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Review

Targeted temperature management in adult cardiac arrest: Systematic review and meta-analysis

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Abstract

Aim: To perform a systematic review and meta-analysis on targeted temperature management in adult cardiac arrest patients.

Methods: PubMed, Embase, and the Cochrane Central Register of Controlled Trials were searched on June 17, 2021 for clinical trials. The population included adult patients with cardiac arrest. The review included all aspects of targeted temperature management including timing, temperature, duration, method of induction and maintenance, and rewarming. Two investigators reviewed trials for relevance, extracted data, and assessed risk of bias. Data were pooled using random-effects models. Certainty of evidence was evaluated using GRADE.

Results: The systematic search identified 32 trials. Risk of bias was assessed as intermediate for most of the outcomes. For targeted temperature management with a target of 32–34 °C vs. normothermia (which often required active cooling), 9 trials were identified, with six trials included in meta-analyses. Targeted temperature management with a target of 32–34 °C did not result in an improvement in survival (risk ratio: 1.08 [95%CI: 0.89, 1.30]) or favorable neurologic outcome (risk ratio: 1.21 [95%CI: 0.91, 1.61]) at 90 to 180 days after the cardiac arrest (low certainty of evidence). Three trials assessed different hypothermic temperature targets and found no difference in outcomes (low certainty of evidence). Ten trials were identified comparing prehospital cooling vs. no prehospital cooling with no improvement in survival (risk ratio: 1.01 [95%CI: 0.92, 1.11]) or favorable neurologic outcome (risk ratio: 1.00 [95%CI: 0.90, 1.11]) at hospital discharge (moderate certainty of evidence).

Conclusions: Among adult patients with cardiac arrest, the use of targeted temperature management at 32–34 °C, when compared to normothermia, did not result in improved outcomes in this meta-analysis. There was no effect of initiating targeted temperature management prior to hospital arrival. These findings warrant an update of international cardiac arrest guidelines.

Keywords: Cardiac arrest, Targeted temperature management, Hypothermia, Cooling, Systematic review

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Introduction

Out-of-hospital cardiac arrest (OHCA) affects over 350,000 individuals in the United States,[1] and 275,000 individuals in Europe[2,3] each year. In-hospital cardiac arrest (IHCA) occurs in an estimated 290,000 patients per year in the United States.[4] The mortality remains high for both conditions with only approximately 10% surviving OHCA and 30% surviving IHCA.[1,5,6]

Cardiac arrest causes whole body ischemia with subsequent reperfusion injury during cardiopulmonary resuscitation (CPR) and return of spontaneous circulation (ROSC). This elicits a complex pathophysiological response that has been termed the post-cardiac arrest syndrome.[7] In order to mitigate organ dysfunction inflicted by the post-cardiac arrest syndrome, post-resuscitation care has received considerable attention and is now incorporated into international guidelines.[8,9] Post-resuscitation care includes therapies aimed at optimizing ventilation and circulation, preserving organ/tissue function, and reducing post-resuscitation injury.

Targeted temperature management (TTM) with a target of 32–34 °C has been a mainstay of post-resuscitation care since early trials in 2002 suggested a beneficial effect after OHCA.[10,11] Since then, many studies have investigated different aspects of TTM including timing, temperature targets, duration, and methods. After publication of the "TTM1 trial" in 2013, which did not demonstrate a benefit with a target of 33 °C compared to a target of 36 °C, there has been debate about the optimal target temperature for post–cardiac arrest patients.[12] The topic was last addressed by the International Liaison Committee on Resuscitation (ILCOR) in 2015.[13] With new evidence available from multiple randomized trials including the large "TTM2 trial".[14,17] an updated systematic review of the evidence is warranted.

The aim of this study was to perform a systematic review and meta-analysis of all aspects of TTM including timing, temperature, duration, method, and rewarming in order to inform international cardiac arrest guidelines.

Methods

Protocol and registration

The protocol was prospectively submitted to the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42020217954) on October 28, 2020 and is provided in the Supplementary Content. This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[18] The PRISMA checklist is provided in the Supplementary Content. The review was commissioned by the International Liaison Committee on Resuscitation (ILCOR).

Eligibility criteria and outcomes

The review focuses on adult patients with cardiac arrest in any setting (in-hospital or out-of-hospital) and includes all aspects of TTM. This includes 1) TTM at 32–34 °C compared with no TTM or TTM with a normothermic target, 2) the timing of initiating TTM, 3) the specific target temperature, 4) the duration of TTM, 5) the method used for TTM, and 6) the rewarming rate in cooled patients. The specific study questions were framed using the PICO (Population, Intervention, Comparison, Outcome) format and are provided in the protocol.

Relevant outcomes were prioritized by the ILCOR Advanced Life Support Task Force based on the available outcomes reported in the literature. We included short-term survival (ROSC or alive at admission), mid-term survival (survival at discharge or 28/30 days), mid-term favorable neurologic outcome, long-term survival, and long-term favorable neurologic outcome. A favorable neurologic outcome was generally defined as a modified Rankin Scale score of 0–3 or a Cerebral Performance Category score of 1 or 2. These scores generally indicate that the patient does not need assistance with activities of daily living. Although these scores indicate both neurologic and functional outcomes, we use the term "favorable neurologic outcome" throughout for simplicity. We also included outcomes related to health-related quality of life, cognitive function, and anxiety and depression.

We included controlled trials in humans including randomized and non-randomized trials (e.g., pseudo-randomized trials). Observational studies, ecological studies, case series, case reports, reviews, abstracts, editorials, comments, letters to the editor, and unpublished studies were not included. Studies assessing cost-effectiveness were included. All years and all languages were included as long as there was an English abstract or an English full-text article.

Information sources and search strategy

On October 30, 2020, and again on June 17, 2021, we searched the following databases: PubMed, Embase, and the Cochrane Central Register of Controlled Trials. The search included a combination of various text and indexing search terms for cardiac arrest and TTM. To identify randomized trials, the Cochrane sensitivity-maximizing search strategy was used.[19] The search strategy for each database is provided in the protocol. The reference lists of included articles were reviewed for potential additional articles. For key outcomes included in meta-analyses, we contacted the authors for the data if the outcome was not reported.

To identify registered ongoing or unpublished trials, we searched the International Clinical Trials Registry Platform and ClinicalTrials.gov on February 1st, 2021. Additional details are provided in the Supplementary Content.

Study selection

Two reviewers independently screened all titles and abstracts retrieved from the systematic search. Any disagreements regarding inclusion or exclusion were resolved via discussion between the reviewers and with a third reviewer as needed. Two reviewers then independently reviewed the full texts of all potentially relevant publications passing the first level of screening. Any disagreement regarding eligibility was resolved via discussion. The Cohen's Kappa values for inter-observer variance were calculated.

Data collection

Two reviewers, using a pre-defined standardized data extraction form, extracted data from individual manuscripts. Any discrepancies in the extracted data were identified and resolved via discussion.

Risk of bias in individual studies

Two reviewers independently assessed risk of bias for individual studies using version 2 of the Cochrane risk-of-bias tool for randomized trials.[20] Disagreements were resolved via discussion. Risk of bias was assessed for each outcome within a trial but is reported at the trial level as the highest risk of bias score across all outcomes. In most included trials, the risk of bias was the same across all out-

comes. If the bias was different for different outcomes, this was noted. Additional considerations about bias assessment are provided in the Supplementary Content.

Data synthesis

Studies were evaluated for clinical (i.e., participants, interventions, and outcomes) and methodological (i.e., study design and risk of bias) heterogeneity. Statistical heterogeneity was assessed using forest plots, Chi-squared statistics, and I-squared statistics.[21] DerSimonian and Laird random effects meta-analyses with the Mantel-Haenszel method were conducted using RevMan version 5 (The Cochrane Collaboration, 2020). Results are reported as risk ratios with 95% confidence intervals.

We considered trial groups using no TTM, no clear description of TTM, or TTM to maintain normothermia (generally 36.5–38 °C) to be comparable. This group is labeled as "normothermia" throughout the manuscript and additional details about the individual trials are provided in the text and tables. For the comparison of TTM at 32–34 °C and normothermia, we performed a number of post-hoc sensitivity analyses. First, we conducted meta-analyses after excluding trials with a high risk of bias and trials more than 10 years old, respectively. Second, since 36 °C can be considered to be within the normothermic range,[22] we conducted a sensitivity analysis where targeting 36 °C was considered to be equivalent to normothermia.

Based on data availability, pre-specified subgroup analyses were conducted according to the reported initial cardiac arrest rhythm categorized as shockable (ventricular fibrillation and pulseless ventricular tachycardia) or non-shockable (asystole and pulseless electrical activity). Other pre-specified subgroups were not feasible based on the available data.

Confidence in cumulative evidence

The certainty of the overall evidence for a given comparison and outcome was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology and classified within one of four categories: very low, low, moderate, or high certainty of evidence.[23] GRADEpro (McMaster University, 2020) was used for drafting of the GRADE tables.

Results

Overview

The search identified 2328 unique records of which 139 full-text articles were assessed for eligibility. Thirty-eight manuscripts representing 31 trials were identified (Fig. 1). One additional trial was identified after review of references, yielding a total of 32 trials published between 2001 and 2021. The search identified one cost-effectiveness analysis from 2009.[24] The search for registered ongoing or unpublished trials identified nine trials although many were registered multiple years ago and had unknown recruitment status (eTable 1). We did not identify any trials assessing rewarming rate.

Targeted temperature management at 32–34 °C

Nine trials compared TTM at 32–34 °C with normothermia (Table 1).[10,14,17,25–30] Most trials were small feasibility or pilot trials and only three trials included more than 100 patients.[14,17,27] There was some heterogeneity in the patient populations and interventions although most trials exclusively included patients with OHCA and tested TTM in the range 32 to 34 °C for approximately 24 hours. Only two trials included a small proportion of patients with in-hospital cardiac arrest.[14,27] Management of the control group varied between the trials although most targeted normothermia in the range of 36.5 to 38 °C. While older trials provided little information of how normothermia was maintained, newer trials used active device cooling in approximately half of the patients in the normothermia group.[14,17] Additional details about the trials are provided in eTable 2–3.

Three small trials were assessed to have a high risk of bias whereas the remaining were considered to have an intermediate risk of bias primarily due to lack of blinding of the treating clinicians (eTable 4).

Meta-analyses were conducted, including six trials that were deemed to be comparable, for outcomes at hospital discharge or 30 days, and for long-term outcomes.[10,14,17,27,29,30] TTM at 32 to 34 °C for 12 to 24 hours compared with normothermia did not result in a statistically significant improvement in any of the outcomes (Fig. 2). Results were similar when trials with high risk of bias were excluded (eFig. 1), when the analyses were restricted to the two trials published within the last 10 years (both of which used active treatments in the control group) (eFig. 2),[14,17] and when considering TTM at 36 °C as normothermia (eFig. 3). For most of the outcomes, the results from the sensitivity analyses were attenuated towards the null. Results were consistent in pre-defined subgroups defined by the initial rhythm (shockable and non-shockable) (eFig. 4 + 5). Additional details on outcomes are provided in eTable 5–7.

Of the remaining trials not included in meta-analyses, three very small trials included a very short duration of TTM (≤4 hours),[25,26,30] while one very small trial included 72 hours of TTM.[28] None of these trials found a difference in outcomes.

Using GRADE, the overall certainty in the evidence for TTM at 32–34 °C vs. normothermia was low for all included outcomes (eTable 8).

Hypothermic temperature targets

Three trials compared different temperature targets (Table 2 and eTables 9 and 10).[12,31,32] The trials were assessed as having an intermediate risk of bias primarily due to lack of blinding (eTable 11). The trials found no difference in outcomes (eTables 12–14). This includes the "TTM trial" published in 2013 that included 950 patients and found no difference in outcomes between 33 °C and 36 °C.[12] The two other trials found no difference between 32 °C, 33 °C, and 34 °C.[31,32]

Using GRADE, the overall certainty in the evidence for these temperature target comparisons was low for all included outcomes (eTables 15–18).

Timing of targeted temperature management initiation

Eleven trials assessed timing of TTM initiation (Table 3).[15,33–42] Specifically, 10 trials compared prehospital with no prehospital cooling for patients with OHCA.[15,33–38,40–42] Six trials tested post-cardiac arrest rapid intravenous cold fluid infusion,[33–35,37,38,42] two tested intra-cardiac arrest intravenous cold fluid infusion,[40,41] and two tested intra-cardiac arrest intra-nasal cooling.[15,42] The use of in-hospital TTM after the prehospital intervention varied across trials (Table 3). Additional details about the trials are provided in eTables

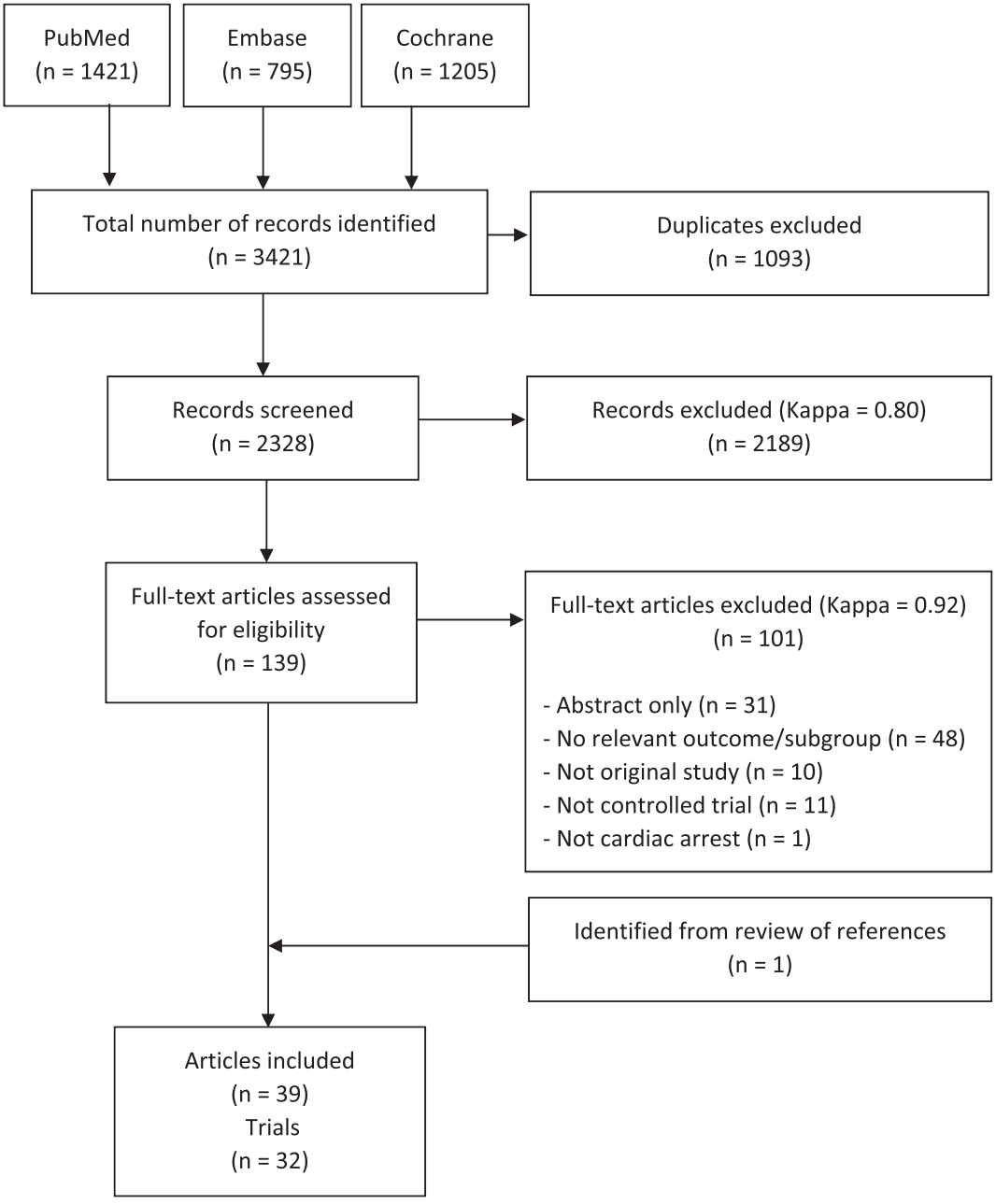


Fig. 1 – PRISMA diagram. Chart illustrating the flow of articles.

19 and 20. All trials were assessed as having an intermediate risk of bias primarily due to a lack of blinding (eTable 21).

Meta-analysis of prehospital vs. no prehospital cooling, with subgroups based on the type of cooling, is provided in Fig. 3. Prehospital cooling did not result in improved survival to hospital discharge (risk ratio: 1.01 [95%CI: 0.92, 1.11]) or survival to hospital discharge with a favorable neurologic outcome (risk ratio: 1.00 [95%CI: 0.90, 1.11]). There was no indication of effect measure modification according to the cooling method (P = 0.61 and P = 0.40 for the two outcomes). For trials testing intra-cardiac arrest cooling, prehospital cooling did not result in a difference in ROSC/admission alive (risk ratio: 0.95 [95%CI: 0.84, 1.07], eFig. 6). For all the outcomes, results were similar in subgroups according to initial rhythm (shockable and non-shockable, eFig. 7 + 8). Additional details on outcomes are provided in eTable 22. Three trials reported outcomes after hospital discharge and found no difference between groups (eTable 23).[15,40,43]

Using GRADE, the overall certainty in the evidence for prehospital vs. no prehospital cooling was assessed as moderate for both survival to hospital discharge and survival to hospital discharge with a favorable neurologic outcome (eTable 24).

Method and duration of targeted temperature management

Seven trials compared different methods of TTM, while one trial compared different TTM durations (Table 4). The majority of the trials were small feasibility or pilot trials with six out of eight trials including fewer than 100 patients. Additional information about the trials is pro-

Table 1 – Use of targeted temperature management at 32–34 °C.

Study	Time of patient inclusion	Main inclusion criteria	Patients	Intervention	Control	Risk of bias[c]
Hachimi-Idrissi, 2001[25]	NR	OHCA, non-shockable rhythm	30	TTM, 34 °C, 4 hours	No TTM, < 38 °C with acetaminophen	Intermediate
Callaway, 2002[26]	1996–1998	OHCA	22	TTM intra-arrest, 34 °C, until ROSC	No TTM	High
HACA, 2002[27]	1996–2001	OHCA or IHCA, shockable rhythm, witnessed	275	TTM, 32–34 °C, 24 hours	No TTM, "normothermia" without further details	Intermediate
Bernard, 2002[10]	1996–1999	OHCA, VF	77	TTM, 33 °C, 12 hours[a]	No TTM, 37 °C without further details	High
Zhang, 2005[28]	2002	Cardiac arrest	16	TTM, 33 °C, 72 hours	No TTM	High
Laurent, 2005[29b]	2000–2002	OHCA	42	TTM, 32–33 °C, 16 hours	No TTM	Intermediate
Hachimi-Idrissi, 2005[30]	1999–2002	OHCA, non-shockable rhythm	33	TTM, 33 °C, 4 hours[a]	No TTM, 37 °C without further details	Intermediate
Hachimi-Idrissi, 2005[30]	1999–2002	OHCA, shockable rhythm, witnessed	28	TTM, 33 °C, 24 hours	No TTM, 37 °C without further details	Intermediate
Lascarrou, 2019[14]	2014–2018	OHCA or IHCA, non-shockable rhythm	584	TTM, 33 °C, 24 hours	TTM 36.5–37.5°C[d,e]	Intermediate
Dankiewicz, 2021[17]	2017–2020	OHCA	1861	TTM, 33 °C, 28 hours	Only TTM if > 37.8 °C, then 37.5°C[d]	Intermediate

TTM: Targeted temperature management, OHCA: out-of-hospital cardiac arrest, IHCA: in-hospital cardiac arrest, NR: not reported, VF: ventricular fibrillation, ROSC: return of spontaneous circulation, HACA: "Hypothermia after Cardiac Arrest"

[a]Cooling was initiated in the pre-hospital setting.

[b]The trial included three groups. Here we focus on the two groups that received hemofiltration.

[c]Detailed bias assessment is provided in eTable 4.

[d]Approximately half of the patients received cooling using a dedicated device.

[e]Patients were actively warned if they were < 36.5 °C.

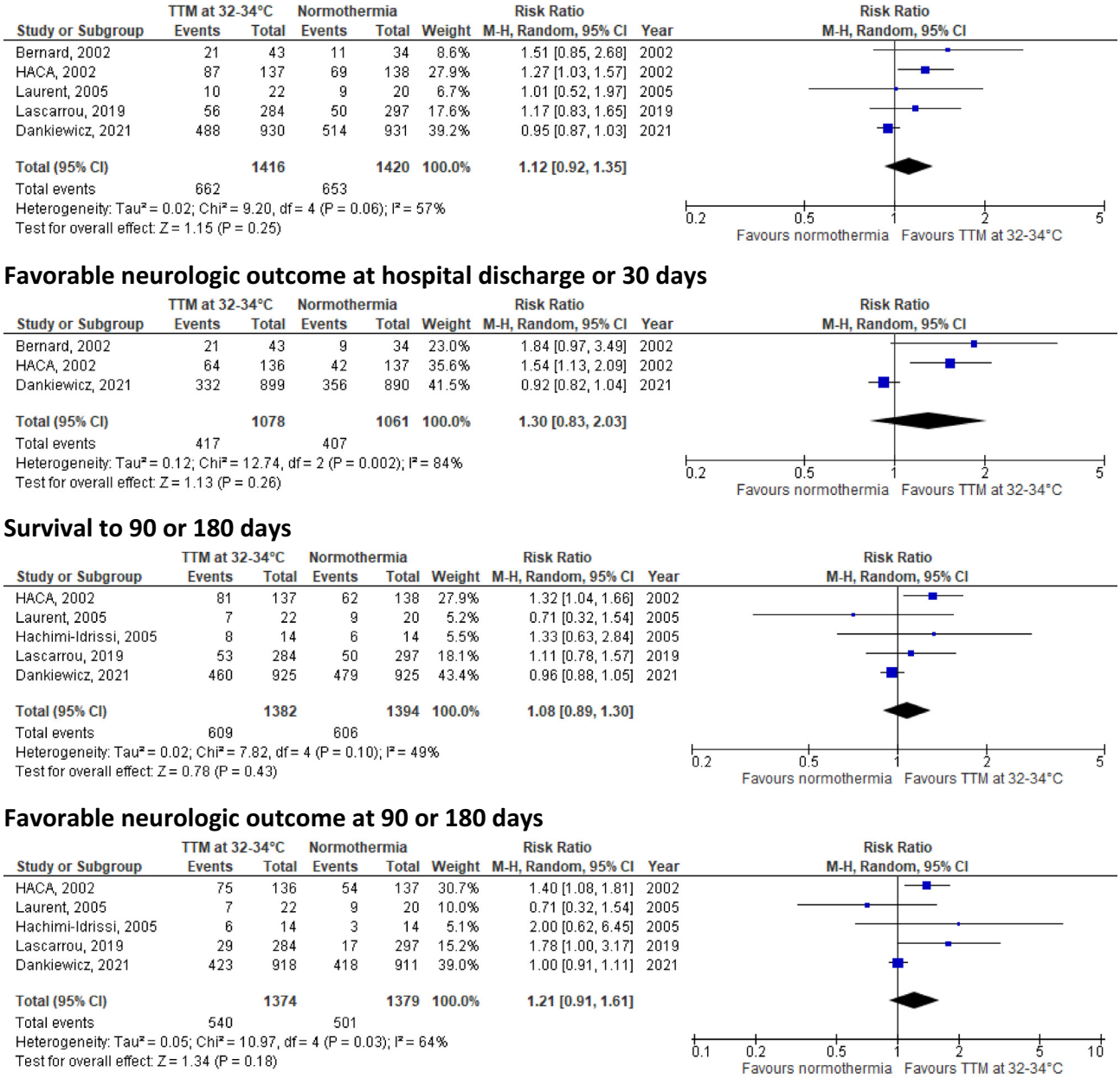


Fig. 2 – Meta-analyses of targeted temperature management. Random-effects meta-analyses of TTM at 32–34 °C compared to normothermia for outcomes at hospital discharge or 30 days and 90 or 180 days.

vided in eTable 25 and 26. One trial was assessed as having a high risk of bias whereas the others were at an intermediate risk (eTable 27). Additional details on outcomes are provided in eTable 28–30.

Three trials, targeting 33 or 34 °C, compared endovascular with surface cooling and were included in a meta-analysis.[44–46] Endovascular cooling did not result in a statistically significant improvement in survival to hospital discharge/28 days (risk ratio: 1.14 [95%CI: 0.93, 1.38]) or survival with a favorable neurologic outcome (risk ratio: 1.22 [95%CI: 0.95, 1.56]) (Fig. 4).

The trial on TTM duration, which included 355 patients, targeted 32–34 °C, and compared 48 with 24 hours of TTM, found no difference in outcomes.[16]

Using GRADE, the overall certainty in the evidence for endovascular vs. surface cooling was assessed as low for both survival to hospital discharge and survival to hospital discharge with a favorable neurologic outcome (eTable 31). The overall certainty in the evidence for 48 compared with 24 hours of TTM at 32–34 °C was also low (eTable 32).

Discussion

The current systematic review, including 32 randomized clinical trials, provides an update on multiple aspects of TTM including timing, target temperature, duration, method, and rewarming. Meta-

Table 2 – Different temperature targets.

Study	Time of patient inclusion	Main inclusion criteria	Patients	Intervention	Control	Risk of bias[b]
Lopez-de-Sa, 2012[31]	2008–2011	OHCA, witnessed	36	TTM, 32 °C, 24 hours	TTM, 34 °C, 24 hours	Intermediate
Nielsen, 2013[12]	2010–2103	OHCA	950	TTM, 33 °C, 28 hours	TTM, 36 °C, 28 hours	Intermediate
Lopez-de-Sa, 2018[32a]	2014–2016	OHCA, shockable rhythm, witnessed	150	TTM, 32 or 33 °C, 24 hours	TTM, 34 °C, 24 hours	Intermediate

TTM: Targeted temperature management, OHCA: out-of-hospital cardiac arrest, IHCA: in-hospital cardiac arrest, NR: not reported, VF: ventricular fibrillation, ROSC: return of spontaneous circulation, HACA: "Hypothermia after Cardiac Arrest"
[a]The trial included three groups.
[b]Detailed bias assessment is provided in eTable 11.

analyses did not identify any differences in outcomes when comparing TTM at 32 to 34 °C with normothermia, prehospital with no prehospital initiation of cooling, or different methods of achieving and maintaining TTM at 32–34 °C.

TTM, originally termed therapeutic hypothermia, for the treatment of post-cardiac arrest brain injury originates from clinical case series in the 1950s.[47] The detrimental effects of systemic cooling at that time precluded widespread clinical implementation. The use of TTM with a hypothermic target was later revived by several animal studies demonstrating a protective effect on brain injury.[48,49] Recently, two systematic reviews on TTM in animals were published demonstrating a consistent and strong protective effect across animal species and models.[50,51] The mechanisms involved in the potential protective effect of TTM were not clear at the time of the first clinical trials, although they were partly attributed to a reduction in cerebral metabolism.[52] Subsequently, many studies have investigated the protective effects of TTM and have demonstrated an array of potential mechanistic pathways, including anti-oxidant, anti-apoptotic and anti-inflammatory effects and a decrease in the accumulation or release of excitotoxic amino acids.[53,54] The positive results from animal studies led to several non-randomized pilot studies[55,56] before the publication of the two landmark trials in 2002.[10,11] This led to inclusion of TTM in the 2005 European and North American cardiac arrest guidelines.[57,58]

The results of the meta-analyses indicated no benefit of TTM at 32–34 °C as compared to normothermia, although the certainty in the evidence was rated as low. This low rating was primarily driven by a risk of bias due to no blinding of the clinical team and inconsistency in the results from the different trials and the related imprecision (i.e., wide confidence intervals) of the estimated effects. While some smaller trials found a potential benefit of TTM at 32–34 °C,[10,14,27] the recent, large "TTM2 trial" by Dankiewicz et al. found no benefit of TTM at 33 °C compared to maintenance of normothermia, a finding that was consistent across outcomes and subgroups.[17] Similarly, the large "TTM1 trial" found no benefit of TTM at 33 °C compared to TTM at 36 °C.[12] Some differences exists between the trials comparing TTM at 32–34 °C to normothermia and included in the meta-analyses, for example in patient characteristics and details of the intervention. Time to target temperature differed between the trials and control of temperature in the normothermia group varied, with some of the older trials providing no information on avoidance of fever, while newer trials provided detailed protocols and reported the number of patients actively cooled using devices to achieve normothermia (approximately 50% of patients in Lascarrou et al.[14] and Dankiewicz et al.[17]. Furthermore, two decades have passed since the initial trials with multiple changes in management, including more protocolized neurological prognostication, and improved survival rates over time.[59,60] However, as these differences were inconsistent between trials reporting no effect of TTM at 32–34 °C or reporting a potential protective effect, the impact of these differences on the results are unclear. Given the limited number of trials, it was not possible to explore this heterogeneity further (e.g., by performing meta-regression). A potential limitation of the majority of the included trials, including the four large trials,[11,12,14,17] is a prolonged time to reaching target temperature. Although this likely reflects current clinical practice in many places,[16,61–65] it is possible that more rapid in-hospital cooling could influence outcomes.

The optimal timing of TTM has been of interest since the publication of the landmark trials in 2002. In the "HACA trial", which demonstrated a strong protective effect of TTM, the median time to initiation of cooling after the ROSC was approximately 2 hours and the median time to the target temperature (32–34 °C) was 8 hours.[11] Following the HACA trial, animal studies challenged this delay in initiating TTM by demonstrating that TTM was more effective if started earlier.[66,67] This led to a clinical pilot trial by Kim et al. demonstrating that rapid infusion of cold saline prehospital was feasible and effective in lowering body temperature.[33] Subsequently, multiple trials, including a cumulative total of almost five thousand patients, have tested various methods of prehospital cooling. In meta-analyses of these trials, we found no difference in outcomes between groups and no indication that the method of cooling in the prehospital setting modified this. In the subgroup of patients with an initial shockable rhythm, the results favored intra-cardiac arrest intra-nasal cooling (eFig. 6), but the confidence intervals were wide, and the results should be interpreted carefully. An important limitation of some of the included trials is the lack of a standardized in-hospital TTM protocol to ensure that all included patients received TTM in the hospital.

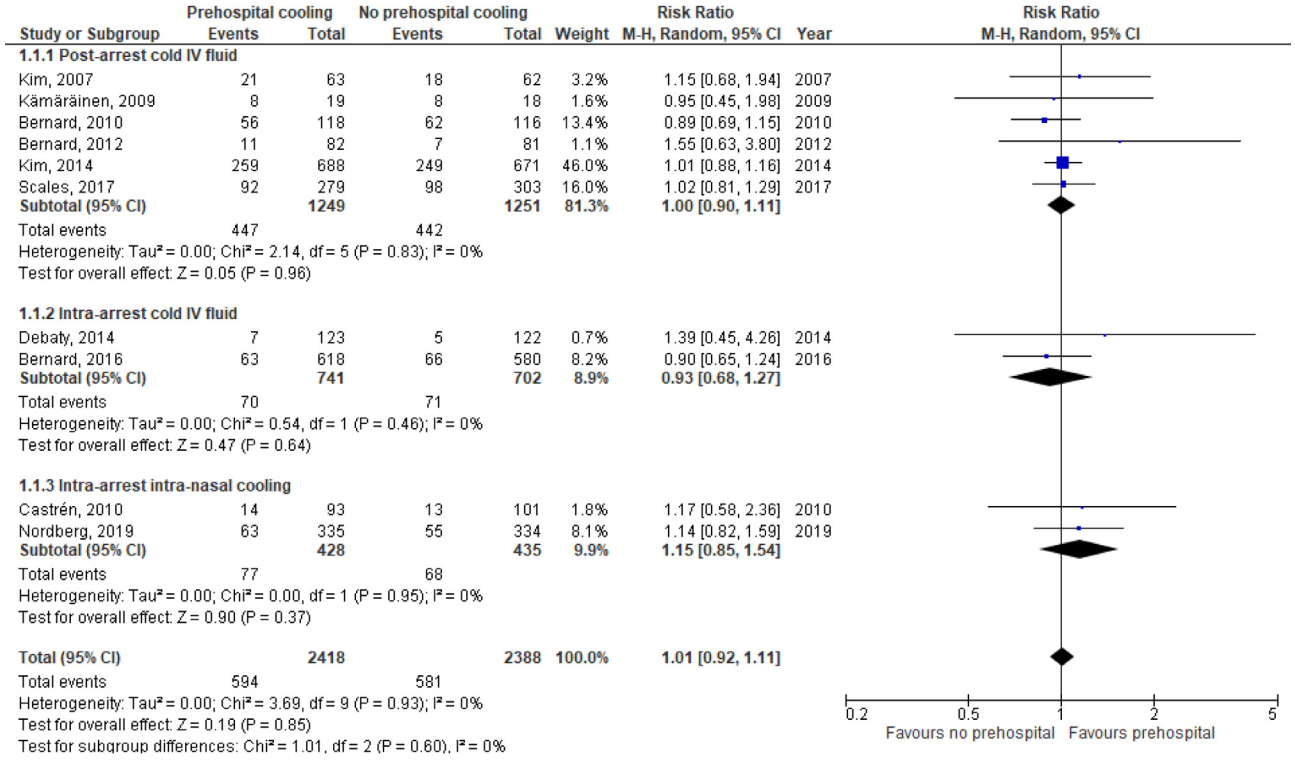
TTM can be achieved by several different methods, including simple interventions such as rapid infusion of cold fluids and application of ice packs, cooling blankets or gel-adhesive pads with feedback mechanisms, or automated endovascular devices. Endovascular devices might theoretically improve outcomes by a reduction in time to target temperature, by maintaining a consistent target temperature, and by controlling re-warming. Despite these theoretical advantages, endovascular cooling did not improve outcomes in the meta-analyses. These results are in contrast to a recent

Table 3 – Timing of targeted temperature management.[a]

Study	Time of patient inclusion	Main inclusion criteria	Patients	Intervention[b]	Control	Patients receiving in-hospital TTM
Kim, 2007[33]	2004–2006	OHCA	125	Prehospital cold IV fluid	No prehospital cooling	62%
Kämäräinen, 2009[34]	2005–2008	OHCA	37	Prehospital cold IV fluid	No prehospital cooling	53% vs. 72%
Bernard, 2010[35]	2005–2007	OHCA, shockable rhythm	234	Prehospital cold IV fluid	In-hospital cold IV fluid	NR
Castrén, 2010[36]	2008–2009	OHCA, witnessed	200	Prehospital transnasal intra-arrest cooling	In-hospital cooling	NR
Bernard, 2012[37]	2005–2007	OHCA, non-shockable rhythm	163	Prehospital cold IV fluid	In-hospital cold IV fluid	93% vs. 79%
Kim, 2014[38]	2007–2012	OHCA	1364	Prehospital cold IV fluid	No prehospital cooling	65%
Takeda, 2014[39]	2009–2013	OHCA or IHCA, witnessed	113	Intra- or post-arrest pharyngeal cooling in the ED	No pharyngeal cooling	72% vs. 65%
Debaty, 2014[40]	2009–2012	OHCA	245	Prehospital intra-arrest cold IV fluid + cooling pads	In-hospital cooling	NR
Bernard, 2016[41]	2010–2014	OHCA	1324	Prehospital intra-arrest cold IV fluid	No prehospital cooling	NR
Scales, 2017[42]	2012–2016	OHCA	585	Prehospital cold IV fluid + ice packs	No prehospital cooling	68% vs. 56%
Nordberg, 2019[15]	2010–2018	OHCA, witnessed	677	Prehospital transnasal intra-arrest cooling	In-hospital cooling	NR

TTM: Targeted temperature management, OHCA: out-of-hospital cardiac arrest, IHCA: in-hospital cardiac arrest, NR: not reported, IV: intravenous.
[a]All trials were assessed as having an overall intermediate risk of bias. Additional detail is provided in eTable 21.
[b]Unless otherwise noted, the intervention was started after return of spontaneous circulation.

Survival to hospital discharge



Favorable neurologic outcome at hospital discharge

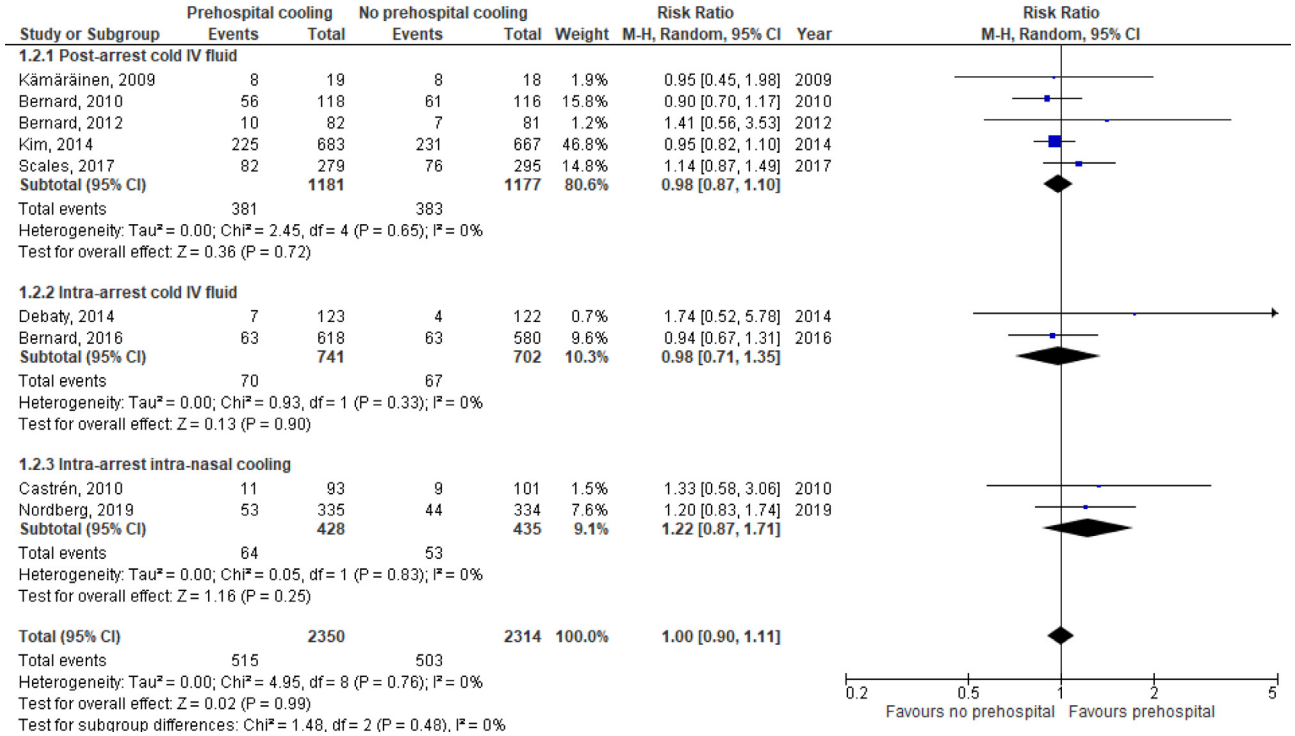


Fig. 3 – Meta-analyses of prehospital cooling. Random-effects meta-analyses of prehospital cooling compared to no prehospital cooling for outcomes at hospital discharge. Trials are subgrouped according to the type of cooling method.

Table 4 – Methods and duration of targeted temperature management at 32–34 °C.

Study	Time of patient inclusion	Main inclusion criteria	Patients	Intervention[a]	Control[a]	Risk of bias[d]
Method						
Heard, 2010[72]	2004–2007	OHCA	64	Cooling pads	Cooling blankets + ice packs	Intermediate
Rana, 2011[73]	NR	OHCA	50	Cooling sleeves[b]	Cold IV fluid + ice/cold packs	Intermediate
Pittl, 2013[44]	2008–2009	OHCA or IHCA	80	Endovascular cooling	Cooling pads	Intermediate
Islam, 2015[74]	2013–2014	OHCA	74	Intranasal	cooling + cooling blanket	Cooling blanket
Intermediate						
Li, 2015[75]	2011–2013	OHCA	45	Cold IV saline	Ice packs	High
Deye, 2015[45]	2006–2009	OHCA	400	Endovascular cooling	Fans, ice packs	Intermediate
Look, 2018[46]	2008–2014	OHCA or IHCA	45	Endovascular cooling	Cooling pads	Intermediate
Duration						
Kirkegaard, 2017[16c]	2017	OHCA	355	48 hours	24 hours	Intermediate

OHCA: out-of-hospital cardiac arrest, IHCA: in-hospital cardiac arrest, NR: not reported, IV: intravenous.
[a]All studies used TTM with a target temperature within the range 32–34 °C for 24 hours unless noted otherwise.
[b]Two interventional groups were included (0.35 or 0.7 m2 surface area of colling sleeves).
[c]Both invasive and noninvasive methods of cooling were used in both groups.
[d]Detailed bias assessment is provided in eTable 27.

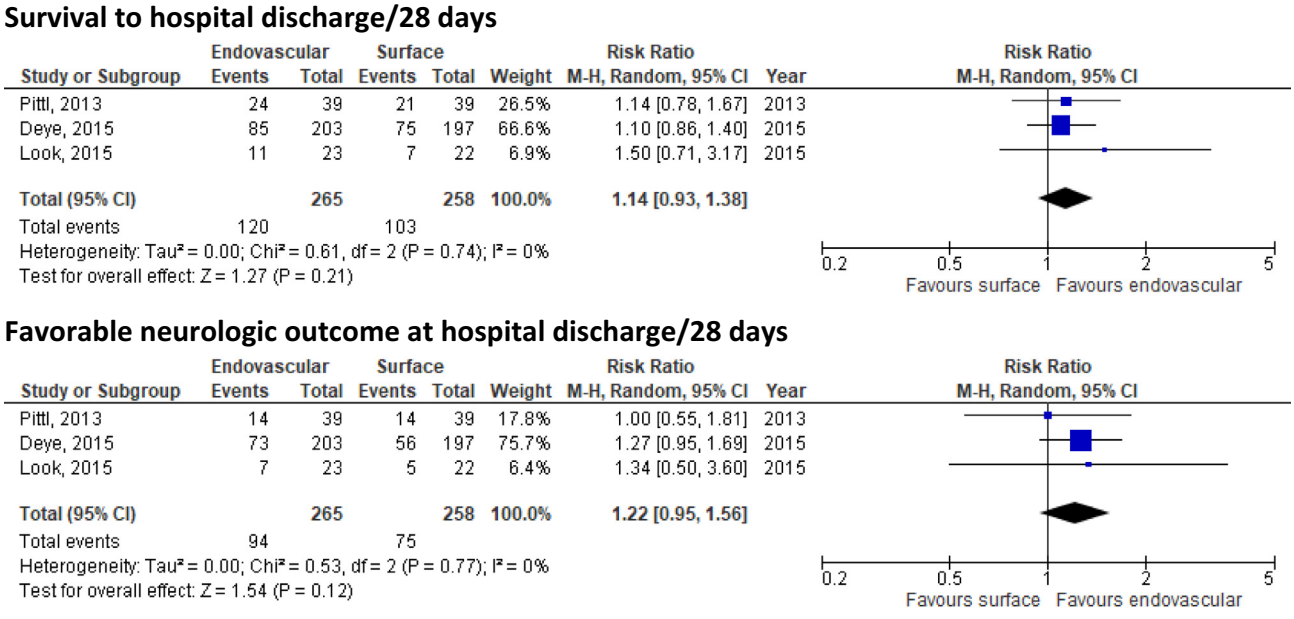


Fig. 4 – Meta-analyses of endovascular vs. surface cooling. Random-effects meta-analyses for endovascular compared to surface cooling for outcomes at hospital discharge/28 days.

systematic review, which concluded that endovascular cooling improved neurologic outcomes.[68] Contrary to this current review, that review included observational studies.[68] We decided a priori not to include observational studies in the current review because of the inherent high risk of bias in such studies and the availability of randomized trials.

The 12- and 24-hour durations of TTM, used in the early trials, were based on balancing the time needed for an effect and potential side effects of prolonged TTM at hypothermic targets.[10,11] After publication of the TTM trial, the recommendation on the duration of TTM in international guidelines was changed to at least 24 hours, although this recommendation was not based on any direct evidence that one duration is superior to another.[9,12] Despite this limited evidence, we identified only one randomized trial comparing different durations of TTM.[16] The trial compared 24 and 48 hours of TTM and found no difference in outcomes between durations.[16] One large trial investigating different durations of TTM is currently ongoing (ClinicalTrials.Gov: NCT04217551).

This systematic review and the results of the meta-analyses should be interpreted in light of some considerations. First, we had originally planned to conduct all analyses separately for IHCA and OHCA. However, most of the trials included only patients with OHCA. It was therefore not feasible to conduct separate analyses. Whether results from the OHCA setting can be generalized to the in-hospital setting is unclear, as there are both similarities and differences between the two populations.[69] Second, for many of the outcomes and prespecified subgroups, data were not reported for all relevant trials. We tried to address this by contacting authors for additional outcome data for the key meta-analyses, but data were not available in most instances. Third, the meta-analyses are limited by the heterogeneity of the included trials. Despite using random-effects methods, the results should therefore be interpreted carefully. Fourth, for some of the meta-analyses, only a few trials were included. Meta-analyses of only a few trials are methodologically challenging when there is heterogeneity among the trials.[70,71] Although the results could depend on the method used, alternative methods (e.g., the Knapp-Hartung method) tend to be more conservative (i.e., with wider confidence intervals) and would therefore not have changed our conclusions.[70,71]

In conclusion, among adult patients with cardiac arrest, the use of TTM at 32–34 °C, when compared to normothermia, did not result in improved outcomes in this meta-analysis. Similarly, there was no effect of initiating TTM prior to hospital arrival. These findings warrant an update of international cardiac arrest guidelines.

CRediT authorship contribution statement

Asger Granfeldt: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing, Visualization. **Mathias J. Holmberg:** Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing, Visualization. **Jerry P. Nolan:** Conceptualization, Methodology, Writing – review & editing. **Jasmeet Soar:** Conceptualization, Methodology, Writing – review & editing. **Lars W. Andersen:** Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing, Visualization. **:** .

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: None of the authors have any financial conflicts of interests and none of the authors have academic conflicts related to ongoing or planned trials. Lars W. Andersen was compensated in his role as a systematic reviewer by the American Heart Association on behalf of ILCOR for his work related to this systematic review. Jerry Nolan is the editor-in-chief of Resuscitation. Jasmeet Soar is an editor at Resuscitation.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2021.08.040.

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