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Review

Efficacy of the cooling method for targeted temperature management in post-cardiac arrest patients: A systematic review and meta-analysis

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Abstract

Objective: This review aimed to compare the efficacy of endovascular cooling devices (ECD), such as Thermogard®, with surface cooling devices (SCD), such as Arctic Sun®, in reducing mortality and improving neurological status for patients with post-cardiac arrest undergoing targeted temperature management.

Data sources: A systematic literature search was conducted using MEDLINE, EMBASE, and the Cochrane Library to identify randomized controlled trials (RCT) and observational studies (OS) comparing mortality and neurological status for patients treated with ECD or SCD.

Results: The meta-analysis comprised 4,401 patients from 2 RCT and 7 OS. For mortality, the overall pooled analysis showed no statistically significant difference between ECD and SCD recipients (RR, 0.93; 95% CI 0.86–1.00; $I^2 = 0\%$). Further, no statistically significant difference was observed between RCT (RR, 0.80; 95% CI 0.56–1.14; $I^2 = 0\%$) and OS (RR, 0.94; 95% CI 0.85–1.04; $I^2 = 18\%$) for in-hospital mortality.

For good neurological status of survivors after TTM, the overall pooled analysis showed no statistically significant difference between ECD and SCD (RR, 1.08; 95% CI 0.99–1.18; $I^2 = 71\%$). No statistically significant difference was found between ECD and SCD at hospital discharge in RCT (RR, 0.88; 95% CI 0.61–1.28; $I^2 = 0\%$) and at 6 months in OS (RR, 1.03; 95% CI 0.99–1.09; $I^2 = 32\%$).

Conclusions: The study findings could not show that either ECD or SCD was more effective in terms of survival and improved neurological status for post-cardiac arrest patients.

Systematic review registration number: CRD42019129770.

Keywords: Hypothermia, induced, Heart arrest, Patient outcome assessment, Meta-analysis

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Introduction

Targeted temperature management (TTM) is used to reduce neurological injury and improve the survival of patients following cardiac arrest (CA).[1] Several different methods and technical devices[2–5] have been used to induce and maintain hypothermia and control rewarming; however, there is no consensus on the most optimal cooling method.[1,6]

The 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care[1] state that temperature control is best achieved using devices that have a continuous temperature feedback control mechanism. TTM may be achieved through body exposure, using cooling pads or packs, and through administration of cold fluids intravenously.[7] Although these easy-to-use methods are inexpensive, they can result in unpredictable changes and variations in body temperature[8] as they lack a temperature feedback control mechanism.[8–12]

Up-to-date endovascular cooling devices (ECD), or surface cooling devices (SCD) with cold-water circulating blankets or hydrogel pads,[9,11,13] have been shown to rapidly achieve target temperature and maintain targeted therapeutic temperature ranges for a longer duration using a temperature feedback control mechanism.[14,15]

The cooling technique in ECD is based on convection. Heat is exchanged between a catheter placed in the vena cava and the blood. In contrast, SCD conduct heat through the tissues, with heat transfer from the core of the body to the surface.[3] Differences between these 2 cooling methods could affect the prognosis of patients undergoing TTM.

Several studies have compared ECD and SCD methods;[1,8,10,16–21] however, the efficacy of these devices in reducing mortality and improving neurological outcomes remains controversial. No systematic review or meta-analysis has been undertaken to compare the efficacy between these 2 types of cooling devices, which are both equipped with a temperature feedback control mechanism. Therefore, we undertook the first systematic review and meta-analysis aiming to evaluate the comparative efficacy of ECD and SCD in reducing in-hospital mortality and improving neurological outcomes in patients undergoing TTM.

Methods

Reporting guidelines and protocol registration

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines to report information from randomized control trials (RCT)[22] and we followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines to report information from observational studies (OS) in conducting this review.[23] The review protocol is registered at http://www.crd.york.ac.uk/PROSPERO/ (CRD42019129770).

Eligibility criteria

Our review applied the population, intervention, comparison, and outcome (PICO) search strategy. Using the PICO acronym, population (P) = adult CA patients who received TTM; intervention (I) = endovascular cooling devices; comparator (C) = surface cooling devices, and; outcome (O) = in-hospital mortality and poor neurological outcome following hospital discharge.

ECD included cooling devices, such as Coolgard® and Thermogard® that circulate water in a closed system through an endovascular catheter with water temperature controlled via a 'closed-loop' temperature feedback mechanism for the patient.[24] The SCD included cooling devices, such as Arctic Sun®, Meditherm®, Blanketrol®, Criticool®, ThermoWrap®, EMCOOLS®, and GAYMAR®, that function in an analogous manner except that water is circulated through a system of blankets or pads that work to cool a patient's skin.

Information sources and literature search strategy

Two experienced researchers undertook a literature search on February 28, 2019. The search was conducted using MEDLINE and EMBASE databases (MEDLINE: from September, 1969 to February, 2019; EMBASE: from October, 1993 to September, 2013) via the Ovid interface, in addition to a Cochrane library search (from May, 2013 to January, 2018) without language restriction (Supplementary Table S1).

Additionally, we manually checked the reference lists of all eligible studies to identify other relevant studies. The search terms used were: 'cardiac arrest', 'cardiopulmonary resuscitation', 'CPR', 'return of spontaneous resuscitation', 'ROSC', or 'advanced cardiac life support', and; 'targeted temperature management', 'TTM', 'hypothermia', 'hypothermia therapy', or 'hypothermia treatment' or 'cooling technique' or 'mechanical cooling', and; 'intravascular cooling' or 'endovascular cooling' or 'internal targeted temperature management' or 'internal device cooling' or 'intravascular cooling technique' or 'intravascular cooling' or 'invasive intravascular cooling', and; 'surface cooling device' or 'external cooling device' or 'surface cooling technique' or 'external targeted temperature management' or 'external temperature control unit' or 'non-invasive surface devices cooling' or 'non-invasive surface cooling'. We only included RCT and OS relevant to our PICO search strategy.

Study selection

We selected studies in accordance with methods described in the Cochrane Handbook for Systematic Reviews of Interventions (Chapter 7).[25] All studies identified in the literature search were entered into reference management software, i.e., Endnote X8 (Clarivate Analytics, Philadelphia, United States). Two reviewers assessed the title, abstract, and study type of each identified studies and irrelevant studies were excluded. They then independently assessed the full texts of all potentially relevant trials and studies for possible inclusion in this meta-analysis if: (1) the research included adult patients with CA who had received TTM using ECD or SCD, and; (2) the research included documentation of mortality and neurological outcome data during admission or post-discharge. We excluded reviews, case reports, editorials, letters, comments, animal studies, duplicate studies, and studies involving paediatric populations. In the event of disagreement between reviewers, a third reviewer facilitated discussion until consensus was reached.

Kappa statistics were used to evaluate agreement on relevance between the reviewers. Fair agreement was observed for titles and abstracts (0.81) with disagreement concerning 15 studies, and perfect agreement was observed for full articles (1.0), in the 237 studies selected.

We recorded reasons why potentially relevant studies failed to meet the eligibility criteria (Supplementary Table S2) and the results of

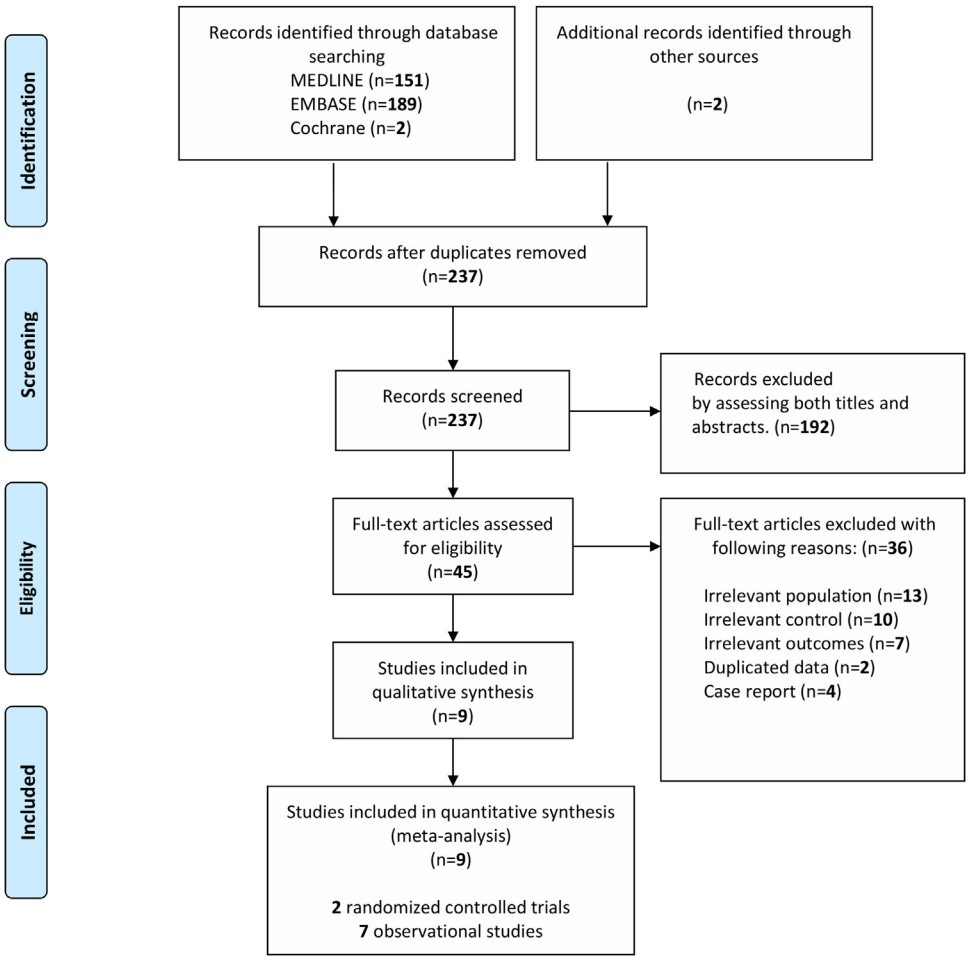

Fig. 1 – Flow diagram for identification of relevant studies.

the search are shown in a PRISMA flowchart (Fig. 1). After excluding ineligible studies, we retrieved the full texts of the selected articles, which we then rescreened and evaluated in detail using the same criteria.

Data extraction

Two reviewers conducted data extraction from selected studies according to the Cochrane guidelines.[25] Any unresolved disagreements were further reviewed by a third reviewer. The following variables were collected from all studies: author, year of publication, study design and centre, country, sample size, CA type, out-of-hospital CA (OHCA) rate, and type of cooling device. We also collected patient baseline characteristics including age, sex, severity status, and other treatments except for TTM, information concerning TTM including target temperature, cooling duration time, complications, manufacture of TTM devices and clinical outcomes (mortality and neurological outcome) using either means and standard deviations (SD) or median and interquartile ranges. Where variables of interest had not been described in the studies, we requested further details concerning them from the corresponding author of each study via email.

Risk of bias in individual studies

Two reviewers independently assessed the methodological quality of each study. Discordance was resolved through discussion and consensus.

We evaluated the quality of the RCT included in our review using methods described in the Cochrane Handbook for Systematic Reviews of Interventions regarding RCT.[26] We assessed potential sources of bias (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting). Intervention blinding when using a cooling method for TTM is either difficult or impossible; therefore, we considered blinding adequate if the outcome assessors had been blinded to the allocation group. RCT were defined as having a low risk of bias if they fulfilled the above criteria. The Risk of Bias Assessment Tool for Non-randomized Studies (RoBANS) was used to evaluate risk of bias in the selected OS studies.[22] The methodological scores of these OS studies were assigned values of 2, 1, and 0 for low-, unclear-, and high-risk, respectively. OS studies achieving >9 points after totalling each 6-domain score were considered to be of high quality.

Outcome measures

The primary outcomes were in-hospital mortality and mortality at 6 months, and good neurological status for survivors after TTM at hospital discharge, at 6 months and at 12 months. The secondary outcomes were to compare complications of ECD and SCD. The neurological outcome scores were dichotomised as good or poor based on Cerebral Performance Category Scale (1−2: good outcome; 3−5: poor outcome). Complications were defined as any adverse event potentially related to cooling such as infection, cardiac arrhythmias, seizures, bleeding, electrolyte abnormalities (potassium or sodium derangements), renal failure and venous thrombosis.

Statistical analysis and summary

Individual and pooled statistics were calculated as risk ratios (RR) with 95% confidence intervals (CI). A random effects model was used to determine pooled outcome measures from individual data of included studies, based on diversity of countries, medical systems, and inclusion periods. To measure heterogeneity, I^2 statistics were used to estimate the proportion of between-study inconsistencies, with values of 25%, 50%, and 75% considered to be low, moderate, and high, respectively.[27]

We also conducted planned subgroup analyses on extracted subgroup variables, namely, sample size ($\geq$160 vs. $<$ 160 patients), study quality (low vs. high), place of cardiac arrest (all OHCA vs. OHCA or in-hospital CA [IHCA]), the number of study centres (single vs. multiple), vasoactive drugs (reported vs. not reported), coronary reperfusion therapy (reported vs. not reported), intra-aortic balloon pump (IABP) (reported vs. not reported), implantable cardioverter-defibrillator (ICD) (reported vs. not reported), extracorporeal membrane oxygenation (ECMO) (reported vs. not reported), and conflicts of interest (yes vs. no).

A statistically significant subgroup effect indicates that the covariate considered in the subgroup analysis modifies the treatment effect significantly. To determine whether a statistically significant subgroup difference (interaction) was detected, the p-value from the test for subgroup differences was considered. A p-value of $<$0.1 indicates a statistically significant subgroup effect for this test.[28]

For specific confounders such as sample size, we used the median value of the reported rates or the total patient number across the 9 studies as a reference. Patients with IHCA have been reported to have higher survival than patients with OHCA.[29] Therefore, we compared all OHCA to OHCA + IHCA in the subgroup analysis to evaluate the effect of IHCA for in-hospital mortality and poor neurological outcome.

We used RevMan version 5.3 (Cochrane Collaboration, Oxford, UK) to perform the statistical analysis for both main and subgroup analyses, and a P-value of $<$0.05 was considered statistically significant.

Publication bias and quality of study evidence

Publication bias was assessed using a funnel plot and Egger's test. Asymmetry of the funnel plot and a P-value of $<$0.05 were indicators of bias. Analysis was performed using R packages 'meta' (R version 3.3.2).

We used GRADEpro GDT (GRADEpro Guideline Development Tool [Software] McMaster University, 2015 [developed by Evidence Prime, Inc.]) for evaluating the quality of evidence of each study. Evidence was summarised according to GRADE levels (high, moderate, low, and very low) through evaluating design, risk of bias, consistency, precision, directness, and possible publication bias of the included studies.

Results

Study selection

Our literature search identified 9 eligible studies as follows: 342 studies were identified from the database search while 2 additional studies were identified from other sources (Fig. 1). After removing 107 duplicates, 237 studies were screened for eligibility. Following this, 192 studies were excluded when assessing both titles and abstracts, as they were not relevant to our study, with 45 potentially relevant studies remaining. The full-text articles of these 45 studies were then retrieved. We excluded 36 studies for irrelevant population (n = 13), irrelevant control group (n = 10), irrelevant outcome measure (n = 7), data duplicated from the same studies (n = 2), and case reports (n = 4), leaving 9 studies (4,401 patients) for inclusion in the final meta-analysis.[1,8,10,16–21]

Study characteristics

Of 9 studies, there were 2 RCT and 7 OS, and the main attributes are summarised in Table 1. Patient baseline characteristics are summarised in Supplementary Table S3. TTM characteristics including target temperature, cooling duration time, complications and manufacture of TTM devices and other patient information such as patient severity status and supportive care are summarised in Supplementary Tables S4, S5 and S6. The 2 RCT were small and single-centred, comprising a total of 123 patients, whereas the 7 OS comprised 5 retrospective OS and 2 prospective OS, involving 4,278 patients in total.

Risk of bias and quality assessment

Risk of bias in the RCT

Using Cochrane methodology, the 2 RCT showed a low risk of bias (Supplementary Fig. S1 . and Supplementary Table S7). Blinding of participants and personnel was uncertain in one study,[20] and blinding of outcome assessors, participants, and personnel was uncertain in the other study.[19]

Quality assessment of the OS

We used the aforementioned quality scoring system to assess the 7 OS, with 3 OS rated as low quality[1,10,17] and 4 OS rated as high quality.[8,16,18,21] A summary of our risk of bias assessment is shown in Supplementary Fig. S1 and Supplementary Table S7.

Quality of evidence according to GRADE levels

The 2 RCT had substantial imprecision with limited total sample size and wide CI spanning. The OS had wide CI spanning and a substantial risk of bias, also suggesting serious imprecision. The RCT had a moderate quality of evidence for in-hospital mortality and good neurological status for survivors at hospital discharge; the OS had a moderate quality of evidence for in-hospital mortality and good neurological status for survivors at hospital discharge and at 6 months,

Table 1 – Characteristics of studies included in the review.

Authors	Year	Study design	Country	Sample size, n	CA type	Cooling devices of TTM		Clinical outcomes, Event/Total (%)				Time point of outcome measurement	
						ECD	SCD	Mortality		GNS of survivors			
								ECD	SCD	ECD	SCD	Mortality	Neurological status
Randomized controlled trials													
Look	2018	sRCT	Singapore	45	OHCA + IHCA	Thermogard®	Arctic Sun®	12/23 (52.2)	15/22 (68.2)	7/11 (63.6)	5/7 (71.4)	In-hospital	Hospital discharge
Pittl	2013	sRCT	Germany	78	OHCA + IHCA	Coolgard®	Arctic Sun®	15/39 (38.5)	18/39 (46.2)	14/24 (58.3)	14/21 (66.6)	In-hospital	Hospital discharge
Observational studies													
De Fazio	2019	mROS	Europe	352	All OHCA	–	–	65/218 (29.8)	43/134 (32.1)	149/153 (97.3)	83/91 (91.2)	6 months	6 months
de Waard	2015	mROS	Netherland	173	OHCA + IHCA	Coolgard®	Meditherm®	38/97 (39.2)	38/76 (50.0)			In-hospital	–
Glover	2016	mROS	Europe, Australia	934	All OHCA	Thermogard®	CritiCool® Arctic Sun® Blanketrol®	111/240 (46.3)	347/694 (50)	123/129 (95.3)	318/347 (91.6)	In-hospital	6 months
Fink	2008	sROS	Germany	49	OHCA + IHCA	Coolgard®	ThermoWrap®	18/26 (69.2)	14/23 (60.9)			In-hospital	–
Kim	2018	mROS	South Korea	2483	All OHCA	–	Arctic Sun® Blanketrol III ® GAYMAR®	186/376 (49.5)	1085/2107 (51.5)	101/189 (53.4)	486/1022 (47.5)	In-hospital	Hospital discharge
Sonder	2018	mPOS	USA	120	OHCA + IHCA	Thermogard®	Arctic Sun® Blanketrol® Meditherm®	24/48 (50.0)	42/72 (58.3)	23/24 (95.8)	30/30 (100)	In-hospital	6 months
Tomte	2011	sPOS	Norway	167	All OHCA	Coolgard®	Arctic Sun®	40/75 (53.3)	38/92 (41.3)	34/35 (97.1)	34/54 (97.1)	In-hospital	6-12 months

CA = cardiac arrest; TTM = targeted temperature management; ECD = endovascular cooling devices; SCD = surface cooling devices; GNS = good neurologic status; sRCT = single center randomized controlled trial; OHCA = out-of-hospital cardiac arrest; IHCA = in-hospital cardiac arrest; mROS = multicenter retrospective observational study; sROS = single center retrospective observational study; mPOS = multicenter prospective observational study; sPOS = single center prospective observational study.

and a very low quality of evidence for mortality at 6 months and good neurological status for survivors at 12 months (Supplementary Table S8).

Results of meta-analyses

Mortality for recipients of ECD vs. SCD (at in-hospital vs. at 6 months)

Mortality was assessed in 9 studies. The overall pooled analysis showed no statistically significant difference between ECD and SCD recipients (RR, 0.93; 95% CI 0.86–1.00; $I^2 = 0\%$). Concerning the in-hospital mortality, no statistically significant difference was found between RCT (RR, 0.80; 95% CI 0.56–1.14; $I^2 = 0\%$) and OS (RR, 0.94; 95% CI 0.85–1.04; $I^2 = 18\%$, Fig. 2).

Good neurological status in ECD vs. SCD survivors (at hospital discharge vs. at 6 months vs. at 12 months)

The overall pooled analysis showed no statistically significant difference in good neurological status between ECD and SCD survivors (RR, 1.08; 95% CI 0.99–1.18; $I^2 = 71\%$). There was no statistically significant difference between the ECD and SCD in the RCT studies (RR, 0.88; 95% CI 0.61–1.28; $I^2 = 0\%$) for good neurological status for survivors at hospital discharge. Concerning good neurological status for survivors at 6 months, the pooled analysis from 3 OS showed there was no statistically significant difference between ECD and SCD (RR, 1.03; 95% CI 0.99–1.09; $I^2 = 32\%$, Fig. 3).

Complications in ECD vs. SCD recipients

Complications were reported in 2 RCT and 3 OS. Reported complications included infection, arrhythmia, seizure, bleeding, electrolyte abnormalities (potassium or sodium derangements), renal failure, and venous thrombosis (Supplementary Table S4).

The overall pooled analysis showed no statistically significant difference between ECD and SCD recipients. Similarly, no statistically significant difference was observed for infections, arrhythmia, seizure, bleeding, and renal failure. In the analysis for electrolyte abnormalities, hypokalaemia was higher in the ECD than in the SCD (RR, 1.40; 95% CI 1.04–1.88; $I^2 = 0\%$, Fig. 4).

Subgroup analysis

For subgroup analysis for mortality, the test for subgroup differences indicate that there is no statistically significant subgroup effect, suggesting that sample size, study quality, places of cardiac arrest, number of study centres, vasoactive drugs, coronary reperfusion therapy, IABP, ICD, ECMO, and conflicts of interest do not modify the effect of ECD compared to the effect of SCD (Supplementary Table S9).

For subgroup analysis for good neurological status for survivors, the test for subgroup differences suggests that there is a statistically significant subgroup effect (sample size: $p = 0.02$; place of cardiac arrest; $p = 0.02$), demonstrating that sample size and places of cardiac arrest significantly modifies the effect of ECD significantly in comparison to that of SCD (Supplementary Table S9).

However, a smaller number of trials and patients contributed data to the sample size <160 subgroup (sample size; 3 trials, 117 participants) than to the sample size ≥160 subgroup (4 trials, 2020 participants) in subgroup analysis on sample size, indicating that the analysis is unlikely to produce useful findings (Supplementary Fig. S2).

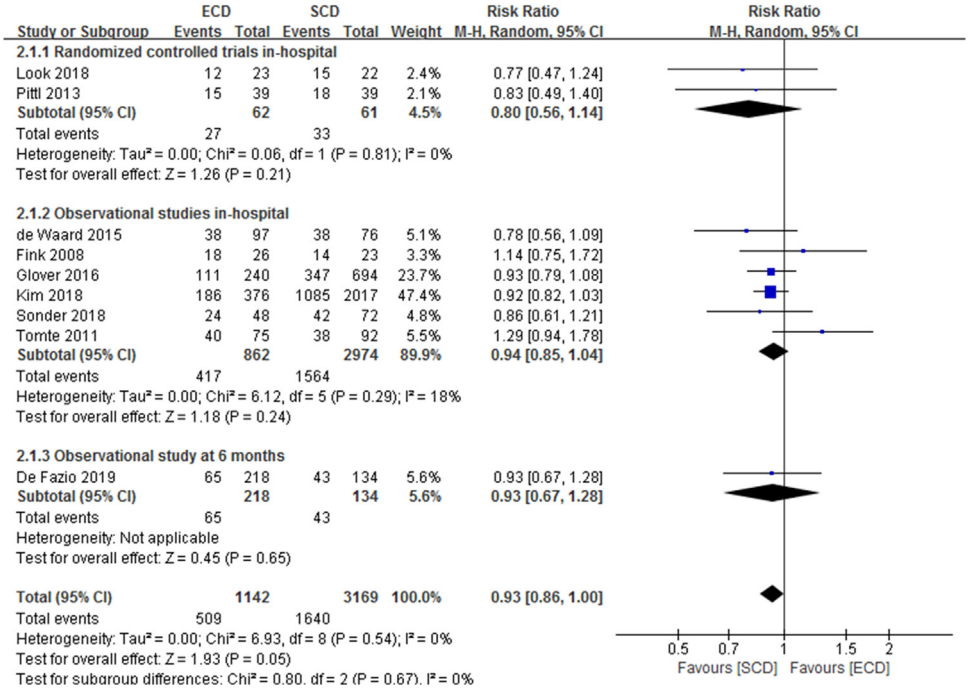

Fig. 2 – Forest plot comparing the effect of ECD to SCD concerning mortality.
Abbreviations: CI, confidence interval; ECD, endovascular cooling devices; SCD, surface cooling devices; SD, standard deviation.

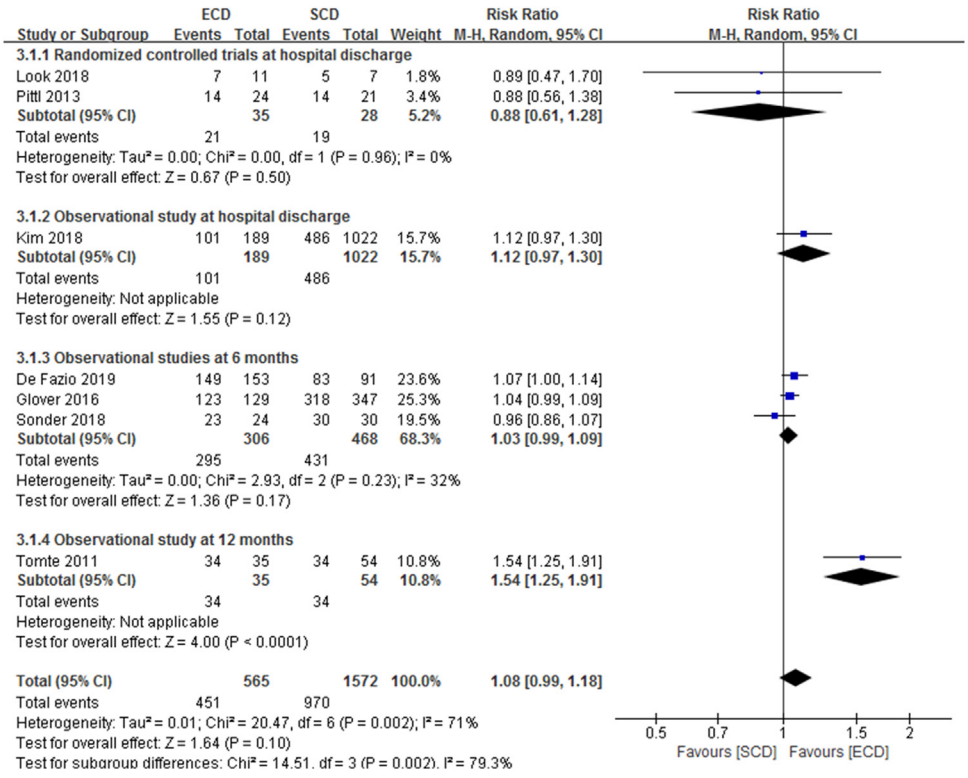

Fig. 3 – Forest plot comparing good neurological status in ECD vs. SCD survivors.
Abbreviations: CI, confidence interval; ECD, endovascular cooling devices; SCD, surface cooling devices; SD, standard deviation.

Similarly, in the subgroup analysis for the place of cardiac arrest, the trials and patients of OHCA or IHCA subgroups (sample size; 3 trials, 117 participants) is far smaller than those of the All OHCA subgroup (4 trials, 2020 participants), meaning that the analysis is unlikely to produce useful findings (Supplementary Fig. S3)

Publication bias

There was no definite asymmetry in the funnel plot. We did not observe any publication bias in studies concerning mortality and good neurological status for survivors, based on Egger's regression test (mortality, P = 0.9431; good neurological status for survivors, P = 0.5987, Fig. 5).

Study blinding

Of 2 RCT concerning participant and personnel blinding, one study lacked relevant detail,[19] and the other was assessed as at low risk for blinding in terms of outcome assessment.[20] Of 7 OS, one study was low risk,[18] one was high risk,[17] and the remainder were of indeterminate risk for blinding of outcome assessment[1,8,10,16,21] (Supplementary Tables S5 & S7).

Discussion

This review found no statistically significant difference between ECD and SCD in terms of mortality and good neurological status of survivors. ECD also showed no statistically significant difference in terms of complication compared to SCD except for hypokalaemia. However, most of the data was obtained from OS, potentially leading to a high risk of bias.

Stanger et al. (2017)[30] reported no statistically significant difference in mortality and neurological outcomes when endovascular cooling methods were compared to surface cooling methods. However, that review was limited to 6 studies (total, n = 920 patients) and included 2 studies concerning conventional surface cooling methods without temperature feedback control mechanisms. Five other studies comparing ECD to SCD have been published, comprising 4 OS and 1 RCT.[1,8,10,18,19] We aimed to evaluate the efficacy of ECD compared to SCD when temperature feedback control mechanisms were involved specifically.

The 2015 AHA guidelines recommended that comatose adult patients with ROSC post-CA receive TTM.[31] TTM decreases the harmful effects of ischemia through reducing a body's need for oxygen and also contributes to limiting reperfusion injury due to oxidative stress when blood supply to tissue is restored.[32]

Either ECD or SCD should be selected when administering TTM, but both devices have specific advantages and disadvantages. ECD achieves rapid cooling and maintains body temperature within specified ranges with less shivering, but is an invasive technique, and patients are vulnerable to infection and may bleed at the puncture site.[33] SCD is a non-invasive procedure but takes longer to induce hypothermia, and body temperature can fluctuate during TTM.

Shinozaki et al. (2012) reported that a longer duration of well-controlled core temperature was associated with better patient

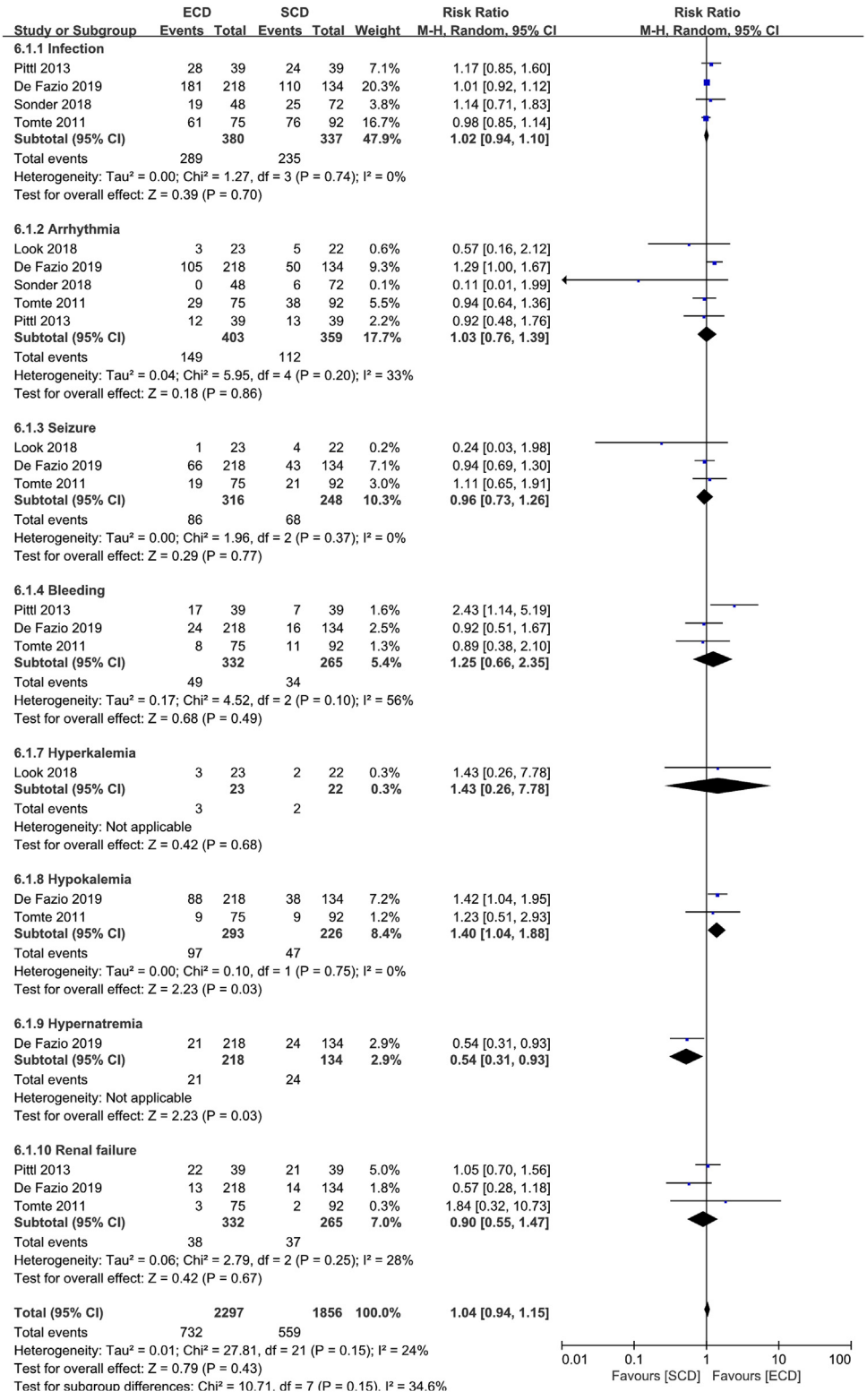

Fig. 4 – Forest plot comparing complications of TTM between ECD and SCD.

Abbreviations: CI, confidence interval; ECD, endovascular cooling devices; SCD, surface cooling devices; SD, standard deviation; TTM, targeted temperature management.

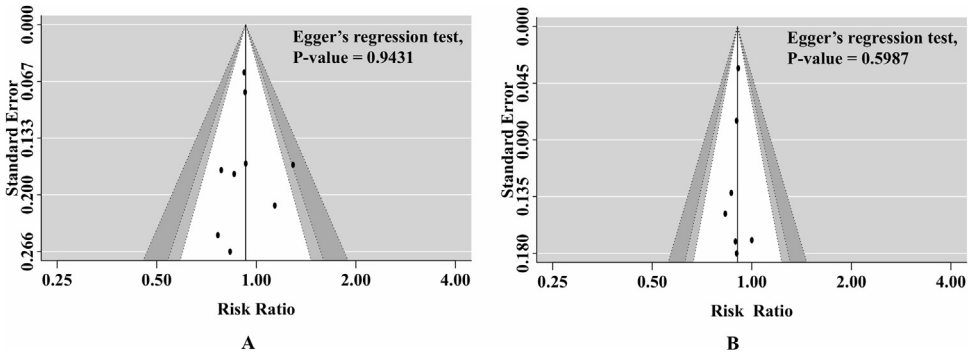

Fig. 5 – Funnel plot and Egger's regression test to assess for publication bias.
A: Publication bias for mortality, B: Publication bias for good neurological status for survivors.

outcomes,[34] whereas fluctuations in the core temperature over a long duration during TTM can lead to poor patient outcomes. Excessive core temperature fluctuation may cause overcooling or brain hypothermia. Look et al. (2018) reported that ECD had less frequent overcooling events than SCD.[19] Overcooling events during TTM can induce atrial or ventricular arrhythmia, coagulopathy, and increase the risk of infection.[35–39]

In the meta-analysis for neurological outcome, as a poor neurological status included those patients who have died, we reported the good neurological status of patients who survived until hospital discharge. ECD showed no statistically significant difference in terms of good neurological status for survivors compared to SCD. Regarding TTM complications, ECD did not differ according to 6 complications (infection, arrhythmia, seizure, bleeding, hyperkalaemia, and hypernatremia) except for hypokalaemia, when compared with SCD.

Post-resuscitation care for patients with CA, such as coronary reperfusion therapy and ECMO, may been a confounding factor in the better neurological outcome of ECD recipients, and should be considered when comparing SCD and ECD. Reperfusion therapy such as PCI could contribute to better neurological outcomes in TTM recipients through eliminating the presumed cause of OHCA. The use of ECMO can also contribute to better neurological outcomes through supporting a patient's hemodynamic status during post-resuscitation care.[40–42] Therefore, the high rates of use of coronary reperfusion therapy or ECMO in ECD recipients in this study may have contributed to better neurological outcomes among patients who used ECD (Supplementary Table S6).

The TTM protocol, patient mental status, and patient severity post-CA prior to TTM may have been confounding factors in the outcome concerning TTM recipients. In the target temperature of TTM, 8 of 9 studies showed the same target temperature in both cooling devices. All studies adhered to the international 2010–2015 American Heart Association guidelines (target temperature, 32–36 °C; maintenance time, 12–24 h).[43,44] However, differences in target temperature might have had a significant effect on patient outcomes.

Only 2 studies reported the time interval from CPR to cooling of TTM; therefore, the effect of earlier cooling on TTM patient outcome was not evaluated in this study. Previous human studies that have assessed the relationship between cooling time and outcomes have shown inconsistent results concerning the benefits of earlier cooling.[45–53] Therefore, we postulated that the time to cooling could affect the outcome for TTM patients but not significantly.

Other possible factors that affected the outcome for TTM recipients were mental status and the severity status of patients with CA prior to TTM treatment, which were not assessed due to insufficient data. However, the influence of the mental status and the severity status of a TTM recipient should be considered when interpreting the reported outcomes in this study.

The statistical heterogeneity (I^2) between the studies was low or moderate for in-hospital mortality and good neurological status of survivors at hospital discharge and at 6 months. However, heterogeneity across the studies included all differences between individual studies such as study design, populations included, treatment strategies, co-interventions, and outcomes.[54] Furthermore, I^2 statistics could have had low statistical power, potentially resulting in misleading results, especially as the number of studies reviewed was limited.[55] Therefore, the I^2 values reported in this study should be interpreted with caution.

In terms of cost and resource implications, ECD required the insertion of a central venous line and was more expensive than SCD.[3] ECD showed a marginal benefit over SCD but relevant evidence was limited.

Our study findings could not show that either ECD or SCD was more effective in TTM recipients. Clinicians should consider individual patient factors, resource availability, and cost in the selection of cooling devices. More RCT are needed to compare ECD and SCD to determine their actual benefits.

This study had some limitations. First, there were heterogeneities between CA location (OHCA vs. IHCA) and CA causes (cardiac vs. non-cardiac origin) (Table 1 and Supplementary Table S3). Generally, patients with OHCA have worse neurological outcomes than patients with IHCA. Furthermore, patients with CA of non-cardiac origin have worse neurological outcomes than patients with CA of cardiac origin.[56] This heterogeneity may have contributed to in-hospital mortality and poor neurological outcomes for TTM recipients. To resolve this heterogeneity, data from future studies should be more detailed and categorized according to CA location and type. Second, the results of our study could not be generalized to other populations because more than half the patients were from South Korea. Our results may have been different if cohorts from other countries or ethnicities had been included. For more robust conclusions, further analyses should include populations of diverse origins. Third, only 4 studies reported neurological outcome 6 months post-hospital discharge, and early CPC measured at discharge could change within the first 6 months; therefore, this suggests that the results may

have been different had a long-term CPC measurement been taken after 6 months.[57,58] Fourth, in contrast to RCT where cooling devices were randomized, ECD or SCD were selected for TTM recipients based on hospital protocols, availability of cooling devices, or physician preference concerning cooling devices in OS. The non-randomized selection of cooling devices could have caused significant selection bias. Therefore, the results of this study should be cautiously interpreted, and well-designed studies that include randomized clinical trials are required.

Conclusion

The study findings could not show that either ECD or SCD was more effective in terms of survival and improved neurological status for post-CA patients due to substantial risks of bias and the limited quality of evidence in the RCT and OS. Further high-quality RCT are needed to confirm the comparative benefits of ECD and SCD.

Conflicts of interest and sources of funding

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None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.12.025.

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