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Temperature Management in Patients After Cardiac Arrest

Rapid Review

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Abbreviations

AAN	American Academy of Neurology
CCCS	Canadian Critical Care Society
CCS	Canadian Cardiovascular Society
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
ICU	intensive care unit
NMA	network meta-analysis
OCHA	out-of-hospital cardiac arrest
RCT	randomized controlled trial
ROSC	return of spontaneous circulation
SR	systematic review
TTM	targeted temperature management

Key Messages

- Two systematic reviews (1 with a network meta-analysis and 1 with a meta-analysis), 1 randomized controlled trial, and 7 non-randomized studies were identified about the comparative clinical effectiveness of normothermia versus hypothermia in adult patients after cardiac arrest.
- Normothermia was found to be similar to hypothermia for several clinical- and patient-related outcomes, such as survival, hospital mortality, and quality of life. There was limited evidence to suggest that either type of targeted temperature management was more efficacious, with findings suggesting that normothermia may be associated with greater protocol adherence and decreased prescription medication use coming from low-quality non-randomized studies.
- Four evidence-based guidelines were identified regarding targeted temperature management (normothermia or hypothermia) in adult patients after cardiac arrest. All guidelines strongly recommend targeted temperature management for eligible patients, particularly for patients resuscitated following out-of-hospital cardiac arrest. Identified guidelines from the Canadian Cardiovascular Society and American Academy of Neurology present strong recommendations for hypothermic targeted temperature management.

Context and Policy Issues

An estimated 35,000 cardiac arrests occur annually in Canada, with the majority of them occurring outside of hospital settings.[1] The abrupt loss of cardiac function is associated with poor clinical outcomes; the rate of survival to hospital discharge for out-of-hospital cardiac arrest (OCHA) ranges between 3.9% and 7.1%.[2] Survival after cardiac arrest not only requires the coordination of emergency services to facilitate immediate resuscitation and return of circulation, but also critical care over the next 24 hours to ensure that the brain is adequately supplied with oxygenated blood.[3] Fever is common among patients following cardiac arrest and resuscitation, and is thought to worsen brain damage.[4] Brain injury is a major cause of both mortality and decreased function, therefore its prevention is an imperative aspect of post–cardiac arrest care.[5]

Hypothermic targeted temperature management (TTM) has been widely practised within this patient population to control body temperature.[4] Also known as therapeutic hypothermia, the intervention involves the use of feedback-controlled intravascular cooling techniques in comatose patients to achieve a target body temperature typically in the range of 32°C to 34°C.[3] Canadian guidelines have recommended therapeutic hypothermia for unresponsive patients following OCHA; however, the evidence base has been largely inconclusive.[2] Results from a recently published randomized controlled trial (RCT)[6] showed that hypothermic TTM may not provide significantly clinical improvements over targeted normothermia at 37°C, which raises the question of whether existing hypothermic TTM protocols in critical care settings are of clinical value to this patient population.

The objective of this report is to identify and review current evidence regarding the comparative clinical effectiveness of normothermia versus hypothermia in adult patients after cardiac arrest and summarize identified evidence-based guidelines and recommendations regarding TTM.

Research Questions

1. What is the comparative clinical effectiveness of normothermia versus hypothermia for targeted temperature management in adult patients after cardiac arrest?
2. What are the evidence-based guidelines regarding targeted temperature management (normothermia or hypothermia) in adult patients after cardiac arrest?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. For question 1, the main search concepts were cardiac arrest, hypothermia, and normothermia. No filters were applied to limit the retrieval by study type. For question 2, the main search concepts were cardiac arrest and temperature management. Search filters were applied to this search to limit retrieval to guidelines. When possible, retrieval was limited to the human population. The search was also limited to English-language documents published between January 1, 2016, and December 16, 2021.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, were duplicate publications, or were published before 2016. Systematic reviews (SRs) in which all relevant studies were captured in other more recent or more comprehensive systematic reviews were excluded. Primary studies retrieved by the search were excluded if they were captured in 1 or more included SR. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)[7] for SR, the Professional Society for Health Economics and Outcomes Research (ISPOR) questionnaire[8] for network meta-analyses, the Downs and Black checklist[9] for randomized and non-randomized studies, and the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument[10] for guidelines. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 280 citations were identified in the literature search. Following screening of titles and abstracts, 228 citations were excluded and 52 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 40 publications were excluded for various reasons and 14 publications met the inclusion criteria and were included in this report. These comprised 2 SRs, 1 RCT, 7 non-randomized studies, and 4 evidence-based guidelines. Appendix 1 presents the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA)[11] flow chart of the study selection. Additional references of potential interest are provided in Appendix 6.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

Two SRs were identified, both published in 2021.[5,12] The authors of 1 SR, which included RCTs published up to June 21, 2021, conducted a network meta-analysis (NMA) of 10 RCTs.[5] Similarly, the other SR included RCTs that were published up to June 17, 2021, and included a meta-analysis of 9 RCTs.[12] A table outlining the overlap between included primary studies within the 2 SRs included in this report is provided in Appendix 5.

Table 1: Selection Criteria

Criteria	Description
Population	Adult patients treated in critical care (intensive or critical care units) after out-of-hospital or in-hospital cardiac arrest
Intervention	Q1: Normothermia, also known as targeted normothermia (i.e., maintenance of a normal core body temperature) Q2: TTM (normothermia or hypothermia)
Comparator	Q1: Hypothermia, also known as targeted hypothermia, therapeutic hypothermia, or protective hypothermia Q2: Not applicable
Outcomes	Q1: Clinical effectiveness (e.g., health-related quality of life, degree of disability or dependence, functional status, mortality) and harms (e.g., pneumonia, sepsis, bleeding, arrhythmia, skin complications associated with the device used to achieve TTM) Q2: Recommendations regarding TTM (normothermia or hypothermia) in adult patients after cardiac arrest (e.g., use of normothermia versus hypothermia, temperature range, time to reach normothermic or hypothermic range, duration of normothermia or hypothermia, management of fever and/or shivering, starting point of timing of therapy for patient within goal temperature when hypothermia is used)
Study designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, evidence-based guidelines

Q = question; TTM = targeted temperature management.

The included RCT, published in 2016, was of non-blinded, parallel design.[13] Seven non-randomized studies published between 2016 and 2021 were also identified, including 6 retrospective cohort studies[14-19] and 1 observational post hoc analysis of an RCT.[20]

Additionally, 4 guidelines with recommendations regarding post–cardiac arrest TTM were included in this report.[2,21-23] The most recent guideline, published in 2018, was developed by the French Intensive Care Society (FICS) and French Society of Anesthesia and Intensive Care Medicine.[21] Two of the included guidelines were published in 2017, 1 by the American Academy of Neurology (AAN),[22] and the other developed jointly by the Canadian Cardiovascular Society (CCS), Canadian Cardiovascular Critical Care Society, and Canadian Association of Interventional Cardiology.[2] The final guideline from 2016 was developed by the Canadian Critical Care Society (CCCS), Canadian Neurocritical Care Society, and Canadian Critical Care Trials Group.[23] Methods for the collection, selection, and synthesis of evidence informing the recommendations were reported in 3 guidelines, stating that a comprehensive literature search was performed[2,22,23] and that the evidence was reviewed by committee members.[2,22] Two guidelines classified the level of evidence for a recommendation from "very low" or "low" to "high."[21,23] The AAN guideline graded evidence as Class I, II, III, or IV.[22] The authors of the CCS guideline used Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology to assess the quality of evidence.[2] Final recommendations were made using Delphi methodology,[21,23] GRADE methodology,[2,21] and nominal group technique.[23] The strength of recommendations was classified in various ways; 2 of the included guidelines referred to them as either "strong" or "conditional,"[2,23] 1 graded them as A, B, C, or U (insufficient evidence),[22] and the other organized them as positive or negative and as strong or weak.[21]

Country of Origin

One of the SRs listed first authors from Canada,[5] and the other listed first authors from Denmark.[12] The included primary clinical studies were conducted in Israel,[17] Singapore,[13,18] South Korea,[16] Switzerland,[14] the Netherlands,[20] and Turkey.[15] Two of the included guidelines were Canadian,[2,23] 1 was from the US,[22] and 1 was from France.[21]

Patient Population

Both SRs[5,12] included RCTs with adult patients after cardiac arrest, with the SR by Fernando et al. (2021)[5] limiting inclusion to patients with OCHA who remained unresponsive following signs of return of spontaneous circulation (ROSC). The SR by Fernando et al. (2021)[5] included 4,218 participants across 10 RCTs, and the SR by Granfeldt et al. (2021)[12] included 2,968 participants from 9 RCTs.[12] Patients' mean age was similar between the 2 SRs (approximately 63 years[5] and 64[12] years). The majority of the included population in both SRs were male, ranging from 60% to 88.9% in 1 SR[5] and from 56% to 100% in the other.[12]

There was some variation in the patient population among the 8 primary studies included in this report. All studies included adult patients hospitalized following cardiac arrest.[13-20] The mean age of the patients ranged between 52.5 years and 65 years.[13-20] Sex was reported in 7 of the 8 primary studies, and the majority of patients across the studies were male, ranging from 53.4% to 81.5%. One retrospective cohort study[16] and 1 observational post hoc analysis[20] limited inclusion to patients with OCHA, whereas the others did not specify between in-hospital and out-of-hospital cardiac arrest. The RCT[13] and retrospective cohort study[18] by Pang et al. included primarily patients who had an in-hospital cardiac arrest (90.5% to 92.4% of participants) and specifically comprised patients on extracorporeal life support. Three

of the included retrospective cohort studies[15,17,19] reviewed patient data from patients in the intensive care unit (ICU).

The relevant target population of the 4 included guidelines[2,21-23] in this report was adult patients with cardiac arrest. One guideline[21] contained recommendations for a broader population: both adult and pediatric patients with cardiac arrest, traumatic brain injury, stroke or other brain injuries, and shock. Authors of the CCS guideline[2] specified that the recommendations pertained to patients with OCHA. The guideline developed by FICS[21] was broadly intended for clinicians who provide neurologic care to critically ill patients. The intended users of the 3 other included guidelines[2,22,23] were clinicians who provide care for patients with cardiac arrest; the AAN guideline[22] is specifically for nontraumatic cardiac arrest and the CCS is guideline for OCHA.[2]

Interventions and Comparators

The SR with NMA by Fernando et al. (2021)[5] compared normothermia (37°C to 37.8°C) with 3 temperature ranges of hypothermia: 31°C to 32°C (which they referred to as "deep hypothermia"), 33°C to 34°C ("moderate hypothermia"), and 35°C to 36°C ("mild hypothermia"). The SR with meta-analysis by Granfeldt et al. (2021)[12] compared normothermia, whether it involved active cooling as part of TTM or not, with hypothermic TTM (32°C to 34°C).

Normothermia was defined in various ways in the included primary clinical studies. Therapeutic normothermia was described as a body temperature maintained at 36°C,[14,19] 37°C,[13] 36°C to 37°C,[20] or higher than 35.5°C.[16] Three retrospective studies[15,17,18] considered normothermia as a comparison group but did not specify a temperature range; however, 1[15] of the studies considered normothermia as a non-TTM intervention. Targeted normothermia was specified to be maintained for 28 hours in the retrospective cohort study by Casamento et al. (2016).[19]

Hypothermia was also defined in various ways in the included primary studies. Targeted hypothermia was described as body temperature maintained at 33°C,[14] 34°C,[13] 32°C to 34°C,[17,19,20] 33°C to 35°C,[15] or lower than 35.5°C.[16] Hypothermia was specified as maintained for 24 hours in the studies by Pang et al.[13,18] and Casamento et al. (2016).[19]

All included guidelines presented recommendations regarding TTM as part of in-hospital care following cardiac arrest.[2,21-23] The AAN guideline defined therapeutic hypothermia, or hypothermic TTM, as cooling to a core body temperature of 32°C to 34°C.[22] The CCS guideline broadly defined the intervention considered, TTM, as a strategy of intentional temperature management of a patient after cardiac arrest, which consists of active patient cooling, subsequent rewarming, and extended fever control.[2]

Outcomes

Several clinical outcomes of relevance were described in the studies included in this review. These outcomes included the following: survival with good neurologic outcome,[5,12,13,18] overall survival,[5,12,13,15-20] mortality,[13-15,17,19] ICU or hospital length of stay,[13-15,18,19] neurologic status,[13-16,20] protocol adherence,[14] quality of life,[20] time spent in temperature target range,[19] medication prescription,[14,19] and adverse events.[5,13,14,17-19]

The modified Rankin Scale, Cerebral Performance Categories scale, and Pittsburgh Cardiac Arrest Category scale were the validated measures used to describe neurologic outcomes in 2 SRs,[5,12] 1 RCT,[13] and 5 non-randomized studies.[14-16,18,20] The modified Rankin Scale is

commonly used to measure the degree of disability of people who have suffered a stroke or other causes or neurologic disability.[24] The scale ranges from 0 to 6, with 0 for no symptoms, 3 for moderate disability (requires some help but able to walk without assistance), and 6 for dead.[24] The Cerebral Performance Categories are the gold standard for describing the level of function and impairment after cardiac arrest.[25] The categories, which rank from 1 to 5, are as follows: good cerebral performance, moderate cerebral disability, severe cerebral disability, coma or vegetative state, and brain death.[25] Finally, the Pittsburgh Cardiac Arrest Category is a 4-level illness severity score with the following rankings: awake, coma with mild cardiopulmonary failure, coma with severe cardiopulmonary failure, and deep coma.[26] Studies that investigated survival with good neurologic outcome defined a favourable neurologic outcome as any of the following: modified Rankin Scale score of 0 to 3,[5,12] Cerebral Performance Categories scale score of 1 or 2,[5,12,13,18] Pittsburgh Cardiac Arrest Category score of 1 or 2,[5] or blinded assessment from a health professional indicating no, mild, or moderate disability.[5]

The authors of 1 retrospective cohort study[14] reported protocol adherence as a primary outcome, and patients were considered to have adhered to the protocol if their body core temperature was within a range of 1°C around the target temperatures of 33°C and 36°C for the hypothermia and normothermia groups, respectively.

The authors of 2 retrospective cohort studies[14,19] reported several outcomes related to the prescription and dose of catecholamines, sedatives, and relaxants administered to patients in the targeted normothermia and hypothermia groups.

The 4 guidelines included in this report regarded survival with good neurologic function as an outcome for consideration when developing recommendations.[2,21-23]

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of the included publications are provided in Appendix 2.

Systematic Reviews and Network Meta-Analyses

Both SRs[5,12] used comprehensive search and selection strategies, which is evident because most RCTs relevant to this report were excluded on the basis of inclusion within the SRs. Both SRs by Fernando et al. (2021)[5] and Granfeldt et al. (2021)[12] had registered published protocols with detailed search strategies. Fernando et al. (2021)[5] searched 6 databases (MEDLINE, PubMed, Embase, Scopus, Web of Science, and the Cochrane Database of Systematic Reviews), conducted further surveillance searches, and performed a grey literature search, including the reference lists of all included studies and existing SR on TTM. Granfeldt et al. (2021) searched 3 databases (PubMed, Embase, and the Cochrane Central Register of Controlled Trials) as well as the International Clinical Trials Registry Platform and ClinicalTrials.gov for registered ongoing and unpublished trials. However, it is unclear whether content experts were consulted during the review process of either of the SRs[5,12] and, in the case of Fernando et al. (2021),[5] it is unclear whether trial registries were searched as part of the grey literature search outlined in the published protocol. Research questions and inclusion criteria were clearly reported and consisted of components of population, intervention, comparison, and outcomes.[5,12] Although Fernando et al. (2021)[5] explained their selection of RCTs for inclusion in the review, Granfeldt et al. (2021)[5,12] did not justify their selection of randomized and non-randomized controlled studies for inclusion. The study selection and data extraction processes were performed in duplicate, and the included studies were

described in adequate detail in supplementary materials.[5,12] Reasons for exclusion cannot be easily verified because neither of the SRs published a list of excluded studies.

In terms of conducting meta-analyses, authors of both SRs[5,12] justified combining the data in a meta-analysis or NMA and used assessment tools by Cochrane to assess the risk of bias of included studies. Statistical heterogeneity among trials were assessed using visual inspection of forest plots, the I^2 statistic, and the Chi-square test.[5,12] Heterogeneity was observed in the results of the reviews, but the authors investigated the potential sources of any heterogeneity in the results and discussed its impact in the findings.[5,12]

Fernando et al. (2021)[5] initially performed pairwise MA using the random-effects model, and then evaluated the feasibility of conducting an NMA by checking the availability of evidence, transitivity assumption, connectivity, and agreement between direct and indirect evidence. With the assumption of a common heterogeneity parameter, the frequentist random-effects model was chosen to combine the included data.[5] However, the authors did not provide a justification about why the analyses were performed with a frequentist instead of a Bayesian approach. Due to insufficient data, the authors were unable to conduct subgroup analyses or meta-regression to explain statistical heterogeneity.[5] The authors presented a network graph of included studies, and given the geometry of the NMA, the comparisons between normothermia and deep and moderate hypothermia were direct, and the comparison between normothermia and mild hypothermia was indirect.[5] In addition, Fernando et al. (2021)[5] provided a clear summary of the main findings but did not perform any sensitivity analyses.

Randomized Controlled Trial

Several aspects of the included RCT[13] were clearly described, such as the study objective, primary and secondary outcomes, patient characteristics, interventions, potential confounders, main findings, estimates of random variability, and adverse events. However, in reviewing the results section, it was unclear whether 1 of the 12 participants in the normothermia group was lost to follow-up given the discrepancy between the total number of participants and the number of patients discharged or deceased. The single-centre study was conducted in a tertiary referral centre, which may not be representative of where most patients seek immediate care after a cardiac arrest. In addition, due to the non-blinded design, investigators, outcomes assessors, and patients were aware of the treatment administered, which may have increased the risk of performance bias and detection bias. It is unclear whether the study was adequately powered because of its sample size of 21 participants. This RCT was also published as a letter to the editor, thus it is unclear whether the methodology and findings have been subject to peer review.

Non-Randomized Studies

Overall, the reporting was clear across the 7 non-randomized studies[14-20] in terms of study objectives, patient characteristics, potential confounders, interventions, and estimates of random variability. In 3 studies,[14,19,20] the characteristics of the patients lost to follow-up were not described. The authors of 2 studies[17,18] did not specify a temperature range for the normothermia group. In Kocayigit et al. (2021),[15] it was unclear when the survival and good neurologic results outcomes were measured. The external validity of the study findings to other similar settings was generally considered poor because 4 of the included non-randomized studies[14,15,17,18] were single-centre, retrospective cohort studies. The other 3 studies consisted of patient data derived from either multiple centres[19,20] or national registries,[16] which may have increased generalizability. None of the included studies were conducted in Canada, which may limit relevance of the results in the Canadian context.

Threats to the internal validity of the studies were primarily due to the non-randomized nature of the studies: 6 of the included studies[14-19] were of retrospective cohort design, which means the investigators, outcome assessors, and patients may have been aware of the intervention. Additionally, there is uncertainty about whether there was a high level of compliance with the intervention and whether the recorded patient data are accurate. Participants across the intervention and comparator groups appeared to be recruited at the same sites or from the same population and over the same periods of time. Some studies[16,17,19,20] considered potential confounders when adjusting main outcomes, whereas other studies[15,18] did not take into account baseline differences between the groups. Only 1 included study[19] provided power calculations, but sample size was noted to be a limitation in 3 studies.[14,17,18]

Guidelines

All included guidelines described a clear scope and purpose.[2,21-23] Evidence of some stakeholder involvement was evident in the development of all guidelines; however, it was unclear whether the views and preferences of the target patient population were sought.[2,21-23] In terms of rigour of development, all included guidelines conducted a comprehensive search to collect evidence to support recommendations and did not specify whether other systematic methods, such as screening and study selection in duplicate, were undertaken.[2,21-23] The guidelines also did not provide a procedure for future updates.[2,21-23] Nonetheless, the supporting evidence was clearly appraised and used to support recommendations, and there was an evident process and methodology for the development of recommendations.[2,21-23] There was an explicit link between the recommendations and the supporting evidence, with varying strengths of recommendations associated with different levels of evidence.[2,21-23] All relevant recommendations were easily identifiable and clearly presented.[2,21-23] The authors of the guidelines adequately described potential facilitators and barriers to application of recommendations but did not provide intended users with additional guidance on how to implement the recommendations and monitor the implementation of relevant interventions.[2,21-23] Finally, all the included guidelines appeared to have editorial independence, with clear disclosures of competing interests.[2,21-23]

Summary of Findings

Appendix 4 presents the main study findings and authors' conclusions.

Clinical Effectiveness of Normothermia Versus Hypothermia

Survival

Two SRs,[5,12] 1 RCT,[13] and 1 retrospective cohort study[18] evaluated the effect of TTM on survival rate with good neurologic or functional outcome. A favourable neurologic or functional outcome was defined as any of the following: modified Rankin Scale score of 0 to 3,[5,12]; Cerebral Performance Categories scale score of 1 or 2,[5,12,13,18]; Pittsburgh Cardiac Arrest Category score of 1 or 2,[5] or blinded assessment from a health professional indicating no, mild, or moderate disability.[5] No statistically significant differences were identified in the survival rate with good neurologic outcome between the normothermia and hypothermia groups.[5,12,13,18] The SRs with NMA and meta-analysis reported odds ratios[5] and risk ratios,[12] respectively; however, the estimates were not statistically significant, suggesting no differences between interventions.

Two SRs, 1 RCT, 5 retrospective cohort studies, and 1 observational post hoc analysis of an RCT also evaluated overall survival, recorded at an unspecified time point,[15,17] at hospital discharge,[5,12,16,18,19] or within 30 days,[12] 90 days,[5,12,20] 6 months,[5,12,13] or 1 year after discharge.[20]

The authors of 1 retrospective cohort study[19] found a significantly greater proportion of survivors at discharge in the normothermia group compared with the hypothermia (TTM 32°C to 34°C) group, but no statistically significant differences were reported in the other studies.[5,12,13,15-18,20]

Mortality

Hospital and ICU mortality rates were evaluated in 1 RCT[18] and 4 of the retrospective cohort studies[14,15,17,19] included in this report. There were no statistically significant differences between the normothermia and hypothermia groups.

ICU or Hospital Length of Stay

One RCT[13] and 4 retrospective cohort studies[14,15,18,19] reported the average length of ICU[14,19] or hospital[13,15,18] stay as either a mean with standard deviation[14] or median with interquartile range.[13,15,18,19] The authors of 1 retrospective cohort study found that patients in the normothermia group who received standard supportive therapy experienced significantly longer hospital stays compared with patients in the hypothermia (TTM at 33°C to 35°C) group.[15] There were no significant differences between the groups reported in the other studies.[13,14,18,19]

Neurologic Status

Neurologic status and function were measured in the studies included in this report using Cerebral Performance Categories scale scores[13-16,20] and modified Rankin Scale scores.[14] The authors of 1 retrospective cohort study[15] found that a significantly greater proportion of patients in the hypothermia (TTM at 33°C to 35°C) group had good neurologic results, defined as a Cerebral Performance Categories scale score of either 1 or 2, compared with patients in normothermia (non-TTM) group. Although this finding was in favour of targeted hypothermia, no statistically significant differences were identified among the groups in other studies that also investigated this outcome.[13,14,16,20]

Protocol Adherence

One retrospective cohort study by Duggelin et al. (2021)[14] investigated the proportion of patients adherent to the TTM protocol at 24 hours. Using a Cox proportional hazard model, it was demonstrated that a significantly higher proportion patients in the normothermia (36°C) group were adherent to the TTM protocol compared with patients in the hypothermia (33°C) group.[14]

Quality of Life

Quality of life at 1-year follow-up, measured using the 36-Item Short Form Survey, was reported in 1 included observational post hoc analysis.[20] Patients in both groups reported similar physical and mental component scores.[20] The risk ratio estimates were not statistically significant, suggesting no differences between interventions.

Time Spent in Temperature Target Range

The authors of 1 retrospective cohort study[19] evaluated the median proportion of time spent in the prescribed temperature range among patients in the hypothermia (TTM 32 to 34°C) versus normothermia (TTM 36°C) groups and found no statistically significant differences.

Medication Prescription

The proportion of patients receiving sedatives and relaxants and the mean or median doses prescribed were reported in 2 retrospective cohort studies.[14,19] There were no statistically significant differences in the proportion of patients receiving propofol, morphine, midazolam, fentanyl, and pethidine for sedation, but 1 of the studies found that a significantly lower proportion of patients in the normothermia (TTM 36°C) group received at least 1 dose of muscle relaxant compared with patients in the hypothermia (TTM 32 to 34°C) group. Patients in the normothermia (TTM 36°C) group were reported to have received significantly lower doses of midalozam[14,19] and fentanyl[19] compared with patients in the hypothermia (TTM 32 to 34°C) group.

Adverse Events

Several adverse events were reported in the studies included in this report: arrhythmia,[5,13,14,19] bleeding,[5,13,14,18,19] pneumonia,[5,13,14] sepsis,[5] seizures,[5,17] limb ischemia,[13,18] acute renal failure,[13,18] continuous renal replacement therapy,[13,18,19] thrombosis,[14] bradycardia,[14] hypoxic ischemia encephalopathy,[18] stroke,[18] ischemic hepatitis,[18] cardiovascular instability,[19] and mechanical ventilation.[19] The authors of Duggelin et al. (2021)[14] found that there was a significantly lower incidence of bradycardia among patients in the normothermia (TTM 36°C) group compared with patients in the hypothermia (TTM 33°C) group. However, no statistically significant differences were identified among the groups in other studies or for other adverse events.[5,13,17-19]

Guidelines

Among the 4 included guidelines, all strongly recommended the use of TTM to improve survival and neurologic outcome in patients resuscitated from OCHA with a shockable cardiac rhythm (ventricular tachycardia or ventricular fibrillation).[2,21-23] The CCCS guideline[23] extended the strong recommendation to patients presenting with pulseless ventricular tachycardia. In terms of patients with in-hospital cardiac arrest, the FICS guideline issued a positive recommendation for TTM at the level of expert opinion.[21] However, the CCCS guideline contained a strong recommendation supported by low-level evidence in favour of TTM for patients with in-hospital cardiac arrest.[23]

The CCS guideline strongly recommended hypothermia (between 33°C and 36°C) for eligible patients who undergo TTM. The AAN guideline[22] similarly specified in their recommendation that the TTM intervention should be hypothermia (32°C to 34°C for 24 hours); however, they also issued a lower-level recommendation supported by the same level of evidence for normothermia (36°C for 24 hours followed by 8 hours of rewarming to 37°C and temperature maintenance below 37.5°C until 72 hours) in patients who are comatose with either a shockable or non-shockable initial cardiac rhythm. The FICS guideline[21] contains a weak recommendation for hypothermic (32°C to 36°C) TTM. Recommendations in the CCCS guideline[23] do not state target temperature ranges for TTM.

With regard to specific technical recommendations, the CCS issued a lower-level recommendation supporting the use of surface cooling or intravascular cooling techniques.[2]

Limitations

Although there was a high quantity of eligible publications identified in this report for the clinical effectiveness question, the quality of the included primary studies[5,12-20] was low. Some limitations were explicitly acknowledged by authors of the individual studies included in this

review, such as the lack of generalizability of a single-centre retrospective cohort study and small sample sizes. Moreover, the critical appraisal performed as part of this review identified some important limitations of the included studies. For example, some of the included non-randomized studies represented outcomes with unclear time points and follow-up periods and lacked detail on important adverse events. With the exception of 1 RCT included in the SR by Fernando et al. (2021),[5] none of the studies included in this report were conducted in a Canadian setting, which could be a limitation.

Furthermore, there was a significant amount of overlap identified across the 2 SRs included in this report; much of the available evidence identified in this review is based on the same trials. The 1 RCT included in this report that did not overlap with the SRs is a preliminary study with 21 participants. This limits the available evidence base to address research questions regarding the clinical effectiveness of targeted and non-targeted normothermia for patients in critical care after cardiac arrest.

The SRs included in this report had several strengths in methodology, but authors of both SRs[5,12] reported heterogeneity in study characteristics, such as patient populations and interventions, among the included RCTs and did not perform subsequent meta-regression or subgroup analyses to investigate the heterogeneity due to insufficient data. The NMA by Fernando et al. (2021)[5] also lacked direct comparative evidence evaluating the differences between normothermia and mild hypothermia (35°C to 36°C).

Although the guidelines included in this report were generally of high quality, some relevant recommendations regarding TTM were categorized as conditional and supported by low-quality evidence, as stated by guideline authors. The guidelines did not contain any recommendations pertaining to the management of fever and shivering or specifics on the timing of TTM therapy.

Conclusions and Implications for Decision- or Policy-Making

This report identified 2 SRs (1 with an NMA[5] and 1 with a meta-analysis[12]), 1 RCT,[13] and 7 non-randomized studies[14-20] published since 2016 informing the comparative clinical effectiveness of normothermia versus hypothermia for adult patients after cardiac arrest. Overall, there were no statistically significant differences across all the studies for several clinical effectiveness and patient-related outcomes: survival with good neurologic outcome, overall survival, hospital mortality, quality of life, and time spent in the temperature target range. There was an indication that targeted normothermia at 36°C may offer slight benefits over hypothermic TTM. Outcomes in favour of normothermia, such as greater proportion of survivors at discharge, protocol adherence, and decreased dose and use of prescribed sedatives and relaxants, were identified in 2 retrospective cohort studies.[14,19] However, the studies[14,19] were characterized to be of low quality and with potentially limited generalizability to the Canadian context. Therefore, there is limited evidence to suggest that normothermic TTM may provide more clinical benefits over hypothermic TTM.

In addition, 4 evidence-based guidelines published since 2016 were identified regarding the use of TTM for adult patients after cardiac arrest. In general, TTM was strongly recommended by all included guidelines, particularly for adult patients resuscitated from OCHA. Patients

presenting with shockable initial cardiac rhythm versus non-shockable cardiac rhythm were also more strongly recommended for TTM. Unlike the clinical evidence identified in this report, guidelines — particularly those developed by Canadian and American organizations — strongly recommended the use of hypothermia for eligible patients, either in the 33°C to 36°C or 32°C to 34°C ranges. The guidelines included in this report were found to be of moderate to high quality. It is important to acknowledge that these guidelines are older compared with some of the clinical studies included in this report, with the latest 1 published in 2018, which may be the cause of discrepancies between the evidence used to inform the recommendations and the current literature on the topic.

Baseline characteristics, such as age, location of cardiac arrest (in hospital vs. out of hospital), and initial cardiac rhythm, may play a role in determining which patients are mostly likely to benefit from either modality of TTM. Larger RCTs and additional SRs with less heterogeneity may allow for the necessary means to identify such subgroups.

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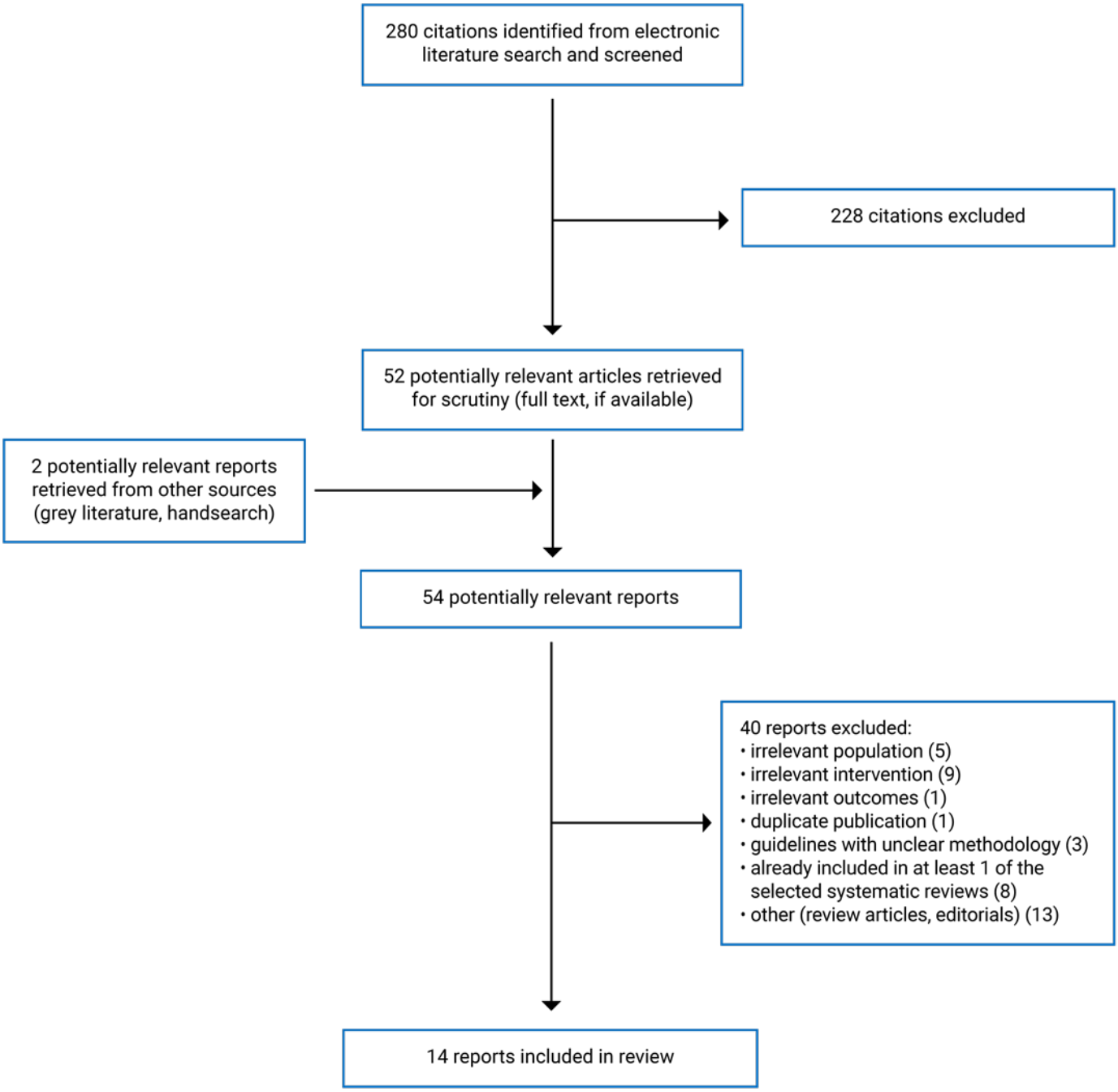
Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Review and Network Meta-Analysis

Study, country, funding	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Fernando et al. (2021)[5] **Canada** **Funding: No funding received**	SR with NMA Total: 10 RCTs (N = 4,218; range 30 to 1,861) included in NMA Year of publication: 2000 to 2021	Adult patients with OHCA who remained unresponsive following ROSC Range of mean age: (56 to 75) years Range of % male: 60 to 88.9 Initial rhythm: any, VF, VF/VT, VF/VT/asystole, VF/asystole, asystole/PEA	Normothermia (37°C to 37.8°C) (n = 1,390) Deep hypothermia (31°C to 32°C) (n = 276) Moderate hypothermia (33°C to 34°C) (n = 2,086) Mild hypothermia (35°C to 36°C) (n = 466)	Primary outcome: • Survival with good functional outcome[a] at discharge, or the latest time point reported up until 6 months post-discharge Secondary outcomes: • Overall survival (i.e., survival at discharge, or the latest time point reported up until 6 months post-discharge) • AEs related to TTM during hospitalization Follow-up: NR
Granfeldt et al. (2021)[12] **Denmark** **Funding: NR**	SR with MA Total 9 RCTs (N = 2,968; range: 16 to 1,861) Year of publication: 2001 to 2021	Adult patients with cardiac arrest in any setting (in-hospital or out-of-hospital) underwent TTM Range of mean age: • Normothermia: 51 to 80 years • Hypothermia: 52 to 77 years Range of % male: • Normothermia: 63 to 80 • Hypothermia: 56 to 100 Initial rhythm: Shockable (VF/VT), non-shockable (asystole/PEA)	Normothermia (e.g., no TTM, no clear description of TTM, or TTM to maintain normothermia [generally 36.5°C to 38°C]) Hypothermia (TTM at 32°C to 34°C)	Survival with favourable neurological outcome at hospital discharge or 30 days Survival with favourable neurological outcome at 90 or 180 days Overall survival to hospital discharge or 30 days Overall survival at 90 or 180 days Follow-up: 90 or 180 days

AE = adverse event; MA = meta-analysis; NMA = network met-analysis; NR = not reported; OHCA = out-of-hospital cardiac arrest; PEA = pulseless electrical activity; ROSC = return of spontaneous circulation; SR = systematic review; TTM = targeted temperature management; VF = ventricular fibrillation; VT = ventricular tachycardia.

Note: This table has not been copy-edited.

[a]Good functional outcome was defined on the basis of any of the following: (1) modified Rankin Scale score of 0 (no symptoms) to 3 (moderate disability); (2) Cerebral Performance Categories scale score of 1 (good cerebral performance) or 2 (moderate cerebral disability); (3) Pittsburgh cerebral performance category of 1 (good recovery) or 2 (moderate disability); or (4) blinded assessment from a health professional indication no, mild, or moderate disability.

Table 3: Characteristics of Included Primary Clinical Studies

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Randomized controlled trial				
Pang et al. (2016)[13] **Singapore** Funding: SingHealth Foundation	Non-blinded, parallel (1:1) RCT Sample size calculation provided: No ITT: NR	Adult patients receiving ECLS for cardiac arrest Mean age: 52.5 years % Male: 81.0 % In-hospital cardiac arrest: 90.5 % Acute coronary syndrome: 81.0 Mean duration of CPR: 25.7 minutes Mean duration of ECLS: 4.4 days Initial rhythm: Any	Normothermia (37°C) (n = 12) Targeted hypothermia (34°C maintained for 24 hours in the ICU) (n = 9) Cooling to 34°C was performed by modulating the heat exchanger component of the ECLS circuit.	Primary outcome: Survival to hospital discharge with good neurological function (defined as a CPC[a] of 1 or 2) Secondary outcomes: • Survival at 6 months • In-hospital death • Length of hospital stay • Severe neurological dysfunction • AEs (i.e., ECLS-related complications within 7 days) Follow-up: 6 months

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Non-randomized studies				
Duggelin et al. (2021)[14] **Switzerland** Funding: No funding received	Retrospective cohort study Sample size calculation provided: No Adjustment for confounders conducted: No	Adult patients successfully resuscitated after out-of-hospital or in-hospital cardiac arrest Mean age: 61 years % Male: 81.5 Mean time to ROSC: 17.6 minutes % OHCA: 83.0 Initial rhythm: Any	• Normothermia (TTM at 36°C) (n = 64) • Hypothermia (TTM at 33°C) (n = 69) TTM was initiated by application of 30 mL/kg body weight of saline cooled to 4°C for TTM 33°C or no cooled saline for TTM 36°C. TTM was maintained for 24 hours.	Outcomes: • Protocol adherence (considered fulfilled if body core temperature was within a range of ±1°C around the target temperature of 33°C or 36°C) • Neurological outcome (assessed using CPC score[a] or the modified Rankin score[b]. A CPC score of 3 to 5 or a modified Rankin score of 4 to 5 was considered as poor neurological outcome) • ICU/hospital mortality • ICU/hospital length of stay • Medication prescription • AEs Follow-up: NA
Kocayigit et al. (2021)[15] **Turkey** Funding: NR	Retrospective cohort study Sample size calculation provided: No Adjustment for confounders conducted: No	Adult patients hospitalized in the ICU for cardiac arrest due to myocardial infarction receiving TTM Mean age: 58.1 years Median duration of CPR: 20 minutes % OHCA: 59.8 Initial rhythm: VF/asystole	Normothermia (non-TTM; temperature not specified) (n = 31) Hypothermia (TTM at 33°C to 35°C for 24 hours)	Outcomes: • Survival • 30-day Mortality • Neurological status (using CPC scores[a]) • Length of hospital/ICU stay Follow-up: NA

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Spoormans et al. (2021)[20] **The Netherlands** Funding: The Netherlands Heart Institute, Biotronik, and AstraZeneca	Observational post hoc analysis of an RCT Sample size calculation provided: No Adjustment for confounders conducted: Yes	Adult patients successfully resuscitated after OHCA with an initial shockable rhythm Mean age: 65 years % Male: 78.6 Median time to ROSC: 15 minutes Median time arrest to basic life support: 2 minutes Initial rhythm: Shockable (VF/VT)	Normothermia (TTM at 36 to 37°C) (n = 190) Hypothermia (TTM at 32°C to 34°C) (n = 269) Cooling methods of TTM: Body surface cooling, intravascular cooling device	Primary outcome: • 90-Day survival Secondary outcomes: • Neurologic outcome at ICU discharge (using CPC scores[a]) • Neurologic outcome at 90-day follow-up • QoL at 1-year follow-up (using SF-36-Item Health Survey) Follow-up: 90 days, 1 year
Kim et al. (2020)[16] **South Korea** Funding: National Fire Agency of Korea and the Korea Centers for Disease Control and Prevention	Retrospective cohort study Sample size calculation provided: No Adjustment for confounders conducted: Yes	OHCA patients who were hospitalized and underwent TTM Mean age: 59.8 years % Male: 76.7 Initial rhythm: Any	Normothermia (TTM at ≥35.5°C) (n = 116) Hypothermia (TTM at <35.5°C) (n = 628) Cooling methods of TTM: External conventional cooling, external device cooling, intra-cavity cooling, unknown)	Primary outcome: • Survival to hospital discharge Secondary outcome: • Good neurological status (defined as a CPC[a] of 1 or 2) Follow-up: NA
Eilam et al. (2017)[17] **Israel** Funding: NR	Retrospective cohort study Sample size calculation provided: No Adjustment for confounders conducted: Yes	Comatose adult patients post-CPR hospitalized in the ICU Mean age: 56.3 years % Male: 53.4 Initial rhythm: Any	Normothermia (temperature not specified) (n = 62) Targeted hypothermia (32°C to 34°C maintained for 24 hours in the ICU) (n = 26)	Outcomes: • Seizures (defined as generalized tonic-clonic, myoclonic, or partial seizures) • In-hospital death/survival Follow-up: NA

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Pang et al. (2017)[18] **Singapore** Funding: Sing Health Foundation	Retrospective cohort study Sample size calculation provided: No Adjustment for confounders conducted: No	Adult patients received CPR for refractory cardiac arrest and being treated with ECLS Mean age: 49.9 years % Male: 78.5 % In-hospital cardiac arrest: 92.4 Mean duration of CPR: 32.0 minutes Mean duration of ECLS: 5.4 days Initial rhythm: VT/VF, PEA, asystole	Normothermia (temperature not specified) (n = 65) Targeted hypothermia (34°C maintained for 24 hours in the ICU) (n = 14) Cooling to 34°C was performed by modulating the heat exchanger component of the ECLS circuit.	Outcomes: • Survival with good neurological recovery (CPC[a] of 1 or 2) • Overall survival to discharge • Hospital length of stay • AEs (ECLS-related complications) Follow-up: 60 days
Casamento et al. (2016)[19] **Australia, New Zealand** Funding: NR	Retrospective cohort study Sample size calculation provided: Yes Adjustment for confounders conducted: Yes	Adult patients with cardiac arrest admitted to ICU Mean age: 62.5 years % Male: 78.3 Mean time to ROSC: 21 minutes Initial cardiac rhythm: EMD, VT/VF, asystole	Strict therapeutic normothermia (36°C for 28 hours) (n = 69) Therapeutic hypothermia (32 to 34°C for 24 hours) Cooling methods were performed using external cooling devices.	Primary outcome: • % Time spent in temperature target range Secondary outcomes: • Medication prescription • ICU/hospital length of stay • ICU/hospital mortality • Survival to discharge • AEs (complications)

AE = adverse events; CPC = cerebral performance category; CPR = cardiopulmonary resuscitation; ICU = intensive care unit; ECLS = extracorporeal life support; EMD = electromechanical dissociation; NA = not applicable; NR = not reported; OHCA = out-of-hospital cardiac arrest; PEA = pulseless electrical activity; QoL = quality of life; RCT = randomized controlled trial; ROSC = return of spontaneous circulation; VF = ventricular fibrillation; VT = ventricular tachycardia.

Note: This table has not been copy-edited.

[a]CPC is a 5-category scale for measuring neurological status after cardiac arrest ranging from 1 (conscious, alert, able to work and lead a normal life) to 5 (brain dead, circulation preserved).

[b]The modified Rankin Scale is commonly used to measure the degree of disability of people who have suffered a stroke or other causes or neurological disability. It is a scale runs from 0 to 6, with 0 for no symptoms and 6 for dead.

Table 4: Characteristics of Included Guidelines

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
SRLF/SFAR, Cariou et al. (2018)[21]						
Intended users: Clinicians who provide neurological care to critically ill patients. **Target population: Adult and pediatric patients with cardiac arrest, traumatic brain injury, stroke, other brain injuries, and shock.**	TTM in the ICU as a primary neuroprotective method.	Survival with good neurological outcome.	Methods for collection, selection and synthesis of evidence were not reported.	The quality of evidence was rated as high, moderate, low, and very low.[a] The strength of recommendation was either positive or negative, and strong or weak.[b]	Recommendations were developed by a group of experts for the SRLF and the SFAR. The committee defined a list of questions and assigned designated experts to address each questions. The recommendations were developed using the GRADE method. The strength of recommendation was determined and validated by the experts through a vote, using the Delphi and GRADE Grid method.	The guideline was reviewed by internal and external experts and published in peer-reviewed journal.
AAN, Geocadin et al. (2017)[22]						
Intended Users: Clinicians who provide care for patients with nontraumatic cardiac arrest. **Target Population: Adult patients who are comatose after successful CPR after cardiac arrest.**	TTM for neuroprotective interventions in adult patients who are comatose after successful CPR. Therapeutic hypothermia is defined as cooling to a core body temperature of 32°C to 34°C.	Survival with good neurological outcome	A comprehensive literature search was taken. Evidence was reviewed by the committee members.	The level of evidence was classified as Class I, II, III or IV.[c] The strength of the recommendations was classified as A, B, C, or U[d].	The committee members reviewed the articles and classified the level of evidence using the AAN classification scheme for therapeutic articles. Recommendations were formulated and linked to the strength of the evidence.	The guideline was reviewed by AAN committees and published in peer-reviewed journal.

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
CCS/CCCCS/CAIC, Wong et al. (2017)[2]						
Intended Users: Clinicians who provide in-hospital care for OHCA patients. **Target Population: OHCA patients.**	TTM for in-hospital care of OHCA patients. TTM was defined as a strategy of intentional temperature management of a postarrest patient comprising active patient cooling, subsequent rewarming, and extended fever control.	Survival with good neurological outcome.	A comprehensive literature search was taken. Evidence was reviewed by the committee.	GRADE methodology was used to assess the quality of evidence[a] The strength of recommendations was either "Strong" (desirable effects clearly outweigh undesirable effects or clearly do not) or "Conditional" (when trade-offs are less certain, either because of low-quality evidence or because the evidence suggests that desirable and undesirable effects are closely balanced).	The Writing Panel composed of cardiologists and critical care specialists developed a set of clinical questions. The members review the evidence and formulate the recommendations with the help of GRADE. Final recommendations were made by majority vote based on the quality of the available evidence.	The guideline was reviewed by internal and external experts and published in peer-reviewed journal.

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
CCCS/CNCCS/CCCTG, Howes et al. (2016)[23]						
Intended Users: Clinicians who provide care for patients with cardiac arrest. **Target Population: Adult patients with cardiac arrest.**	TTM use after cardiac arrest in adult patients.	Survival with good neurological outcome.	A comprehensive literature search was taken.	The level of evidence for a recommendation was graded as high, moderate, or low.[a] The "low" and "very low" designations were combined to a single "low" category. The strength of recommendation was defined as "Strong" or "Conditional," based on consideration of the quality of evidence, balance between benefits and risks, feasibility, and cost.[e]	A committee composed of experts in neurocritical care created a set of clinical questions. Each section lead coordinated the work with its team to search, extract and grade the literature, and formulate the draft recommendations. The final recommendations were made using a combination of Delphi methodology and nominal group technique.	The guideline was reviewed by internal and external experts and published in peer-reviewed journal.

AAN = American Academy of Neurology; CPR = cardiopulmonary resuscitation; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; ICU = intensive care unit; NCS = Neurological Care Society; OHCA = out-of-hospital cardiac arrest; SFAR = Société française d'anesthésie et de réanimation; SRLF = Société de réanimation de langue française; TTM = targeted temperature management.

Note: This table has not been copy-edited.

[a]Level of evidence: High = Further research is very unlikely to change the confidence in the estimate of the effect; Moderate = Further research is likely to have an impact on the confidence in the estimate of the effect and may change the estimate of the effect itself; Low = Further research is likely to have an impact on the confidence in the estimate of the effect and is likely to change the estimate of the effect itself; Very low = Any estimate of the effect is very unlikely.

[b]Strength of recommendation: Strong = We recommend (GRADE 1+) or we do not recommend (GRADE 1-); Weak = We suggest (GRADE 2+) or we do not suggest (GRADE 2-).

[c]Level of evidence: Class I = A randomized, controlled clinical trial of the intervention of interest with good methodology and masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. Class II = A randomized, controlled clinical trial of the intervention of interest in a representative population with moderate quality and with masked or objective outcome assessment, relevant baseline characteristics are presented and substantially equivalent among treatment groups, or there is appropriate statistical adjustment for differences. Class III = All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement. Class IV = Studies not meeting Class I, II, or III criteria, including consensus or expert opinion.

[d]Strength of recommendation: A = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least 2 consistent Class I studies.) B = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or 2 consistent Class II studies.) C = Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or 2 consistent Class III studies.) U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven. *In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome > 5 and the lower limit of the confidence interval is > 2).

[e]Strength of recommendation: Strong = The panel is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects; Conditional = The panel concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects but is not confident.

Appendix 3: Critical Appraisal of Included Publications

Note that this appendix has not been copy-edited.

Table 5: Strengths and Limitations of Systematic Reviews and Network Meta-Analysis Using AMSTAR 2[7] and the ISPOR Questionnaire[8]

Strengths	Limitations
Fernando et al. (2021)[5]	
• Research questions and inclusion criteria for the • review included the components of population, • intervention, comparison, and outcomes. • A published protocol was established prior to the conduct of the review. The Open Science Framework registration was provided in the report. • The review authors explained their selection of RCTs for inclusion in the review. • Study selection and data extraction were performed in duplicate by 2 reviewers. • Included studies were described in adequate detail. • The authors used a satisfactory technique, a modified Cochrane Collaboration tool (Guyatt and Busse), for assessing the risk of bias of included individual studies. • The authors initially performed pairwise MA using random-effects model. The statistical heterogeneity among trials were assessed using visual inspection of forest plots, I^2 statistics, and the Chi-squared test. • The authors evaluated the feasibility of conducting NMA by checking the availability of evidence, transitivity assumption, connectivity, and coherence in network. • The authors performed frequentist random-effects NMA using multivariate meta-analysis. • The relative effect estimates were described as odds ratios with 95% CI. • The presence of incoherence between direct and indirect estimates of the effect was assessed using the node splitting method. • The certainty of evidence for each comparison was assessed using the GRADE approach, which addresses the risk of bias, imprecision, inconsistency, indirectness, intransitivity, publication bias, and incoherence. • Satisfactory explanation and discussion were provided for heterogeneity observed in the results of the review.	• It was unclear whether content experts were consulted or trial registries were searched during the review process. • A list of excluded studies was not published; therefore, reasons for exclusion cannot be verified. • Sources of funding for the included studies were not reported. • The researchers attempted to include all relevant RCTs based on a comprehensive search of multiple databases but did not specify whether the grey literature search included trial registries and conference proceedings. • Although the authors performed frequentist random-effects NMA using multivariate meta-analysis assuming a common heterogeneity parameter, there were substantial clinical heterogeneity across trials in terms of study characteristics (e.g., initial rhythm, etiology of arrest, time to cooling, duration of cooling). • The authors provided no justification of why the analyses were performed with a frequentist instead of a Bayesian approach. • The authors did not provide raw data by study and treatment as used in the analysis or model. • The authors did not perform subgroup analysis or meta-regression due to insufficient data. • No sensitivity analyses were performed in the description of the findings.

Strengths	Limitations
• The authors presented direct estimates, indirect estimates, and network estimates with 95% CI. • The authors provided a clear summary of main findings. • The authors discussed the strengths and limitations at study and outcome level. Internal validity and external validity were discussed. • The authors provided a general interpretation of the results in the context of other evidence, and implications for future research, and considered the relevance of the findings to heath care providers, patients, and clinical practice guidelines. • Potential sources of conflict of interest and funding were disclosed.	
Granfeldt et al. (2021)[12]	
• Research questions and inclusion criteria for the • review included the components of population, • intervention, comparison, and outcomes. • A published protocol was established prior to the conduct of the review. The PROSPERO registration number was provided in the report. • Study selection and data extraction were performed in duplicate by 2 reviewers. • Included studies were described in adequate detail. • The review authors used a satisfactory technique, the Cochrane Risk of Bias Assessment Tool, for assessing the risk of bias of included individual studies. • The authors conducted DerSimonian and Laird random-effects MA with the Mantel-Haenszel method. • The authors justified combining the data in an MA, and statistical heterogeneity was assessed using • forest plots, Chi-squared statistics, and I^2 statistics. Discussion and explanation of heterogeneity observed in the results of the review were reported. • The certainty of evidence for each comparison was assessed using the GRADE approach. • The review authors assessed the potential impact of risk of bias in individual studies on the results of the MA and accounted for it when discussing results. • Satisfactory explanation and discussion were provided for heterogeneity observed in the results of the review. • The review authors performed graphical and statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias. • **Potential sources of conflict of interest and funding were disclosed.**	• The review authors did not explain their selection of randomized and non-randomized controlled trials for inclusion in the review. • It was unclear whether content experts were consulted during the review process. • A list of excluded studies was not published. • Sources of funding for the included studies were not reported.

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2; CI = confidence interval; GRADE = Grading of Recommendations, Assessment, Development and Evaluations; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; MA = meta-analysis; NMA = network meta-analysis; NR = not reported; RCT = randomized controlled trial.

Table 6: Strengths and Limitations of Clinical Studies Using the Downs and Black Checklist[9]

Strengths	Limitations
Randomized controlled trial	
Pang et al. (2016)[13]	
Reporting: • Clearly described: objective, primary and secondary outcomes in the Methods section, inclusion/exclusion criteria, demographics, and baseline clinical data of included patients, interventions, confounders, main findings, IQR for main outcomes, adverse events • Actual P values were reported. **Internal validity (bias, confounding):** • No evidence of data dredging was apparent. • Statistical tests were used appropriately, and the main outcome measures were accurate and reliable. • **Participants in different groups were recruited from the same site and over the same period of time.**	**Reporting:** • Unclear/missing follow-up data for 1 patient in normothermia group **External validity:** • Non-Canadian sample (Singapore) • Participants were treated at a tertiary referral centre, which may not be representative of most hospitals. **Internal validity (bias, confounding):** • This was a non-blinded, parallel-group RCT in which investigators and patients were aware of the treatment. This may have resulted in high risk of bias. **Power:** • Power calculations were not provided. • Sample size was noted as a limitation of the study.
Non-randomized studies	
Duggelin et al. (2021)[14]	
Reporting: • Clearly described: aim, hypotheses, main outcomes in the Methods section, inclusion/exclusion criteria, patient characteristics, interventions of interest, confounders, main findings, SD for main outcomes, adverse events • Patients with missing data were excluded. • Actual P values and effect sizes were reported. **Internal validity (bias, confounding):** • No evidence of data dredging was apparent. • Statistical tests were used appropriately, and the main outcome measures were accurate and reliable. • Survival analysis for the protocol adherence outcome was conducted using the Cox proportional hazards model. • **Participants in different groups were recruited from the same site and over the same time periods.**	**Reporting: c**haracteristics of patients lost to follow-up NR **External validity:** • Non-Canadian centre • The study was conducted in a single hospital. • It is unclear whether participants are representative of the cardiac arrest patient population in Switzerland. **Internal validity (bias, confounding):** • This was a retrospective cohort study in which investigators and patients may have aware been of the treatment. This may have resulted in high risk of bias. • As this was a retrospective study relying on historical patient data, compliance with the intervention is uncertain. However, missing application of strict TTM was an exclusion criterion. **Power:** • Power calculations were not provided. • Sample size in the hypothermia group was noted as a limitation of the study.

Strengths	Limitations
Kocayigit et al. (2021)[15]	
Reporting: • Clearly described: aim, primary and secondary outcomes in the Methods section, inclusion/exclusion criteria, baseline characteristics, interventions, confounders, main findings, IQR and SD for main outcomes • Patients with missing data were excluded. • Actual P values were reported. **Internal validity (bias, confounding):** • No evidence of data dredging was apparent. • Statistical tests were used appropriately. • **Participants in different groups were recruited from the same site and over the same period of time.**	**Reporting:** • Unclear timepoints for survival and good neurologic results outcomes • Adverse events NR **External validity:** • Non-Canadian centre • The study was conducted in a single hospital. • It is unclear whether participants are representative of the cardiac arrest patient population in Turkey. **Internal validity (bias, confounding):** • Unclear follow-up periods for survival and good neurologic results outcomes • This was a retrospective cohort study in which investigators and patients may have been aware of the treatment. This may have resulted in high risk of bias. • Significant differences in APACHE score and number of patients with witnessed arrest between the groups at baseline were reported, but no adjustments were conducted for these confounders. • As this was a retrospective study relying on historical patient data, compliance with the intervention is uncertain. **Power:** power calculations were not provided, but sample size was not noted as a limitation of the study.
Spoormans et al. (2021)[20]	
Reporting: • Clearly described: objective, primary and secondary outcomes in the Methods section, inclusion/exclusion criteria, patient demographics, interventions, confounders, main findings, percentages for main categorical outcomes • Actual P values and effect sizes were reported. External validity: observational post hoc analysis of COACT trial conducted in 19 hospitals in the Netherlands **Internal validity (bias, confounding):** • No evidence of data dredging was apparent. • Follow-up periods were the same across groups. • Statistical tests were used appropriately, and the main outcome measures were accurate and reliable. • Patients were randomized to study assignment. • Participants in different groups were recruited from the same population and over the same period of time. • **Logistic regression accounted for confounders (witnessed arrest, time to ROSC, academic/non-academic centre, ECMO/non-ECMO centre, ICU capacity, patient characteristics).**	**Reporting:** • Unclear reporting of important adverse events • Authors did not describe the characteristics of >50% patients lost to follow-up for the 1-year quality of life outcome. **External validity:** non-Canadian sample **Internal validity (bias, confounding):** • This was a substudy of a larger open-label trial in which investigators and patients were aware of the treatment. This may have resulted in high risk of bias. **Power:** This was a substudy of a larger trial, and therefore sample size calculations were not performed.

Strengths	Limitations
Kim et al. (2020)[16]	
Reporting: • Clearly described: aim, hypothesis, primary and secondary outcomes in the Methods section, inclusion/exclusion criteria, patient demographics, interventions, confounders, main findings, effect sizes for main categorical outcomes • Patients with missing data were excluded. • Actual P values and effect sizes were reported. External validity: • Patient data were collected from the national OHCA database operated by the Korea Centers for Disease Control & Prevention. Internal validity (bias, confounding): • No evidence of data dredging was apparent. • Statistical tests were used appropriately, and the main outcome measures were accurate and reliable. • Participants in different groups were recruited from the same population and over the same period of time. • Main outcomes were adjusted for confounders (age, sex, diabetes, hypertension, place of arrest, witness status, bystander cardiopulmonary resuscitation, initial shockable rhythm, response time, level of emergency department, reperfusion therapy, interaction term).	**Reporting:** adverse events NR **External validity:** non-Canadian sample **Internal validity (bias, confounding):** • This was a retrospective cohort study, in which investigators and patients may have been aware of the treatment. This may have resulted in high risk of bias. • As this was a retrospective study relying on historical patient data, compliance with the intervention is uncertain. However, the OCHA database is monitored regularly by quality management committees. • Specific TTM protocol may differ among sites. **Power:** power calculations were not provided, but sample size was not noted as a limitation of the study.

Strengths	Limitations
Eilam et al. (2017)[17]	
Reporting: • Clearly described: objective, main outcomes in the Introduction section, inclusion/exclusion criteria, patient characteristics, interventions, confounders, main findings, percentages for main categorical outcomes, one adverse event (seizures) • Actual P values were reported. **Internal validity (bias, confounding):** • No evidence of data dredging was apparent. • Statistical tests were used appropriately, and the main outcome measures were accurate and reliable. • Participants in different groups were recruited at the same site and over the same period of time. • **Logistic regression accounted for confounders (age, gender).**	**Reporting:** • Temperature range for normothermia comparator group NR • Adverse events (other than seizures) NR **External validity:** • Non-Canadian centre • The study was conducted in a single urban, academic medical centre. • It is unclear whether participants are representative of the cardiac arrest patient population in Israel. **Internal validity (bias, confounding):** • Most baseline characteristics were not reported separately for each group. • This was a retrospective cohort study, in which investigators and patients may have been aware of the treatment. This may have resulted in high risk of bias. • Patients were not randomized to study assignment. • As this was a retrospective study relying on historical patient data, compliance with the intervention is uncertain. **Power:** • Power calculations were not provided. • Sample size was noted as a limitation of the study.

Strengths	Limitations
Pang et al. (2017)[18]	
Reporting: • Clearly described: objective, inclusion/exclusion criteria, patient characteristics, confounders, main findings, IQR and SD for main outcomes, adverse events, characteristics of patients lost to follow-up • Actual P values and effect sizes were reported. **Internal validity (bias, confounding):** • No evidence of data dredging was apparent. • Statistical tests were used appropriately, and the main outcome measures were accurate and reliable. • **Participants in different groups were recruited at the same site and over the same period of time.**	**Reporting:** • Temperature range for normothermia comparator group NR • Main outcomes were not clearly reported in the Introduction or Methods section. **External validity:** • Non-Canadian centre (Singapore) • Included patients were treated at a tertiary referral centre, which may not be representative of most hospitals. **Internal validity (bias, confounding):** • This was a retrospective cohort study, in which investigators and patients may have aware of the treatment. This may have resulted in high risk of bias. • As this was a retrospective study relying on historical patient data, compliance with the intervention is uncertain. • Significant differences in cardiac arrest location and left ventricular ejection fraction between groups at baseline were reported, but no adjustments were conducted for these confounders. **Power:** • Power calculations were not provided. • Sample size in the hypothermia group was noted as a limitation of the study.
Casamento et al. (2016)[19]	
Reporting: • Clearly described: aim, primary and secondary outcomes in the Methods section, inclusion/exclusion criteria, baseline characteristics, interventions. principal confounders, main findings, IQR for main outcomes, adverse events • Actual P values were reported. External validity: Multi-centre, international (Australia and New Zealand) retrospective review **Internal validity (bias, confounding):** • No evidence of data dredging was apparent. • Statistical tests were used appropriately, and the main outcome measures were accurate and reliable. • Participants in different groups were recruited at the same sites and over the same time periods. • Regression analysis adjusted for confounders (age, adjusted APACHE III score, time to ROSC, shockable [versus non-shockable] rhythm). **Power:** power calculations provided	**Reporting:** • Authors acknowledged that some data points pertaining to the primary outcome were missing but did not describe characteristics of those patients. **External validity:** • Non-Canadian sample • Included patients were treated at tertiary university-affiliated hospitals, which may not be representative of most hospitals. **Internal validity (bias, confounding):** • This was a retrospective cohort study, in which investigators and patients may have been aware of the treatment. This may have resulted in high risk of bias. • As this was a retrospective study relying on historical patient data, compliance with the intervention is uncertain.

APACHE = Acute Physiologic Assessment and Chronic Health Evaluation; COACT = Coronary Angiography after Cardiac Arrest; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; IQR = interquartile range; NR = not reported; OCHA = out-of-hospital cardiac arrest; ROSC = return of spontaneous circulation; SD = standard deviation.

Table 7: Strengths and Limitations of Guidelines Using AGREE II[10]

Item	SRLF/SFAR, Cariou et al. (2018)[21]	AAN, Geocadin et al. (2017)[22]	CCS/CCCCS/CAIC, Wong et al. (2017)[2]	CCCS/CNCCS/CCCTG, Howes et al. (2016)[23]
Domain 1: Scope and purpose				
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	Yes	Yes	Yes
3. The population (e.g., patients, public) to whom the guideline is meant to apply is specifically described.	Yes	Yes	Yes	Yes
Domain 2: Stakeholder involvement				
4. The guideline development group includes individuals from all relevant professional groups.	Yes	Yes	Yes	Yes
5. The views and preferences of the target population (e.g., patients, public) have been sought.	Unclear	Unclear	Unclear	Unclear
6. The target users of the guideline are clearly defined.	Yes	Yes	Yes	Yes
Domain 3: Rigour of development				
7. Systematic methods were used to search for evidence.	Only a comprehensive search reported	Only a comprehensive search reported	Only a comprehensive search reported	Only a comprehensive search reported
8. The criteria for selecting the evidence are clearly described.	Yes	Yes	Yes	Yes
9. The strengths and limitations of the body of evidence are clearly described.	Yes	Yes	Yes	Yes
10. The methods for formulating the recommendations are clearly described.	Yes	Yes	Yes	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes	Yes	Yes	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	Yes	Yes	Yes	Yes
13. The guideline has been externally reviewed by experts prior to its publication.	Yes	Yes	Yes	Yes

Item	SRLF/SFAR, Cariou et al. (2018)[21]	AAN, Geocadin et al. (2017)[22]	CCS/CCCCS/CAIC, Wong et al. (2017)[2]	CCCS/CNCCS/CCCTG, Howes et al. (2016)[23]
14. A procedure for updating the guideline is provided.	Unclear	Unclear	Unclear	Unclear
Domain 4: Clarity of presentation				
15. The recommendations are specific and unambiguous.	Yes	Yes	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes	Yes	Yes	Yes
17. Key recommendations are easily identifiable.	Yes	Yes	Yes	Yes
Domain 5: Applicability				
18. The guideline describes facilitators and barriers to its application.	Yes	Yes	Yes	Yes
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Unclear	Unclear	Unclear	Unclear
20. The potential resource implications of applying the recommendations have been considered.	Unclear	Unclear	Yes	Unclear
21. The guideline presents monitoring and/or auditing criteria.	Unclear	Unclear	Unclear	Unclear
Domain 6: Editorial independence				
22. The views of the funding body have not influenced the content of the guideline.	Yes	Yes	Yes	Yes
23. Competing interests of guideline development group members have been recorded and addressed.	Yes	Yes	Yes	Yes

AGREE II = Appraisal of Guidelines for Research and Evaluation II.

Appendix 4: Main Study Findings and Authors' Conclusions

Note that this appendix has not been copy-edited.

Table 8: Summary of Findings by Outcomes for Survival

Study citation, study design, and patient model	Study findings
Survival with good neurological outcome	
Fernando et al. (2021)[5] SR (10 RCTs included in NMA) Adult patients with OHCA who remained unresponsive following ROSC	NMA estimate (OR [95% CI]) compared hypothermia with normothermia (i.e., 37°C to 37.8°C): Survival with good functional outcome at hospital discharge, or the latest time point reported up until 6 months post-discharge: • Deep hypothermia (i.e., 31°C to 32°C): 1.30 (0.73 to 2.30) • Moderate hypothermia (i.e., 33°C to 34°C): 1.34 (0.92 to 1.94) • Mild hypothermia (i.e., 35°C to 36°C): 1.44 (0.74 to 2.80)
Granfeldt et al. (2021)[12] SR (9 RCTs included in MA) Adult patients with cardiac arrest in any setting (in-hospital or out-of-hospital) underwent TTM	MA estimate (RR [95% CI]) compared hypothermia (i.e., 32°C to 34°C) with normothermia (e.g., no TTM, no clear description of TTM, or TTM to maintain normothermia [generally 36.5°C to 38°C]): • Survival with favourable neurological outcome at hospital discharge or 30 days: 1.30 (0.83 to 2.03) • Survival with favourable neurological outcome at 90 or 180 days: 1.21 (0.91 to 1.61)
Pang et al. (2016)[13] RCT Adult patients receiving ECLS for cardiac arrest	Survival rate to hospital discharge with good neurological function in hypothermia (TTM 34°C) versus in normothermia (37°C) groups: • 22.2% versus 8.3%; P = 0.368
Pang et al. (2017)[18] Retrospective cohort study Adult patients received CPR for refractory cardiac arrest and being treated with ECLS	Survival rate with good neurological recovery (i.e., CPC of 1 or 2) in hypothermia (TTM 34°C) versus normothermia (temperature not specified) groups: • 42.9% versus 15.4%; P = 0.020
Overall survival	
Fernando et al. (2021)[5] SR (10 RCTs included in NMA) Adult patients with OHCA who remained unresponsive following ROSC	NMA estimate (OR [95% CI]) compared with normothermia (37°C to 37.8°C): Overall survival (i.e., survival at hospital discharge, or the latest time point reported up until 6 months post-discharge): • Deep hypothermia (31°C to 32°C): 1.27 (0.70 to 2.32) • Moderate hypothermia (33°C to 34°C): 1.23 (0.86 to 1.77) • Mild hypothermia (35°C to 36°C): 1.26 (0.64 to 2.49)
Granfeldt et al. (2021)[12] SR (9 RCTs included in MA) Adult patients with cardiac arrest in any setting (in-hospital or out-of-hospital) underwent TTM	MA estimate (RR [95% CI]) compared hypothermia (i.e., 32 to 34°C) with normothermia (e.g., no TTM, no clear description of TTM, or TTM to maintain normothermia [generally 36.5°C to 38°C]): • Survival to hospital discharge or 30 days: 1.12 (0.92 to 1.35) • Survival at 90 or 180 days: 1.08 (0.89 to 1.30)

Study citation, study design, and patient model	Study findings
Pang et al. (2016)[13] RCT Adult patients receiving ECLS for cardiac arrest	Survival rate until 6 months in hypothermia (TTM 34°C) versus normothermia (37°C) groups: • 33.3% versus 18.2%; P = 0.436
Kocayigit et al. (2021)[15] Retrospective cohort study Adult patients hospitalized in the ICU for cardiac arrest due to myocardial infarction receiving TTM	Survival rate in hypothermia (TTM at 33°C to 35°C) versus normothermia (non-TTM; temperature not specified) groups: • 51.9% versus 35.5%; P = 0.209
Spoormans et al. (2021)[20] Observational post hoc analysis of an RCT Adult patients successfully resuscitated after OHCA with an initial shockable rhythm	Survival in hypothermia (TTM at 32°C to 34°C) versus normothermia (TTM at 36°C to 37°C) groups: • Until 90 days: HR (95% CI) = 0.86 (0.62 to 1.18); P = 0.35 • Until 1 year: HR (95% CI) = 0.81 (0.59 to 1.11); P = 0.18
Kim et al. (2020)[16] Retrospective cohort study OHCA patients who were hospitalized and underwent TTM	Survival to hospital discharge in hypothermia (TTM at <35.5°C) versus normothermia (TTM at ≥35.5°C) groups: • 57.2% versus 62.9%; P = 0.248 • Adjusted OR (95% CI) = 0.85 (0.53 to 1.37)
Eilam et al. (2017)[17] Retrospective cohort study Comatose adult patients post-CPR hospitalized in the ICU	Survival rate in hypothermia (TTM 32°C to 34°C) versus Normothermia (temperature not specified): • 39% versus 40%; P = 0.52
Pang et al. (2017)[18] Retrospective cohort study Adult patients received CPR for refractory cardiac arrest and being treated with ECLS	Survival rate to discharge in hypothermia (TTM 34°C) versus normothermia (temperature not specified) groups: • 50.0% versus 21.5%; P = 0.029
Casamento et al. (2016)[19] Retrospective cohort study Adult patients with cardiac arrest admitted to ICU	Survival rate to discharge in hypothermia (TTM 32°C to 34°C) versus normothermia (TTM 36°C) groups: • 52.5% versus 77.8%; P = 0.02

CI = confidence interval; ECLS = extracorporeal life support; HR = hazard ratio; ICU = intensive care unit; MA = meta-analysis; NMA = network meta-analysis; OHCA = out-of-hospital cardiac arrest; OR = odds ratio; RCT = randomized controlled trial; ROSC = return of spontaneous circulation; RR = risk ratio; SR = systematic review; TTM = targeted temperature management.

Table 9: Summary of Findings by Outcomes for Mortality

Study citation, study design, and patient model	Study findings
ICU/In-hospital death	
Pang et al. (2016)[13] RCT Adult patients receiving ECLS for cardiac arrest	Hospital mortality rate in hypothermia (TTM 34°C) versus normothermia (37°C) groups: • 66.7% versus 75.0%; P = 0.676

Study citation, study design, and patient model	Study findings
Duggelin et al. (2021)[14] Retrospective cohort study Adult patients successfully resuscitated after out-of-hospital or in-hospital cardiac arrest	Hospital mortality rate in hypothermia (TTM 33°C) versus normothermia (TTM 36°C) groups: • 59% versus 45%; P = 0.15 ICU mortality rate in hypothermia (TTM 33°C) versus normothermia (TTM 36°C) groups: • 41% versus 34%; P = 0.58
Kocayigit et al. (2021)[15] Retrospective cohort study Adult patients hospitalized in the ICU for cardiac arrest due to myocardial infarction receiving TTM	30-day mortality rate in hypothermia (TTM at 33°C to 35°C) versus normothermia (non-TTM; temperature not specified) groups: • 44.4% versus 41.9%; P = 0.847
Eilam et al. (2017)[17] Retrospective cohort study Comatose adult patients post-CPR hospitalized in the ICU	Hospital mortality rate in hypothermia (TTM 32°C to 34°C) versus Normothermia (temperature not specified): • 61% versus 60%; P > 0.05
Casamento et al. (2016)[19] Retrospective cohort study Adult patients with cardiac arrest admitted to ICU	ICU mortality rate in hypothermia (TTM 32°C to 34°C) versus normothermia (TTM 36°C) groups: • 36.2% versus 40.6%; P = 0.60 Hospital mortality rate in hypothermia (TTM 32°C to 34°C) versus normothermia (TTM 36°C) groups: • 42.0% versus 47.8%; P = 0.49

CPR = cardiopulmonary resuscitation; ECLS = extracorporeal life support; ICU = intensive care unit; RCT = randomized controlled trial; TTM = targeted temperature management.

Table 10: Summary of Findings by Outcomes for ICU and Hospital Length of Stay

Study citation, study design, and patient model	Study findings
Pang et al. (2016)[13] RCT Adult patients receiving ECLS for cardiac arrest	Median (range) length of hospital stay in hypothermia (TTM 34°C) versus normothermia (37°C) groups: • 6 (2, 23) days versus 7 (2, 22) days; P = 0.772
Duggelin et al. (2021)[14] Retrospective cohort study Adult patients successfully resuscitated after out-of-hospital or in-hospital cardiac arrest	Mean (SD) of ICU length of stay in hypothermia (TTM 33°C) versus normothermia (TTM 36°C) groups: • 7.9 (7.1) days versus 8.4 (8.5) days; P = 0.70 Mean (SD) of hospital length of stay in hypothermia (TTM 33°C) versus normothermia (TTM 36°C) groups: • 13.4 (12.5) days versus 15.5 (13.7) days; P = 0.42
Kocayigit et al. (2021)[15] Retrospective cohort study Adult patients hospitalized in the ICU for cardiac arrest due to myocardial infarction receiving TTM	Median (range) length of hospital stay in hypothermia (TTM at 33°C to 35°C) versus normothermia (non-TTM; temperature not specified) groups: • 17 (4, 29) days versus 39 (10, 69) days; P = 0.074 Hospital stay before discharge (SD) in hypothermia (TTM at 33°C to 35°C) versus normothermia (non-TTM; temperature not specified) groups: • 43.1 (35.5) days versus 87.2 (33.1) days; P = 0.004

Study citation, study design, and patient model	Study findings
Pang et al. (2017)[18] Retrospective cohort study Adult patients received CPR for refractory cardiac arrest and being treated with ECLS	Median (range) length of hospital stay in hypothermia (TTM 34°C) versus normothermia (temperature not specified) groups: • 11.0 (2.8, 30.8) days versus 7.0 (2.0, 21.0) days; P = 0.487
Casamento et al. (2016)[19] Retrospective cohort study Adult patients with cardiac arrest admitted to ICU	Median (range) of ICU length of stay in hypothermia (TTM 32°C to 34°C) versus normothermia (TTM 36°C) groups: • 5 (4, 7) days versus 4 (3, 6) days; P = 0.11 Median (range) of hospital length of stay in hypothermia (TTM 32°C to 34°C) versus normothermia (TTM 36°C) groups: • 15 (9, 25) days versus 12 (8, 16) days; P = 0.26

ECLS = extracorporeal life support; ICU = intensive care unit; SD = standard deviation; RCT = randomized controlled trial; TTM = targeted temperature management.

Table 11: Summary of Findings by Outcomes for Neurological Status

Study citation, study design, and patient model	Study findings
Pang et al. (2016)[13] RCT Adult patients receiving ECLS for cardiac arrest	Severe neurological dysfunction (CPC 3 to 5) rate in hypothermia (TTM 34°C) versus normothermia (37°C) groups: • 66.7% versus 58.3%; P = 0.697
Duggelin et al. (2021)[14] Retrospective cohort study Adult patients successfully resuscitated after out-of-hospital or in-hospital cardiac arrest	Proportion of patients with modified Rankin Score < 4 in hypothermia (TTM 33°C) versus normothermia (TTM 36°C) groups: • 91% versus 96%; P = 0.88 Proportion of patients with CPC < 3 in hypothermia (TTM 33°C) versus normothermia (TTM 36°C) groups: • 35% versus 45%; P = 0.34
Kocayigit et al. (2021)[15] Retrospective cohort study Adult patients hospitalized in the ICU for cardiac arrest due to myocardial infarction receiving TTM	Proportion of patients with good neurologic results (i.e., CPC 1 or 2) in hypothermia (TTM at 33°C to 35°C) versus normothermia (non-TTM; temperature not specified) groups: • 40.7% versus 6.5%; P = 0.002
Spoormans et al. (2021)[20] Observational post hoc analysis of an RCT Adult patients successfully resuscitated after OHCA with an initial shockable rhythm	Patients with good neurological function at 90-day follow-up in hypothermia (TTM at 32°C to 34°C) versus normothermia (TTM at 36°C to 37°C) groups: • Adjusted OR (95% CI) = 0.80 (0.41 to 1.55); P = 0.50 CPC scores did not significantly differ between hypothermia (TTM at 32 to 34°C) versus normothermia (TTM at 36 to 37°C) groups: • At ICU discharge (P = 0.053) • At 90-day follow-up (P = 0.26)
Kim et al. (2020)[16] Retrospective cohort study OHCA patients who were hospitalized and underwent TTM	Good neurological status (i.e., a CPC score of 1 or 2) in hypothermia (TTM at <35.5°C) versus normothermia (TTM at ≥35.5°C) groups: • 32.6% versus 38.8%; P = 0.198 • Adjusted OR (95% CI) = 0.83 (0.50 to 1.40)

CPC = cerebral performance category; ECLS = extracorporeal life support; ICU = intensive care unit; OR = odds ratio; RCT = randomized controlled trial; TTM = targeted temperature management.

Table 12: Summary of Findings by Outcomes for Protocol Adherence

Study citation, study design, and patient model	Study findings
Duggelin et al. (2021)[14] Retrospective cohort study Adult patients successfully resuscitated after out-of-hospital or in-hospital cardiac arrest	Proportion of patients adherent to the protocol at 24 hours in hypothermia (TTM 33°C) versus normothermia (TTM 36°C) groups: • 30% versus 83%; P < 0.0001

TTM = targeted temperature management.

Table 13: Summary of Findings by Outcomes for Quality of Life

Study citation, study design, and patient model	Study findings
Spoormans et al. (2021)[20] Observational post hoc analysis of an RCT Adult patients successfully resuscitated after OHCA with an initial shockable rhythm	Quality of life at 1-year follow-up (using SF-36-Item Health Survey) in hypothermia (TTM at 32°C to 34°C) versus normothermia (TTM at 36°C to 37°C) groups: • Physical component: RR (95% CI) = 0.97 (0.91 to 1.04) • Mental component : RR (955 CI) = 0.99 (0.93 to 1.06)

CI = confidence interval; OHCA = out-of-hospital cardiac arrest; RCT = randomized controlled trial; RR = risk ratio; TTM = targeted temperature management.

Table 14: Summary of Findings by Outcomes for Time Spent in Temperature Target Range

Study citation, study design, and patient model	Study findings
Casamento et al. (2016)[19] Retrospective cohort study Adult patients with cardiac arrest admitted to ICU	Median proportion (range) of time spent in the prescribed temperature range in hypothermia (TTM 32°C to 34°C) versus normothermia (TTM 36°C) groups: • 60% (45 to 74) versus 53% (38 to 72); P = 0.12

ICU = intensive care unit; TTM = targeted temperature management.

Table 15: Summary of Findings by Outcomes for Medication Prescription

Study citation, study design, and patient model	Study findings
Duggelin et al. (2021)[14] Retrospective cohort study Adult patients successfully resuscitated after out-of-hospital or in-hospital cardiac arrest	Hypothermia (TTM 33°C) versus normothermia (TTM 36°C): • Mean (SD) dose of catecholamine used during the first 24 hours: ◦ Norepinephrine (µg/min): 9.5 (12.5) versus 8.3 (10.8); P = 0.17 ◦ Epinephrine (µg/min): 0.9 (2.7) versus 1.0 (3.4); P = 0.91 ◦ Dobutamine (µg/min): 49 (108) versus 36 (68); P = 0.94 ◦ Vasopressin (µg /min): 0.05 (0.22) versus 0.04 (0.17); P = 0.77 • Cumulative mean (SD) dose of sedatives and relaxants used during the first 24 hours: ◦ Propofol (mg): 157 (99) versus 177 (96); P = 0.24 ◦ Midazolam (mg): 4.4 (7.6) versus 1.9 (4.3); P = 0.04 ◦ Rocuronium (mg): 1.6 (3.2) versus 1.4 (3.1); P = 0.39 • No significant differences between groups in proportion of patients receiving any sedatives or Pethidine during the first 24 hours.

Study citation, study design, and patient model	Study findings
Casamento et al. (2016)[19] Retrospective cohort study Adult patients with cardiac arrest admitted to ICU	Hypothermia (TTM 32°C to 34°C) versus normothermia (TTM 36°C): • No significant differences between groups in proportion of patients receiving propofol, morphine, midazolam, fentanyl, and pethidine for sedation (P > 0.05) • Patients in the hypothermia group received significantly higher dose of midazolam (median [range] = 37 mg [11, 68]) compared to those in the normothermia group (median [range] = 9 mg [2, 76]); P = 0.02 • Patients in the hypothermia group received significantly higher dose of fentanyl (median [range] = 883 µg [330, 2720]) compared to those in the normothermia group (median [range] = 310 µg [120, 700]); P = 0.01 • Significantly higher proportion of patients in the hypothermia group (84.1%) received at least 1 dose of muscle relaxant compared to those in the normothermia group (59.4%); P = 0.001

ICU = intensive care unit; TTM = targeted temperature management.

Table 16: Summary of Findings by Outcomes for Adverse Events

Study citation, study design, and patient model	Study findings
Fernando et al. (2021)[5] SR (10 RCTs included in NMA) Adult patients with OHCA who remained unresponsive following ROSC	NMA estimate (OR [95% CI]) compared hypothermia with normothermia (i.e., 37°C to 37.8°C): • Arrhythmia: ◦ Deep hypothermia (31°C to 32°C): 3.58 (1.77 to 7.26) ◦ Moderate hypothermia (33°C to 34°C): 1.45 (1.08 to 1.94) ◦ Mild hypothermia (35°C to 36°C): 1.16 (0.76 to 1.78) • Bleeding: ◦ Deep hypothermia (31°C to 32°C): 1.21 (0.68 to 2.15) ◦ Moderate hypothermia (33°C to 34°C): 1.10 (0.78 to 1.55) ◦ Mild hypothermia (35°C to 36°C): 1.21 (0.66 to 2.21) • Pneumonia: ◦ Deep hypothermia (31°C to 32°C): 0.91 (0.42 to 2.09) ◦ Moderate hypothermia (33°C to 34°C): 1.24 (0.79 to 1.95) ◦ Mild hypothermia (35°C to 36°C): 1.21 (0.41 to 2.33) MA estimate (OR [95% CI]) compared hypothermia with normothermia (i.e., 37°C to 37.8°C): • Sepsis: ◦ Deep hypothermia (31°C to 32°C): Not available ◦ Moderate hypothermia (33°C to 34°C): 1.36 (0.88 to 2.10) ◦ Mild hypothermia (35°C to 36°C): Not available • Seizure: ◦ Deep hypothermia (31°C to 32°C): Not available ◦ Moderate hypothermia (33°C to 34°C): 0.95 (0.67 to 1.35) ◦ Mild hypothermia (35°C to 36°C): Not available

Study citation, study design, and patient model	Study findings
Pang et al. (2016)[13] RCT Adult patients receiving ECLS for cardiac arrest	AE incidence in hypothermia (TTM 34°C) versus normothermia (37°C) groups (i.e., ECLS-related complications within 7 days): • Bleeding: 22.2% versus 25.0%; P = 0.882 • Arrythmia: 22.2% versus 16.7%%; P = 0.748 • Limb ischemia: 22.2% versus 33.3%; P = 0.577 • Acute renal failure: 88.9% versus 91.7%; P = 0.830 • Continuous renal replacement therapy: 77.8% versus 91.7%; P = 0.368 • Pneumonia : 11.1% versus 50%; P = 0.061
Duggelin et al. (2021)[14] Retrospective cohort study Adult patients successfully resuscitated after out-of-hospital or in-hospital cardiac arrest	Proportion of patients with at least 1 AE in hypothermia (TTM 33°C) versus normothermia (TTM 36°C) groups: • 96% versus 92% • RR (95% CI) = 0.93 (0.88 to 1.05); P = 0.50 AE incidence in hypothermia (TTM 33°C) versus normothermia (TTM 36°C) groups: • Pneumonia: 42% versus 44%; P = 0.98 • Thrombosis: 1% versus 9%; P = 0.09 • Catheter-associated bleeding: <1% versus 5%; P = 0.56 • Systemic bleeding: 10% versus 8%; P = 0.87 • Arrythmia: 78% versus 66%; P = 0.11 • Bradycardia: 71% versus 38%; P < 0.001
Eilam et al. (2017)[17] Retrospective cohort study Comatose adult patients post-CPR hospitalized in the ICU	Rate of seizure in hypothermia (TTM 32°C to 34°C) versus Normothermia (temperature not specified): • 23% versus 16%; P = 0.70
Pang et al. (2017)[18] Retrospective cohort study Adult patients received CPR for refractory cardiac arrest and being treated with ECLS	AE incidence in hypothermia (TTM 34°C) versus normothermia (temperature not specified) groups: • Hypoxic ischemia encephalopathy: 42.9% versus 56.9%; P = 0.338 • Stroke: 21.4% versus 16.9%; P = 0.689 • Bleeding: 35.7% versus 44.6%; P = 0.542 • Limb ischemia: 9.5% versus 33.3%; P = 0.540 • Acute renal failure: 71.4% versus 69.2%; P = 0.871 • Continuous renal replacement therapy: 57.1% versus 58.5%; P = 0.928 • Ischemic hepatitis: 21.4% versus 29.2%; P = 0.555

Study citation, study design, and patient model	Study findings
Casamento et al. (2016)[19] Retrospective cohort study Adult patients with cardiac arrest admitted to ICU	AE incidence in hypothermia (TTM 32°C to 34°C) versus normothermia (TTM 36°C): • Composite (bleeding, arrhythmia, and cardiovascular instability): 66.7% versus 47.8%; P = 0.03 ◦ Bleeding: 2.9% versus 4.3%; P = 1.0 ◦ Arrhythmia: 33.3% versus 20.3%; P = 0.08 ◦ Cardiovascular instability: 53.6% versus 37.7%; P = 0.06 • Renal replacement therapy: 7.2% versus 4.3%; P = 0.72 • Median (range) time in mechanical ventilation: 56 (37, 98) hours versus 53 (30, 91) hours; P = 0.15

AE = adverse event; CI = confidence interval; ECLS = extracorporeal life support; HR = hazard ratio; ICU = intensive care unit; MA = meta-analysis; NMA = network meta-analysis; OHCA = out-of-hospital cardiac arrest; OR = odds ratio; RCT = randomized controlled trial; ROSC = return of spontaneous circulation; RR = risk ratio; SR = systematic review; TTM = targeted temperature management.

Table 17: Summary of Recommendations in Included Guidelines

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
SRLF/SFAR, Cariou et al. (2018)[21]	
"We recommend using TTM in order to improve survival with good neurological outcome in patients resuscitated from out-of-hospital cardiac arrest (OHCA) with shockable cardiac rhythm (ventricular fibrillation and pulseless ventricular tachycardia) and who remain comatose after return of spontaneous circulation (ROSC)."[21] (p.483) **Evidence supporting this recommendation came from 7 MAs and 4 SRs assessed studies on TTM after CA.**	Strength of recommendation: Grade 1+
"We suggest considering TTM in order to improve survival with good neurological outcome in patients resuscitated from OHCA with non-shockable cardiac rhythm (asystole or pulseless electrical activity) and who remain comatose after ROSC."[21] (p.483) **This recommendation was developed based on evidence from 8 MAs and 4 reviews on TTM after CA.**	Strength of recommendation: Grade 2+
"We suggest considering TTM in order to increase survival with good neurological outcome in patients resuscitated from in-hospital cardiac arrest (IHCA) who remain comatose after ROSC."[21] (p.483) **There were no published RCTs with patients presenting in-hospital cardiac arrest (IHCA) patients.**	Strength of recommendation: Expert opinion
"We suggest considering TTM between 32 and 36 °C in order to improve survival with good neurological outcome after CA."[21] (p.483) **One RCT and 1 SR of 6 RCTs provided evidence for this recommendation. However, it was not possible to define the optimal temperature within this range.**	Strength of recommendation: Grade 2+

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
AAN, Geocadin et al. (2017)[22]	
"For patients who are comatose after an initial cardiac rhythm of VT/VF, TH (32–34°C for 24 hours) is highly likely to be effective in improving neurologic outcome and survival compared with non-TH and should be offered."[22] (p. 2142) **The recommendation was developed based on 2 Class I studies.**	Level of evidence: Class I Strength of recommendation: A
"For patients who are comatose with an initial cardiac rhythm of either VT/VF or PEA/asystole, TTM (36°C for 24 hours followed by 8 hours of rewarming to 37°C and temperature maintenance below 37.58C until 72 hours) is likely as effective as TH in improving neurologic outcome and survival and is an acceptable alternative to TH. "[22] (p. 2142-2143) **The recommendation was developed based on 1 Class I study.**	Level of evidence: Class I Strength of recommendation: B
"For patients who are comatose with an initial rhythm of VF, there is insufficient evidence to support or refute the use of 32°C vs 34°C TH because of lack of statistical precision."[22] (p. 2143) **The recommendation was developed based on Class III studies.**	Level of evidence: Class III Strength of recommendation: U
"For patients who are comatose in whom the initial rhythm is PEA/asystole, treatment with TH vs non-TH possibly improves functional neurologic outcome and survival at hospital discharge and may be offered."[22] (p. 2143) **The recommendation was developed based on 2 MAs of Class III studies.**	Level of evidence: Class III Strength of recommendation: C
"For patients who are comatose after cardiac arrest, prehospital cooling as an adjunct to in-hospital cooling is highly likely to be ineffective in further improving neurologic outcome and survival and should not be offered."[22] (p. 2144) **The recommendation was developed based on multiple Class I studies.**	Level of evidence: Class I Strength of recommendation: A
CCS/CCCCS/CAIC, Wong et al. (2017)[2]	
"We recommend that TTM be used in unresponsive OHCA survivors with an initial shockable rhythm after ROSC."[2] (p.3) **The recommendation was developed based on 3 RCTs of low quality.**	Level of evidence: Low Strength of recommendation: Strong
"We suggest TTM be used in unresponsive OHCA survivors with an initial nonshockable rhythm after ROSC."[2] (p.3) **The recommendation was developed based on 7 observational studies.**	Level of evidence: Very low Strength of recommendation: Conditional
"We suggest that TTM be considered in unresponsive survivors of in-hospital cardiac arrest with any rhythm after ROSC."[2] (p.3) **The recommendation was developed based on 3 observational studies.**	Level of evidence: Very low Strength of recommendation: Conditional
"We recommend that a temperature between 33°C and 36°C, inclusively, be selected and maintained for patients who undergo TTM."[2] (p.3) **The recommendation was developed based on 2 RCTs.**	Level of evidence: Moderate Strength of recommendation: Strong

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
"We do not recommend the use of chilled intravenous fluids for prehospital cooling after ROSC."[2] (p.3) **The recommendation was developed based on 2 RCTs.**	Level of evidence: Moderate Strength of recommendation: Strong
"We suggest that either surface cooling or intravascular cooling techniques may be used to induce and maintain TTM."[2] (p.4) **The recommendation was developed based on 2 RCTs and 2 observational studies.**	Level of evidence: Low Strength of recommendation: Conditional
"We suggest that the cooling temperature selected for TTM be maintained for at least 24 hours."[2] (p.4) "We suggest TTM be continued beyond 24 hours from ROSC to prevent fever."[2] (p.4) **The recommendations were developed based on 2 RCTs and 1 retrospective study.**	Level of evidence: Very low Strength of recommendation: Conditional
CCCS/CNCCS/CCCTG, Howes et al. (2016)[23]	
"We recommend that Targeted Temperature Management (TTM) be used for neuro-protection in eligible adult patients after resuscitation from cardiac arrest."[23] (p.52) **The recommendation was developed based on 2 RCTs of high quality.**	Level 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."[23] (p.52) **The recommendation was developed based on 4 RCTs of high quality.**	Level 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."[23] (p.52) **The recommendation was developed based on 1 RCT and 1 retrospective study.**	Level of evidence: Low Strength of recommendation: Conditional
"We recommend that patients who suffer out-of-hospital cardiac arrest are eligible for TTM."[23] (p.53) **The recommendation was developed based on 2 RCTs of high quality.**	Level of evidence: High Strength of recommendation: Strong
"We recommend that patients who suffer in-hospital cardiac arrest are eligible for TTM."[23] (p.53) **The recommendation was developed based on 4 low-quality studies.**	Level of evidence: Low Strength of recommendation: Strong
"We recommend that patients who suffer a cardiac arrest of known cardiac cause or of an unknown cause are eligible for TTM."[23] (p.53)	Level of evidence: High Strength of recommendation: Strong

CA = cardiac arrest; MA = meta-analysis; OHCA = out-of-hospital cardiac arrest; PEA = pulseless electrical activity; RCT = randomized controlled trial; ROSC = return of spontaneous circulation; SR = systematic reviews; TH = therapeutic hypothermia; TTM = targeted temperature management; VF = ventricular fibrillation; VT = ventricular tachycardia.

Appendix 5: Overlap Between Included Systematic Reviews

Note that this appendix has not been copy-edited.

Table 18: Overlap in Relevant Primary Studies Between Included Systematic Reviews

Primary study citation	Fernando et al. (2021)[5]	Granfeldt et al. (2021)[12]
Bernard SA et al. N Engl J Med 2002; 346:557–563	Yes	Yes
Dankiewicz J et al. Engl J Med 2021; 384:2283–2294	Yes	Yes
Hypothermia After Cardiac Arrest Study Group 2002; N Engl J Med 346:549–556	Yes	Yes
Hachimi-Idrissi S 2001; Resuscitation 51:275–281	Yes	Yes
Lascarrou JB et al. 2019; N Engl J Med 81:2327–2337	Yes	Yes
Laurent I et al. 2005; Am Coll Cardiol 46:432–437	Yes	Yes
Le May M et al. 2021; JAMA 326 : 1494-1503	Yes	No
Lopez-de-Sa E et al. 2012; Circulation 126:2826–2833	Yes	No
Lopez-de-Sa E et al. 2018; Intensive Care Med 44:1807–1815	Yes	No
Nielsen N et al. 2013; N Engl J Med 369:2197–2206	Yes	No
Callaway CW et al. 2002; Resuscitation 52(2):159–65	No	Yes
Zhang J 2005; Chin J Clin Rehabilitation 9:136–8	No	Yes
Hachimi-Idrissi S ewt al. 2005; Resuscitation 64:187–92	No	Yes

Appendix 6: References of Potential Interest

Note that this appendix has not been copy-edited.

Previous CADTH Reports

Temperature settings for therapeutic hypothermia: guidelines. *(CADTH rapid response report: summary of abstracts)*. Ottawa (ON): CADTH; 2016: https://www.cadth.ca/sites/default/files/pdf/htis/june-2016/RB0993%20Therapeutic%20Hypothermia%20Final.pdf. Accessed 2022 Jan 27.

Normothermia versus therapeutic hypothermia for adult patients after cardiac arrest: clinical evidence. *(CADTH rapid response report: summary of abstracts)*. Ottawa (ON): CADTH; 2014: https://www.cadth.ca/media/pdf/htis/dec-2014/RB0727%20Normothermia%20Final.pdf. Accessed 2022 Jan 27.

Additional References

National Institute for Health and Care Excellence. Arctic Sun 5000 for therapeutic hypothermia after cardiac arrest. *(Medtech innovation briefing MIB112)* 2017; https://www.nice.org.uk/advice/mib112. Accessed 2022 Jan 27.