassium levels dropped to below 3.5 mmol l^{-1} in 78% of TTM patients.[141] Both of these studies recommended that potassium levels be kept above 3.0 mmol l^{-1} during the hypothermic phase of TTM. The strength of recommendation was based on the low quality of supporting evidence.

We suggest against the routine use of prophylactic antibiotics in patients treated with TTM.

Quality of evidence: **Low**

Strength of recommendation: **Conditional**

A recent meta-analysis examined the risk for infection during TTM for any indication.[142] Twenty-three RCTs randomized to TTM or usual care, including 2820 patients were included. The prevalence of all infections was not increased (rate ratio, 1.21 [95% CI, 0.95–1.54]), but there was an increased risk of pneumonia and sepsis (risk ratios, 1.44 [95% CI, 1.10–1.90]; 1.80 [95% CI, 1.04–3.10]). In a retrospective review of 641 patients, 500 (78%) were treated for early onset pneumonia defined as within 3 days of admission.[143] However, although early onset pneumonia was associated with increased duration of mechanical ventilation and ICU stay, it was not associated with increased mortality or worsened neurologic outcome.

One study addressed the issue of prophylactic antibiotics. Davies et al.[144] retrospectively reviewed 138 patients, 88% of whom were treated with TTM. The use of antibiotics in the first week of admission was associated with reduced mortality (56.6% vs. 75.3%; $p = 0.025$).

The committee found the retrospective nature of the evidence insufficient to support the routine use of antibiotics, but the Davies article is provocative and the issue requires further study.

We recommend against the use of procalcitonin (PCT) for the diagnosis of infection in patients treated with TTM.

Quality of evidence: **Low**

Strength of recommendation: **Strong**

There has been increasing interest in the utility of PCT for the diagnosis of infection and for guiding antibiotic utilization. PCT has been retrospectively studied in TTM patients and found to be non-specifically elevated.[145,146]

The potential harm from using a diagnostic test that appears to have very low positive and negative predictive values led the committee to a strong recommendation despite the low overall quality of evidence.

We suggest that standard order sets and care bundles be utilized for the initiation and care of patients undergoing TTM.

Quality of evidence: **Low**

Strength of recommendation: **Conditional**

The committee found the overall quality of the evidence around this issue to be low. Walters et al. implemented a care bundle that included TTM and hemodynamic optimization targets.[147] In a pre-post design of 55 patients, the implementation of the care bundle was associated with a trend towards reduced mortality and improved neurological outcome. Kilgannon et al.[148] reported on the successful implementation of an order set for TTM.

The committee concluded that although the use of these clinical tools may simplify the clinical application of TTM, there is currently no good evidence of improved patient outcomes. Centers lacking order sets and care bundles should continue to provide TTM while the tools are developed.

Feeding

We recommend that patients undergoing TTM receive enteral nutrition.

Quality of evidence: **Moderate**

Strength of recommendations: Strong

We suggest that caloric intake targets be calculated as 75% of normothermic targets during the hypothermic phase of TTM, if calorimetry is not being used.

Quality of evidence: **Low**

Strength of recommendations: Conditional

There were no high-quality studies that directly addressed the issue of how much patients who are undergoing TTM should be fed. The recommendation is based on extrapolation of nutrition research for critically ill patients, studies from other populations, and physiologic studies.

Three small observational studies compared indirect calorimetry measurements to basal metabolic rate calculated by the Harris–Benedict equation in patients undergoing TTM.[149–151] All were for indications other than post-cardiac arrest, the majority of patients being victims of traumatic brain injury. Measured energy expenditure was 71%, 70% and 85% that of calculated energy expenditure. There was no high quality data on the effect of TTM on absorption. A recent longitudinal cohort analysis suggests patients undergoing TTM tolerate a significant volume of enteral feeds.[152]

The committee felt that there was sufficient evidence supporting the use of enteral nutrition in other critically ill patients to give a strong recommendation. The caloric target was downgraded to a conditional recommendation because of uncertainty and a marginal expectation of benefit for this time period. There were concerns of harm if aggressive pursuit of enteral feeding was to be combined with prokinetic agents that may prolong the QTc interval.

Rewarming

We suggest that rewarming should begin 24 h after the patient reaches the target temperature.

Quality of evidence: **Low**

Strength of recommendation: **Conditional**

Eight RCTs[1,2,8,43,104,115,117,153] informed this recommendation. None of the studies addressed the clinical question with a direct comparison. The reference point for the start of the rewarming period was variable amongst the studies and included time from hospital arrival, time from start of cooling procedures, and time from achievement of target temperature (TT).

In four RCTs, rewarming was commenced 24 h after achievement of TT.[2,115,117,153] Laurent et al.,[43] randomized 61 patients into 3 groups (hemofiltration, hemofiltration with hypothermia, and control). Cooled patients were passively rewarmed after 16 h of hypothermia. In the Bernard trial[1] rewarming began 18 h after arrival to hospital. In a study assessing the feasibility of a helmet cooling device,[104] 16 patients were cooled while 14 received normothermia. In the helmet group, participants were allowed to spontaneously rewarm over an 8-h period after achieving TT or after 4 h, whichever came first. In the Nielsen trial[8] passive rewarming commenced 28 h after the start of cooling. A recently published systematic review and meta-analysis of RCTs, observational studies, and case reviews summarizes the evidence on duration of cooling.[140] The majority (74%) of included studies report 24 h of hypothermia.

The committee's consensus was that patients be kept at the target temperature for 24 h, but acknowledged that the quality of the evidence was low due to limitations in design, inconsistency in application, and indirectness of the findings. The committee identified concerns of potential harm due to infection from more prolonged hypothermia. Moreover, there was significant debate about whether shorter time periods might also be acceptable in certain clinical situations. The low quality of evidence led to the conditional recommendation.

We suggest that patients should be rewarmed at a rate of 0.25–0.5 °C Celsius per hour.

Quality of evidence: **Low**

Strength of recommendation: Conditional

The review did not find any high level evidence that directly addressed this issue. A retrospective cohort study by Bouwes[154] compared patients who were rewarmed at a rate ≥0.5 °C to <0.5 °C and found a non-significant trend toward poor outcome in the rapidly warmed patients (OR 2.61, $p = 0.08$).

Achieving consensus on this recommendation was challenging. The quality of the evidence was low, and there was significant practice variation amongst committee members. There was general agreement that rewarming should be controlled, if available methods of temperature control allow for this. There was concern of harm from patients overshooting normothermia when warmed at a rapid rate. The committee felt there was insufficient evidence to recommend a specific rewarming method or device.

We suggest that hyperthermia (core temperature > 37.5 °C) should be prevented for at least 72 h post arrest.

Quality of evidence: **Low**

Strength of recommendation: **Conditional**

There is no direct evidence to support a recommendation on fever management in this population. In the recent RCT by Nielsen and colleagues, the protocol advised fever control measures be used on a site-specific basis to maintain body temperature at or below 37.5 °C for 72 h post-arrest.

Harm has not been demonstrated from fever in this population. Amongst 177 patients in a prospective cohort of TTM post cardiac arrest,[155] fever (>38 °C) was prevalent (76%) but not associated with in-hospital mortality ($p = 0.45$). In the retrospective study by Bouwes et al.,[154] development of fever within 72 h of admission was not associated with poor neurologic outcome (OR 0.64 (0.31–1.30), $p = 0.22$). This finding was consistent after adjustment for confounders (OR 0.94 (0.40–2.17), $p = 0.88$). In a retrospective, multicenter clinical registry study Leary et al.[156] found rebound pyrexia in 41% of TTM-treated patients but no association with lower survival to discharge (54% versus 52%, $p = 0.88$) or worsened neurologic outcomes (70% versus 82%, $p = 0.21$). However, among patients with fever, higher maximum temperature (>38.7 °C) was associated with worse neurologic outcomes among survivors to hospital discharge.

The committee found the quality of evidence around this issue to be low. Despite the lack of demonstrated harm from pyrexia in this patient population, the committee considered indirect evidence from other populations with neurologic injury.[157–159] The potential for benefit, lack of harm, societal value of neurologic outcome, low cost and feasibility of fever prevention led the committee to suggest avoidance of hyperthermia.

Prognostication

We recommend that a clinical neurologic examination for the purpose of prognostication not be performed earlier than 72 h after return of spontaneous circulation.

Quality of evidence: **Moderate**

Strength of recommendation: **Strong**

We suggest that when there is a concern of residual medication effect, clinical neurologic examination for prognostication should be deferred until the clinician is confident that the confounding effects are no longer present.

Quality of evidence: **Low**

Strength of recommendation: **Conditional**

Three recent meta-analyses have addressed neurological prognosis after TTM.[160–162]

The current evidence suggests that the longer we wait, the more specific diagnostic tests become at predicting a poor neurological outcome.[163,164] 72 h after ROSC, many of the simple bedside clinical exams predict poor neurological outcome with a false positive rate approaching 0% with narrow confidence intervals.[160,165]

Studies evaluating elements of the prognostic neurologic examination in TTM patients have found the most useful clinical exam findings are bilaterally absent pupillary reflexes or bilaterally absent corneal reflexes.[160,166] At the recommended time 72 h after ROSC, the presence of either finding is sufficient to predict a poor outcome, defined as a Cerebral Performance Category (CPC) 3–5.

Sedation is recommended for patients undergoing TTM, but has increasingly been shown to alter the accuracy and recommended timing of the tests commonly used to predict neurological outcomes.[167] Samaniego et al. observed that 83% of TTM patients in their study had received sedation within 12 h of their 72 h prognostic neurologic exam.[127]

The committee gave particular consideration to societal concerns around false prognosis of poor outcome. This was balanced with resource costs and emotional toll on family members that come from a prolonged time interval. The committee reached consensus for a strong recommendation that prognostication be delayed for a minimum of 72 h after ROSC.

In situations where there is suspicion of residual drug effect at 72 h we suggest extending the timing of these diagnostic tests. The duration of the extension will depend on the sedatives and analgesics used, their dosing, and the patient's ability to clear them. Any patient requiring ongoing sedation should not have prognostic assessments for the purpose of limiting therapy.

We suggest that adjunctive testing is not routinely required to identify poor neurological outcome in patients after TTM

Quality of evidence: **Low**

Strength of recommendation: **Conditional**

We suggest that somatosensory evoked potentials (SSEP) and electroencephalography (EEG) can facilitate prognostication in specific circumstances.

Quality of evidence: **Low**

Strength of recommendation: **Conditional**

Given the predictive accuracy of delayed clinical testing (corneal reflexes and pupillary reflexes) at 72 h post-arrest, combined with the limited availabilities of advanced neuromodalities such as SSEP and continuous EEGs, the committee chose to suggest against the routine use of adjunctive testing. In certain circumstances, however, these modalities may offer benefit. SSEP testing has demonstrated high specificity 24 h post-cardiac arrest,[160,161] and its prognostic results improve 72 h post-arrest.[160,165] For the purposes of prognostication, the only definitive SSEP result is bilaterally absent N20 responses. All other findings are considered indeterminate.

EEG has a marginally higher false positive rate than SSEP,[160,165] but may still provide useful information in some circumstances. The only acceptable result for prognostication is "unfavorable EEG", defined by at least one of burst suppression pattern, status epilepticus, generalized suppression, or unreactive pattern.[160]

There is insufficient data on the use of CT or MRI, and we do not recommend that either be used for prognostication. Most studies are small with low precision estimates and a high likelihood of selection bias.[160,165]

We recommend that a neurologic consultation is not routinely required for prognostication.

Quality of evidence: **low**

Strength of recommendation: **Strong**

There was no evidence upon which to base this recommendation. The committee based its recommendation on the ability of clinicians caring for cardiac arrest patients to perform simple bedside clinical examinations and the lack of access to timely specialty consultation in most centers.

Specialist consultation may be very helpful in some situations and is encouraged in complex or confounded situations.

Discussion

The recommendations that we have developed for the use of TTM after cardiac arrest build on previous work.[168] We address issues faced by clinicians, with recommendations based on comprehensive systematic literature reviews. The committee also considered societal values, clinical benefit, risk of harm, cost, feasibility and variations in clinical practice environment. The guidelines were developed using GRADE methodology,[7] with consideration of the AGREE II instrument[14] and guideline attributes most highly valued by emergency health practitioners.[169]

There are important strengths to this guideline. This guideline was developed by a multidisciplinary committee, which included nurses, dietitians and physicians with specialty training in critical care, emergency medicine and neurology. Representatives from the four sponsoring Societies were involved at all stages of development. Extensive efforts were made to avoid conflict of interest and bias. Because one of our main objectives was to develop a practical and clinically useful guideline, we endeavored to offer a recommendation for each clinical question despite low quality evidence. A significant number of the recommendations are informed by or based on expert opinion, and where this is the case it is transparently indicated.

The guideline is limited to the use of targeted temperature management after cardiac arrest in adults. We did not consider its use in other clinical situations, or in the pediatric age group. The definitions used by the committee to assign quality of evidence (Fig. 2) have been updated.[170] The revised definitions improve the clarity of the terms, but do not substantively change their meaning.

Implementation of the recommendations made within this guideline will require active dissemination strategies and education.[171,172] It is beyond the scope of this paper to provide such strategies. However, it is the intention of the group to provide tools for implementation that can be shared among the broader community. Ideally, clinicians would be best served by a 'living guideline' that is continuously maintained and updated. The challenges of creating such a clinical tool include finding a home for the document, ongoing financial support, and contributor fatigue. In the face of those limitations it is our intention to update the guideline every five years.

Overall, we found that the majority of questions the clinicians we surveyed had about the application of TTM have not been clearly answered by the research. There are many clinical questions yet to be adequately addressed, but there are some fundamental knowledge gaps that should be prioritized by researchers. These include patient selection, optimal cooling rate, optimal target temperature, duration of hypothermia, and optimal rewarming rate.

Conclusions

Targeted temperature management (also referred to as therapeutic hypothermia) is an important component of post-resuscitation care for the patient with return of spontaneous circulation after cardiac arrest. We have provided clinically relevant recommendations for the provision of this therapy in the emergency department and critical care unit, and for prognostication after its use.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.resuscitation.2015.07.052.

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