SYSTEMATIC REVIEW AND META-ANALYSIS OF INTRAVASCULAR TEMPERATURE MANAGEMENT VERSUS SURFACE COOLING IN COMATOSE PATIENTS RESUSCITATED FROM CARDIAC ARREST

EMILY BARTLETT MD, MS*[1]

TERENCE VALENZUELA MD, MPH[2,3]

AHAMED IDRIS MD[4]

NICOLAS DEYE MD, PHD[5]

GUY GLOVER MD[6]

MICHAEL GILLIES MD[6]

FABIO SILVIO TACCONE MD, PHD[7]

KJETIL SUNDE MD, PHD[8,9]

ALEXANDER FLINT MD, PHD[10,11]

HOLGER THIELE MD[12]

JASMIN ARRICH MD[13,14]

CLAUDE HEMPHILL MD[15]

MICHAEL HOLZER MD[13]

MARKUS B SKRIFVARS MD, PHD[16]

UNDINE PITTL MD[12]

KEES POLDERMAN MD[17,18]

MARCUS EH ONG MD, MPH[19,20]

KI HONG KIM MD[21]

SANG HOON OH, MD[22]

SANG DO SHIN MD, PHD[23,24]

HANS KIRKEGAARD MD, PHD[25]

GRAHAM NICHOL MD, MPH, FRCP©[1, 26,27]

1 Department of Emergency Medicine, University of Washington, Seattle, Washington, United States of America

2 Department of Emergency Medicine, University of Arizona, Tucson, Arizona, United States of America

3 Tucson Fire Department, Tucson, Arizona, United States of America

4 Departments of Emergency and Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, United States of America

5 Medical Intensive Care Unit, Inserm U942, Lariboisiere Hospital, APHP, F-75019, Paris, France

6 Department of Critical Care, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom

7 Department of Intensive Care, Cliniques Universitaires de Bruxelles Hopital Erasme, Université Libre de Bruxelles (ULB), Brussels, Belgium

8 Department of Anaesthesiology, Division of Emergencies and Critical Care, Oslo University Hospital, Oslo, Norway

9 Institute of Clinical Medicine, University of Oslo, Oslo, Norway

10 Divison of Research, Kaiser Permanente, Oakland, California, United States

11 Neuroscience Department, Kaiser Permanente, Redwood City, California, United States

12 Department of Internal Medicine/Cardiology, Heart Center Leipzig at University of Leipzig, Leipzig, Germany

13 Department of Emergency Medicine, Medical University of Vienna, Vienna, Austria

14 Center of Emergency Medicine, University of Jena, Faculty of Medicine, Jena , Germany

15 Department of Neurology, University of California, San Francisco, California, United States

16 Department of Emergency Care and Services, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

17 Essex Cardiothoracic Centre, Basildon, Essex, SS16 5NL, United Kingdom

18 Anglia Ruskin School of Medicine, Chelmsford, CM1 1SQ, United Kingdom

19 Health Services and Systems Research, Duke-NUS Medical School, Singapore, Singapore

20 Department of Emergency Medicine, Singapore General Hospital, Singapore, Singapore

21 Department of Emergency Medicine, Seoul National University Hospital, Seoul, Republic of Korea

22 Department of Emergency Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

23 Department of Emergency Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea

24 Laboratory of Emergency Medical Services, Seoul National University Hospital Biomedical Research Institute, Seoul, Republic of Korea

25 Research Center for Emergency Medicine, Department of Emergency Medicine and Department of Clinical Medicine, Aarhus University Hospital and Aarhus University, Aarhus, Denmark

26 Department of Internal Medicine, University of Washington, Seattle, Washington, United States of America

27 University of Washington-Harborview Center for Prehospital Emergency Care, Seattle, Washington, United States of America

* Corresponding author

Contact:

emilysb2@uw.edu

301-502-4551

Box 359702
325 9th Avenue
Seattle, WA
98104
United States of America

Manuscript Word Count: 3,257

Disclosures:

Bartlett – Principal investigator (PI) of a feasibility trial of remote ischemic conditioning funded by ZOLL Foundation, Chelmsford, MA.

Deye- Travel reimbursement and speakers fees, Bard Medical Inc., Covington, GA and ZOLL Circulation, San Jose, CA.

Flint- Patents in United States and elsewhere on technology for automated shivering detection and treatment.

Gillies - Chief Scientist's Office (Scotland) NHS Research Scheme Clinician.

Glover- Consultant and travel reimbursement, Bard Medical Inc., Covington, GA.

Hemphill- Member of Data Safety Monitoring Board, INTREPID trial of fever prevention using Arctic Sun surface method in patients with strokes, funded by BARD Medical Inc.

Holzer- PI, Cool AMI EU Pivotal trial of intravascular cooling in patients with STEMI, funded by ZOLL Circulation Inc. PI, trial of cooling with CaerVest device in patients resuscitated from cardiac arrest, funded by Bodychilz Inc., Gatwick, Sussex, United Kingdom; Received speaker fees and travel reimbursement from Bard Medical Inc. and ZOLL Circulation Inc.

Idris - member of the HeartSine (Stryker Belfast) Clinical Advisory Board

Nichol- Consultant and PI, STEMI COOL trial of intravascular cooling in patients with ST-elevation myocardial infarction, funded by ZOLL Circulation Inc; Consultant, QOOL Therapeutics Inc, Mountain View, CA.

Ong- Scientific Advisor to Global Healthcare SG, Singapore.

Polderman- Travel reimbursement and speakers fees from Bard Medical Inc., Stryker Inc., ZOLL Medical Inc.

Skrifvars: Research funding from GE, Lecture fees from COVIDIEN, MEDTRONIC and BARD.

Sunde- Travel reimbursement and speakers fees from Bard Medical Inc., Stryker Inc.

Taccone: Lecture fees from BARD and ZOLL

All other authors report no disclosures.

This review was not funded or sponsored.

ABSTRACT

Objective: To systematically review the effectiveness and safety of intravascular temperature management (IVTM) versus surface cooling methods (SCM) for induced hypothermia (IH).

Methods: Systematic review and meta-analysis. English-language PubMed, Embase and the Cochrane Database of Systematic Reviews were searched on May 27, 2019. The quality of included observational studies was graded using the Newcastle-Ottawa Quality Assessment tool. The quality of included randomized trials was evaluated using the Cochrane Collaboration's risk of bias tool. Random effects modeling was used to calculate risk differences for each outcome. Statistical heterogeneity and publication bias were assessed using standard methods.

Eligibility: Observational or randomized studies comparing survival and/or neurologic outcomes in adults aged 18 years or greater resuscitated from out-of-hospital cardiac arrest receiving IH via IVTM versus SCM were eligible for inclusion.

Results: In total, 12 studies met inclusion criteria. These enrolled 1,573 patients who received IVTM; and 4,008 who received SCM. Survival was 55.0% in the IVTM group and 51.2% in the SCM group [pooled risk difference 2% (95% CI -1%, 5%)]. Good neurological outcome was achieved in 40.9% in the IVTM and 29.5% in the surface group [pooled risk difference 5% (95% CI 2%, 8%)]. There was a 6% (95% CI 11%, 2%) lower risk of arrhythmia with use of IVTM and 15% (95% CI 22%, 7%) decreased risk of overcooling with use of IVTM versus SCM. There was no significant difference in other evaluated adverse events between groups.

Conclusions: IVTM was associated with improved neurological outcomes vs. SCM among survivors resuscitated following cardiac arrest. These results may have implications for care of patients in the emergency department and intensive care settings after resuscitation from cardiac arrest.

Background

Out-of-hospital cardiac arrest (OHCA) affects more than 400,000 individuals in the United States (US)[1] and 624,000 individuals in Europe[Extrapolated from (2)] annually. Of these, nearly 90% die. Timely restoration of blood flow after the onset of cardiac arrest (CA) is critical to survival but the act of restoring flow is associated with cell injury, termed reperfusion injury.[3] Studies in animal models of CA demonstrated that mild therapeutic hypothermia, also referred to as induced hypothermia (IH) or targeted temperature management (TTM), reduces the inflammation and other harmful processes that occur immediately following reperfusion.[4-8] Also, briefer time from the onset of arrest or initiation of therapeutic reduction of core body temperature to achieving moderate hypothermia is associated with significantly better outcome.[5, 9-12] In humans resuscitated from CA, briefer time to target temperature appears to be associated with better survival.[13-15] Two randomized trials have demonstrated that IH improves outcomes in comatose patients resuscitated from cardiac arrest, [16, 17] and mild therapeutic hypothermia between 32°C and 36°C is currently recommended by evidence-based practice guidelines for use in post-cardiac arrest care.[18-20] However, the optimal dose, duration and method for IH or TTM have not been fully determined.[21]

Multiple methods of IH are in clinical use in patients resuscitated from CA. Intravascular temperature management (IVTM), also sometimes referred to as endovascular temperature management, requires insertion of catheters into a large vein. Current commercially available catheters have multiple balloons on their external surface that provide a large surface area in contact with the patient's blood. A console is used to circulate chilled saline in a closed loop, and heat exchange occurs between the surface of the balloons and the blood so as to induce and maintain IH. Surface cooling methods (SCM) require application of ice packs, cooling blankets or gel-adhesive pads to one or more areas of skin so as to induce and maintain IH. Each method has differing capabilities of extracting heat, which translate to different rates of achieving the intended target temperature. Methods of IH may also differ in their ability to maintain a consistent target temperature as well as to control the rewarming phase at the completion of the IH protocol.[22] The different methods of IH may also have distinct types and rates of adverse events. Small randomized trials have compared temperature control and outcomes in patients who received IH via IVTM vs SCM.[23-25] However, these trials lacked sufficient power to detect a small but potentially important difference in outcomes. To date, the effectiveness and safety of IVTM vs. SCM of IH in this high-impact population is incompletely defined. Therefore, we conducted a systematic review and meta-analysis to assess the effectiveness and safety of IVTM vs. SCM of IH in patients resuscitated from CA. We hypothesized that IVTM would be associated with improved survival and neurological outcome compared with SCM.

Methods

The methods of this review were registered prospectively (PROSPERO 2018 CRD42018112541).[26] A Boolean search strategy was applied to the PubMed database (See Online Supplement). In response to a request by a peer-reviewer, this was also applied to the Embase and Cochrane systematic reviews databases. This was supplemented by application of the Cochrane sensitivity- and precision-maximizing search strategy for randomized controlled trials, and modified for clinical studies of hypothermia devices rather than drugs.[27]

Included were observational or interventional studies that described use of IVTM and SCM of IH in adults aged 18 years or greater who were resuscitated from CA, and that reported survival and/or neurologic outcomes for both IVTM and SCM groups. Studies that described only IVTM or SCM without a comparison group were not included. If a study described use of multiple means of achieving IH (IVTM or SCM), these data were aggregated prior to inclusion in the systematic review.

Unique citations were reviewed to confirm eligibility by two individuals (GN, TV, EB), and relevant data extracted (GN, EB). The primary author of each included study was asked to confirm that the data had been extracted correctly. The primary author for one study was unable to do so,[28] so the data extracted for that study were confirmed by a second a member of the review team (EB). Differences in either study eligibility or data abstraction were resolved by consensus. The methodological quality of included observational studies was assessed independently by two individuals (GN, EB) with differences resolved by consensus using the Newcastle-Ottawa Quality Assessment form.[29] This is scored by a star system along the domains of representativeness of the groups, comparability of the groups and outcomes assessment, with a higher star score indicating better quality. Included randomized trials were evaluated in a similar manner using the Cochrane Collaboration's risk of bias tool.[30] This includes seven domains of potential bias and is scored as low, high or uncertain risk of bias.

The primary outcome evaluated by this review was survival to hospital discharge. If vital status at discharge was not available, we substituted survival to 28 or 30 days or end of study follow-up. A key secondary outcome was good neurologic outcome at discharge (or 28 or 30 days or end of study follow-up). Good neurologic outcome was defined as Cerebral Performance Category 1 or 2 or modified Rankin score less than or equal to 3. Adverse events of interest included: shivering, temperature overcooling, local or skin injury, deep venous thrombosis (DVT), serious bleeding requiring transfusion, arrhythmias, pneumonia or sepsis (see Online Supplement for definitions). We sought to abstract sufficient information to be able to stratify outcomes by first recorded rhythm. If relevant data were not included in the primary publication, we contacted the primary author to request that they provide the missing information.

Results were summarized qualitatively and quantitatively by using standard meta-analytic techniques.[31] Analyses were performed for the overall results as well as grouped by randomized vs. observational design. Statistical heterogeneity was assessed using tau^2, inconsistency index I^2 and a test of heterogeneity with the related p value. A random effects model (DerSimonian-Laird) was used to calculate pooled risk differences for each outcome. All planned analyses delineated in the prospectively registered systematic review protocol were performed. Additionally, rate of arrhythmia in IVTM vs SCM was included as a post-hoc analysis. Funnel plots were used to visually check for possible selection or publication bias in combination with a test for funnel plot asymmetry based on a linear weighted regression. Secondary analysis used a fixed effects model (Mantel-Haenszel) to calculate pooled risk differences for survival and neurologic outcome. The level of statistical significance was set *a priori* at alpha = 0.05. Meta-analysis was performed by using jamovi (Version 0.9, retrieved from https://www.jamovi.org) with its 'major' package. This was supplemented by using R (Version 3.5.0, retrieved from https://www.r-project.org/) with its 'meta' package.

Results

Literature Search

The results of the literature search are summarized in Figure 1. On May 27, 2019, 244 unique candidate citations were identified by the search strategy. Four additional candidate citations were identified by the authors of this meta-analysis based on their prior knowledge of the literature.[22, 24, 32, 33] Of these 248 citations, 15 studies were identified as being eligible for inclusion. After full text review of each eligible article, three studies were excluded. One evaluated use of IH in patients with multiple disorders including but not limited to CA.[34] Another applied fever control methods but not active IH to patients who did not receive IVTM.[35] Another did not disaggregate outcomes by IVTM vs. SCM.[36] Twelve studies (overall n=5,581 patients) were included in the meta-analysis.

Included Studies

The characteristics of included studies and their enrolled patients and outcomes are summarized in Table 1. Three studies were randomized trials;[23-25] four were prospective cohort studies;[22, 28, 32, 33] and three were retrospective case-control studies.[37-39] Two were secondary analyses of randomized trials: one compared two target temperature ranges and another compared two protocols for duration of IH in patients resuscitated from CA.[40,41] Note that we considered outcomes in each temperature range and IH duration in these articles separately. All studies enrolled patients with OHCA; some also enrolled patients with in-hospital CA. Methodological quality was rated as moderate among included observational studies (Online Supplement). The risk of bias was rated as moderate among included trials.

The majority of included studies originated from outside the US. The SCM of IH that were used in each study varied, and consisted of ice packs, fans, tents, non-adherent cooling blankets or gel adhesive cooling pads. Some also administered chilled fluids intravenously. The majority of included studies used a target temperature of 32-34 °C or less, but two randomized trials used a target temperature of 36 °C.[24, 40] One cohort study used target temperatures of 32, 33, 34 or 35 °C, depending on patient characteristics and provider preference.[22] The age and gender distribution of enrolled patients was typical of patients with OHCA. Most studies predominantly enrolled patients with a first recorded rhythm that was shockable. Insufficient information was available about patient characteristics, EMS processes of care, time from activation of emergency medical services to initiation of hypothermia or achievement of target temperature, use of sedation or paralytics to reduce shivering, or rate of rewarming to pool these data to make any inferences about the relationship between these factors and outcomes. As well, there was insufficient information regarding the precision and variability of induced hypothermia in each study to assess the association between these factors and patient outcomes. 1,573 patients (28%) received IVTM; 4,008 received SCM (71.8%). Survival data were available for all patients included. Neurological outcomes data were available for 1,514 patients in the IVTM group and 3,962 in the SCM group. Survival was 55.0% in the IVTM group and 51.2% in the SCM group. Good neurological outcome was achieved in 40.9% in the IVTM and 29.5% in the SCM group.

Pooled Effects

Pooled data from included studies demonstrated that use of IVTM was associated with an absolute 2% (95% CI -1%, 5%) greater chance of survival as compared to SCM. There was an absolute 5% (95% CI 2%, 8%) greater chance of good neurological outcome associated with use of IVTM compared to SCM. These results are summarized in Figure 2.

There was no significant statistical heterogeneity among studies that reported survival data (p value=0.74) or in those that reported the incidence of good neurological outcome (p value=0.82). There was no evidence of publication bias among studies that reported survival data (regression test for funnel plot asymmetry p value=0.24) or in those that reported the incidence of good neurological outcome (regression test for funnel plot asymmetry p value=0.94).

Secondary analysis using a fixed effects model demonstrated that use of IVTM was associated with an absolute 2% (95% CI -1%, 5%) greater chance of survival as compared to SCM (Online Supplement). There was an absolute 5% (95% CI 2%, 8%) greater chance of good neurological outcome associated with use of IVTM compared to SCM using this method of analysis as well.

There was a 6% (95% CI 11%, 2%) lower risk of arrhythmia with IVTM versus SCM and an 15% decreased risk of temperature overcooling with use of IVTM versus SCM (95% CI 22%, 7%) (See Online Supplement). There was no significant difference between groups with regards to the risk of shivering, skin injury, clinically significant bleeding, DVT, pneumonia or sepsis.

There was no evidence of a differential effect of IVTM upon survival to discharge or neurological outcome at discharge in studies that employed a randomized vs. observational design. There were insufficient data available to evaluate for a differential effect of IVTM as compared with SCM in studies of US vs. ex-US origin, first recorded rhythm, no-flow time (EMS call to sustained restoration of flow in minutes), time to target temperature (EMS call to target temperature in minutes), use of feedback control, precision or overshoot.

There were insufficient data available for a post hoc analysis to evaluate the differential effect of IVTM as compared to SCM of IH with target temperature 34°C or less vs. 36 °C.

Discussion

This systematic review of randomized trials and observational studies from multiple geographically separate locations reported over a decade-long period suggested that IH using IVTM as compared to SCM is associated with a significant and important beneficial effect on neurological outcome in patients resuscitated from OHCA. Treatment of 20 (95% CI 13, 50) patients with IVTM as compared to SCM was associated with one more individual with good neurologic outcome. As well, there was a significant decrease in the rate of arrhythmias and of temperature overcooling with use of IVTM as compared to SCM. There was no significant difference in the rate of shivering, skin injury, serious bleeding, DVT, pneumonia, or sepsis between IVTM and SCM. Several of the latter comparisons were limited by sparse data. The overall quality of the included studies was moderate. There was no evidence of statistical heterogeneity or publication bias.

An insufficient number of patients resuscitated from CA (overall n=352) have been randomized to IH vs. normothermia to have sufficient power to detect small but important differences in outcome between the two interventions.[16, 17] Due to lack of clinicians' equipoise,[18-20] a US-based trial of IH vs. normothermia is likely infeasible. In the absence of a larger amount of additional randomized evidence of the effect of IH vs. normothermia in patients resuscitated from CA, this systematic review and meta-analysis could inform ongoing debate among providers about whether IH improves outcomes compared to normothermia in patients resuscitated from CA. Prior randomized trials of IH as compared to normothermia in patients with CA yielded mixed results. Two trials that monitored adherence to IH and achieved target temperature quickly observed improved outcomes with IH vs. normothermia.[16, 17] In contrast, IH without early achievement of target temperature was not associated with benefit.[42, 43] These discordant results may be due in part to variation in the time to achieving target temperature between trials or drugs used to reduce shivering.[3]

Due to discordant information about whether a target temperature of 34°C or less is necessary, many providers have adopted target temperature of 36°C. However, multiple large retrospective analyses of data collected for reasons unrelated to IH (overall n=100,085) suggest that among patients resuscitated from CA, a target temperature of 36°C is associated with worse outcomes as compared to a target of 34 °C or less.[44-46] Although the present analysis had limited power to detect differences in outcome between different target temperatures, our observation that IVTM is associated with better neurological outcome than SCM of IH could provide indirect evidence that there is an association between active use of IH as opposed to normothermia and better outcomes in patients resuscitated from OHCA.

This study has some limitations. First, we considered only citations written in English. This reduced the number of eligible citations and hence the overall number of patients included in the analysis. However, reported effects may be larger in non-English as opposed to English studies,[47] and restriction to English-language studies is unlikely to bias the results of a systematic review.[48]

Second, our strict eligibility criteria reduced the overall number of studies and patients included in our systematic review. While the present analysis was undergoing revision after its initial peer review, another systematic review the effect of different methods of IH was published.[49] The latter included 22 studies (overall n=8,027). Of these, one study compared IVTM vs SCM and reported survival to discharge but not neurologic outcome in the English language (overall n=69).[50] A post hoc analysis including this additional study did not suggest that IVTM significantly improved survival vs. SCM (details available from authors). In contrast to the other systematic review, we separated IVTM and SCM groups in trials of mild vs. moderate IH as well as brief vs. prolonged IH, and emphasized random effects rather than fixed effects analysis. Thus our methods avoid underestimating uncertainty (i.e., had wider confidence intervals in effect estimates) than the other analysis. As well, we evaluated differences in adverse events as well as effectiveness outcomes with IVTM vs. surface. Thus we believe that the results of the present study are more robust than those of the other systematic review.

Third, the majority of patients included in this analysis were enrolled in observational rather than randomized studies. As such, we can infer association between use of IH and outcomes after OHCA, rather than causation. However, a subgroup analysis of the results of data derived from randomized studies did not demonstrate a significant difference in effects found for either neurological outcomes or overall survival.

Fourth, multiple factors are associated with outcome after OHCA. There was insufficient information about time to target temperature in each study to be able to relate it to outcome. The SCM employed in studies included in this analysis were heterogeneous, but we were unable compare the effect of specific SCM. In addition to method of IH, important prognostic factors may include initial rhythm (i.e., ventricular fibrillation versus pulseless electrical activity or asystole),[51] site of initiation of IH (pre-hospital or emergency department),[52-55] duration of IH,[52] and concurrent medications to reduce shivering and sedation. Multi-center observational studies and a systematic review suggest that the outcomes of patients resuscitated from OHCA are associated with the components of care administered after transportation to a receiving hospital.[53-56] These include emergency coronary angiography and selective percutaneous coronary intervention, as well as deferred prognostic assessment and withdrawal of life-sustaining treatment in addition to IH. Included articles lacked information regarding these components of resuscitation after OHCA so we cannot draw conclusions about their relative contributions to patient outcomes based on the results of this systematic review and meta-analysis.

Fourth, there was a significant difference in neurologic outcome but not survival with IVTM vs. SCM. It is possible that the latter may be attributable to a lack of survival benefit from IH. Alternatively, the lack of significant survival benefit may reflect that effective post-resuscitation care has several necessary elements, and that the included studies generally did not try to mitigate the competing risk of premature prognosis assessment and withdrawal of life sustaining treatments upon survival.[57]

This study has some strengths. First, to the best of our knowledge, the overall sample size of the present study is larger than any prior controlled assessments of use of IH in individual patients with CA. This yields more precise effect estimates than previous studies. Second, treatment effects were pooled using a random-effects statistical model. Meta-analyses commonly use a fixed effect or a random-effects model. The former assumes all studies are estimating the same (i.e., fixed) treatment effect, whereas the latter allows for differences in the treatment effect from study to study.[58] Although both methods are criticized,[59] random-effects models are less likely to overstate certainty (i.e., underestimate confidence interval around the pooled treatment effect).

Third, included studies were widely separated by geography, time and method of IH. Ordinarily, this would be expected to attenuate differences between treatment and outcome. Instead, we observed significant differences. We therefore infer that the observed differences are likely generalizable to other settings.

Conclusions

Temperature management following CA using IVTM as compared to SCM is associated with a significant and important beneficial effect on neurological outcome but not on overall survival. Our findings suggest that use of IVTM may be preferable to use of SCM to reduce morbidity in this population. Future research on induced hypothermia after cardiac arrest should report cooling method(s) used, characteristics of cooling (including time to target temperature, temperature precision and duration of cooling) as well as the characteristics of EMS and in-hospital care.

Figure 1: PRISMA Flow Diagram of Included and Excluded Studies

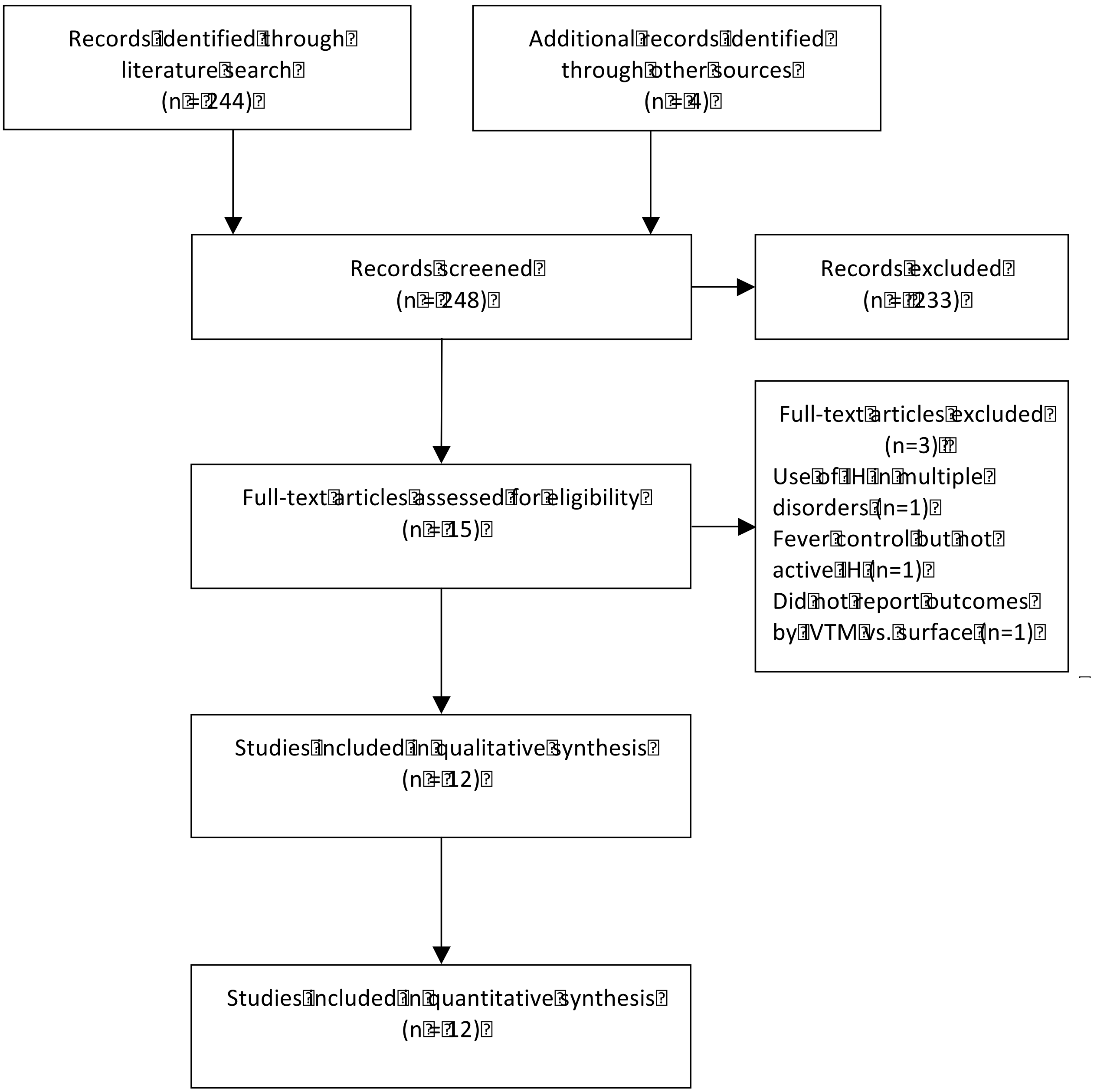
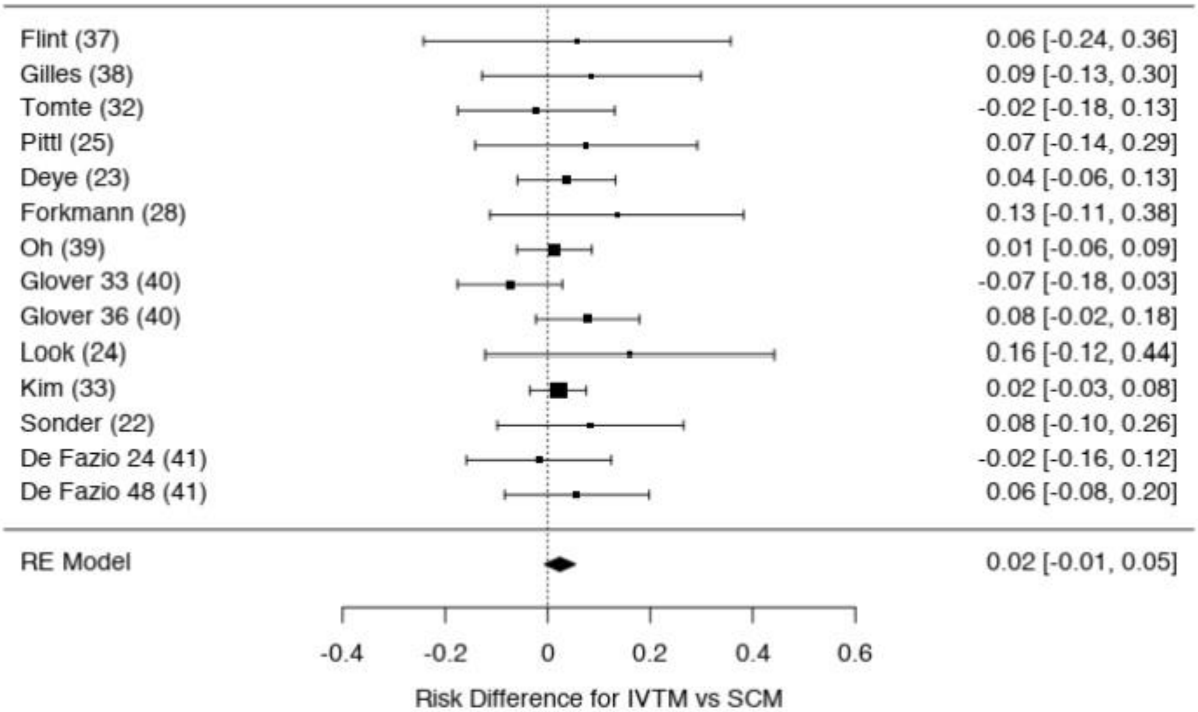


Figure 2: Random-Effects Forrest Plots for Risk Difference in Survival and Good Neurologic Outcome

A) Survival



Random-Effects Model (k = 14)

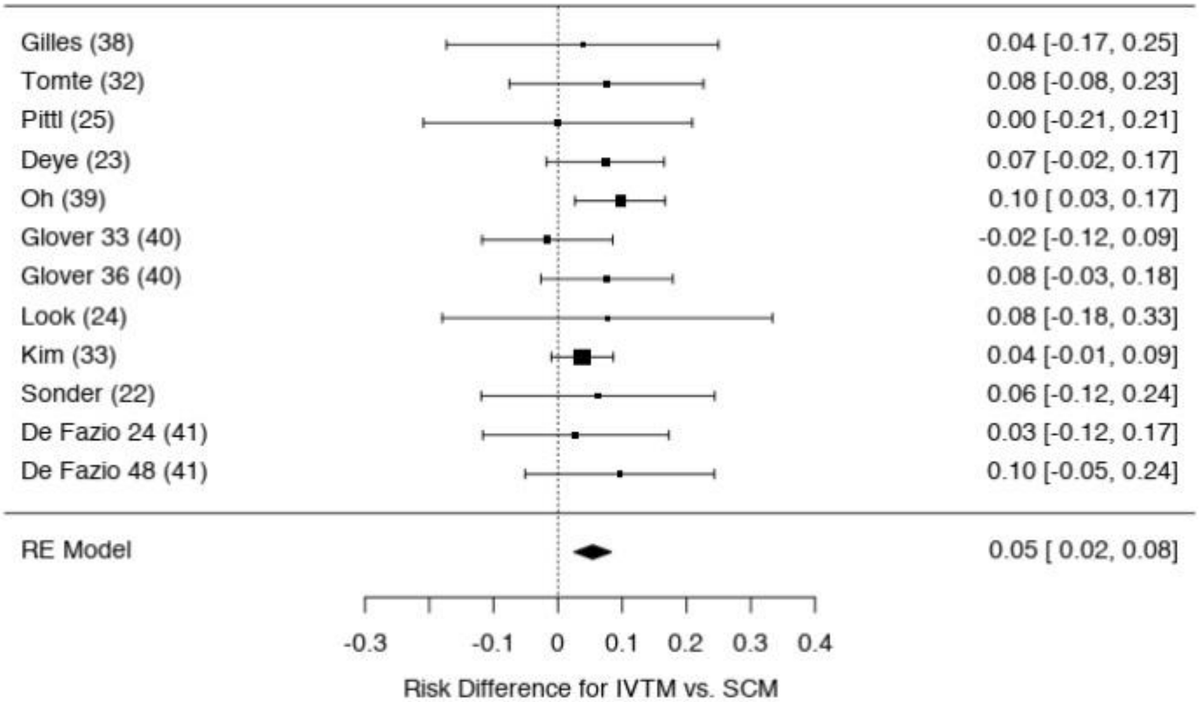
	Estimate	se	Z	p	CI Lower Bound	CI Upper Bound
Intercept	0.0238	0.0155	1.53	0.126	–0.007	0.054
	.	.	.	.	.	.

Note. Tau² Estimator: DerSimonian-Laird

Heterogeneity Statistics

Tau	Tau²	I²	H²	R²	df	Q	p
0.000	0 (SE= 0.0015)	0%	1.000	.	13.000	8.328	0.822

B) Good Neurologic Outcome



Random-Effects Model (k = 12)

	Estimate	se	Z	p	CI Lower Bound	CI Upper Bound
Intercept	0.0541	0.0149	3.64	<.001	0.025	0.083
	.	.	.	.	.	.

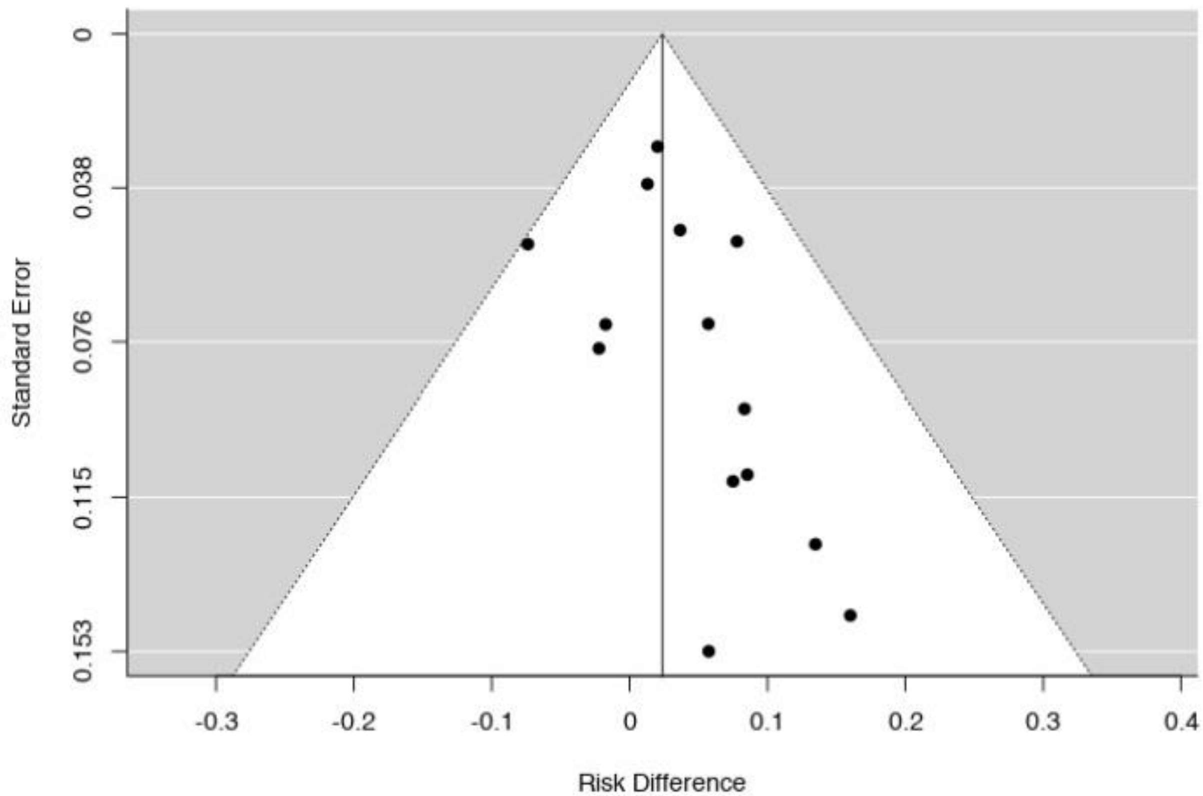
Note. Tau² Estimator: DerSimonian-Laird

Heterogeneity Statistics

Tau	Tau²	I²	H²	R²	df	Q	p
0.000	0 (SE= 0.0013)	0%	1.000	.	11.000	4.898	0.936

Figure 3: Funnel Plots for Survival and Good Neurologic Outcome

A) Survival



Fail-Safe N Analysis (File Drawer Analysis)

Fail-safe N	p
5.000	0.029

Note. Fail-safe N Calculation Using the Rosenthal Approach

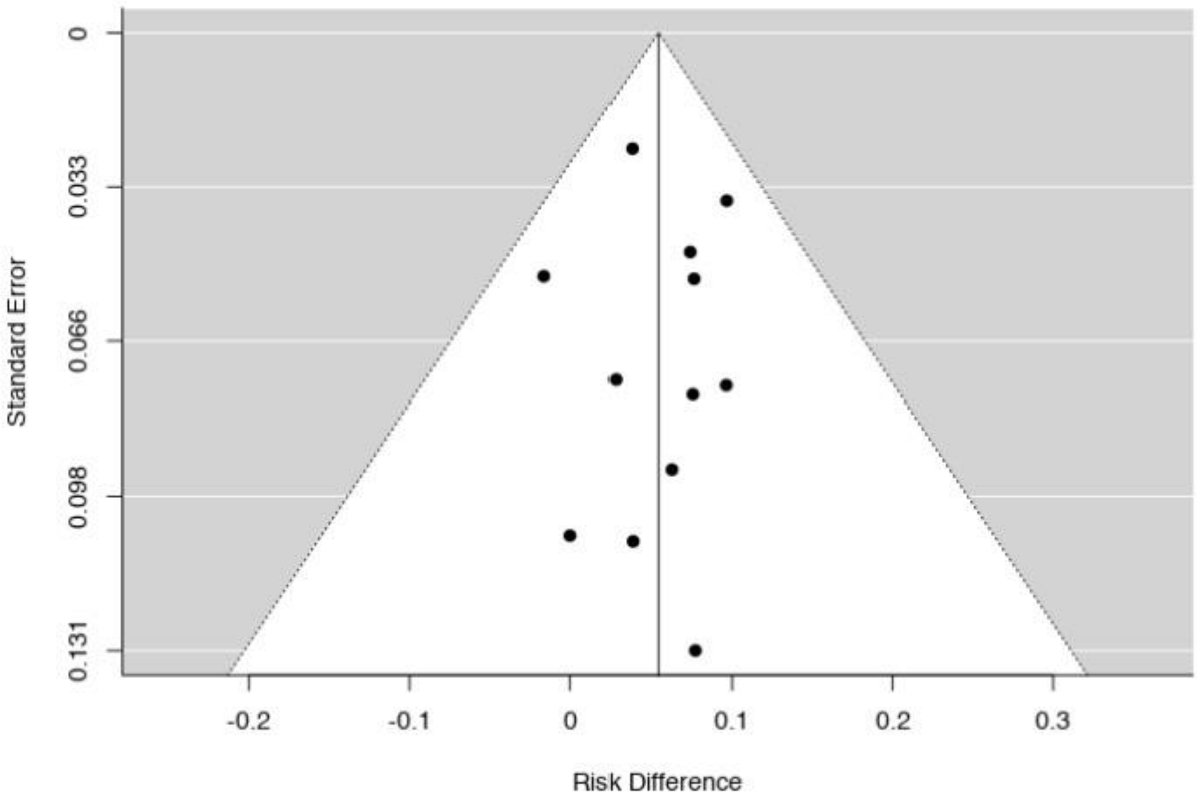
Rank Correlation Test for Funnel Plot Asymmetry

Kendall's Tau	p
0.253	0.233

Regression Test for Funnel Plot Asymmetry

Z	p
1.165	0.244

B) Good Neurologic Outcome



Fail-Safe N Analysis (File Drawer Analysis)

Fail-safe N	p
35.000	<.001

Note. Fail-safe N Calculation Using the Rosenthal Approach

Rank Correlation Test for Funnel Plot Asymmetry

Kendall's Tau	p
−0.121	0.638

Regression Test for Funnel Plot Asymmetry

Z	p
0.070	0.944

Table 1: Characteristics of Included Studies and Patients

(See attached)

Table 2: Outcomes

(See attached)

References

1. Benjamin EJ, Virani SS, Callaway CW, et al. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. Circulation 2018;137:e67-e492.
2. Grasner JT, Lefering R, Koster RW et al. EuReCa ONE-27 Nations, ONE Europe, ONE Registry: A prospective one month analysis of out-of-hospital cardiac arrest outcomes in 27 countries in Europe. Resuscitation 2016;105:188-95.
3. Madathil RJ, Hira RS, Stoeckl M, Sterz F, Elrod JB, Nichol G. Ischemia reperfusion injury as a modifiable therapeutic target for cardioprotection or neuroprotection in patients undergoing cardiopulmonary resuscitation. Resuscitation 2016;105:85-91.
4. Fan J, Cai S, Zhong H et al. Therapeutic hypothermia attenuates global cerebral reperfusion-induced mitochondrial damage by suppressing dynamin-related protein 1 activation and mitochondria-mediated apoptosis in a cardiac arrest rat model. Neurosci Lett. 2017;647:45-52.
5. Yuan W, Wu JY, Zhao YZ et al. Comparison of early sequential hypothermia and delayed hypothermia on neurological function after resuscitation in a swine model. Am J Emerg Med 2017;35:1645-52.
6. Wu J, Yuan W, Li J et al. Effects of Mild Hypothermia on Cerebral Large and Small Microvessels Blood Flow in a Porcine Model of Cardiac Arrest. Neurocrit Care 2017;27:297-303.
7. Li J, Li C, Yuan W et al. Therapeutic hypothermia attenuates brain edema in a pig model of cardiac arrest: Possible role of the angiopoietin-Tie-2 system. Am J Emerg Med 2017;35:993-9.
8. Wu L, Sun HL, Gao Y et al. Therapeutic Hypothermia Enhances Cold-Inducible RNA-Binding Protein Expression and Inhibits Mitochondrial Apoptosis in a Rat Model of Cardiac Arrest. Mol Neurobiol 2017;54:2697-705.
9. Janata A, Weihs W, Bayegan K et al. Therapeutic hypothermia with a novel surface cooling device improves neurologic outcome after prolonged cardiac arrest in swine. Crit Care Med 2008;36:895-902.
10. Yu T, Yang Z, Li H, Ding Y, Huang Z, Li Y. Short Duration Combined Mild Hypothermia Improves Resuscitation Outcomes in a Porcine Model of Prolonged Cardiac Arrest. Biomed Res Int 2015;2015:279192.
11. Hutin A, Lidouren F, Kohlhauer M et al. Total liquid ventilation offers ultra-fast and whole-body cooling in large animals in physiological conditions and during cardiac arrest. Resuscitation 2015;93:69-73.
12. Bayegan K, Janata A, Frossard M et al. Rapid non-invasive external cooling to induce mild therapeutic hypothermia in adult human-sized swine. Resuscitation 2008;76:291-8.
13. Mooney MR, Unger BT, Boland LL et al. Therapeutic hypothermia after out-of-hospital cardiac arrest: evaluation of a regional system to increase access to cooling. Circulation 2011;124:206-14.
14. Uribarri A, Bueno H, Perez-Castellanos A et al. Impact of time to cooling initiation and time to target temperature in patients treated with hypothermia after cardiac arrest. Eur Heart J Acute Cardiovasc Care 2015;4:365-72.
15. Goury A, Poirson F, Chaput U et al. Targeted temperature management using the "Esophageal Cooling Device" after cardiac arrest (the COOL study): A feasibility and safety study. Resuscitation 2017;121:54-61.
16. Bernard SA, Gray TW, Buist MD et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346:557-63.
17. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346:549-56.
18. Donnino MW, Andersen LW, Berg KM et al. Temperature Management After Cardiac Arrest: An Advisory Statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Circulation 2015;132:2448-56.
19. Callaway CW, Donnino MW, Fink EL et al. Part 8: Post-Cardiac Arrest Care: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2015;132:S465-82.
20. Geocadin RG, Wijdicks E, Armstrong MJ et al. Practice guideline summary: Reducing brain injury following cardiopulmonary resuscitation: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology 2017;88:2141-9.
21. Kleinman ME, Perkins GD, Bhanji F et al. ILCOR Scientific Knowledge Gaps and Clinical Research Priorities for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care: A Consensus Statement. Resuscitation 2018;127:132-46.
22. Sonder P, Janssens GN, Beishuizen A et al. Efficacy of different cooling technologies for therapeutic temperature management: A prospective intervention study. Resuscitation 2018;124:14-20.
23. Deye N, Cariou A, Girardie P et al. Endovascular Versus External Targeted Temperature Management for Patients With Out-of-Hospital Cardiac Arrest: A Randomized, Controlled Study. Circulation 2015;132:182-93.
24. Look X, Li H, Ng M et al. Randomized controlled trial of internal and external targeted temperature management methods in post- cardiac arrest patients. Am J Emerg Med 2018;36:66-72.

25. Pittl U, Schratter A, Desch S et al. Invasive versus non-invasive cooling after in- and out-of-hospital cardiac arrest: a randomized trial. Clin Res Cardiol 2013;102:607-14.
26. Booth A, Clarke M, Ghersi D, Moher D, Petticrew M, Stewart L. An international registry of systematic-review protocols. Lancet 2011;377:108-9.
27. Zhang L, Ajiferuke I, Sampson M. Optimizing search strategies to identify randomized controlled trials in MEDLINE. BMC Med Res Methodol 2006;6:23.
28. Forkmann M, Kolschmann S, Holzhauser L et al. Target temperature management of 33 degrees C exerts beneficial haemodynamic effects after out-of-hospital cardiac arrest. Acta Cardiol 2015;70:451-9.
29. Zeng X, Zhang Y, Kwong JS et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. J Evid Based Med 2015;8:2-10.
30. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.02011. http://handbook-5-1.cochrane.org
31. Liberati A, Altman DG, Tetzlaff J et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700.
32. Tomte O, Draegni T, Mangschau A, Jacobsen D, Auestad B, Sunde K. A comparison of intravascular and surface cooling techniques in comatose cardiac arrest survivors. Crit Care Med 2011;39:443-9.
33. Kim KH, Shin SD, Song KJ et al. Cooling methods of targeted temperature management and neurological recovery after out-of-hospital cardiac arrest: A nationwide multicenter multi-level analysis. Resuscitation 2018;125:56-65.
34. Hoedemaekers CW, Ezzahti M, Gerritsen A, van der Hoeven JG. Comparison of cooling methods to induce and maintain normo- and hypothermia in intensive care unit patients: a prospective intervention study. Crit Care 2007;11:R91.
35. Holzer M, Mullner M, Sterz F et al. Efficacy and safety of endovascular cooling after cardiac arrest: cohort study and Bayesian approach. Stroke 2006;37:1792-7.
36. Arrich J, European Resuscitation Council Hypothermia After Cardiac Arrest Registry Study Group. Clinical application of mild therapeutic hypothermia after cardiac arrest. Crit Care Med 2007;35:1041-7.
37. Flint AC, Hemphill JC, Bonovich DC. Therapeutic hypothermia after cardiac arrest: performance characteristics and safety of surface cooling with or without endovascular cooling. Neurocrit Care 2007;7:109-18.
38. Gillies MA, Pratt R, Whiteley C, Borg J, Beale RJ, Tibby SM. Therapeutic hypothermia after cardiac arrest: a retrospective comparison of surface and endovascular cooling techniques. Resuscitation 2010;81:1117-22.
39. Oh SH, Oh JS, Kim YM et al. An observational study of surface versus endovascular cooling techniques in cardiac arrest patients: a propensity-matched analysis. Crit Care 2015;19:85.
40. Glover GW, Thomas RM, Vamvakas G et al. Intravascular versus surface cooling for targeted temperature management after out-of-hospital cardiac arrest - an analysis of the TTM trial data. Crit Care 2016;20:381.
41. DeFazio C, Skrifvars M, Soreide E et al. Intravascular versus surface cooling for targeted temperature management after out-of-hospital cardiac arrest: an analysis of the TTH48 trial. Critical Care 2019;23:61.
42. Nielsen N, Wetterslev J, Friberg H, Group TTMTS. Targeted temperature management after cardiac arrest. N Engl J Med 2014;370:1360.
43. Nichol G, Huszti E, Kim F et al. Does induction of hypothermia improve outcomes after in-hospital cardiac arrest? Resuscitation 2013;84:620-5.
44. Salter R, Bailey M, Bellomo R et al. Changes in Temperature Management of Cardiac Arrest Patients Following Publication of the Target Temperature Management Trial. Crit Care Med 2018;46:1722-30.
45. Khera R, Humbert A, Leroux B et al. Hospital Variation in the Utilization and Implementation of Targeted Temperature Management in Out-of-Hospital Cardiac Arrest. Circ Cardiovasc Qual Outcomes 2018;11:e004829.
46. Bradley SM, Liu W, McNally B et al. Temporal Trends in the Use of Therapeutic Hypothermia for Out-of-Hospital Cardiac Arrest. JAMA Netw Open 2018;1:e184511.
47. Hartling L, Featherstone R, Nuspl M, Shave K, Dryden DM, Vandermeer B. Grey literature in systematic reviews: a cross-sectional study of the contribution of non-English reports, unpublished studies and dissertations to the results of meta-analyses in child-relevant reviews. BMC Med Res Methodol 2017;17:64.
48. Morrison A, Polisena J, Husereau D et al. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. Int J Technol Assess Health Care 2012;28:138-44.
49. Calabró L, Bougouin W, Cariou A et al. Effect of different methods of cooling for targeted temperature management on outcome after cardiac arrest: a systematic review and meta-analysis. Critical Care 2019;23:1-2.
50. Flemming K, Simonis G, Ziegs E et al. Comparison of external and intravascular cooling to induce hypothermia in patients after CPR. Ger Med Sci Flemming, Kerstin et al. “Comparison of external and intravascular cooling to induce hypothermia in patients after CPR.” German medical science : GMS e-journal 2006;4:Doc04.
51. Nichol G, Thomas E, Callaway CW et al. Regional variation in out-of-hospital cardiac arrest incidence and outcome. JAMA 2008;300:1423-31.

52. Kirkegaard H, Soreide E, de Haas I et al. Targeted Temperature Management for 48 vs 24 Hours and Neurologic Outcome After Out-of-Hospital Cardiac Arrest: A Randomized Clinical Trial. JAMA 2017;318:341-50.
53. Stub D, Schmicker RH, Anderson ML et al. Association between hospital post-resuscitative performance and clinical outcomes after out-of-hospital cardiac arrest. Resuscitation 2015;92:45-52.
54. Callaway CW, Schmicker R, Kampmeyer M et al. Receiving hospital characteristics associated with survival after out-of-hospital cardiac arrest. Resuscitation 2010;81:524-9.
55. Callaway CW, Schmicker RH, Brown SP et al. Early coronary angiography and induced hypothermia are associated with survival and functional recovery after out-of-hospital cardiac arrest. Resuscitation 2014;85:657-63.
56. Yeung J, Matsuyama T, Bray J, Reynolds J, Skrifvars MB. Does care at a cardiac arrest centre improve outcome after out-of-hospital cardiac arrest? - A systematic review. Resuscitation 2019;137:102-15.
57. Geocadin RG, Wijdicks E, Armstrong MJ et al. Practice guideline summary: Reducing brain injury following cardiopulmonary resuscitation: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology 2017. 88:2141-9.
58. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. BMJ. 2011;342:d549.
59. Serghiou S, Goodman SN. Random-Effects Meta-analysis: Summarizing Evidence With Caveats. JAMA. 22;321:301-2.