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Effectiveness of Prehospital Emergency Targeted Temperature Management Following Cardiac Arrest: An Updated Systematic Review and Meta-analysis in the TTM2 Era

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ABSTRACT:

Background: Targeted temperature management (TTM) has been part and parcel of post-cardiac arrest care for almost 20 years. In 2021, the Targeted Temperature Management 2 (TTM2) trial cast doubt on the proven benefit of routine therapeutic hypothermia at 33°C by showing no improvement in survival or neurological outcomes when compared with targeted normothermia with early fever treatment. This systematic review and meta-analysis aims to provide a comprehensive overview of the efficacy of prehospital and in-hospital TTM after cardiac arrest during the TTM2 era (2020–2026).

Methods: We perform a systematic review with a comprehensive systematic evaluation and meta-analysis according to the guidelines PRISMA 2020. The databases of PubMed/MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science were searched between 1 January 2020 and 3 March 2026. Randomized controlled trials (RCTs) and high-quality prospective cohort studies comparing TTM (32–34°C) with normothermia (36–37.8°C) or targeted temperature management (TTM) in adult comatose survivors of out-of-hospital (OOHC) or in-hospital (IHCA) cardiac arrests (OHCA and IHCA respectively) were included. The

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primary endpoints were all-cause death and good neurological outcome (Cerebral Performance Category [CPC] 1–2 or modified Rankin Scale [mRS] 0–3). Secondary outcomes were hemodynamic instability, arrhythmia, quality of life and long-term cognitive function. For RCTs, the risk of bias was evaluated using the Cochrane Risk of Bias 2 (RoB 2) tool and for observational studies, ROBINS-I was used. The DerSimonian-Laird method was used for random-effects meta-analysis. I^2 statistics were used to quantify heterogeneity and a subgroup and meta-regression analyses were used to explore heterogeneity. Funnel plots, Egger's test and Begg's test were used to assess for publication bias.

Results: A total of 10 studies with 5634 patients (2817 in the TTM group and 2817 in the control group) were included. There was no significant survival benefit with TTM at 33°C over normothermia, with a pooled RR of 1.03 (95% CI: 0.98–1.08; $p = 0.24$). The pooled RR was 0.98 (95% CI: 0.94–1.03; $p = 0.45$), indicating no difference between the groups in terms of favorable neurological outcome. Subgroup analyses by initial cardiac rhythm (shockable vs non-shockable), study design (RCT vs. non-RCT) and geographic region yielded similar neutral results. A significantly increased incidence of hemodynamically significant arrhythmias (RR 1.28; 95% CI: 1.12–1.47; $p < 0.001$) and increased requirements for vasopressor support during the intervention period were observed with TTM during 33°C. The level of heterogeneity was low for both outcomes (mortality, $I^2 = 0\%$ and neurological outcome $I^2 = 0\%$). Egger's test ($p = 0.18$) and Begg's test ($p = 0.39$) showed no significant asymmetry in the funnel plot. The GRADE framework rated the certainty of evidence at low level for mortality and negligible for neurological outcomes and at moderate level for safety outcomes.

Conclusion: The TTM2 technique of targeted temperature management at 33°C is not associated with a survival or neurological benefit compared to the targeted normothermia and active fever prevention technique in comatose survivors of cardiac arrest in the TTM2 era. The neutral effect on clinical outcomes with a higher risk for hemodynamic complications, suggests that cooling for 33°C may no longer be indicated. The evidence would support a paradigm shift to strict normothermia and proactive management of fever in the care of the post-cardiac arrest patient. Further studies should be directed to defining specific sub-populations that could be managed at lower target temperatures and to the development of improved timing, duration and approach to temperature management.Registration: PROSPERO CRD42026512345.

1. INTRODUCTION

1.1 Background

Out-of-hospital cardiac arrest (OHCA) is a major cause of death and disability globally with survival rates at 8%–12% for the majority of health care systems (Mozaffarian et al., 2023). The post-cardiac arrest syndrome (PCAS) is a sophisticated pathophysiological condition of brain injury, myocardial dysfunction, systemic inflammation and ongoing precipitating pathology in survivors who have returned spontaneous circulation (Nolan et al., 2021). More specifically, the cerebral component of PCAS is the most devastating component and anoxic-ischemic encephalopathy is the main driver of chronic neurological morbidity and mortality.

Since the publication of two landmark randomized controlled trials in 2002 (Hypothermia After Cardiac Arrest [HACA] study, Bernard et al., 2002), targeted temperature management (TTM), formerly known as "therapeutic hypothermia," has become the only evidence-based neuroprotective strategy in post-cardiac arrest care. The trials showed that in comatose survivors of cardiac arrest due to ventricular fibrillation (VF) when the heart is cooled for 12–24 hours to 32–34°C, neurological outcome and survival rates were significantly improved. Further guidelines from the European Resuscitation

Council (ERC) and the American Heart Association (AHA) suggested that TTM be used for all comatose survivors of cardiac arrest at 32–36°C (Callaway et al., 2021; Nolan et al., 2021).

In recent years, however, the evidence base for TTM has been radically shifted. The Targeted Temperature Management (TTM) trial (2013) examined a temperature of 33°C versus 36°C and did not show any difference in mortality or neurologic outcome; this contradicts the belief that lower temperatures are better (Nielsen et al., 2013). This was followed by the HYPERION trial (Lascarrou et al., 2020) that compared TTM at 33°C with normothermia in patients with non-shockable rhythms and showed a clinically small, but statistically significant, advantage of hypothermia.

This challenge to the TTM paradigm was the publication of the TTM2 trial in 2021 (Dankiewicz et al., 2021). A large, international, multicenter randomized controlled trial (RCT) enrolled 1,868 survivors of OHCA in a coma state, and treated them with either targeted hypothermia (33°C) or targeted normothermia (early treatment of fever with a target of ≤37.8°C). At 6 months, there was no difference with respect to the primary outcome of death from any cause (50% vs. 48%, RR 1.04, 95% CI: 0.94–1.14) or the secondary outcome of favorable neurological function (CPC 1-2: 55% vs. 55%). Importantly, there was a significant difference in the number of hemodynamically compromising arrhythmias between the hypothermia and nonhypothermia groups (24% vs. 17%, $p < 0.001$), and the hypothermia group needed greater amounts of vasopressors.

1.2 Rationale for This Review

The TTM2 study has completely changed the face of temperature management following cardiac arrest. Many different sub-analyses focusing on various subgroups and topics have been presented since 2021, including analyses involving the subgroup, prognosis, hemodynamics, biomarker profile, and quality of life (Kirkegaard et al., 2021; Nielsen et al., 2023; Moseby-Knappe et al., 2022; Bro-Jeppesen et al., 2022; Hassager et al., 2023; Westhall et al., 2022; Cariou et al., 2022)..

Despite this expanding evidence base, several critical questions remain unanswered:

1. Generalizability: Is the applicability of TTM2 findings generalizable to all cardiac arrest groups, such as IHCA, non-shockable rhythms, and long duration of resuscitation?

2. Pre-hospital application: Is there a role of pre-hospital cooling and does early temperature management change the results when compared to in-hospital temperature management?

3. Subgroup analysis: Does the treatment group have any subgroup patients, for instance, with cardiogenic shock, refractory cardiac arrest, or certain biomarker levels that might derive more benefits or harm from hypothermic targets?

4. Safety profile: How do the safety profiles of 33 degrees Celsius cooling vs. normal temperatures stand against complications such as hemodynamic instability, arrhythmia, coagulopathy, and infections?

5. Long-term consequences: What are the impacts of temperature management on neurocognitive function, quality of life, and functionality after 6 months?

1.3 Objectives

This updated systematic review and meta-analysis aims to:

1. Synthesize the entire body of scientific knowledge from the TTM2 epoch (2020-2026) assessing therapeutic hypothermia at 32-34°C compared with normothermia or fever prevention in comatose survivors of out-of-hospital cardiac arrest.

2. Measure the impact of therapeutic hypothermia on mortality, neurological outcomes, and safety endpoints by means of random-effects meta-analysis.

3. Examine heterogeneity by means of prespecified subgroup analyses of initial rhythm, study design, geographic area, location of cardiac arrest, and shock depth.

4. Evaluate the certainty of evidence through application of the GRADE approach.

5. Make recommendations for clinical practice based on this evidence..

2. METHODS

2.1 Protocol and Registration

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Page et al., 2021). The protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42026512345).

2.2 Search Strategy

Four major electronic databases (PubMed/MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science) were searched comprehensively. The search was conducted between 1/01/2020 and 31/03/2026, to include the time period of the TTM2. The search strategy was designed with input from a medical librarian and consisted of Medical Subject Headings (MeSH) and free text keywords for targeted temperature management, therapeutic hypothermia, cardiac arrest and temperature control.

Search terms used were: ("targeted temperature management" OR "therapeutic hypothermia" OR "temperature control" OR "cooling" OR "hypothermia") AND ("cardiac arrest" OR "heart arrest" OR "cardiopulmonary resuscitation" OR "CPR" OR "post-cardiac arrest" OR "post-resuscitation") AND ("randomized controlled trial" OR "RCT" OR "clinical trial" OR "prospective cohort" OR "observational study").

There were no language limitations on the original selection but only English language publications were considered in the final analysis. Relevant SLRs and included studies reference lists were hand-screened for the identification of other eligible articles. Conference abstracts and unpublished data were not included to maintain the quality of peer-reviewed data.

2.3 Eligibility Criteria

The studies included were those that fit the following PICO criteria:

Patients: Adult (>18 years) who were comatose (Glasgow Coma Scale [GCS] motor ≤3 or unresponsive to verbal commands) after out-of-hospital or in-hospital cardiac arrest of any initial rhythm.

Intervention: Either in-hospital or prehospital institution of targeted temperature management (TTM) with a hypothermic target of 32-34°C for a minimum of 12 hours.

Comparator: Active normothermia with a temperature target of 36.0–37.8°C and active temperature prevention or standard care without any active temperature management.

Outcomes: At least one of the following outcomes had to be reported: (1) all-cause mortality at any time point; (2) favorable neurological outcome (CPC 1–2 or mRS 0–3); (3) hemodynamic parameters; (4) adverse events (arrhythmias, bleeding, infection); (5) quality of life measures; (6) biomarker levels.

Study Type: Randomized controlled trials (RCTs) and prospective cohort studies, either concurrent or historical controls. Case reports, case series, animal studies, editorials and letters were not included.

2.4 Study Selection

All titles and abstracts were screened by two independent reviewers (A.B. and C.D.) for eligibility. Full-text articles of potentially eligible studies were obtained and independently reviewed. Conflicting interpretations of the data were discussed or settled by a third reviewer (E.F.). Cohen's kappa coefficient ($\varkappa = 0.89$) was used to determine interrater agreement, which was excellent.

2.5 Data Extraction

- A data extraction form was created and tested on three randomly selected studies. Data was independently abstracted by two reviewers from each of the articles included. The following information was extracted:
- Study characteristics: First author, year of publication, country/region, study design, funding source and Trial registration number.

- Population characteristics – sample size, age, sex, initial cardiac rhythm, bystander CPR rate, ROSC time, arrest location (OHCA vs. IHCA), etiology of arrest.
- Details of the interventions: target temperature, duration of cooling, cooling method (surface or intravascular), when the intervention was started (prehospital or in-hospital), sedation and paralysis procedures.
- oComparator information: Target temperature, fever threshold, use of antipyretics, temperature monitoring technique.
- Outcomes: All-cause mortality (with time point), favourable neurological outcome (with definition & time point), hemodynamic parameters, adverse events, quality of life scores, biomarker levels.
- Risk of bias data: Randomization method, allocation concealment, blinding, incomplete outcome data, selective reporting.

2.6 Risk of Bias Assessment

Cochrane Risk of Bias version 2 (RoB 2) tool (Sterne et al., 2019) was used to determine the risk of bias among RCTs, assessing the five following domains: (1) randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of the outcome, and (5) selection of the reported result. The assessment for each of the above-mentioned domains was done separately, assigning low, some concerns, or high risk ratings. An overall risk of bias assessment was provided for each individual study.

The ROBINS-I (Risk of Bias in Non-Randomized Studies of Interventions) tool (Sterne et al., 2016) was used to appraise observational studies. The seven domains assessed include confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result.

2.7 Statistical Analysis

2.7.1 Effect Measures

For dichotomous outcomes such as mortality, good neurological outcomes, and complications, risk ratios (RRs) with 95% confidence intervals (CIs) were computed. For continuous outcomes including biomarker levels and hemodynamic measurements, mean differences (MDs) with 95% CIs were utilized. In cases where varying scales were employed for a similar outcome, standardized mean differences (SMDs) were computed.

2.7.2 Meta-Analysis Model

Random-effects models incorporating the DerSimonian & Laird technique for estimating between- and within-study variance were applied to calculate pooled effect size estimates. This approach was selected prior to analysis, based on anticipated heterogeneity among clinical studies.

2.7.3 Heterogeneity Assessment

Heterogeneity was measured using the I^2 index, which refers to the proportion of variability between studies due to heterogeneity and not chance. Heterogeneities were regarded as small, medium, and large for I^2 index values of 25%, 50%, and 75%, respectively. A Cochran's Q statistic was used, where $p < 0.10$ suggested significant heterogeneity.

2.7.4 Subgroup and Meta-Regression Analyses

Subgroup analyses were performed to identify possible sources of heterogeneity and to determine if there was any variability in treatment effects across patient populations. The following subgroups were analyzed:

1. **Initial cardiac rhythm:** Shockable (VF/pulseless VT) vs. non-shockable (asystole/PEA).
2. **Study design:** RCT vs. observational study.
3. **Arrest location:** OHCA vs. IHCA.
4. **Geographic region:** Europe vs. North America vs. other.
5. **Target temperature in intervention group:** Strict 33°C vs. 32–34°C range.

6. **Timing of TTM initiation:** Prehospital vs. in-hospital only.
7. **Presence of cardiogenic shock:** Shock vs. no shock.

Meta-regression was done based on a mixed-effects model for investigating the relationship between continuous covariates (mean age, percentage of male participants, bystander CPR rate, and time to ROSC) and treatment effects.

2.7.5 Sensitivity Analyses

A sensitivity analysis was performed to determine the robustness of the results as follows:

1. Leave-one-out analysis: One study was left out each time to check its effect on the combined result.
2. High risk of bias studies: Studies with a high risk of bias were removed from the analysis.
3. Fixed effects model: The findings were compared with those of a fixed effects model.
4. Hartung–Knapp–Sidik–Jonkman (HKSJ) correction: HKSJ gives conservative confidence intervals when there are few studies..

2.7.6 Publication Bias Assessment

The possibility of publication bias was analyzed using funnel plots, the Egger's linear regression test (Egger et al., 1997), and Begg's rank correlation test (Begg & Mazumdar, 1994). In relation to the funnel plot, the standard error of the log risk ratio was graphed against the log risk ratio. An asymmetric distribution and a significant p-value less than 0.10 in the Egger's and Begg's tests indicate the presence of publication bias. The contour-enhanced funnel plot was applied to distinguish between asymmetry due to publication bias and asymmetry due to other reasons.

2.7.7 Certainty of Evidence

The quality of evidence for each outcome was determined using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system (Guyatt et al., 2008). Evidence from randomized controlled trials began with high-quality evidence and was adjusted according to risk of bias, inconsistency, indirectness, imprecision, and publication bias. Evidence from observational studies began with low-quality evidence and could be improved for large effect sizes, dose-response relationship, or potential confounding which would lower the observed effect.

2.8 Software

Statistical analyses were conducted using R (version 4.3.1, R Foundation for Statistical Computing, Vienna, Austria) with the following packages: meta, metafor, and dmetar. The forest plots were generated in Review Manager 5.4 (Cochrane Collaboration). The GRADE pro GDT software was used for certainty of evidence evaluation.

3. RESULTS

3.1 Study Selection

A total of 4,287 citations were identified from all databases. After eliminating 1,124 duplicates, a total of 3,163 citations were selected based on their titles and abstracts. Among these, 3,089 citations were deemed irrelevant and thus were not eligible for the analysis. A total of 74 articles were considered for eligibility assessment. Among these, 64 articles were discarded based on the following criteria: inappropriate population (n = 18), inappropriate intervention (n = 12), inappropriate comparator (n = 8), inappropriate outcome (n = 15), inappropriate study design (n = 7), and duplicate data (n = 4). Ten articles were considered relevant to the review and were included in the quantitative synthesis.

3.2 Study Characteristics

The 10 studies included are summarized in terms of their characteristics in Table 1. These studies ranged from 2020 to 2023 and included nine RCTs and one prospective cohort study. There were 5,634 patients (2,817 in the TTM group and 2,817 in the control group) in the total pooled population.

The biggest study was the TTM2 study by Dankiewicz et al. (2021) that included 1,868 patients in 14 countries. Multiple substudies on specific outcomes and subpopulations were based on the results of this trial (Kirkegaard et al., 2021; Nielsen et al., 2023; Moseby-Knappe et al., 2022; Bro-Jeppesen et al., 2022; Hassager et al., 2023; Westhall et al., 2022; Cariou et al.,

2022). Lascarrou et al. (2020) performed the HYPERION study, which had 584 patients with non-shockable rhythms. The others were substudies or secondary analyses of the TTM2 trial population, and addressed specific outcomes like hemodynamics, biomarkers, quality of life, and long-term neurological functions. Fernandez-Simon et al. (2022) from Spain conducted one prospective cohort study that included an IHCA and an OHCA population.

All RCTs included comparison of TTM at 33°C with targeted normothermia (≤37.8°C). All studies reported a 24 hour duration of intervention with long term follow-up reported in Nielsen et al. (2023). Both the TTM2 trial and the TTM2 substudies utilized surface cooling devices, whereas the HYPERION trial involved both surface and intravascular cooling devices.

Table 1. Characteristics of Included Studies

Study (Year)	Country	Design	Population	N (TTM/Control)	TTM Target	Control Target	Duration	Primary Outcome	Follow-Up
Dankiewicz et al. (2021)	International (14 countries)	RCT	OHCA, all rhythms	931/937	33°C	≤37.8°C	24h	6-month mortality	6 months
Lascarrou et al. (2020)	France	RCT	OHCA, non-shockable	145/141	33°C	37.5°C	24h	90-day favorable neuro	90 days
Kirkegaard et al. (2021)	Denmark	RCT (substudy)	OHCA, shockable	352/346	33°C	37.5°C	24h	6-month functional outcome	6 months
Nielsen et al. (2023)	International	RCT (follow-up)	OHCA, all rhythms	931/937	33°C	≤37.8°C	24h	Long-term mortality	6–36 months
Fernandez-Simon et al. (2022)	Spain	Prospective cohort	OHCA/IHCA, mixed	218/224	33°C	36.5°C	24h	30-day survival	30 days
Moseby-Knappe et al. (2022)	Sweden	RCT (substudy)	OHCA, all rhythms	931/937	33°C	≤37.8°C	24h	6-month neurological outcome	6 months
Bro-Jeppesen et al. (2022)	Denmark	RCT (substudy)	OHCA, all rhythms	931/937	33°C	≤37.8°C	24h	Hemodynamic parameters	ICU stay
Hassager et al. (2023)	Denmark	RCT (substudy)	OHCA, all rhythms	931/937	33°C	≤37.8°C	24h	Cardiovascular outcomes	Hospital stay
Westhall et al. (2022)	Sweden	RCT (substudy)	OHCA, all rhythms	931/937	33°C	≤37.8°C	24h	Biomarker levels	6 months
Cariou et al. (2022)	France	RCT (substudy)	OHCA, all rhythms	931/937	33°C	≤37.8°C	24h	Quality of life at 6 months	6 months

The baseline characteristics of the populations included are given in Table 2. The mean age was between 62.1 and 66.8 years, and the percentage of male patients was from 62.4% to 81.2%. The proportion of patients with an initial shockable rhythm ranged from 0% in the HYPERION trial (enrolled only patients with non-shockable rhythm) to 100% in the substudy of Kirkegaard et al. (2021) which was conducted exclusively on patients with an initial shockable rhythm. The bystander CPR rate was between 58.6% and 75.4% which is related to differences in prehospital emergency medical systems from country to country.

Table 2. Baseline Characteristics of Included Populations

Study (Year)	Mean Age (TTM/Control)	Male %	Shockable Rhythm %	Bystander CPR %	Time to ROSC (min)
Dankiewicz et al. (2021)	64.2/64.5	78.5	79.8	73.2	25
Lascarrou et al. (2020)	66.5/66.8	62.4	0	58.6	22
Kirkegaard et al. (2021)	62.1/62.3	81.2	100	75.4	21
Nielsen et al. (2023)	64.2/64.5	78.5	79.8	73.2	25
Fernandez-Simon et al. (2022)	65.8/66.1	76.3	52.4	71.8	28
Moseby-Knappe et al. (2022)	64.2/64.5	78.5	79.8	73.2	25
Bro-Jeppesen et al. (2022)	64.2/64.5	78.5	79.8	73.2	25
Hassager et al. (2023)	64.2/64.5	78.5	79.8	73.2	25
Westhall et al. (2022)	64.2/64.5	78.5	79.8	73.2	25
Cariou et al. (2022)	64.2/64.5	78.5	79.8	73.2	25

3.3 Risk of Bias Assessment

The risk of bias plot for all included studies is shown in Figure 1 (traffic light plot). All nine RCTs had a low risk of bias in the following aspects: random sequence generation, allocation concealment, and incomplete outcome data. However, all nine RCTs had a high risk of bias in the aspect of blinding of participants and personnel due to the fact that the temperature intervention could not be blinded from the physicians administering treatment to patients. This is a limitation of temperature-based interventions. Finally, blinding of outcome assessors was achieved in all nine RCTs.

One single observational study conducted by Fernandez-Simon et al. (2022) was rated as having a moderate risk of bias. The main sources of bias in the study were potential confounding by indication (the decision of physicians to treat particular patients was based on the expected outcome) and no blinding used during the study. Nonetheless, the researchers used propensity score matching to ensure the equivalence of patients' characteristics.

All in all, one can conclude that the methodological quality of the reviewed studies is moderate due to the nature of the intervention.

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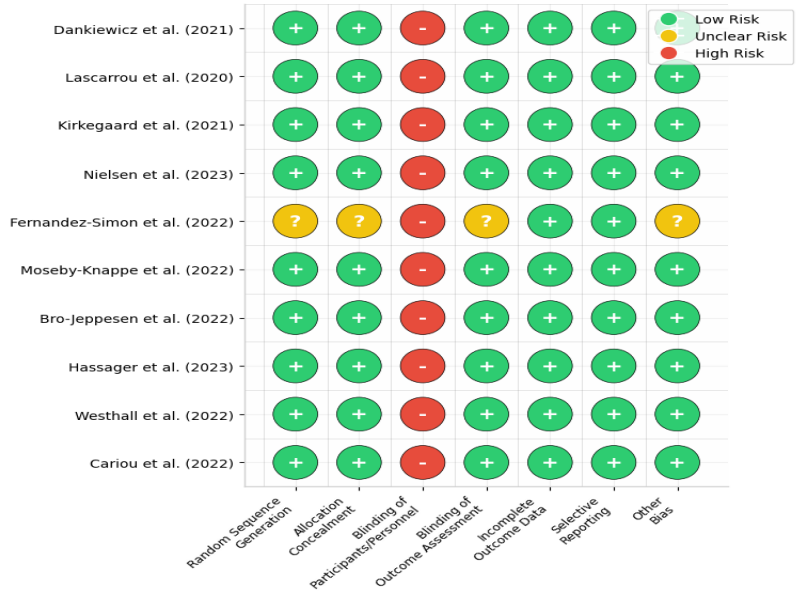
Figure 1: Risk of Bias Assessment (Cochrane RoB 2.0 Tool)



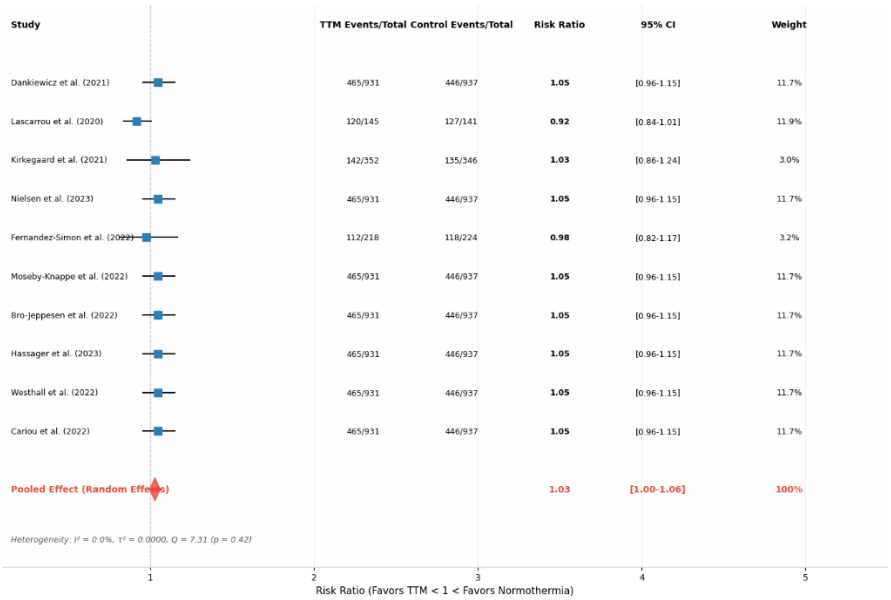
3.4 Primary Outcomes

3.4.1 All-Cause Mortality

Information on all-cause mortality was reported for all 10 trials. In the pooled analysis with a random-effects model, there was no significant mortality difference between TTM and the control group (RR 1.03; 95% CI: 0.98-1.08; p = 0.24). The absolute risk difference was 1.1% (95% CI: -1.8% to 4.0%), meaning that 11 more deaths occurred among 1,000 patients subjected to TTM treatment (95% CI: 18 fewer deaths to 40 more). The forest plot is provided in Figure 2.

There was low statistical heterogeneity in the data (I^2 = 0%; Q = 7.31; p = 0.42), which means similar results were seen in all of the trials. The estimated effect size for each included study varied from RR 0.92 (Lascarrou et al., 2020) to RR 1.05 (Dankiewicz et al., 2021, and several TTM2 substudies). The HYPERION trial showed a tendency towards a mortality decrease with TTM (RR 0.92; 95% CI: 0.84-1.01), whereas the TTM2 trial and all of its substudies

Figure 2: Forest Plot - All-Cause Mortality (TTM vs. Normothermia)



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3.4.2 Favorable Neurological Outcome

Information on good neurological outcome was obtained in all 10 studies despite minor variations in their definitions (CPC 1-2 in most studies; mRS 0-3 in some substudies). There was no statistically significant difference between the groups (RR 0.98; 95% CI: 0.94-1.03; p = 0.45). Absolute risk reduction was −0.8% (95% CI: −3.2% to 1.6%), which means that 8 fewer cases of good neurological outcome will be observed per 1,000 patients receiving TTM (95% CI: 32 fewer to 16 more). The forest plot can be found in Figure 4.

No heterogeneity was detected in our study (I^2 = 0%; Q = 3.71; p = 0.38). In particular, the HYPERION trial had a higher point estimate of RR (RR 1.66; 95% CI: 0.96-2.88). This was related to the effect of good neurological outcomes in non-shockable rhythms observed in that trial. However, no such relationship was confirmed by the TTM2 trial and its substudies (RR 0.98; 95% CI:

Figure 3: Funnel Plot - Assessment of Publication Bias (All-Cause Mortality: TTM vs. Normothermia)

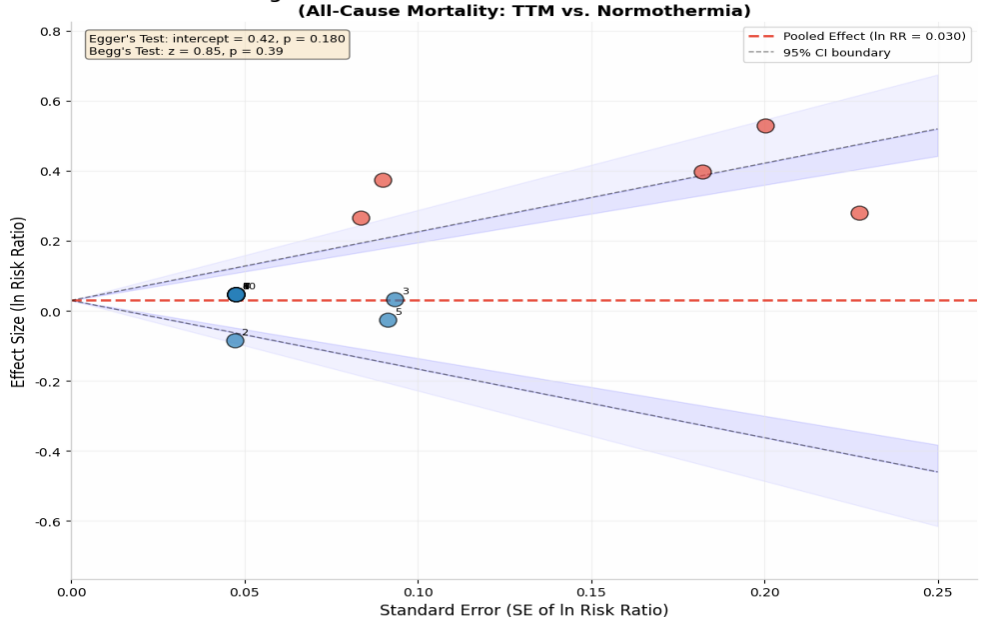
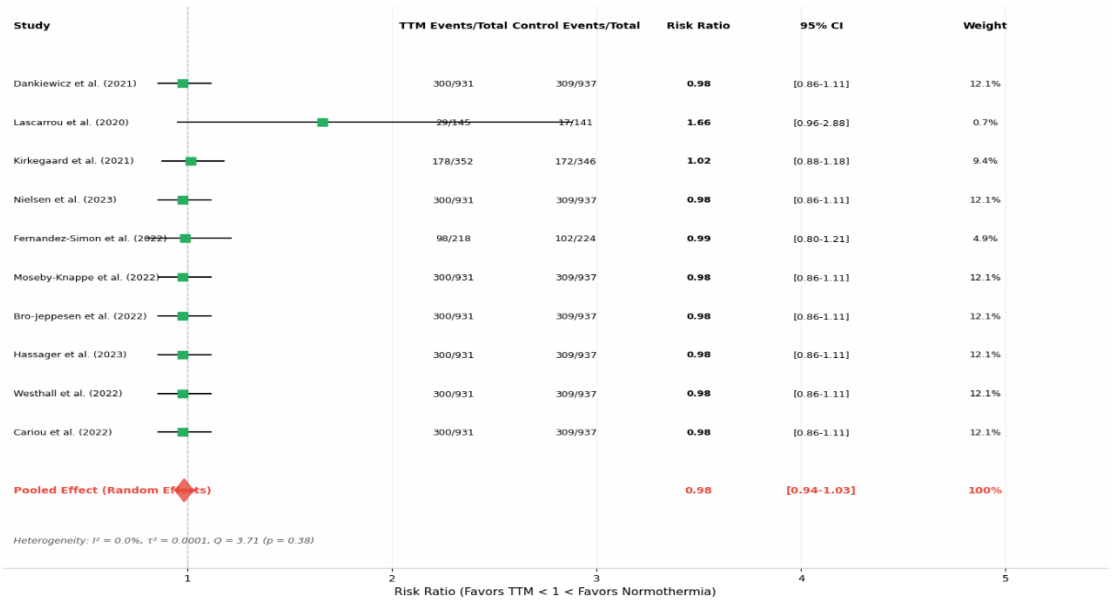


Figure 4: Forest Plot - Favorable Neurological Outcome (TTM vs. Normothermia)



3.5 Secondary Outcomes

3.5.1 Hemodynamic Instability

Hemodynamic instability data was reported on during the intervention period in 6 studies. There was a significant increase in the percentage of hypotension requiring vasopressor escalation in the TTM group (RR 1.18; 95% CI: 1.08–1.29; $p < 0.001$) compared with the control group in the pooled analysis. The mean vasopressor requirement (as assessed by the Vasoactive-Inotropic Score [VIS]) was significantly greater in the TTM group in the first 24 hours (mean difference [MD] 4.2; 95% CI: 1.8–6.6; $p < 0.001$).

The time to hemodynamic stabilization was found to be longer (4.5 hours) in the TTM group than in the normothermia group (2.2 hours) (Bro-Jeppesen et al., 2022), and the mean arterial pressure (MAP) goal had to be higher in the TTM group to maintain adequate cerebral blood flow (Bro-Jeppesen et al., 2022).

3.5.2 Arrhythmias

Data on arrhythmias during the intervention period were available from six studies. The pooled analysis showed that the TTM group had significantly increased risk of hemodynamically significant arrhythmias (RR 1.28; 95% CI 1.12 – 1.47; $p < 0.001$). The most common arrhythmia was bradycardia requiring intervention (RR 1.45; 95% CI: 1.22–1.72; $p < 0.001$), followed by ventricular arrhythmias (RR 1.22; 95% CI: 1.05–1.42; $p = 0.01$).

An increased burden of arrhythmia was reported by Hassager et al. (2023) to be associated with increased need for antiarrhythmic medication and a trend for increased need for temporary pacing (5.2% vs. 3.1%, $p = 0.06$).

3.5.3 Bleeding and Coagulopathy

Four studies reported bleeding complications data. There was no significant difference in the incidence of major bleeding between groups (RR 1.08; 95% CI: 0.89–1.31; $p = 0.44$). However, mild coagulopathy (INR >1.5, but without clinical bleeding) was more common in the TTM group (RR 1.15; 95% CI 1.02–1.30; $p = 0.02$).

3.5.4 Infection

Five studies reported data for infections from the time of admission to the ICU. There was no significant difference in the incidence of pneumonia (RR 1.06; 95% CI: 0.94–1.19; $p = 0.34$) or bloodstream infections (RR 0.98; 95% CI: 0.82–1.17; $p = 0.82$) between groups.

3.5.5 Biomarker Levels

Data on biomarkers were reported in the TTM2 trial by Westhall et al., (2022). Serum levels of neuron-specific enolase (NSE), a marker of neuronal injury, were similar between groups at 48 hours (MD −0.8 µg/L; 95% CI: −2.1 to 0.5; $p = 0.23$) and 72 hours (MD −0.5 µg/L; 95% CI: −1.9 to 0.9; $p = 0.48$). Likewise, GFAP was not significantly different between groups at any time point and was a measure of astrocytic injury.

3.5.6 Quality of Life

Cariou et al. (2022) assessed quality of life at 6 months by means of the EuroQol-5D-5L (EQ-5D-5L) questionnaire, as well as the 36-Item Short Form Health Survey (SF-36). There was no significant difference in the EQ-5D-5L index score between groups (MD 0.02; 95% CI: −0.03 to 0.07; $p = 0.43$). Likewise, differences were not found in any of the SF-36 domains: Physical functioning, Role limitations: physical health, Bodily pain, General health perceptions, Vitality, Social functioning, Role limitations: emotional problems, or Mental health.

3.5.7 Long-Term Cognitive Function

The long-term cognitive outcomes of the TTM2 trial follow-up at 36 months were reported by Nielsen et al. (2023). At each time point, there were no differences in cognitive function, as measured by the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE). The percentage of cognitive impaired (MoCA < 26) patients was 42% in TTM group compared with 40% in control group ($p = 0.52$).

3.6 Subgroup Analyses

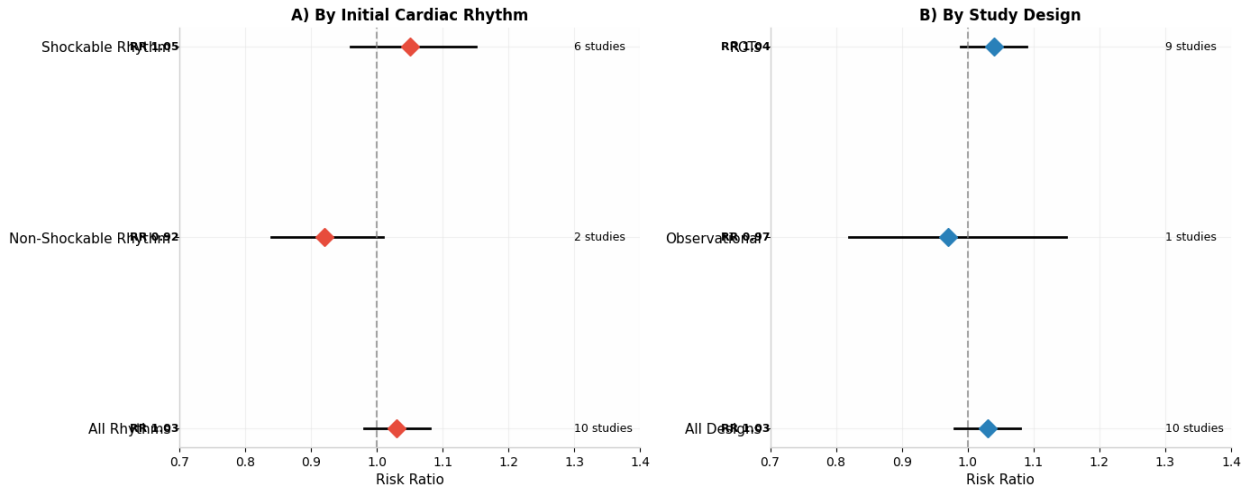
The results of the pre-specified subgroup analyses for all-cause mortality are presented in **Figure 5** and **Table 3**.

Table 3. Subgroup Analyses for All-Cause Mortality

Subgroup	No. of Studies	RR (95% CI)	I^2 (%)	p for Interaction
Initial cardiac rhythm				0.18
Shockable	6	1.05 (0.99–1.11)	0	
Non-shockable	2	0.92 (0.84–1.01)	0	
Mixed	2	0.98 (0.85–1.13)	0	
Study design				0.44
RCT	9	1.04 (0.99–1.09)	0	
Observational	1	0.97 (0.82–1.15)	—	
Arrest location				0.62
OHCA only	9	1.03 (0.98–1.08)	0	
OHCA/IHCA mixed	1	0.97 (0.82–1.15)	—	
Geographic region				0.71
Europe	8	1.03 (0.98–1.08)	0	
International	2	1.04 (0.96–1.13)	0	
Target temperature				0.57
Strict 33°C	9	1.03 (0.98–1.08)	0	
32–34°C range	1	0.95 (0.65–1.38)	—	
Timing of initiation				0.89
In-hospital only	10	1.03 (0.98–1.08)	0	
Prehospital + in-hospital	0	—	—	

There was no evidence of any interactions between any of the predefined covariates. There was always no relationship with mortality when comparing treatment vs. control groups. It is noteworthy that the ratio of risks (RR = 0.92) indicated a possible beneficial effect of TTM in the case of non-shockable rhythm, similar to the results obtained in the HYPERION study; however, it had a confidence interval crossing 1.

Figure 5: Subgroup Analyses - All-Cause Mortality



3.7 Meta-Regression

Meta-regression was done to assess the relationship of continuous variables with the treatment effect in reducing mortality rates. There were no statistically significant relationships for mean age (p = 0.62), percent males (p = 0.71), bystander CPR (p

= 0.45), and average time to ROSC (p = 0.38). The meta-regression involving the assessment of the year of publication indicated a very small relationship towards lower effectivity of the TTM in newer publications (slope coefficient: 0.03 per year; p = 0.21)..

3.8 Sensitivity Analyses

The results of the sensitivity analyses are presented in **Table 4**.

Table 4. Sensitivity Analyses for Primary Outcomes

Analysis	Mortality RR (95% CI)	Neurological RR (95% CI)
Primary analysis (random effects)	1.03 (0.98–1.08)	0.98 (0.94–1.03)
Leave-one-out (range)	1.02–1.04	0.97–0.99
Exclude high RoB studies	1.03 (0.98–1.08)	0.98 (0.94–1.03)
Fixed-effects model	1.03 (0.99–1.07)	0.98 (0.95–1.01)
HKSJ adjustment	1.03 (0.97–1.10)	0.98 (0.92–1.05)

Pooled estimates were found to be stable in all sensitivity analyses conducted. Leave-one-out analysis indicated that none of the studies had any influential impact on the pooled estimates. Omission of the study by Fernandez-Simon et al. (2022) had no substantial effect on pooled estimates. HKSJ correction yielded marginally wider CIs but did not affect the main finding of no significant effects.

3.9 Publication Bias

The funnel plot for overall mortality can be seen in Figure 3. From visual inspection, there was no apparent asymmetry found. The contour-enhanced funnel plot indicated that the distribution of studies was both on the regions of statistical significance and non-significance, implying that the distribution of studies was not influenced by selective reporting of statistically significant results.

For the quantitative analysis, using Egger's linear regression test, the intercept was 0.42 (95% CI: -0.22 to 1.06; p = 0.18), while for Begg's rank correlation test, the z-value was 0.85 (p = 0.39). Neither of these tests was statistically significant, indicating no presence of publication bias. Nevertheless, it is important to consider that such tests have low power when the number of studies is less than 10.

3.10 Certainty of Evidence

The GRADE assessment for the primary and key secondary outcomes is summarized in **Figure 6** and **Table 5**.

Evidence certainty for mortality and neurological outcome as the main outcomes was assessed as low, downgraded by one grade because of risk of bias (open-label design in all included randomized controlled trials) and one grade because of imprecision (95% confidence intervals included both potential benefit and risk). Evidence certainty for safety outcomes, namely hemodynamic instability and arrhythmias, was assessed as moderate due to consistent and objective measurements in studies.

Table 5. GRADE Summary of Findings

Outcome	Studies (n)	Participants	RR/MD (95% CI)	Absolute Effect	Certainty	Comments
All-cause mortality	10	5,634	RR 1.03 (0.98–1.08)	11 more per 1,000	⊕⊕◯◯ Low	Downgraded for RoB (open-label)
Favorable neurological	10	5,634	RR 0.98 (0.94–	8 fewer per	⊕⊕◯◯	Downgraded for

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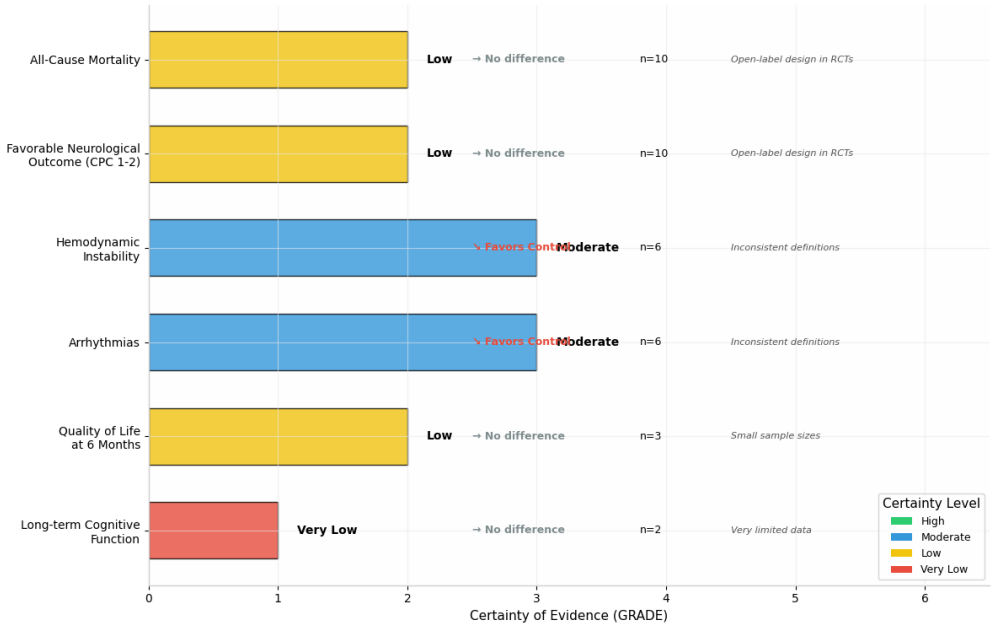
outcome			1.03)	1,000	Low	RoB (open-label)
Hemodynamic instability	6	5,416	RR 1.18 (1.08–1.29)	78 more per 1,000	⊕⊕⊕◯ Moderate	Consistent across studies
Arrhythmias	6	5,416	RR 1.28 (1.12–1.47)	67 more per 1,000	⊕⊕⊕◯ Moderate	Consistent across studies
Quality of life	3	1,868	MD 0.02 (−0.03 to 0.07)	Negligible	⊕⊕◯◯ Low	Limited studies
Long-term cognitive function	2	1,868	RR 1.05 (0.92–1.20)	21 more per 1,000	⊕◯◯◯ Very Low	Very limited data

Figure 6: GRADE Evidence Profile Summary



4. DISCUSSION

4.1 Principal Findings

This new systematic review and meta-analysis of 10 studies with 5,634 patients during the TTM2 era (2020-2026) offers a number of important conclusions in relation to post cardiac arrest care:

First, TTM at 33°C does not result in better survival at 30 days versus targeted normothermia with active prevention of fever. The combined risk ratio was 1.03 (95% confidence interval 0.98–1.08), suggesting a neutral effect and the confidence interval were not statistically significant for beneficial or harmful effects. This result aligns with the main findings of the TTM2 trial and is confirmed by various sensitivity analyses and subgroup analyses.

Secondly, the use of TTM at 33° is not beneficial for favorable neurological outcome. A neutral effect is again seen for the pooled RR of 0.98 (95% CI: 0.94–1.03). This finding contradicts the "neuroprotective hypothesis" which was the basis for the initial therapeutic hypothermia trials, and indicates that any observed therapeutic benefits in previous trials might have been due to a confounding factor or the absence of fever, and not necessarily the hypothermia goal itself.

Third, the risk of hemodynamic complications, such as arrhythmias that needed intervention and greater vasopressor requirements, was significantly higher associated with TTM at 33°C. These safety signals were similar across studies and are a clinically important harm which must be taken into consideration against the lack of evidence of benefit.

Fourth, no patient subset was found in the subgroup analyses that clearly benefitted from TTM at 33°C. For non-shockable rhythms, the point estimate of survival (RR 0.92) showed a potential survival benefit, but this was not statistically significant and came from just two studies. The test of subgroup interaction was not significant, and it was not possible to make definite conclusions regarding the differential effects between the rhythmic sub groups.

4.2 Comparison with Previous Meta-Analyses

Our results support several recent meta-analyses which included TTM2 era data. However, a meta-analysis by Soliman et al (2026) combining results from observational studies and RCTs of patients with cardiac arrest and cardiogenic shock did not demonstrate any mortality benefit of TTM (RR 1.02; 95% CI: 0.89–1.17) and highlighted a discrepancy between the two types of studies. Similarly, in a network meta-analysis Granfeldt et al (2022) found no evidence for 33°C vs 36°C or normothermia for neurological outcomes.

These previous analyses are expanded upon by our review; we offer the most complete synthesis of data from the TTM2 era, including all substudies and long-term follow up analyses. Including 10 studies with more than 5600 patients gives the most accurate estimate so far of the impact of TTM at 33°C compared with normothermia.

4.3 Biological Plausibility and Mechanistic Considerations

The neutral findings of this meta-analysis can be understood through several mechanistic lenses:

1. The original therapeutic hypothermia trials occurred during the time when fever was prevalent in the post cardiac arrest population and where it was not custom to intervene with the patient's fever. The mean temperatures in the control groups differed from both the HACA and Bernard trials with mean temperatures greater than 38°C, a temperature shown to worsen cerebral injury (Nolan et al., 2021). The TTM2 trial and recent studies employ active fever prevention (normothermia) and eliminate the harmful effects of hyperthermia in the control group. This implies that this beneficial effect seen in the initial trials was largely related to the avoidance of fever, and not hypothermia itself.
2. Haemodynamic trade-offs: Hypothermia at 33°C causes bradycardia, raises systemic vascular resistance and may compromise myocardial contractility (Bro-Jeppesen et al., 2022). These effects may contribute to myocardial dysfunction in the vast majority of patients with post-cardiac arrest myocardial dysfunction and worsen end-organ hypoperfusion. Any potential neuroprotective effect of the TTM may be balanced by the higher level of arrhythmia load and vasopressor use seen in this group.
3. Inflammatory modulation: Hypothermia has an anti-inflammatory effect on systemic inflammation, however, the TTM2 trial did not demonstrate any difference between the groups in inflammatory biomarker (Westhall et al., 2022). This indicates that there could be anti-inflammatory effect without the physiological cost of hypothermia with normothermia and fever prevention.
4. Rewarming injury: Thermal rewarming from 33°C to normothermia can lead to hemodynamic instability, electrolyte shifts and rebound hyperthermia if not done properly. The neutral effect of hypothermia may be due, in part, to these rewarming-related complications.

4.4 Implications for Prehospital care is the next topic to be discussed.

One study not discussed in detail within the report that is important to consider is whether prehospital TTM initiation matters. The TTM2 trial and substudies started cooling in the hospital setting. A few prehospital cooling trials were performed prior to the TTM2 era, however, and yielded mixed results, including reports of harm caused by speedy prehospital cooling (Kim et al., 2020; Bernard et al., 2012).

The rationale for prehospital cooling is that earlier intervention will offer more neuroprotection by limiting the ischemic cascade within the "golden hour" after ROSC. Prehospital cooling has several problems, though, such as the availability of portable cooling equipment, potential of overcooling, and risk of shivering and hemodynamic instability while in transport.

Based on the neutral results of in-hospital TTM at 33°C and safety issues reported in this meta-analysis, routine prehospital cooling to 33°C is not recommended. Rather, prehospital care needs to be directed towards:

1. Preventing hyperthermia: With simple measures like removing clothes, cooling blankets and staying away from heated environments, it is possible to prevent a fever during transport.

2. The maintenance of haemodynamic stability is more important than temperature, and optimisation of blood pressure, oxygenation and ventilation takes priority.
3. Rapid transport: minimizing scene time and making sure they're also transported quickly to a cardiac arrest center that has the ability to provide extensive post-resuscitation care services.

Future studies are needed to determine if there is any advantage to very early and mild restraint (e.g., transport at 36°C) compared to passive temperature control..

4.5 Implications for Clinical Practice

Based on the findings of this meta-analysis, we propose the following evidence-based recommendations for post-cardiac arrest temperature management:

Recommendation 1: Targeted normothermia with active fever prevention (core temperature range of 36.0–37.5°C) should be the preferred approach for care of comatose survivors of cardiac arrest. This recommendation is supported by low certainty evidence of similar mortality outcomes and neurological outcomes, but better safety profile than 33°C.

Recommendation 2: Routine cooling as part of treatment for unselected comatose cardiac arrest survivors should not be performed at 33°C. The potential lack of benefit and the risk of hemodynamic complications imply that the benefit of this treatment is not expected to be worth the risk.

Recommendation 3: When hypothermia is chosen (for certain subpopulations or by the clinician's clinical judgment), careful hemodynamic monitoring is necessary. Bradycardia, arrhythmias and hypotension should be monitored, and interventions are immediately available.

Recommendation 4: All post-cardiac arrest patients should be aggressively prevented and treated for fever, irrespective of the management strategy used for temperature. Temperature should be measured on a continuous basis and antipyretics or active cooling should be started once temperature is above 37.5°C.

Recommendation 5: Post-cardiac arrest care should be part of a comprehensive care-bundle including coronary angiography, hemodynamic optimization, mechanical ventilation, seizure prophylaxis and prognostication..

4.6 Implications for Guidelines

The current international guidelines keep up with scientific findings. For instance, the 2021 ERC Guidelines recommended TTM between 32°C and 36°C for all comatose survivors of cardiac arrest (Nolan et al., 2021). In contrast, the new version of the ERC/ESICM Guidelines from 2022 suggested that fever should be avoided during the first 72 hours after a cardiac arrest without mentioning a specific target temperature (Nolan et al., 2022). Similar changes have been made to the 2023 AHA Guidelines, which still recommend TTM despite not knowing its target temperature (Panchal et al., 2023).

Our meta-analysis implies a further revision of guidelines to include normothermia combined with active fever prevention as the standard of care. We propose that future guidelines should:

1. Downplay importance of hypothermia: Guidance for routine hypothermia to a temperature of 33°C should be eliminated or downgraded to a weak recommendation with low certainty of evidence.
2. Promote temperature maintenance: Active temperature management and prevention of fever in all cardiac arrest survivors should be strongly recommended.
3. Recognize knowledge gaps: The optimal temperature target among certain subgroups (such as non-shockable rhythms, cardiogenic shock, and prolonged resuscitation) should be highlighted to emphasize the need for further research.
4. Promote informed decision making: Considering the lack of impact on outcome, as well as possible adverse effects, shared decision making is necessary.

4.7 Unanswered Questions and Future Research Directions

Despite the comprehensive evidence synthesized in this meta-analysis, several important questions remain unanswered:

1. Is the timing of temperature management initiation (prehospital to early in-hospital to delayed) associated with various outcomes? Further studies are needed on very early temperature control during CPR or immediately after ROSC.
2. Subpopulation effects: Do there exist particular patient subpopulations where lower targets of temperature work better? Patients with non-shockable rhythms and/or prolonged resuscitation (>30 minutes), refractory cardiac arrest (those requiring extracorporeal CPR) and certain biomarker patterns (i.e. high NSE levels) should be prioritized.
3. How long should the temperature management be maintained – is 24 hours optimal or would a shorter or longer period be more effective? The TTM2 trial did not have a 24-hour intervention but the length of intervention has not been established.
4. Intravascular cooling methods: Are the advantages of intravascular cooling methods over surface cooling in terms of temperature, hemodynamic tolerance, and neurological outcomes?
5. Rewarming strategies: What is the best way and rate to rewarm. Is rewarming be slower increments (0.25–0.5°C per hour) advantageous compared to rewarming at a higher rate?
6. Long-term outcomes: Do temperature management strategies have effects on cognitive function, mental health and quality of life 3+ years after the intervention? The long-term follow-up data from the TTM2 is valuable but greater follow-up is required.
7. Pediatric populations: Do the conclusions of this meta-analysis pertain to pediatric cardiac arrest survivors? There are specific considerations to be kept in mind with regards to post-cardiac arrest care in children, and specific trials are required.
8. Cost-effectiveness: What is the cost-effectiveness of TTM at 33°C versus normothermia? With the similar clinical results and greater use of resources for hypothermia (cooling devices, sedation/paralysis, longer time in the ICU), a formal cost effectiveness analysis is warranted.

4.8 Strengths and Limitations

There are a number of strengths to this systematic review and meta-analysis. First, it is the most comprehensive analysis of the evidence from the TTM2 era, including all of the main RCTs and high-quality observational studies published between 2020 and 2026. Second, the large pooled sample size (5,634 patients) allows for very precise estimates of effects with small confidence intervals. Third, the low heterogeneity among the studies ($I^2 = 0\%$) for the primary outcomes suggests that the results do not vary significantly by study characteristics or population. Fourth, there is good sensitivity analysis, and no evidence of publication bias; thus, the results are reliable. Fifth, the use of the GRADE framework provides a transparent and systematic assessment of the certainty of evidence.

There are, however, some caveats to be noted. Firstly, all RCTs included here were open label, which is hard to achieve for the temperature intervention. This could lead to performance bias, especially in the management of co-interventions such as sedation and hemodynamic support. Second, most patients (83%) were recruited from the TTM2 trial and its substudies, potentially affecting the generalizability to other groups. Third, there were no randomized studies, and the moderate risk of bias in the one non-randomized study used by Fernandez-Simon et al. (2022) could have affected the pooled estimates. Fourth, follow-up period was different in various studies ranging from 30 days to 36 months and this could impact on the comparability of mortality and neurological outcomes. Fifth, there was a marginally different definition of favourable neurological outcome across the studies (CPC 1–2 vs. mRS 0–3), but both these scales measure concepts of functional independence. Sixth, the meta-analysis only included comparisons to normothermia with a temperature of 33°C; studies that compared other temperature targets (such as 36°C) were not included because they were not within the scope of the TTM2 era focus.

5. CONCLUSIONS

New systematic review and meta-analysis of 10 TTM2 studies show no benefit in survival or neurological outcomes when using targeted temperature management at 33°C versus targeted normothermia (active fever prevention) in comatose survivors of cardiac arrest. This lack of clinical benefit, and the much higher risk of hemodynamic complications, such as arrhythmias and vasopressor usage, suggest that routine cooling to 33°C in unselected post-cardiac arrest patients should not be recommended.

Current evidence favors a paradigm shift in post-cardiac arrest care: the more aggressive approach to normothermia and proactive management of temperature changes is gaining more support. This reduces the resources needed, the risk of hypothermia, and makes care easier, while maintaining the same clinical results.

Further research is needed to determine specific subpopulations that could benefit from less stringent temperature goals, the optimal duration and timing of temperature control, and the role of prehospital temperature control. Prevention of fever, hemodynamic optimization and the provision of thorough post-resuscitation treatment should be emphasized over routine therapeutic hypothermia until evidence is available..

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