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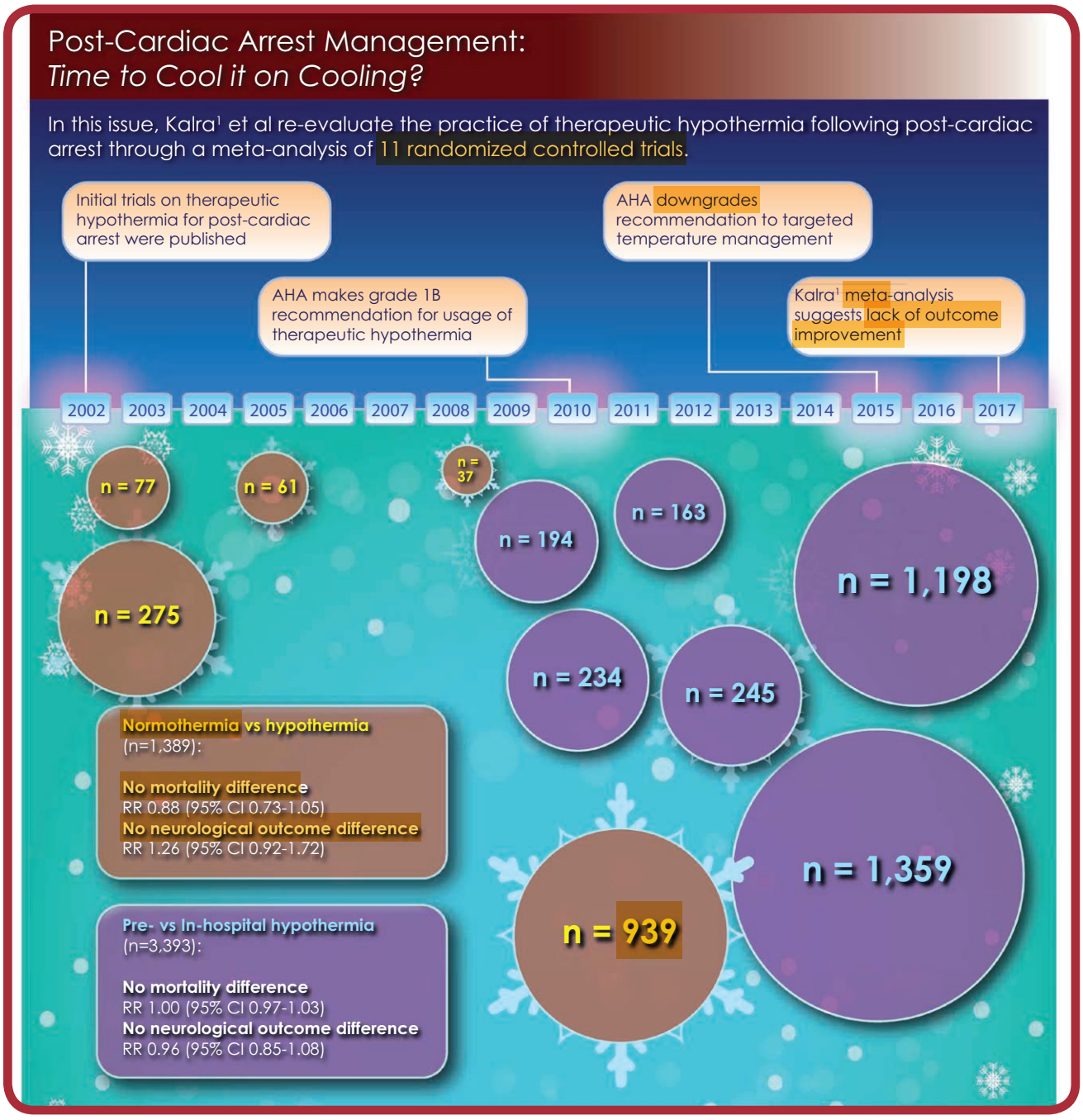

Therapeutic hypothermia after postcardiac arrest has become a recommended component of care for survivors. Despite this recommendation, recent randomized clinical trials have failed to support the benefit of targeted temperature management on important end points such as all-cause mortality and neurological outcomes. In this infographic, we review the timeline of the development of the current recommendations, visualize the clinical trials that have provided data to guide clinical care, and summarize a recent meta-analysis that synthesizes the high-quality data available to date.

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Meta-analysis, Medical Reversal, and Settled Science

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"Medical reversal" describes the publication of clinical data that contradict previously published data and establishes a new "evidence-based" standard. Worrisome at best (and harmful at worst), reversal is surprisingly common, and exists in nearly all medical specialties. Recent high-profile examples include vertebroplasty for spinal fractures[1] and hormone therapy in postmenopausal women.[2] The failure of initial reports of tight glucose control[3] and daily sedative interruption[4] to withstand subsequent scrutiny suggests that the evidence base underlying perioperative critical care may have a similarly unstable foundation.

Although the reasons for reversal are incompletely understood, potential mechanisms include fraud, error, inadequate statistical analysis, mechanistic plausibility,[5] and cognitive biases. Underlying many of these possibilities is a tacit understanding that the later article is "true," and the earlier, "reversed" findings must have been incorrect. But 3 other frames are possible: the earlier studies were correct (and the later studies were wrong), both earlier and later findings were correct (implying that the phenomenon being studied has changed over time), or neither finding is correct, and the truth lies elsewhere. In seeking an explanation for reversal, the choice of frame is not always easy because an adequately powered randomized prospective study design may not protect the finding against the subsequent reversal.[6]

In this issue of *Anesthesia & Analgesia*, Kalra et al[7] publish the results of a meta-analysis of targeted temperature management (TTM) (cooling) after cardiac arrest. The authors identified 11 trials from 1966 to 2016 containing 4782 patients. Individual trials varied in rates of bystander cardiopulmonary resuscitation, cooling protocol, and method. After multivariate random-effects modeling, the authors concluded that TTM had no effect on mortality rates or cerebral performance status.

Anesthesia & Analgesia readers who are familiar with TTM research may wonder why another meta-analysis of TTM is needed. The history of TTM fits a classic reversal scenario: multiple small clinical trials with unclear consensus, followed by high-profile randomized clinical trials establishing a clinical "truth." In the case of TTM, 2 small but high-profile trials were published in the same 2002 issue of the *New England Journal of Medicine*,[8,9] with an accompanying editorial[10] citing as evidence of correctness that the 2 studies were performed on different continents, produced similar effect sizes, and that a plausible mechanism existed for the protective effect. By 2010, cooling to 32°C–34°C was enshrined in American Heart Association guidelines for cardiopulmonary resuscitation[11] and strongly recommended by 5 professional critical care societies.[12]

Then came the reversal. A 2013 study of 950 patients (>4 times the combined number of 213 in the initial 2002 trials) randomized patients to 33°C vs 36°C after cardiac arrest, and found no difference in survival or neurological outcome.[13] Also published in the *New England Journal*, this study was intensely discussed, garnering an Altmetric score of 470 by January 2014[14] and 664 as of August 22, 2017, placing it in the top 5% of all research outputs scored by Altmetric.

Despite this apparent reversal, little has changed regarding the recommended use of temperature management after cardiac arrest in 2017. Both the 2016 Cochrane[15] and the 2015 American Heart Association updates[16] continue to recommend postarrest cooling. Critical care and emergency medicine specialists argue over cooling method, duration, timing, target, and applicability. With TTM, the net result of literature reversal is more, not less cognitive diversity.

In principle, meta-analysis is an ideal solution. By combining the results of several studies, meta-analysis increases statistical power, facilitates understanding of variability between studies, and allows generalization of results to a wider population. The TTM landscape, dotted with multiple small studies and divergent results, is tailor made for meta-analysis, and multiple groups have obliged with both negative[17,18] and positive results.[16] However, meta-analysis also presumes that an absolute truth underlies all studies, but it is detected with varying accuracy and precision. What if that assumption is wrong, and the story of TTM really is one in which one (or more) of the dueling studies is incorrect? Does it then make sense to lump the results of correct and incorrect studies together? In such cases, meta-analyses may result in less, not more, truth.

Even when all studies are correctly performed, repeated meta-analyses raise an issue akin to that encountered during interim analyses of a randomized controlled trial. Stopping early when data are few and the likelihood of an outlier effect is high risks a type 1 error, whereas addition of multiple negative trials with high heterogeneity risks never reaching

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clear significance. Aware of this challenge, meta-analysts have responded with trial sequential meta-analysis (TSA), a Bayesian modification of standard meta-analysis in which thresholds for significance or futility are adjusted based on available data. With TSA, thresholds for significance are raised when few data exist (and the likelihood of a false positive is high) and lowered when a wealth of data are available (and the likelihood of identifying a real effect with further studies is low). A 2017 treatise on TSA[19] includes a sample TSA-based analysis of TTM explaining why early meta-analyses may have found a benefit, why later efforts (including Kalra et al[7]) are more inconclusive, and why future trials or meta-analyses of TTM are likely to be futile.

Deciphering whether the TTM story represents reversal or fertile ground for meta-analysis may not be easy. Kalra et al[7] found considerable variation among studies in age, time to return of spontaneous circulation, percentage of bystander cardiopulmonary resuscitation, a large 12–28-hour variation in cooling duration, and multiple cooling techniques, including helmet, ice packs, and intravenous administration of cold fluid.[11] Which of these elements may affect TTM results (if at all) is unknown. In a 2016 analysis of Cochrane reports, outcomes graded as having a high quality of evidence had no better concordance among individual trials than did outcomes graded as having a low quality of evidence.[20] Observations such as these are disquieting because they suggest that only time can reveal the true answer.

So what should readers of *Anesthesia & Analgesia* make of repeated meta-analyses of TTM (or any other topic)? First, just as readers are critical of individual studies, so should they be appropriately thoughtful about meta-analysis results. Questions of applicability, generalizability, and actual benefit (as opposed to control group harm) are germane to both types of data. To the above, we would add the possibility that meta-analyses in fields in which reversal has occurred may be incorporating the results of not just underpowered, but also flawed research.

Absent a need to clarify 1 or more of the above questions, repeated meta-analyses, especially for low-certainty data, may be an exercise similar to "p hacking," in which analyses are repeatedly run to extract a statistically significant finding, rather than to answer a hypothesis.[21] Alternatively, repeat meta-analyses may serve a useful role in highlighting overlooked gaps in the data and pointing out questions for future investigation. Regardless, the role for repeated meta-analyses remains unclear, and such studies may confuse as much as they clarify.

DISCLOSURES

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Contribution: This author helped prepare the manuscript.
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Contribution: This author helped prepare the manuscript.
Conflicts of Interest: A. Tung is an executive editor, Critical Care and Resuscitation, for *Anesthesia & Analgesia*.
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Targeted Temperature Management After Cardiac Arrest: Systematic Review and Meta-analyses

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BACKGROUND: Targeted temperature management (TTM) with therapeutic hypothermia is an integral component of postarrest care for survivors. However, recent randomized controlled trials (RCTs) have failed to demonstrate the benefit of TTM on clinical outcomes. We sought to determine if the pooled data from available RCTs support the use of prehospital and/or in-hospital TTM after cardiac arrest.

METHODS: A comprehensive search of SCOPUS, Elsevier's abstract and citation database of peer-reviewed literature, from 1966 to November 2016 was performed using predefined criteria. Therapeutic hypothermia was defined as any strategy that aimed to cool post–cardiac arrest survivors to a temperature ≤34°C. Normothermia was temperature of ≥36°C. We compared mortality and neurologic outcomes in patients by categorizing the studies into 2 groups: (1) hypothermia versus normothermia and (2) prehospital hypothermia versus in-hospital hypothermia using standard meta-analytic methods. A random effects modeling was utilized to estimate comparative risk ratios (RR) and 95% confidence intervals (CIs).

RESULTS: The hypothermia and normothermia strategies were compared in 5 RCTs with 1389 patients, whereas prehospital hypothermia and in-hospital hypothermia were compared in 6 RCTs with 3393 patients. We observed no difference in mortality (RR, 0.88; 95% CI, 0.73–1.05) or neurologic outcomes (RR, 1.26; 95% CI, 0.92–1.72) between the hypothermia and normothermia strategies. Similarly, no difference was observed in mortality (RR, 1.00; 95% CI, 0.97–1.03) or neurologic outcome (RR, 0.96; 95% CI, 0.85–1.08) between the prehospital hypothermia versus in-hospital hypothermia strategies.

CONCLUSIONS: Our results suggest that TTM with therapeutic hypothermia may not improve mortality or neurologic outcomes in postarrest survivors. Using therapeutic hypothermia as a standard of care strategy of postarrest care in survivors may need to be reevaluated. (Anesth Analg 2018;126:867–75)

KEY POINTS

- **Question:** Does targeted temperature management affect outcomes after cardiopulmonary arrest?
- **Findings:** Pooled evidence from available randomized control trials indicated that targeted temperature management did not improve all-cause mortality or neurologic outcomes but variability among studies was high.
- **Meaning:** The role of targeted temperature management in postresuscitation care remains unclear.

In recent years, therapeutic hypothermia and targeted temperature management (TTM) have been increasingly used in the postresuscitation care of patients who have suffered cardiac arrest. Many mechanisms have been thought to confer benefit in therapeutic hypothermia after cardiac arrest. These mechanisms are thought to affect all 3 levels of injury after cardiac arrest: ischemic injury, immediate reperfusion injury, and delayed reperfusion injury.[1] Almost a decade ago, 2 large randomized controlled trials (RCTs) in humans demonstrated improvement in mortality and neurologic outcomes with therapeutic hypothermia use after cardiac arrest.[2,3]

On the basis of such evidence, the 2010 American Heart Association guidelines recommended the usage of therapeutic hypothermia as a grade IB recommendation.[4] Conflicting data then began to surface regarding the use

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of therapeutic hypothermia. Multiple investigations were published showing little impact between TTM with the normothermia, prehospital hypothermia, and in-hospital hypothermia strategies on neurologic and mortality outcomes.[5,6] This led to an alteration in the recommendation for the use of therapeutic hypothermia, with the 2015 American Heart Association guidelines[7] for post–cardiac arrest care instead suggesting that TTM be used rather than strictly outlining a therapeutic hypothermia strategy. The grading of the recommendation was also altered to a class IB level B-R recommendation for out-of-hospital pulseless ventricular tachycardia and ventricular fibrillation cardiac arrest. Furthermore, it was changed to a class IB level C-EO recommendation (consensus of expert opinion based on clinical experience) for out-of-hospital pulseless electrical activity and asystole cardiac arrests and in-hospital cardiac arrests.[7] This was also followed by the recommendation against prehospital intravenous cooled fluid infusion.

Due to the conflicting data, we sought to evaluate the effect that TTM had through normothermia, prehospital hypothermia, and in-hospital hypothermia on in-hospital mortality and neurologic outcomes after cardiac arrest through systematic review and meta-analytic comparisons of the RCTs comparing the 3 TTM strategies.

METHODS

We searched SCOPUS from 1966 until November 2016 for English language RCTs detailing the use of TTM after cardiac arrest in adult patients. The SCOPUS database indexes the full Medline database as well as Biobase, Embase, Fluidex, Geobase, and the World Textile Index. Three authors (P.A., N.S.B., and R.K.) used a prespecified list of terms to locate studies. The full search strategy is detailed in Supplemental Digital Content, Section 1, http://links.lww.com/AA/C138. We also reviewed reference lists from original manuscripts and published systematic reviews and meta-analyses to identify trials that were not listed in the original database search. After review of abstracts, full-text manuscripts were retrieved for review.

All English language RCTs evaluating the use of TTM in adults were eligible for inclusion. All combinations of cardiac rhythms (asystole, pulseless electrical activity, ventricular fibrillation, and pulseless ventricular tachycardia), TTM strategies (prehospital hypothermia, in-hospital hypothermia, and normothermia), and target temperatures were included. Hypothermia was defined as being 34°C or less. Normothermia was defined as being 36°C or more. Foreign language studies were excluded unless a full-text English translation of the study was available.

We intended to compare mortality and neurologic outcomes in patients by categorizing the studies into 2 groups: (1) hypothermia versus normothermia and (2) prehospital hypothermia versus in-hospital hypothermia. The prehospital hypothermia versus in-hospital comparison was done to evaluate whether the timing of hypothermia affected outcomes and to alleviate any concerns about the delay in institution of hypothermia as a cause of null results in the primary comparison (therapeutic hypothermia versus normothermia). These comparisons were decided on in an a priori fashion because the RCTs comparing the 2 approaches have conflicting results. The primary outcome measure was in-hospital all-cause mortality after cardiac arrest. The secondary outcome measure was the cerebral performance category (CPC) after TTM.[8] The CPC scale is a 5-point scale graded from 1 to 5, where the outcome of neurologic disability after significant damage is graded into one of the following 5 categories: good recovery (CPC 1), moderate disability (CPC 2), severe disability (CPC 3), persistent vegetative state (CPC 4), or death (CPC 5).[8] Within this scale, good neurologic outcome was defined as CPC categories 1–2 and poor neurologic outcomes were defined as CPC categories 3–5 for meta-analyses. Discharge to rehabilitation facilities was classed as CPC 2 and discharge to a nursing home was classified as CPC 3. A CPC score of 2 or less was considered a favorable neurologic outcome.[2] Where there were multiple studies reporting outcomes for the same cohort, we chose the study with the longest and most complete follow-up.

Four authors (P.A., N.S.B., R.K., and G.A.) searched the titles and abstracts of all studies. Multiple authors (G.A., N.S.B., and R.K.) then performed data extraction. Data were extracted to elucidate baseline characteristics of patients and outcome measures in all of the included studies. All inconsistencies during data extraction were resolved by mutual consensus so that a unanimous decision was made.

Quality assessment of the included studies was performed according to the Jadad scale for RCTs.[9] The Jadad scale evaluates the quality of RCTs through assessment of study randomization, blinding, and description of withdrawals and dropouts. Two authors (N.S.B. and R.K.) independently performed quality assessment of all of the included RCTs using the Jadad scale.[9]

The systematic review and meta-analyses were reported based on the recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[10]

Statistical Analysis

Statistical analyses were performed by Comprehensive Meta-Analysis version 2.2.046 (Biostat, Englewood, NJ) and STATA version 14.1 (StataCorp LP, College Station, TX). To estimate summary effects, a random effects model using the DerSimonian and Laird[11] method was used in our investigation. The Mantel-Haenszel model was then used to estimate the heterogeneity for the meta-analyses.[12] Heterogeneity was estimated using the I^2 statistic proposed by Higgins and Thompson.[12] Summary treatment effects and results were presented as risk ratios (RR) with 95% confidence intervals (CIs). Funnel plots were generated to outline the publication bias. We used log RR as the x-axis variable to exhibit estimated treatment effect for the included studies and plotted standard error as the y-axis variable to provide a measure of sample size.[13] Publication bias was assessed using the Egger regression intercept.[14] The Egger regression test is a simple linear regression to detect asymmetry of the funnel plot on the logarithm scale of the risk ratio.[14] The 1-sided Egger test was used because the 2-sided test may produce a false publication bias or inconsistency in the tail.[15,16] Based on the estimated standard normal deviate (treatment effect size divided by standard error) and the precision (the inverse of standard error) of the included studies, an Egger regression line is generated. If there is symmetry in the funnel plot, the intercept should be nonsignificant. In other words, the intercept value

should be zero or near zero, and deviation of intercept from zero suggests publication bias. However, the power of the Egger regression test proportionally increases with number of studies.[14,16] A limited number of studies may have low power to detect publication bias. In case of significant heterogeneity in primary outcome among either comparison, meta-regression analyses were conducted in post hoc fashion using a mixed-effects (unrestricted maximal likelihood) meta-regression model to explore the reasons for the heterogeneity. The variables used for meta-regression were age, bystander cardiopulmonary resuscitation (CPR), presenting rhythm, and duration of return to spontaneous circulation (ROSC) on treatment effects comparisons between hypothermia and normothermia trials. Power calculations were performed assuming a 20% reduction in mortality and adverse neurologic outcome as a clinically important treatment effect for the hypothermia versus normothermia comparison.[5] Conversely, for the prehospital hypothermia versus in-hospital hypothermia comparison, a 15% reduction mortality and adverse neurologic outcome was considered clinically important.[17] These calculations were based on the assumptions that the number of patients and the outcome rate in the control group are equal to those in our meta-analysis. A 2-sample proportions the Pearson χ^2 test was used to compute power.

RESULTS

Eleven RCTs (Figure 1) with 4782 patients were eligible for analyses (Table 1).[2,3,5,18–25] The results of this systematic review and meta-analyses are presented as per the PRISMA extension statement (Supplemental Digital Content, Table 1, http://links.lww.com/AA/C138).[10] All included studies were graded as good to excellent based on the Jadad scale (Supplemental Digital Content, Table 2, http://links.lww.com/AA/C138).

There was variation in the individual characteristics of the trials. The mean/median age of the patients in the prehospital hypothermia, in-hospital hypothermia, and normothermia arms ranged from 63 to 67, 61 to 67, and 59 to 69 years of age, respectively. Mean/median ROSC time in the prehospital hypothermia, in-hospital hypothermia, and normothermia arms ranged from 26 to 32, 21 to 30, and 22 to 28 minutes, respectively. All combinations of presenting rhythms during out-of-hospital cardiac arrest were studied. There was a predominance of male patients in nearly all study arms (Table 1).

There were also variations in the resuscitation and cooling protocols of the trials. Percentage of bystander CPR varied from 26% to 73% among all study arms. The prehospital and in-hospital hypothermia arms of the trials had target temperatures ranging from 32 to 34°C. The duration of cooling in the prehospital hypothermia and in-hospital hypothermia arms ranged from 12 to 28 hours. Multiple methods of cooling were used, such as cooling via a helmet, ice packs, and intravenous infusion of cooled fluids (Table 1). These interventions were studied in 2 groups: (1) the hypothermia versus normothermia comparison (studies = 5 and patients = 1389)[2,3,5,18,23] and (2) the prehospital hypothermia versus in-hospital hypothermia comparison (studies = 6, patients = 3393).[19–22,24,25]

Hypothermia Versus Normothermia

Among the 5 RCTs that compared the hypothermia and normothermia strategies,[2,3,5,18,23] 702 patients received hypothermia as part of postarrest care, whereas 687 received normothermia. We observed no difference in all-cause mortality rates in the hypothermia versus normothermia comparison (RR, 0.88; 95% CI, 0.73–1.05; Figure 2A). Similarly, we did not observe any difference in the rates of favorable neurologic outcome in the hypothermia versus normothermia comparison (RR, 1.26; 95% CI, 0.92–1.72; Figure 2B).

Prehospital Hypothermia Versus In-Hospital Hypothermia

Among the 6 RCTs that compared the prehospital hypothermia and in-hospital hypothermia strategies,[19–22,24,25] 1722 patients received prehospital hypothermia as part of postarrest care, whereas 1671 received in-hospital hypothermia. We observed no difference in all-cause mortality rates in the prehospital hypothermia versus in-hospital hypothermia comparison (RR, 1.00; 95% CI, 0.97–1.03; Figure 3A). Similarly we did not

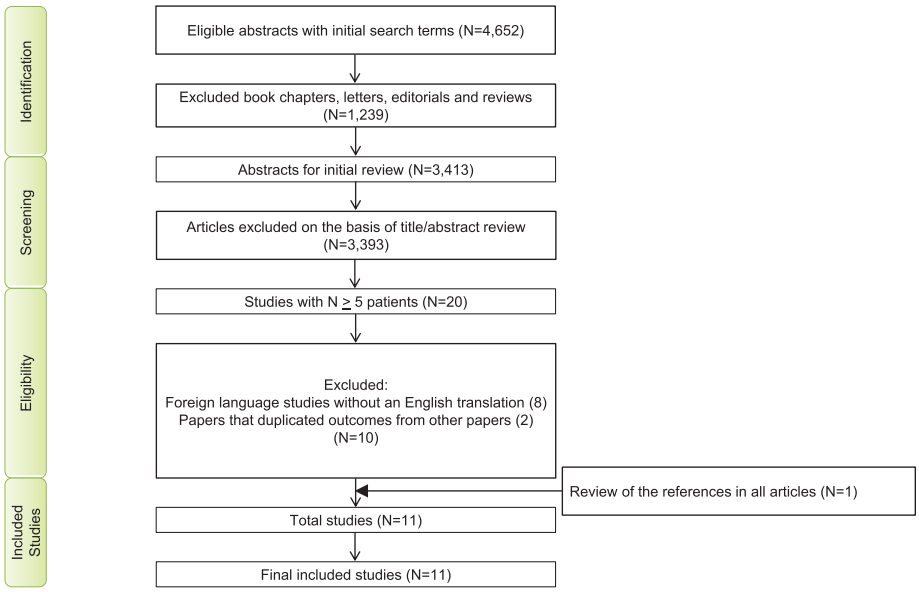

Figure 1. Flow diagram for study selection.

Table 1. Baseline Characteristics of Included Studies

Study (Reference) (IH or PH/NT)	Presenting Rhythm	Method of Cooling	Duration of Cooling	Time That Cooling was Commenced	Target Temperature (°C)	Follow-up Period	ROSC (Time in min) (TTM/NT)	Age (y) (TTM/NT)	Male (%) (TTM/NT)	Patients Receiving Bystander CPR (%) (IH or PH/NT)
Bernard et al (2002)[2] (N = 43 PH/34 NT)	VF	Ice packs	12 h	After ROSC	33	Till discharge	27/25	67/65	58/79	49/71
Holzer et al (2002)[3] (N = 137 IH/138 NT)	VF/pulseless VT	External cooling device	24 h	After ROSC	32–34	6 mo	21/22	59/59	77/75	49/43
Hachimi-Idrissi et al (2005)[18] (N = 30 IH/31 NT)	Asystole/PEA and VF/pulseless VT	Cooling helmet	Up to 24 h	After ROSC	33	6 mo	29/28	67/69	77/68	30/26
Kämäräinen et al (2009)[23] (N = 19 IH/18 NT)	Asystole/PEA and VF/pulseless VT	Cooled intravenous fluid infusion	-	After ROSC	33	Till discharge	23/22	59/63	95/94	58/22
Nielsen et al (2013)[5] (N = 473 IH/466 NT)	Asystole/PEA and VF/pulseless VT	Ice packs and cooled intravenous fluid infusion	28 h	After ROSC	33	8.5 mo	25/25	64/64	83/79	73/73
Study (PH/IH)	Presenting Rhythm	Method of Cooling	Duration of Cooling	Time that Cooling Was Commenced	Target Temperature (°C)	Follow-up Period	ROSC (Time in min) (PH/IH)	Age (y) (PH/IH)	Male (%) (PH/IH)	Patients Receiving Bystander CPR (%) (PH/IH)
Castrén et al (2010)[19] (N = 93/101)	Asystole/PEA and VF/pulseless VT	Transnasal evaporative cooling then systemic cooling	-	Intraarrest	34	7 d	32/30	66/64	67/79	33/46
Bernard et al (2010)[20] (N = 118/116)	VF	Cooled intravenous fluid infusion	24 h	After ROSC	33	Till discharge	26/26	63/63	83/86	69/67
Bernard et al (2012)[21] (N = 82/81)	Asystole/PEA	Surface cooling using machines, blankets, and ice packs; cooled intravenous fluid infusion	24 h	After ROSC	32–34	Till discharge	29/29	64/61	57/48	36/31
Debaty et al (2014)[25] (N = 123/122)	Asystole/PEA and VF/pulseless VT	Cooled intravenous fluid infusion and external cooling	24 h	Intraarrest	32–34	12 mo	27/30	66/69	72/71	50/52
Maynard et al (2015)[24] (N = 688/671)	Asystole/PEA and VF	Cooled intravenous fluid infusion	Up to 24 h	After ROSC	34	12 mo for mortality outcomes and 3 months for neurologic outcomes	27/26	66/65	64/63	57/59
Bernard et al (2016)[22] (N = 618/580)	Asystole/PEA and VF/pulseless VT	Cooled intravenous fluid infusion	24 h	After ROSC	33	Till discharge	23/20	65/64	75/74	66/67

Abbreviations: CPR, cardiopulmonary resuscitation; IH, in-hospital hypothermia; N, number; NT, normothermia; PEA, pulseless electrical activity; PH, prehospital hypothermia; ROSC, return to spontaneous circulation; TTM, targeted temperature management; VF, ventricular fibrillation; VT, ventricular tachycardia.

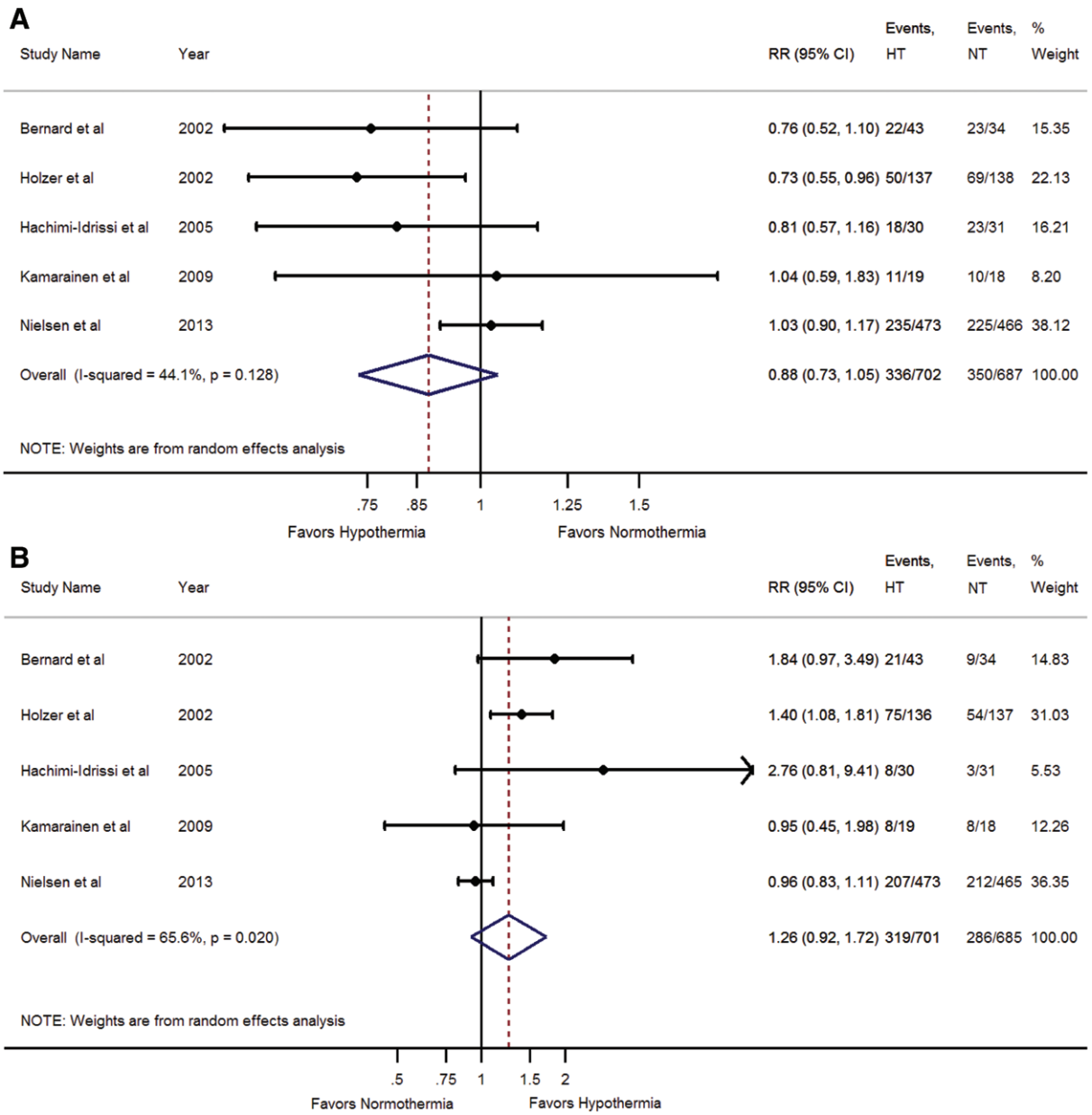

Figure 2. A, Forest plot comparing all-cause mortality between hypothermia and normothermia. B, Forest plot comparing favorable neurologic outcome between hypothermia and normothermia. The blue diamond depicts the point estimate and the 95% confidence interval. The red dotted lines represent a random effects generated overall estimate. This was generated with a random effects model using the method of DerSimonian and Laird,[11] with the estimate of heterogeneity calculated from the Mantel-Haenszel model. Data are presented with risk ratios and 95% confidence intervals. CI indicates confidence interval; HT, hypothermia; NT, normothermia; RR, risk ratio.

observe any difference in the rates of favorable neurologic outcome in the prehospital hypothermia versus in-hospital hypothermia comparison (RR, 0.96; 95% CI, 0.85–1.08; Figure 3B).

Meta-regression to Explore Heterogeneity in All-Cause Mortality Across Trials

We observed a substantial heterogeneity in treatment effect for mortality across trials comparing hypothermia and normothermia (I^2 = 44%; Figure 2A) No heterogeneity was seen in trials comparing prehospital hypothermia and in-hospital hypothermia (I^2 = 0%; Figure 3A).

We conducted a post hoc analysis to see if age, bystander CPR, presenting rhythm, and time to ROSC would explain this heterogeneity. In studies comparing normothermia and hypothermia, we observed a significant trend toward a favorable effect of hypothermia on all-cause mortality with decreasing proportion of patients undergoing bystander CPR (P = .04). The other characteristics were not related to treatment effect of mortality (P > .05; Table 2).

Publication Bias

Publication bias was assessed using the Egger regression intercept for the primary outcome for the normothermia versus hypothermia and prehospital hypothermia versus in-hospital hypothermia comparisons. We did not observe any significant publication bias (Figure 4A, B).

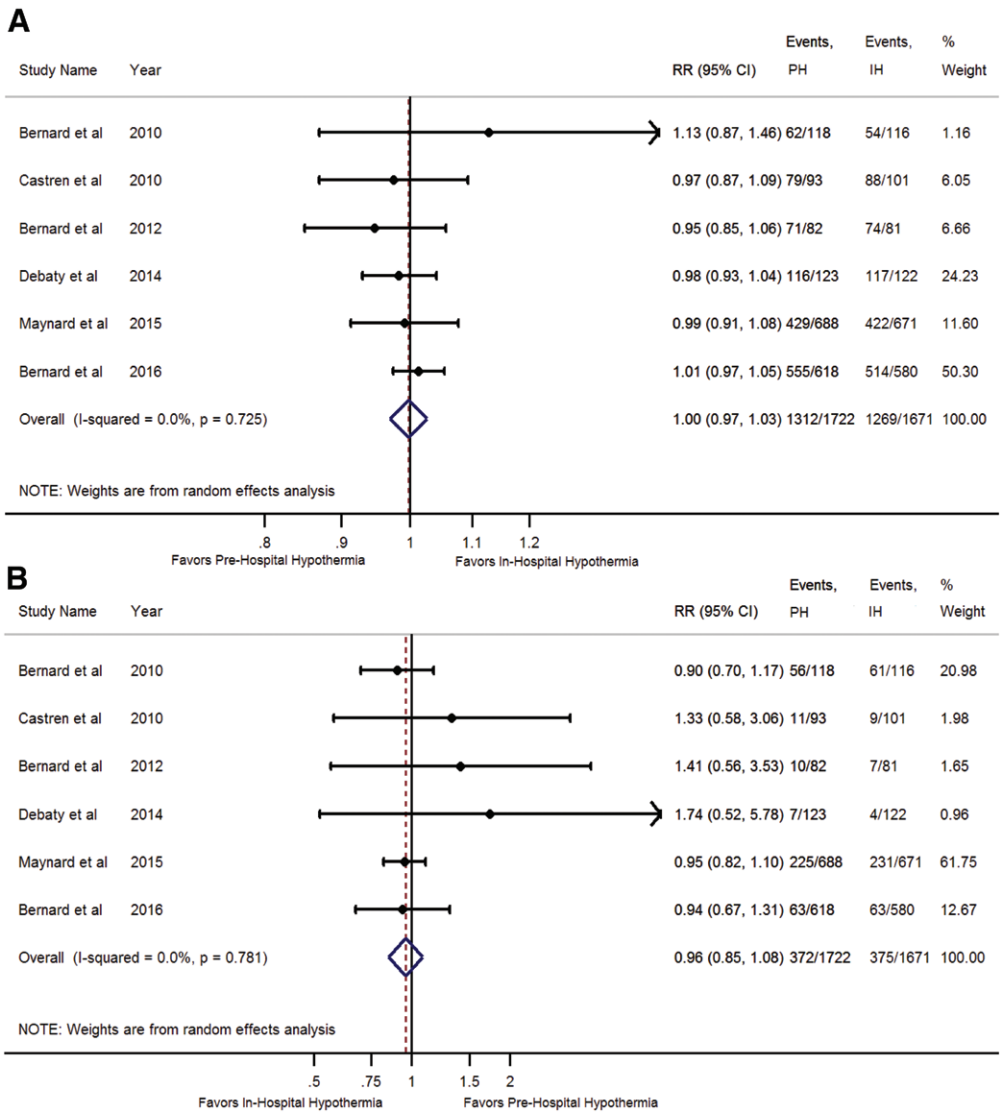

Figure 3. A, Forest plot comparing all-cause mortality between prehospital hypothermia and in-hospital hypothermia. B, Forest plot comparing favorable neurologic outcome between prehospital hypothermia and in-hospital hypothermia. The blue diamond depicts the point estimate and the 95% confidence interval. The red dotted lines represent a random effects generated overall estimate. This was generated with a random effects model using the method of DerSimonian and Laird,[11] with the estimate of heterogeneity calculated from the Mantel-Haenszel model. Data are presented with risk ratios and 95% confidence intervals. CI indicates confidence interval; IH, in-hospital hypothermia; PH, prehospital hypothermia; RR, risk ratio.

Table 2. Meta-regression to Assess the Effect of Predictors of Mortality (Hypothermia Versus Normothermia)

Variable	Range	β Estimate (95% CI) Hypothermia Versus Normothermia	*P* Value
Mean trial age (y)	59–67	0.01 (−0.044 to 0.068)	.671
Mean trial time to ROSC (min)	21–29	0.01 (−0.060 to 0.300)	.764
% trial bystander CPR	28–73	0.007 (0.0001 to 0.014)	.046
% shockable rhythm	46–100	−0.002 (−0.012 to 0.007)	.602

The interpretation is valid in between the specified range of variables. β estimate >0 indicates risk ratio >1. Meta-regression analyses were conducted using a mixed-effects meta-regression (unrestricted maximal likelihood) model.
Abbreviations: CI, confidence interval; CPR, cardiopulmonary resuscitation; ROSC, return to spontaneous circulation.

Power Calculation

We observed that >90% power would be achieved for mortality comparisons for both the hypothermia versus normothermia and prehospital hypothermia versus in-hospital hypothermia comparisons under this premise. For favorable neurologic outcome, the hypothermia versus normothermia comparison would achieve a power of >80%, whereas the prehospital hypothermia versus in-hospital hypothermia comparison would achieve a power of 62%. The prehospital hypothermia versus in-hospital hypothermia comparison

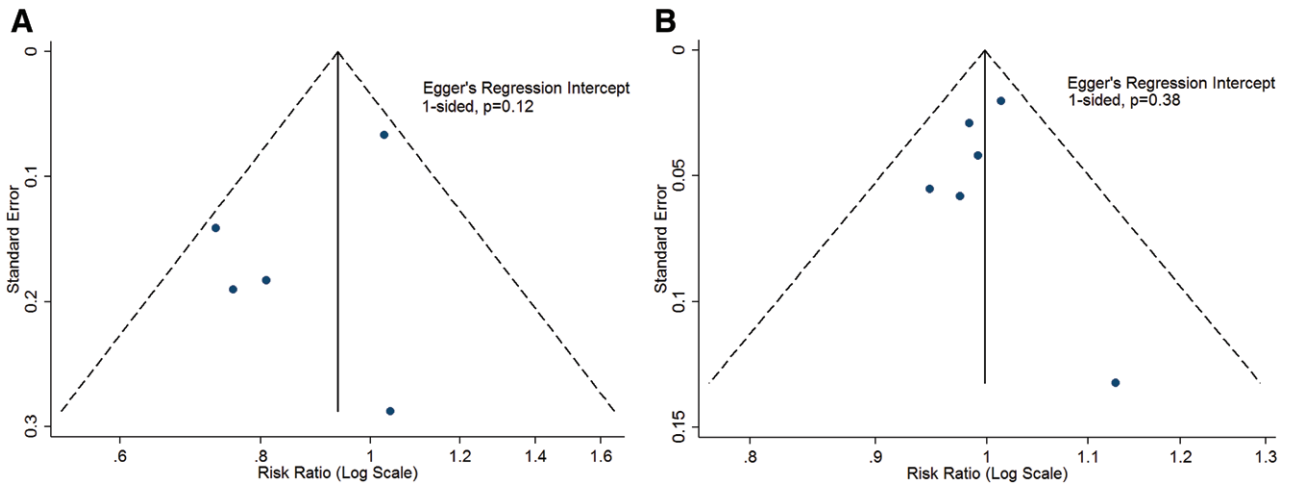

Figure 4. A, Depiction of publication bias for the all-cause mortality comparison between hypothermia and normothermia. B, Depiction of publication bias for the all-cause mortality comparison between prehospital hypothermia and in-hospital hypothermia. Blue circles represent available studies. The dashed lines indicate the triangular region with pseudo 95% confidence interval. The Egger regression intercept for funnel plot was nonsignificant (A, 1-sided, $P = .12$ and B, 1-sided, $P = .38$).

may be affected by a future trial as the power to detect a clinically important treatment effect in neurologic outcome was low (Supplemental Digital Content, Table 3, http://links.lww.com/AA/C138).

DISCUSSION

Our systematic review and meta-analyses explore and compare the mortality and neurologic outcomes in cardiac arrest patients undergoing in-hospital hypothermia, prehospital hypothermia, and the normothermia TTM strategies. Despite heterogeneity in the duration of cooling, target temperatures, and presenting rhythms, we found that there was no difference in mortality or neurologic outcomes when comparing these strategies.

There are likely several mechanistic explanations for our findings. Therapeutic hypothermia and TTM as a whole have been under investigation for well over a decade. Along with the release of a number of high-profile RCTs, consensus guidelines have moved toward protocol-driven post–cardiac arrest care. The emergence of therapeutic hypothermia strategies may have led to the institution of formal protocols for post–cardiac arrest care where they were previously lacking. There are some data to suggest improvement in mortality after implementation of such protocols and this is similar to trends seen elsewhere in medicine, such as in the treatment of sepsis. Hence, we postulate that making post–cardiac arrest care more standardized may well have itself improved the outcomes of post–cardiac arrest patients, thereby neutralizing some of the effects conferred by therapeutic hypothermia strategies. Additionally, the physiologic effect of cooling on cardiac function remains unclear. There are conflicting data on the topic, with some reports to suggest that in transplant patients there is less damage to the donor heart in the absence of profound hypothermia and therefore improvement in cardiac function.[26] Conversely, Shao et al[27] reported benefit after starting a therapeutic hypothermia at lower temperatures in an animal model by potentially reducing cardiac myocyte death through generation of nitric oxide. However, this appears to itself conflict with clinical data by Bernard et al[22] in the form of the recently published Rapid Infusion of Cold Normal Saline (RINSE) trial. These conflicting data raise important questions about the physiologic implications of hypothermia on cardiac function and the timing of institution of hypothermia. We hoped to address the latter question through our investigation. More importantly, it suggests that the mechanisms are largely unclear to us and that manipulating this delicate physiology may induce harm. This is particularly important when a significant proportion of deaths after use of therapeutic hypothermia are due to a cardiac cause. Finally, we note that there is a vast difference in the percentage of patients receiving bystander CPR before initiation of therapeutic hypothermia in the trials. This ranged from 26% to 73% in the included trials.[5,18] Because early and good-quality CPR is very clearly linked to survival after cardiopulmonary arrest,[28,29] we postulate that the large variation in percentage of patients receiving CPR may have been a confounding factor in the mortality and neurologic outcome results attributed to therapeutic hypothermia protocols.

Our findings can also be used to draw interesting conclusions when compared to the existing literature base. There appears to be a significant interest in TTM and this has led to the publication of numerous meta-analyses and a Cochrane review that attempt to summarize the literature. To the best of our knowledge, our investigation remains the first to use meta-analyses to compare mortality and neurologic outcomes between the prehospital hypothermia, in-hospital hypothermia, and normothermia strategies. Most of the other investigations are limited by sole comparisons between the prehospital hypothermia and normothermia strategies.[30–34] Of these published meta-analyses, 1 investigation included only nonshockable rhythms[35] and another primarily included the results of cohort studies.[31] We also note the trend in the meta-analyses published after 2014 to largely suggest that therapeutic hypothermia does not confer a benefit with regards to neurologic outcome or mortality. This may be affected by the inclusion of the investigation authored by Nielsen et al,[5] which was the largest trial to suggest this. We

note that similar results were reflected in the recently published RINSE trial authored by Bernard et al.[22]

There are also important clinical implications of our findings. Induction of therapeutic hypothermia and care of therapeutic hypothermia is associated with a significant cost to modern health care system. This has been estimated to be somewhere between $100,000 and $160,000 per hospitalization per patient treated.[36] In the modern era, this economic concern cannot be discarded if the proven outcome remains unclear. Therapeutic hypothermia is also associated with significant risks during the rewarming period. If patients are able to achieve equally good neurologic and mortality outcomes without the use of the hypothermia strategy, then clinicians may well be able to ameliorate some of these risks through avoidance of therapeutic hypothermia. We also note that there are further trials aiming to examine the future of therapeutic hypothermia.[37] The Therapeutic Hypothermia After Cardiac Arrest in Non Shockable Rhythm (HYPERION) trial[37] is a multicenter randomized controlled superiority trial that aims to compare neurologic status and mortality outcomes in patients with cardiac arrest due to a nonshockable rhythm. This trial aims to compare patients treated with a TTM strategy maintaining a temperature between 32.5°C and 33.5°C to patients treated with a TTM strategy maintaining a temperature between 36.5°C and 37.5°C.[37] We hope that this will yield information as to whether it is therapeutic hypothermia or simply a TTM normothermic strategy with avoidance of fever that confers neurologic or mortality benefit.

Kämäräinen et al[23] note differences in the rates of bystander CPR in the 2 groups and minor differences in the end-tidal carbon dioxide measurements at the time of hospital admission. Hence we evaluated the effect of rates of bystander CPR on treatment effect using meta-regression. Both our meta-analysis and recent evidence suggests that conventional bystander CPR confers a clear mortality benefit over both no compression CPR and no bystander CPR.[38] Such evidence highlights the need to create prediction models to identify who may benefit from hypothermia, such as patients who have not received bystander CPR. Hypothermia has been demonstrated in animal models to reduce ischemia-reperfusion injury, suppress ischemia-induced inflammatory cytokine surge, reduce free radicals, protect blood-brain barrier integrity and resultant brain edema/intracranial hypertension, improve brain glucose metabolism, reduce convulsive activity, and increased expression of immediate early genes which may prevent stress injury.[39–43] The important distinction between animal and human studies is that the former are conducted in a tightly controlled environment with rapid and effective institution of mild hypothermia. On the other hand, human studies often have heterogeneity in the aforementioned. There are also key differences in the "bundle of care" in postarrest settings across human studies. This may also reduce the efficacy of hypothermia in humans. Hence future studies should aim to differentiate the effectiveness of hypothermia from other standard of care treatments that are instituted in postarrest settings to identify individuals who may benefit the most from hypothermia.

We recognize that our analyses also have limitations. Amalgamation of data in the form of meta-analyses has well-recognized limitations.[13] Furthermore, we acknowledge significant differences in the cooling methods, cooling protocols, and even the rewarming protocols of the included trials (Table 1). This remains a topic of great discussion and we hope that future studies will help to derive the optimal protocols for these characteristics. Moreover, in the contemporary trials, therapeutic hypothermia was compared to the standard of care. This was poorly defined given that most of these trials were multicenter trials, some of which took place over multiple countries. We acknowledge that the standard of care likely became more protocol-driven, and therefore more homogeneous, as the trials integrated newer consensus guidelines due to the development of an evidence base for postresuscitation care. However, we feel that this may be a more accurate depiction of modern-day care and this consistency in care provision should be heralded as an important advance in the care of post–cardiac arrest patients.

In conclusion, TTM after cardiac arrest is an integral part of postresuscitation care. Our analyses showed that the normothermic TTM strategy and the prehospital and in-hospital hypothermia TTM strategies produced comparable mortality and neurologic outcomes. More RCTs are required to determine the ideal timing, protocol, and patient population that would benefit from these interventions.

DISCLOSURES

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Name: Navkaranbir S. Bajaj, MD, MPH.
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