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Clinical paper

Does therapeutic hypothermia benefit adult cardiac arrest patients presenting with non-shockable initial rhythms?: A systematic review and meta-analysis of randomized and non-randomized studies☆

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1. Introduction

Out-of-hospital sudden cardiac arrest (OHCA) is a leading cause of death in industrialized countries. The estimated incidence of emergency medical services (EMS)-treated OHCA in the US and Canada is about 50–55/100,000 persons per year and median rate of survival to hospital discharge is 8.4% for any rhythm and 22.0% after ventricular fibrillation (VF).[1] In Europe, the annual incidence of EMS-treated OHCA for all rhythms is 38 per 100,000 populations and survival to hospital discharge is 10.7% for all-rhythms and 21.2% for VF CA.[2] On initial rhythm analysis, only about 25–30% of OHCA victims have shockable rhythms, a percentage that has declined over the last 20 years.[3] The majority of OHCA patients in most Asian countries present to EMS with non-shockable initial rhythms (asystole or pulseless electrical activity [PEA]).[4,5]

Experimental evidence and many clinical studies suggest that mild therapeutic hypothermia (TH) of 32–34 °C for 12–24 h after CA improves survival and neurological recovery. A recent meta-analysis which pooled the data of four randomized trials and one abstract showed that

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TH seems to improve survival and neurological outcome after CA.[6] Mild TH for 12–24 h is now strongly recommended for comatose adult patients with return of pulses after out-of-hospital VF CA.[7,8] However, the benefit of TH after non-shockable CA remain uncertain. Because patients with non-shockable initial rhythms have a lower rate of survival than patients with VF, randomized controlled trials in these patients will require extremely large sample sizes to test the efficacy of TH. Only one very small, randomized trial provided data the efficacy of TH for patients after non-shockable CA.[9]

Some studies have reported outcomes for TH implemented in populations including both shockable and non-shockable CA. However, these studies rarely report individual outcome data for the patients with non-shockable initial rhythms. Taken together, these studies may reveal whether TH is beneficial for non-shockable CA. Therefore, we performed a systematic review and meta-analysis of randomized and non-randomized studies to test whether TH decreases mortality and improves neurologic outcomes in comatose adult survivors resuscitated from non-shockable CA.

2. Methods

We followed the PRISMA guideline[10] for randomized trials and the MOOSE guideline[11] for observational studies to conduct this review.

2.1. Eligibility criteria

We included randomized studies (RS) and non-randomized studies (NRS) in adult CA survivors with non-shockable initial rhythms comparing survival or neurological outcome in TH and standard care or normothermia.

2.2. Information sources and search strategy

We conducted an electronic search of PubMed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), and BIOSIS through March 2010. No languages limits were applied and foreign papers were translated. The search strategy developed for PubMed (Appendix B) was adapted for use in the other databases.

2.3. Study selection and data extraction

One reviewer (YMK) screened all studies that appeared relevant on the basis of "Title" and "Abstract" for full article review. Two reviewers (YMK and CWC) independently selected studies based on the full article for inclusion criteria into the review. Agreement was measured using simple agreement and Cohen kappa statistics. Discordance was resolved by discussion and consensus. We corresponded with 27 authors via email to clarify missing data and for further information that was not available in the publications. When neurological outcome was reported in cerebral performance categories (CPC), we considered CPC 1 or 2 to be "good" and CPC 3–5 to be "poor" outcome. If not reported in CPC categories, we accepted the authors' designation of "good" neurological outcome to be comparable to CPC 1 or 2.

2.4. Meta-analysis

Two authors (HWY and SHJ) performed the meta-analysis using Cochrane Review Manager software (RevMan version 5.0.24). Individual and pooled statistics were calculated as risk ratios (RRs) with 95% confidence interval (CI). Both fixed- and random-effects models (Mantel–Haenszel test) were used for both meta-analyses because of clinical heterogeneity between studies. Heterogeneity between the studies identified by visual inspection of the forest plots and by using a χ^2 test and also expressed as I^2. Statistical heterogeneity was considered relevant if $I^2 > 50\%$. Subgroup analyses for single center studies and location of arrest were also performed. We assessed publication bias and heterogeneity using funnel plots (plotting the effect against precision).

2.5. Assessment of risk of bias and quality in included studies

Two reviewers (YMK and CWC) independently assessed methodological quality of each included study. Discordance was resolved by discussion and consensus. We evaluated potential source of bias (sequence generation, allocation concealment, blinding, outcome reporting, baseline differences, power calculations, interim analysis, stopping rules and sponsor or academic bias) according to the Cochrane Handbook. Blinding of the intervention with TH is inherently difficult or impossible, and we considered blinding adequate if the outcome assessors had been blinded to allocation group. Trials were defined as having a low risk of bias if they fulfilled the above criteria. The quality of NRS was assessed using the Newcastle-Ottawa Scale (NOS). The NOS consists of three categories of quality: selection, comparability, and outcome. The text of some items within each category was customized for the CA and a star can be given for follow up rate ≥90% in outcome. The NOS assigns a maximum of 4 stars for selection, a maximum of 2 stars for comparability and a maximum of 3 stars for outcome. We also used GRADE pro version 3.2.2 for evaluating the quality of evidence of each study and summarized the evidence as one of the GRADE levels (high, moderate, low and very low) by evaluating design, quality, consistency, precision, directness and possible publication bias of the included studies.

3. Results

3.1. Study selection

The search identified a total of 8416 studies, of which 8107 were excluded after screening titles and abstracts. After eliminating duplicates, 169 studies remained for detailed evaluation (full article review). Of these, 138 studies were discarded because they clearly did not meet the criteria. Agreement between reviewers for this selection step was very good ($\kappa = 0.98$). Among 31 remaining studies, 27 studies required additional information from the authors. The published manuscripts requiring additional information reported overall outcomes for groups comprised of both shockable and non-shockable rhythms. We requested the specific outcomes for patients with non-shockable rhythm from the authors. For six studies we were unable to contact the authors or the authors could not provide missing data. We excluded an additional 11 studies that had no available initial rhythms or outcome data. Two randomized controlled trials and 12 observational cohort studies remained for analysis (Fig. 1).

3.2. Characteristics of the included studies

Table 1 summarizes the main characteristics of the 14 included studies. Two randomized controlled trials[12,13] were small, single center trials including only 44 patients. For one trial, we used data from the 2005 report[12], which included three more patients and longer follow-up period (6 months), instead of the feasibility report[9] in 2001. For the other trial, the authors provided the individual survival data for the shockable and non-shockable patients which were not available in the publication.[13] The length of follow-up and the target temperatures were similar, but cooling methods and duration were substantially different between these two RS.

Table 1
Characteristics of studies included in the meta-analysis.

Source	Methods	Participants					Interventions & control						Outcomes				
Authors	Study design	Country	Setting	Location of arrest	No. of total	No. of target rhythms	Location of initiation	Cooling methods	Target temperature	Cooling duration	Rewarming	Control	Length of F/up	Hypothermia		Control	
														No. of survival	No. of good	No. of survival	No. of good
Randomized studies																	
Hachimi-Idrissi et al. (2005)	RCT	Belgium	Single hospital	OHCA	33	33	In-hospital	Surface (helmet)	33 °C	Up to 4 h (from start of cooling)	Passive (0.25 °C/h)	NT	6 months	4/16	2/16	2/17	0/17
Laurent et al. (2005)	RCT	France	Single hospital	OHCA	41	11	In-hospital	CVVH and surface	32–33 °C	24 h (from start of CVVH)	Passive	SC	6 months	1/6		0/5	
Non-randomized studies																	
Holzer et al. (2006)	Retrospective cohort	Austria	Single hospital	Mixed	1038	534	In-hospital	Endovascular with or without cold fluid	32–34 °C	24 h (from start of cooling)	0.5 °C/h to 36 °C	SC	30 days	14/28	8/28	195/506	128/506
Oddo et al. (2006)	Retrospective cohort	Switzerland	Single hospital	OHCA	109	23	In-hospital	Surface	32–34 °C	24 h (at the target temp)	Passive	SC	Discharge	2/12	2/12	1/11	0/11
Arrich, ERC-HACA (2007)	Prospective cohort	Europe (7)	Multi-center (19)	Mixed	587	197	In-hospital	Mixed	32–34 °C	24 h (at the target temperature)	Over 8 h	NT	Discharge	45/124	35/124	14/73	14/73
Sunde et al. (2007)	Prospective cohort	Norway	Single hospital	OHCA	119	15	In-hospital	Cold fluid + surface or endovascular	33 °C	24 h (at the target temperature)	0.5 °C/h	SC	Discharge	2/6	1/6	0/9	0/9
Heer (2007)	Retrospective cohort	Germany	Single hospital	Mixed	76	18	In-hospital	Endovascular	33 °C	24 h (at the target temperature)	0.5 °C/h to 36 °C	SC	Discharge	3/10		2/8	
Rittenberger et al. (2008)	Retrospective cohort	USA	Single hospital	Mixed	241	81	In-hospital	Cold fluid + surface	32–34 °C	24 h (from ROSC)	<1 °C/h	NT	Discharge	7/42	4/42	7/39	4/39
Storm et al. (2008)	Prospective cohort	Germany	Single hospital	OHCA	126	49	In-hospital	Cold fluid + surface	33 °C	24 h (at the target temperature)	0.25 °C/h	SC	Discharge	12/18	9/18	15/31	7/31
Bro-Jeppesen et al. (2009)	Prospective cohort	Denmark	EMS + single hospital	OHCA	61	34	Prehospital or in-hospital	Cold fluid + surface	32.5–33.5 °C	24 h (at the target temperature)	Active (0.5 °C/h to 37 °C)	SC	Discharge	7/13		5/21	
Gaieski et al. (2009)	Prospective cohort	USA	Single hospital	OHCA	38	18	In-hospital	Cold fluid + surface	32–34 °C	24 h (from start of cooling)	Active (0.25 °C/h)	SC	Discharge		3/9		1/9
Whitfield et al. (2009)	Retrospective cohort	Australia	EMS + single hospital	OHCA	123	28	Prehospital or in-hospital	Cold fluid + surface	32.5–33.5 °C	24 h (from hospital presentation)	Over 12 h	SC	Discharge	3/15	3/15	3/13	4/13
Don et al. (2009)	Retrospective cohort	USA	Single hospital	OHCA	491	313	In-hospital	Surface	32–34 °C	24 h (at the target temperature)	Passive	SC	Discharge	37/122	14/122	26/191	17/191
Derwall et al. (2009)	Prospective cohort	Germany	EMS + multi-center (5)	OHCA	68	28	Prehospital or in-hospital	Cold fluid + surface	33 °C	24 h (at the target temperature)	<1 °C/h	NT	14 days		4/13		5/15

RCT, randomized controlled trial; OHCA, out-of-hospital cardiac arrest; CVVH, continuous veno-venous hemofiltration; NT, normothermia; SC, standard care; EMS, emergency medical system; ROSC, return of spontaneous circulation.

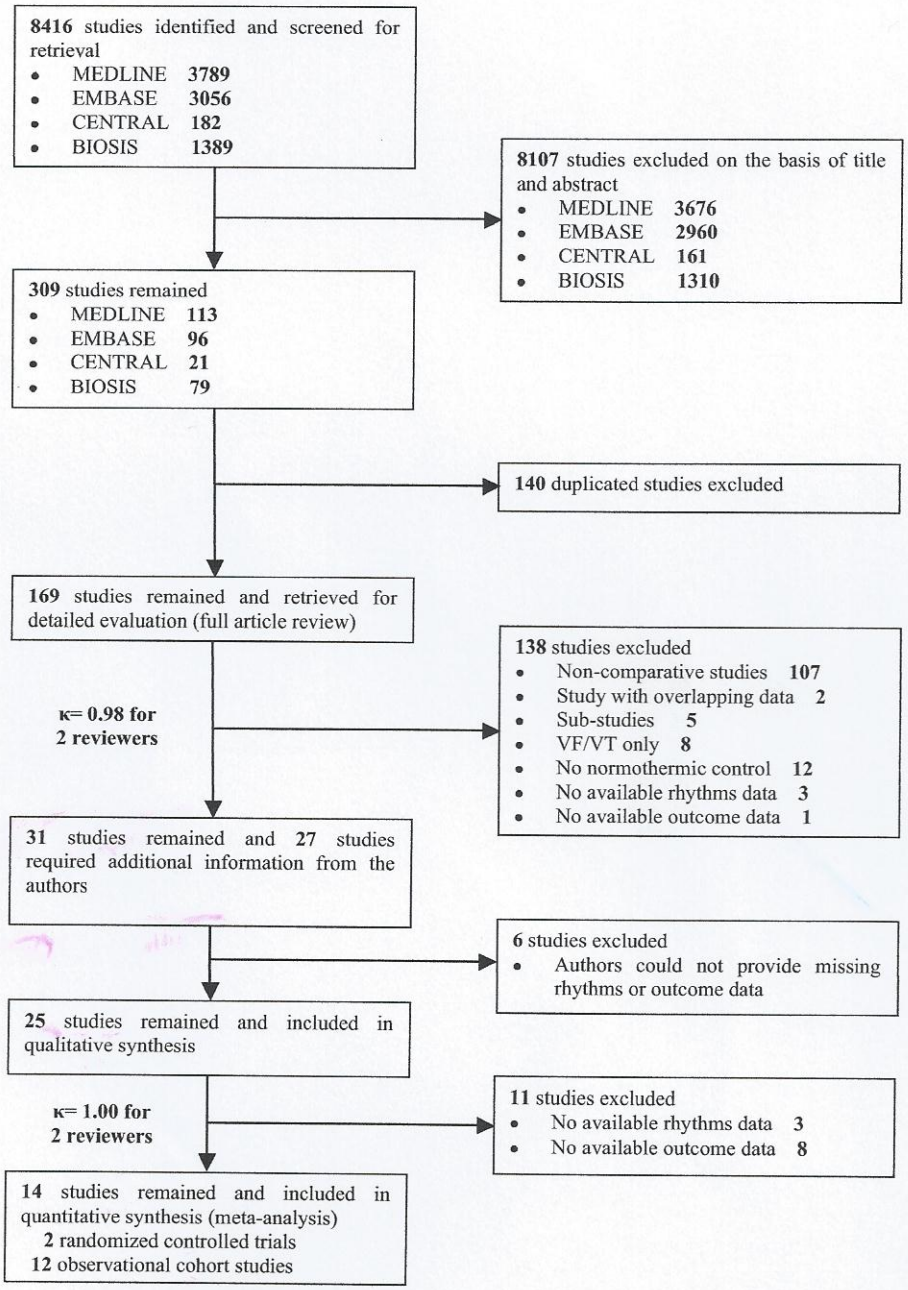

Fig. 1. Flow diagram of study selection process.

Twelve non-randomized studies [14–25] included 1292 patients. There were six retrospective [14,15,18,19,23,24] and six prospective observational cohort studies.[16,17,20–22,25] There were two multicenter studies.[16,25] Four studies [14,16,18,19] included both out-of-hospital and in-hospital CA cases. Only five studies[15,16,18,21,24] reported separate outcome data for shockable and non-shockable CA. The first or corresponding author of the other seven studies provided individual outcome data for the analysis via email. There was clinical heterogeneity in cooling protocols. Most of studies used cold fluid for TH induction and 24 h duration of TH. However, starting points of maintenance were slightly different among the studies. Although the most of studies reported the outcome data at hospital discharge, Holzer et al.[14] assessed outcome at 30 days and Derwall et al.[25] used 14 days follow-up period. We considered the outcome data on 30 or 14 days as outcome at discharge for the analysis. Bro-Jeppesen et al.[21] also reported the outcome data both at discharge and 6 months but we only included data at hospital discharge on the analysis. Ten studies reported in-hospital mortality[14–21,23,24] and ten studies[14–17,19,20,22–25] reported neurological status at hospital discharge.

3.3. *Effects of interventions*

We separately analyzed RS and NRS. With only two RCTs reporting 6-month survival (involving 22 cases and 22 controls), the pooled RR for 6-month mortality was 0.85 but there was no statistical difference (95% confidence interval CI 0.65–1.11; $I^2 = 0\%$) in random-effects model (Fig. 2) In a fixed-effects model of the studies,

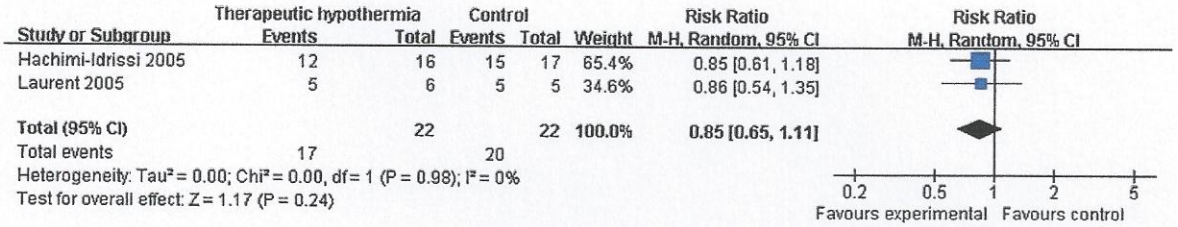

Fig. 2. The effect of therapeutic hypothermia on 6 month mortality in randomized studies.

the RR and 95% CI did not changes substantially. As there was only one study[12] reporting neurological outcome at 6 months, it was not possible to employ meta-analysis. The single study found no statistical difference in neurological outcome (RR, 0.88; 95% confidence interval CI 0.71–1.08).

With 10 NRS (involving 390 cases and 902 controls) reporting survival at hospital discharge, the pooled result showed the hypothermia group had reduced in-hospital mortality (RR, 0.84; 95% CI 0.78–0.92; $I^2 = 0\%$) in random-effects model (Fig. 3). With 10 NRS (involving 389 cases and 897 controls) reporting neurological outcome at hospital discharge, the pooled RR was 0.95 and there was no statistical difference (95% CI 0.90–1.01) in random-effects model (Fig. 4). In a fixed-effects model of the studies, the RR and 95% CI did not change substantially.

3.4. Subgroup analyses

We examined subgroups of patients in NRS for the following parameters: location of arrest (in-hospital versus out-of-hospital), study setting (single center study versus multicenter study), and study design (prospective versus retrospective) (Tables 1 and 2). For the patients with out-of-hospital CA in seven NRS, the pooled result showed the hypothermia group reduced in-hospital mortality (RR, 0.86; 95% CI 0.76–0.99; $I^2 = 19\%$) in random-effects model. With nine NRS performed at single hospital, the pooled result showed the hypothermia group also reduced in-hospital mortality (RR, 0.86; 95% CI 0.78–0.94; $I^2 = 0\%$) in random-effects model. For the patients of four prospective NRS, the pooled result showed the hypothermia group reduced in-hospital mortality (RR, 0.76; 95% CI 0.65–0.89; $I^2 = 0\%$) in random-effects model. In a fixed-effects model of the studies, the RR and 95% CI did not changes substantially.

For the poor neurological outcome at hospital discharge, there was no significant difference between two groups in subgroup analysis for the patients with out-of-hospital CA and included in single center studies. However, in five prospective NRS, the pooled result showed the hypothermia group also decreased poor neurological outcome (RR, 0.86; 95% CI 0.76–0.98; $I^2 = 0\%$) in random-effects model. In a fixed-effects model of the studies, the RR and 95% CI did not changes substantially.

3.5. Risk of bias for included randomized studies

Neither RS had low risk of bias according to Cochrane methodology (Appendix B). Sequence generation, allocation concealment, baseline imbalance, and sample size calculations were uncertain in one study.[12] Blinding of outcome assessors and baseline imbalance were not reported in the other study.[13]

3.6. Quality of included non-randomized studies

The quality of 12 NRS ranged from seven stars ($n = 3$) to nine stars ($n = 5$) (Appendix B). In terms of selection bias, 100% of the studies met all the high quality criteria. The most common comparability bias was the lack of reporting of baseline characteristics (25%) and adjustments (25%). In terms of outcome bias, the length of follow-up of one study was only 14 days.[25]

3.7. Quality of evidence according to GRADE

The two included RS had substantial risks of bias. One trial did not report the number of the screened patients. The other trial included only 17% of the screened patients with ROSC and only a subset (asystole) of the target CA population. Hence there was a questionable directness. Total sample sizes are limited and events rates are low. The two trials had a wide confidence interval spanning both potential for benefit and harm suggesting serious imprecision.

Three NRS (25%) did not report comparability of cohorts. Hence there was a questionable directness. Seven studies (58%) have a wide confidence interval spanning both potential for benefit and harm suggesting serious imprecision.

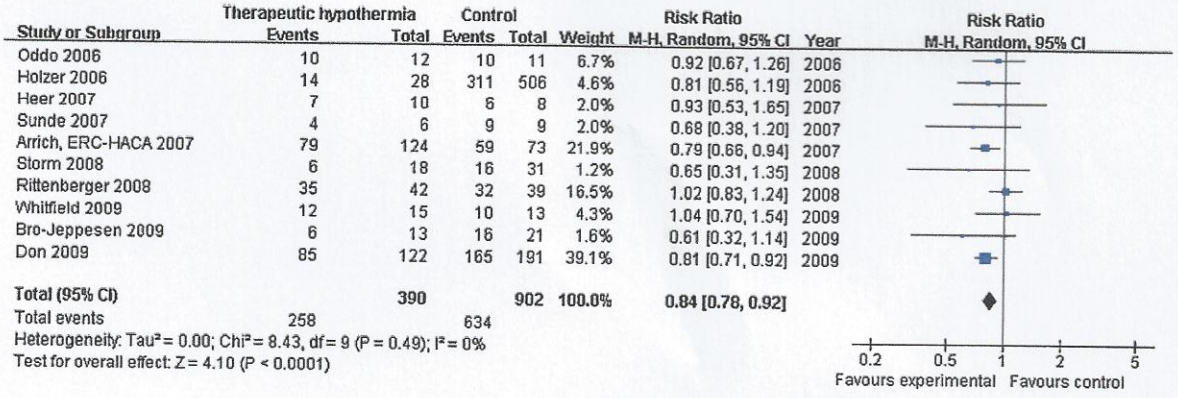

Fig. 3. The effect of therapeutic hypothermia on in-hospital mortality in non-randomized studies.

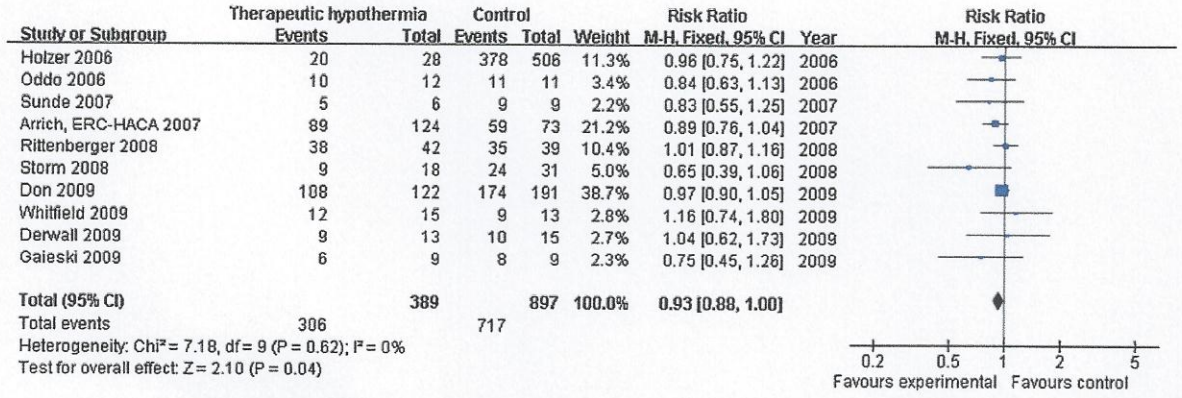

Fig. 4. The effect of therapeutic hypothermia on neurological outcome in non-randomized studies.

Assessment of quality of evidence using GRADE-methodology led us to conclude that the accumulated qualities of evidence are of very low in RS and NRS (Table 3).

4. Discussion

This paper examined the evidence for an effect of TH on in-hospital mortality and neurological outcome after non-shockable CA. Published studies examining the use of TH after non-shockable CA included two RS and twelve NRS. The randomized trials included only 44 subjects in aggregate, had high risk of bias, and were inconclusive about the effects of TH. On the other hand, NRS included survival data for 390 subjects and neurological outcomes for 389 subjects treated with TH after non-shockable CA. These studies were of good to excellent quality, and suggested a decreased risk ratio for in-hospital mortality in patients treated with TH after non-VF CA.

At present, there are only two randomized clinical trials of TH in non-shockable CA.[12,13] Both of these studies were conducted to test devices or innovative strategies rather than the actual benefit of TH. As a consequence, there was substantial risk of bias, and very few subjects were enrolled. Although the point estimate for survival and neurological outcome favored TH in both of these studies, these limitations leave the question unanswered.

The NRS included in this review are of high quality. When pooled together, the RR of in-hospital mortality were significantly lower in the TH groups. However, these studies also have significant limitations that threaten the validity of this conclusion. When assessed with the GRADE criteria, the quality of evidence for TH benefits in non-shockable CA is very low. Although the pooled RR of neurological outcome for five prospective studies including 228 subjects was significantly higher in the TH group on a subgroup analysis, the overall RR of the outcome was not significantly higher than control groups. These results correspond with the results of two large, prospective observational studies that were recently published.[26,27] In these studies, TH was also not associated with good neurological outcome at hospital discharge in non-shockable CA patients. However, cohort studies may be confounded by the changes in resuscitation practice over time. For example, superior acute resuscitation techniques, mechanical devices and improvements in systems of care might result in more awake patients with excellent prognoses reaching the hospital. TH would not be used in these patients, reducing the apparent effectiveness of TH. Ideally, studies should report outcomes stratified by the initial neurological status after cardiac arrest.

Prior studies have examined the published evidence for TH after CA.[6,28–30] These systematic reviews and meta-analyses have focused primarily on the overall efficacy of TH. None of these reviews specifically examined the efficacy of TH in the subset of patients with non-shockable CA. Only one study included subgroup analysis for the non-shockable rhythms concluded that TH did not show a statistically significant effect on good neurological outcome.[6] A recent comprehensive systematic review and meta-analysis, as was done in the present study, concluded that the level of evidence for TH was still inconclusive.[29] Those studies including RS also noted that the quantity of data for TH in non-shockable CA was insufficient to offer a conclusion in this cohort. A recent report from five international critical care societies which assessed the quality of evidence for two key RS including non-shockable CA patients using GRADE methodology concluded that no sufficient evidence exists to make any recommendations regarding the use of TH in these patients.[8] Therefore, our results are consistent with prior analyses of RS, but extend the existing systematic reviews of NRS.

Strengths of the present study include the rigorous data search strategy and standardized criteria used for evaluation of studies. Potential limitations of this study include the possibility that some data, especially published conference abstracts, may have been missed. However, the search strategies were comprehensive and were applied to multiple databases. It is also a limitation that complete data could not be obtained for some studies that appear to meet inclusion criteria. We attempted to minimize this limitation

Table 2
The effect of therapeutic hypothermia on each outcome in subgroup analyses for the non-randomized studies.

Outcome	Subgroup	No. of studies	No. of patients	Summary risk ratios (M-H, random, 95% CI)	Heterogeneity, I^2 (%)
In-hospital mortality	All	10	892	0.84 (0.78–0.92)	0
	Out-of-hospital cardiac arrest	7	389	0.86 (0.76–0.99)	19
	Single center study	9	754	0.86 (0.78–0.94)	0
	Prospective study	4	195	0.76 (0.65–0.89)	0
Poor neurologic outcome at hospital discharge	All	10	1023	0.95 (0.90–1.01)	0
	Out-of-hospital cardiac arrest	8	856	0.96 (0.90–1.02)	0
	Single center study	8	446	0.96 (0.90–1.03)	0
	Prospective study	5	228	0.86 (0.76–0.98)	0

Table 3
GRADE profile for assessing quality of evidence for the studies included in the meta-analysis.

Quality assessment							Summary of findings					Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients		Effect		Quality	
							Therapeutic hypothermia	Control	Relative (95% CI)	Absolute		
Mortality (follow-up 6 months)												
2	Randomized trials	Serious[a]	No serious inconsistency	Serious[b]	Serious[c]	None	17/22 (77.3%)	20/22 (90.9%)	RR 0.85 (0.65 to 1.12)	136 fewer per 1000 (from 318 fewer to 109 more)	⊕◯◯◯ VERY LOW	CRITICAL
Neurological outcome (follow-up 6 months)												
1	Randomized trials	Serious[d]	No serious inconsistency	Serious[e]	Serious[f]	None	14/16 (87.5%)	17/17 (100%)	RR 0.88 (0.71 to 1.08)	120 fewer per 1000 (from 290 fewer to 80 more)	⊕◯◯◯ VERY LOW	CRITICAL
Mortality (at hospital discharge)												
10	Observational studies	Serious[g]	No serious inconsistency	Serious[h]	Serious[i]	None	258/390 (66.2%)	634/924 (68.6%)	RR 0.84 (0.78 to 0.92)	110 fewer per 1000 (from 55 fewer to 151 more)	⊕◯◯◯ VERY LOW	CRITICAL
Neurological outcome (at hospital discharge)												
10	Observational studies	Serious[g]	No serious inconsistency	Serious[j]	Serious[k]	None	306/389 (78.7%)	717/897 (79.9%)	RR 0.95 (0.9 to 1.01)	40 fewer per 1000 (from 80 fewer to 8 more	⊕◯◯◯ VERY LOW	CRITICAL

[a] All trials had substantial risks of bias.
[b] One trial did not report the number of the screened patients. The other trial included only 17% of the screened patients with ROSC and only a subset (asystole) of the target cardiac arrest population.
[c] Total sample sizes are limited and events rates are low. The two trials have a wide confidence interval spanning both potential for benefit and harm.
[d] The trial had substantial risk of bias.
[e] The trial did not report the number of the screened patients.
[f] The sample size of the trial is limited. The trial has a wide confidence interval spanning both potential for benefit and harm.
[g] All studies had substantial risks of bias.
[h] The three studies did not report comparability of cohorts.
[i] The seven studies have a wide confidence interval spanning both potential for benefit and harm.
[j] The two studies did not report comparability of cohorts.
[k] The six studies have a wide confidence interval spanning both potential for benefit and harm.

by contacting many authors directly for supplemental information. Furthermore, subgroup analysis for individual rhythm (asystole or PEA) and analysis for adverse events could not be completed because many studies did not report the outcome and adverse events of the patients separately and the numbers of the patients were too small.

While the available data support the use of TH after non-shockable CA, the quality and type of data are prone to bias. In addition, most data have focused on survival and short-term outcomes rather than long-term neurologically favorable recovery, which is the goal of TH. A randomized study to determine the effects of induced hypothermia on long-term neurological function after non-shockable CA would greatly augment confidence in this therapy for this population. However, such a study would be extremely challenging given the lower rates of survival compared to shockable CA. For example, a study might require over 1250 subjects per group to have 80% power to detect an increase in good outcome from 25% to 30%, which would be an effect similar to the risk ratio of 0.84 estimated in Fig. 3.

Finally, the argument that the beneficial effects of TH would be absent in patients with non-shockable rhythms lacks biological plausibility. First, some non-shockable rhythms such as asystole may result from the deterioration of ventricular fibrillation over time. For this subset of cases, the shockable and non-shockable patient populations differ only in time of discovery, not in terms of physiology. Second, hypothermia is a post-reperfusion intervention that appears to primarily improve neurological recovery. For many patients, the brain will not be able to distinguish whether ischemia-reperfusion resulted from a shockable or non-shockable rhythm. In fact, the animal studies demonstrating the neurological benefits of post-cardiac arrest hypothermia have largely been conducted after PEA and asystole.[31–33]

5. Conclusions

This study concludes that TH after non-shockable CA is associated with reduced in-hospital mortality. However, this study acknowledges that the overall quality of this evidence is limited. The data available at present would support the use of TH for non-shockable CA in clinical practice. However, greater certainty would only be afforded by a high quality randomized clinical trial to test the actual benefit of TH in this population.

Contributions of authors

Young-Min Kim (YMK) developed the initial idea for the review, developed the protocol, selected studies, data extraction, contact the authors, quality assessment of the studies, interpretation of data, drafted the manuscript, and revision of draft. Hyeon-Woo Yim (HWY) developed the protocol, statistical analysis, interpretation of data, and revision of draft. Seung-Hee Jeong (SHJ) developed the protocol, statistical analysis, interpretation of data, and revision of draft. Mary Lou Klem (MLK) developed the protocol, undertook searches, and revision of draft. Clifton W. Callaway (CWC) proposed the review, developed the protocol, data extraction, contact the authors, quality assessment of the studies, interpretation of data, and revision of draft.

Conflicts of interest statement

Clifton W. Callaway (CWC) has had prior research funding from the National Institutes of Health and American Heart Association for studies of hypothermia after cardiac arrest. He is currently funded by NIH (U01-HL077871) in part to help design future clinical trials of hypothermia after cardiac arrest, and has received a loan of equipment, without payment, for laboratory studies of hypothermia from Medivance, Inc. The other authors declare no conflicts of interest and have no financial disclosures for this project.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.resuscitation.2011.07.031.

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