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Therapeutic Hypothermia and Prevention of Acute Kidney Injury: A Meta-Analysis of Randomized Controlled Trials

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Abstract

Background—Therapeutic hypothermia has been shown to reduce neurological morbidity and mortality in the setting of out-of-hospital cardiac arrest and may be beneficial following brain injury and cardiopulmonary bypass. We conducted a systematic review to ascertain the effect of therapeutic hypothermia on development of acute kidney injury (AKI) and mortality.

Methods—We searched for randomized controlled trials in MEDLINE through February 2011. We included trials comparing hypothermia to normothermia that reported kidney-related outcomes including, development of AKI, dialysis requirement, changes in serum creatinine, and mortality. We performed Peto fixed-effect and random-effects model meta-analyses, and meta-regressions.

Results—Nineteen trials reporting on 2,218 patients were included; in the normothermia group, the weighted rate of AKI was 4.2%, dialysis requirement 3.7%, and mortality 10.8%. By meta-analysis, hypothermia was not associated with a lower odds of AKI (odds ratio [OR] 1.01, 95% confidence interval [CI] 0.68, 1.51; $P = 0.95$) or dialysis requirement (OR 0.81; 95% CI 0.30, 2.19; $P = 0.68$); however, by meta-regression, a lower target cooling temperature was associated with a lower odds of AKI ($P = 0.01$). Hypothermia was associated with lower mortality (OR 0.69; 95% CI 0.51, 0.92; $P = 0.01$).

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Conclusions—In trials that ascertained kidney endpoints, therapeutic hypothermia prevented neither the development of AKI nor dialysis requirement, but was associated with lower mortality. Different definitions and rates of AKI, differences in mortality rates, and concerns about the optimal target cooling temperature preclude definitive conclusions.

Keywords

critical illness (or critically ill); hypothermia; acute kidney injury; mortality; meta-analysis

Introduction

On the basis of the published evidence, the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation has adopted therapeutic hypothermia into its guidelines for the treatment of unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest¹. These recommendations are based on a clear demonstrable benefit of therapeutic hypothermia on neurological morbidity and mortality following out-of-hospital cardiac arrest^{2,3}, and some potential benefit in the setting of traumatic brain injury^{4,5} and cardiopulmonary bypass for major cardiovascular surgery⁶. As a result, therapeutic hypothermia has been widely used in critically ill adults in the intensive care unit^{7,8}.

Acute kidney injury (AKI), as defined by a wide range of serum creatinine increments⁹, is a consistent and powerful predictor of in-hospital mortality, and is associated with an increase in hospital length of stay, hospital costs, and resource utilization^{10,11}. Acute kidney injury is commonly observed in patients who have undergone cardiopulmonary bypass^{12,13}, and following resuscitation from spontaneous cardiac arrest^{14,15}, and carries an increased mortality risk¹⁵. Previously published trials comparing the effect of therapeutic hypothermia vs. normothermia on kidney endpoints have yielded conflicting results¹⁶ due in part to the small sample size and low study quality. To shed further light on this question, we conducted a systematic review and meta-analysis of the existing randomized controlled trials (RCTs) comparing the effect of therapeutic hypothermia vs. normothermia in adults on the development of AKI (primary outcome) and all-cause mortality (secondary outcome).

Methods

Data Sources and Search Strategy

We searched Medline (1965 - February 2011) using the following MeSH database search terms: “Hypothermia”, “Hypothermia Induced”, and “Deep Hypothermia Induced”. The search was limited to human RCTs with no language restrictions. We also searched <http://www.ClinicalTrials.gov> for completed trials using similar search terms, reviewed abstracts from the annual scientific meetings of the American Society of Nephrology (2000-2010), and performed a manual search of references in narrative and systematic reviews on therapeutic hypothermia.

Study Selection

We included all RCTs that examined primary or secondary kidney endpoints (as defined below) in adults undergoing therapeutic hypothermia vs. normothermia. We excluded trials of newborns and children, as well as duplicate publications. If authors published more than one manuscript on the same study, data from the most inclusive report were used.

The primary outcome of interest was AKI, as defined by the authors of individual trials. We also assessed other kidney endpoints including continuous changes in serum creatinine,

creatinine clearance and dialysis requirement. The secondary outcome of interest was all-cause mortality, which was only evaluated in the trials reporting kidney endpoints.

Data Extraction and Quality Assessment

Two of the authors independently reviewed and screened the titles and abstracts of all the MEDLINE citations (PS and MA), and the scientific abstracts of the annual meetings of the American Society of Nephrology (ACB and PS). The full-text articles were retrieved for comprehensive review and re-screened, and the data were extracted and tabulated. The following variables were extracted: country of origin, year of publication, study design, population setting, (e.g., out-of hospital cardiac arrest, brain injury, and cardiopulmonary bypass for major cardiovascular surgery), total number of patients, sex, mean age, mean duration of cardiac arrest, mean aortic cross clamp time (for on-pump cardiovascular surgery), cooling target temperature, control arm temperature, cooling technique (including infusate type), duration of cooling, development of AKI, definition of AKI, mean baseline serum creatinine, mean baseline creatinine clearance, mean follow-up serum creatinine, mean follow up creatinine clearance, duration of follow-up, and mortality rate. Disagreements were resolved through consensus and arbitration by a third author (BLJ). In the case of trials with more than 2 groups, separate analyses were performed comparing each therapeutic hypothermia intervention group with the normothermia control group. Corresponding authors of 4 trials were contacted by e-mail for data clarification, and 2 provided additional information.

Study quality was assessed using a modified Jadad scale¹⁷, which is based on the adequacy of randomization, blinding and attrition¹⁸. A score of 0-1, 2-3, and 4-5 corresponds to a study of poor, fair, and good quality, respectively.

Data Synthesis and Analysis

For our primary analysis, due to the low number of events in most studies (often zero in one study group)¹⁹, we performed a Peto fixed-effect meta-analysis to assess the odds ratio (OR) (with 95% confidence interval [CI]) for the development of AKI, dialysis requirement, and mortality in the therapeutic hypothermia group relative to the normothermia group. We also performed a random-effects model meta-analysis as a sensitivity analysis²⁰. Trials with no events in both groups were excluded from the analyses. A random-effects model meta-analysis was also performed to assess the net change in serum creatinine and creatinine clearance in the therapeutic hypothermia group relative to the normothermia group.

Existence of heterogeneity among effect sizes estimated by individual trials was tested using the I^2 index, and chi-squared P value. Heterogeneity was explored by subgroup analyses based on the 3 population settings, mainly traumatic brain injury, out-of hospital cardiac arrest, and cardiopulmonary bypass, as well as the cooling technique, infusion type, study quality and sample size (\leq vs. >100 patients). The Student *t*-test was used to compare subgroups. Meta-regression analyses were also performed to explore heterogeneity including the cooling target temperature, cardiac arrest duration, and duration of cooling against the odds of AKI and mortality rate. Finally, publication bias was formally assessed using funnel plots. The meta-analyses were performed using Comprehensive Meta-Analysis version 2.0 and MetaAnalyst beta version 3.1 (Tufts University, Boston, MA)

Results

Characteristics and Quality of the Studies

A total of 792 potentially relevant citations were identified and screened; 257 articles were retrieved for detailed evaluation, of which 19 fulfilled eligibility criteria (Figure 1)²¹⁻³⁹.

Three trials tested 2 therapeutic hypothermia interventions^{22, 25, 26}, which were each compared with the control group. One parent study providing data on rate of AKI³² had a subsequent report on a subset of patients where changes in serum creatinine were examined³⁴; the latter report was used for the meta-analysis of continuous change in serum creatinine.

Characteristics of the individual trials are displayed in Table 1. The trials spanned more than 10 years, varied in sample size (23-291 patients) and involved the three population settings. All trials had mostly men (range of 53-95%) with a mean age ranging from 29 to 69 years.

Overall study quality was mostly poor^{21-24, 27, 28, 33} to fair^{25, 26, 29-32, 34, 36-39}, with only one study being rated as good³⁵. Reported randomization methods were adequate in only 12 of the 19 trials^{25, 26, 29-32, 34-39}, and 7 trials described the number of withdrawals or dropouts, and used an intention-to-treat analysis^{29, 31, 32, 34, 37-39}.

Effect of Therapeutic Hypothermia on Development of AKI

Twelve RCTs reported on the development of AKI in a total of 1,839 analyzable patients; however 2 of these studies^{22,33} had no patients with AKI in either group and thus did not contribute to the meta-analysis. The overall weighted rate of AKI in the normothermia group was 4.2% (range of 0 to 59%). By meta-analysis, therapeutic hypothermia was not associated with a lowered odds of AKI (OR 1.01, 95% CI 0.68, 1.51; $P = 0.95$; Figure 2). Although the trials differed considerably in their size, quality score, and population setting, the test for heterogeneity was not significant ($I^2 = 0\%$; $P = 0.46$); however, this is largely due to the small number of AKI events in most studies, and thus the very wide confidence intervals.

By meta-regression, a lower target cooling temperature was associated with a lower odds of AKI ($P = 0.01$, Figure 3), whereas the duration of therapeutic hypothermia ($P = 0.31$), and the duration of cardiac arrest were not ($P = 0.49$). Of note, however, after the removal of an influential trial that delivered intra-renal arterial cooling of 15°C³¹, the target cooling temperature was no longer associated with a lower odds of AKI ($P = 0.68$).

Effect of Therapeutic Hypothermia on Serum Creatinine and Creatinine Clearance

Five trials reported changes in serum creatinine^{25, 28, 29, 34, 36} in a total of 522 analyzable patients. By meta-analysis, therapeutic hypothermia resulted in a net decrease in serum creatinine of 0.5 mg/dL (95% CI -1.8, 0.7 mg/dL), which did not reach statistical significance ($P = 0.40$). Three trials reported changes in creatinine clearance^{23, 25, 34}, with a total of 141 analyzable patients. By meta-analysis, therapeutic hypothermia resulted in a net increase in creatinine clearance of 0.4 mL/min (95% CI -2.2, 3.0 mL/min), which was also not significant ($P = 0.76$).

In one study, compared to normothermia, therapeutic hypothermia resulted in higher serum urea nitrogen at day 2 (23 vs. 13 mg/dL) but not at day 7 (16 vs. 15 mg/dL), but there was no significant difference in serum creatinine at the same time points (no reported values)³⁹. In another study, there was no significant difference in the serum creatinine between the normothermia and therapeutic hypothermia group (1.06 vs. 1.05 mg/dL)³⁷.

Effect of Therapeutic Hypothermia on Dialysis Requirement

Three RCTs reported on dialysis requirement totaling 509 analyzable patients^{27, 31, 32}. One study had no patients who required dialysis in either group and thus did not contribute to the meta-analysis³¹. The overall weighted incidence of dialysis requirement in the normothermia group was 3.7% (range of 0 to 4.3%). By meta-analysis, therapeutic

hypothermia was not associated with a significantly lower odds for dialysis requirement (OR 0.81; 95% CI 0.30, 2.19; $P = 0.68$).

Effect of Therapeutic Hypothermia on Mortality

This analysis was restricted to the 16 RCTs that reported kidney and mortality endpoints, totaling 2,077 analyzable patients. Mortality was ascertained post-operatively in 2 trials^{26, 33}, in-hospital in 5 trials^{28, 32, 36-38}, at 15 days in 3 trials^{24, 27, 30}, at 30 days in 2 trials^{29, 31}, and at 90 days in one trial³⁹. The duration of follow up was not documented in the 3 remaining studies^{21, 22, 35}. There was no death in either group in one study, which did not contribute to the meta-analysis²⁸. The overall weighted mortality rate in the normothermia group was 10.8% (range of 0 to 87.5%). By meta-analysis, therapeutic hypothermia was associated with a significant 31% lower odds for mortality (OR 0.69; 95% CI 0.51, 0.92; $P = 0.01$; Figure 4). Although the trials differed considerably in their size, quality score, and population setting, the test for heterogeneity was not significant ($I^2 = 0\%$; $P = 0.63$). By meta-regression, the duration of cardiac arrest, the cooling target temperature, and the duration of hypothermia were not associated with mortality.

Sensitivity and Subgroup Analyses

Despite the absence of significant heterogeneity among the trials, we performed random-effects meta-analyses, which generated similar results (data not shown). Subgroup analyses by population settings, cooling technique, type of fluid, study quality, and sample size did not influence the odds of AKI (data not shown). However, although therapeutic hypothermia was associated with lower odds for mortality in patients suffering from out-of-hospital cardiac arrest (OR 0.64; 95% CI 0.45, 0.91), compared to those with brain injury (OR 0.83; 95% CI 0.43, 1.60) or those undergoing cardiopulmonary bypass surgery (OR 0.75; 95% CI 0.33, 1.68), there was no significant difference between these clinical settings. Subgroup analyses stratified according to the cooling technique, type of fluid, and sample size (>100 patients) did not significantly influence the mortality analysis (data not shown). However, low-quality studies did not demonstrate a mortality benefit of therapeutic hypothermia (OR 0.58; 95% CI 0.25, 1.33) whereas in fair-to-good-quality studies, there was a demonstrable mortality benefit of hypothermia (OR 0.70; 95% CI 0.51, 0.96, $P=0.03$). In addition, compared to studies that excluded patients with pre-existing chronic kidney disease^{26, 30, 36}, those that included patients with chronic kidney disease^{24, 27, 31} displayed lower odd ratio for development of AKI (OR 1.30, 95% CI 0.72-2.35; vs. OR 0.46, 95% CI 0.19-1.14), but this did not reach statistical significance ($P = 0.42$).

Although funnel plots were slightly asymmetric for the development of AKI with 2 unpublished studies favoring hypothermia, they were symmetric for the outcome of dialysis requirement and mortality.

Discussion

The present meta-analysis suggests that therapeutic hypothermia applied in different population settings including out-of-hospital cardiac arrest, major cardiovascular surgery with cardiopulmonary bypass, and brain injury is associated with a reduction in mortality, but has no impact on the prevention of AKI and dialysis requirement.

Acute kidney injury is a common occurrence following out-of-hospital cardiac arrest with spontaneous return of circulation, and on-pump cardiovascular surgery^{12, 14}, and is associated with an increased risk for mortality, dialysis requirement, and prolonged hospital length of stay^{15, 40}. With an incidence of out-of-hospital cardiac arrest estimated at 38 per 100,000 person-years⁴¹, and greater than 163,000 cardiac surgeries performed annually in

the US⁴², several strategies have been explored to prevent AKI including minimization of ischemic time, use of an off-pump technique, and adoption of therapeutic hypothermia^{18, 23, 25, 31, 34}.

Induction of moderate hypothermia has been successfully used since the 1950s to protect the brain against global ischemia after cardiac arrest⁴³, but was subsequently abandoned due to uncertain benefit and difficulties with its use. In more recent years, this strategy has regained recognition following the completion of several RCTs demonstrating a clear benefit on neurological morbidity and mortality following out-of-hospital cardiac arrest^{2, 3, 29, 32}. Although therapeutic hypothermia has been adopted into the treatment guidelines of adults with spontaneous circulation after out-of-hospital cardiac arrest¹, there is scant data on the potential protective benefit of this strategy on kidney endpoints.

Unfortunately, in the present meta-analysis, we were unable to demonstrate a kidney-related benefit of therapeutic hypothermia. That may be due in part to the induction of renal vasoconstriction by systemic therapeutic hypothermia, resulting in possible kidney injury⁴⁴, whereas locally applied therapeutic hypothermia may decrease the metabolic demand of the kidneys⁴⁵ and oxygen consumption^{46, 47}. These effects correlate with the temperature of the kidney. Indeed, following temperature reduction to 30°C, 20°C, and 10°C, the kidney oxygen consumption is reduced to 40%, 15% and less than 5%, respectively⁴⁷.

In the present meta-analysis, we identified only one study that measured kidney temperature, demonstrating a protective effect of hypothermia against AKI³¹. Although our meta-regression analysis suggests that a target cooling temperature cut-off point of 31°C might confer kidney protection, this hypothesis requires formal testing, as this association was highly influenced by a single study³¹. Moreover, therapeutic hypothermia appeared to be associated with a lower risk of AKI in studies that included patients with pre-existing chronic kidney disease, but this still did not reach statistical significance.

Strengths of our synthesis include the demonstrable survival benefit of therapeutic hypothermia especially in studies of fair-to-good quality, which is in agreement with previously published meta-analyses⁴. Mild hypothermia is thought to suppress many of the biological responses associated with ischemia reperfusion injury. These include the generation of free radicals, the release of amino acids, and transcellular calcium shifts, which can lead to mitochondrial injury and apoptosis⁴⁸⁻⁵⁰, especially following out-of-hospital cardiac arrest. The main limitation of our meta-analysis is the variable or lack of definition of AKI reported in the individual studies. The small sample size of most of the trials is also an important limitation of the evidence. The analysis was restricted to adults and excluded newborns and children. Furthermore, the trials included in this analysis were not originally designed to examine the effect of therapeutic hypothermia on kidney endpoints as their primary endpoint. In addition, we were unable to address the safety of therapeutic hypothermia including, the potential risk for the development of arrhythmias, infections, and coagulopathy^{2, 4}. Our analysis of mortality is limited by the lack of inclusion of trials that did not report kidney outcomes.

In conclusion, the currently available trials indicate that therapeutic hypothermia does not prevent AKI including dialysis requirement, but is associated with lower mortality following out-of-hospital cardiac arrest, major cardiovascular surgery and brain injury. The present analysis however, calls for the design of future studies to formally test whether therapeutic hypothermia prevents AKI in the setting of major cardiovascular surgery and out-of-hospital cardiac arrest, two clinical settings known to be associated with this complication. Such studies would need to explore a range of cooling temperatures with the hope of identifying the optimal kidney protective hypothermic strategy, and monitor for adverse effects.

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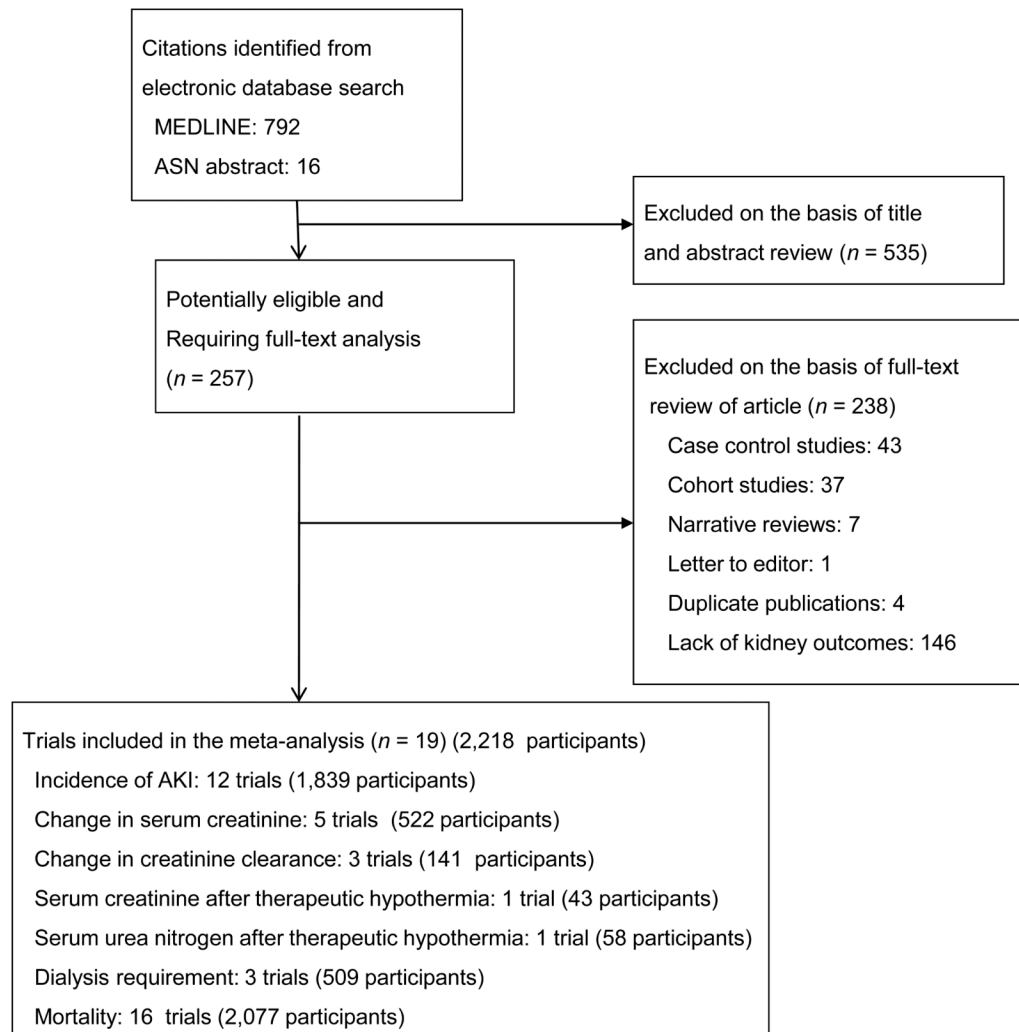


Figure 1.
Study selection flow diagram.

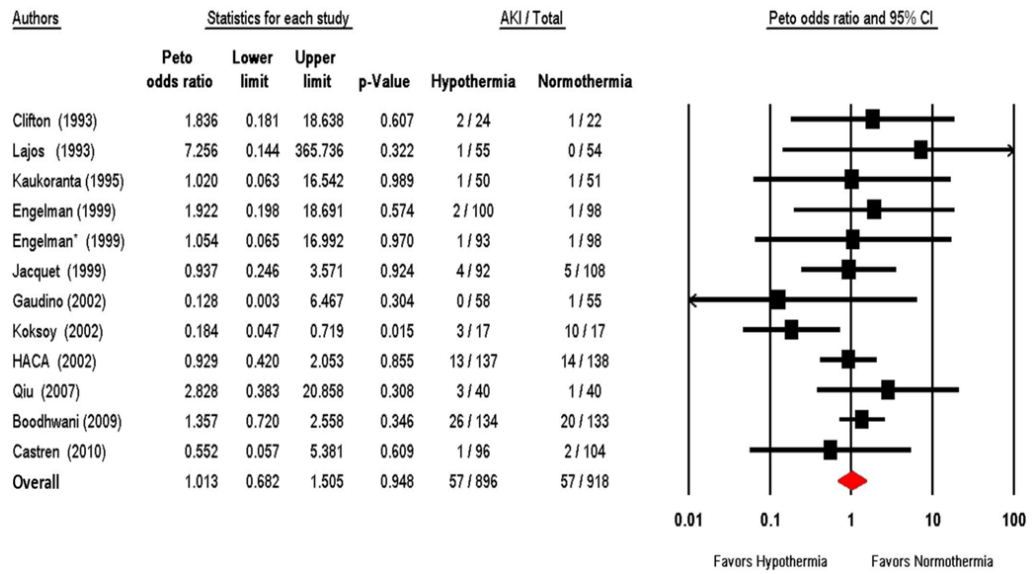


Figure 2. Forest plot of therapeutic hypothermia vs. normothermia on the development of AKI. HACA denotes Hypothermia after Cardiac Arrest Study Group. * Refers to the second therapeutic hypothermia intervention tested in the same trial.

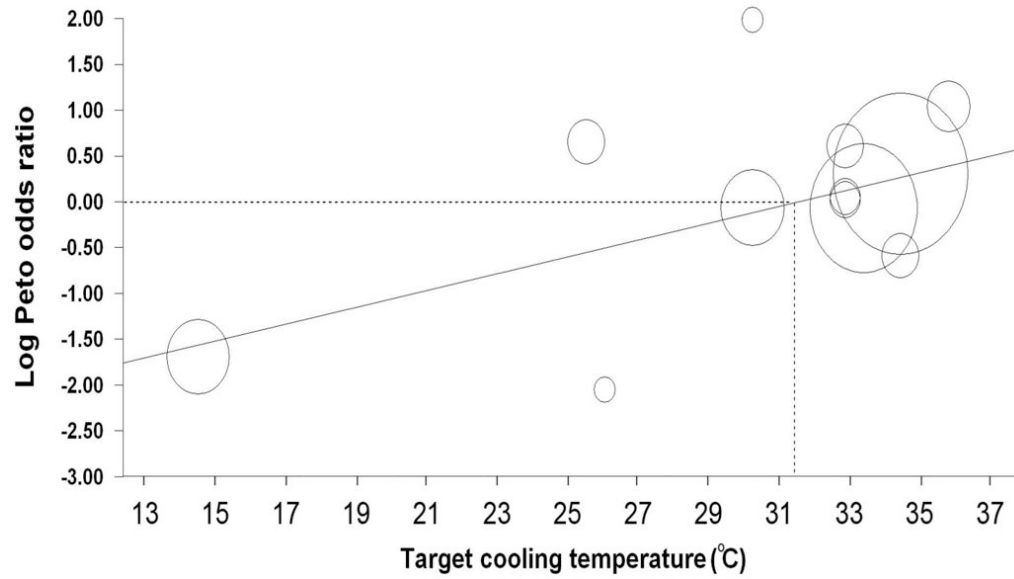


Figure 3. Meta-regression plot examining the relationship between the target cooling temperature and the log of the Peto odds ratio for the development of AKI ($P = 0.011$). The meta-regression equation is as follows: $\text{Log Peto odds ratio} = -3.004 + 0.096(^{\circ}\text{C})$.

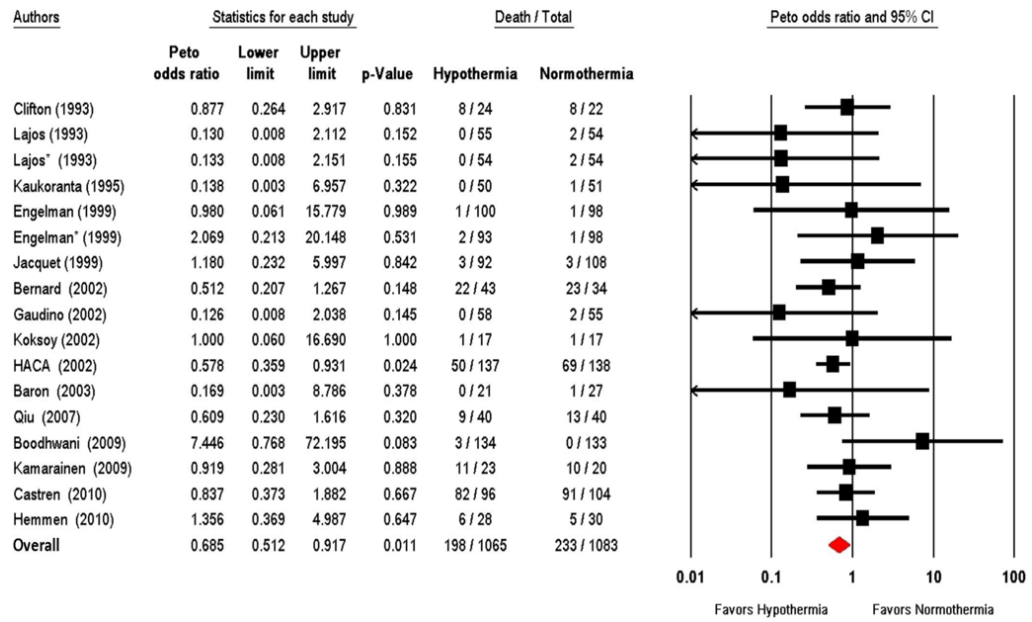


Figure 4. Forest plot of therapeutic hypothermia vs. normothermia on mortality. HACA denotes Hypothermia after Cardiac Arrest Study Group. * Refers to the second therapeutic hypothermia intervention tested in the same trial.

Table 1

Characteristics of the randomized controlled trials included in the meta-analysis

Author	Year	Country	Population setting	Total number of patients	Mean age (years)	Men (%)	Mean cardiac arrest duration (min)	Hypothermia group target temperature (°C)	Normothermia group temperature (°C)	Cooling technique	Infusion type	Duration of cooling (min)	Study Quality	Definition of AKI
Clifton	1993	USA	Traumatic brain injury	46	29	NR	NA	32-33	37	Cooling blanket	NA	2880	1	Not specified
Lajos	1993	USA	CABG-CPB	163	63	71	73	30	37	Fluid infusion	Crystalloid	91	1	Not specified
Ip-Yam	1994	UK	CABG-CPB	23	60	83	62	28	37	Fluid infusion	Hartmann's solution	98	1	Change in Cr clearance
Kaukoranta	1995	Finland	CABG-CPB	101	59	81	103	32-33	37	Fluid infusion	Blood	126	1	Not specified
Regragui	1995	UK	CABG-CPB	30	59	57	35	28	37	Fluid infusion	Crystalloid	75	2	Change in sCr and Cr clearance
Engelman	1999	USA	CABG-CPB	291	63	77	86	23-28	35-36	Fluid infusion	(Blood:crystalloid 4:1)	135	2	Not specified
Jacquet	1999	Belgium	CABG-CPB	200	65	73	65	32-33	35-36	Fluid infusion	(Blood:crystalloid 4:1)	139	1	Change in sCr not specified; need for dialysis
Kuhn-Regnier	1999	Germany	CABG-CPB	60	65	77	55	NR	NR	Fluid infusion	Blood	89	1	Change in sCr
Bernard	2002	Australia	Out-of-hospital cardiac arrest	77	59	67	26	33	37	Ice packs	NA	720	3	Change in sCr
Gaudino	2002	Italy	CABG-CPB	113	NA	93	62	26	37	Fluid infusion	Blood	88	2	Not specified
Koksoy	2002	USA	AAA-CPB	34	64	53	62	15 ^a	37	Fluid infusion	Ringer's solution	23	3	> 50% increase in sCr within first 10 postoperative days; need for dialysis
HACA	2002	European countries	Out-of-hospital cardiac arrest	275	59	76	22	32-34	37	Mattress & ice packs	NA	1440	3	Not specified
Baron	2003	France	CABG-CPB	69	64	87	49	15 ^b	37	Fluid infusion	Blood+ crystalloid	98	1	Not specified
Zeiner	2004	Austria	Out-of-hospital cardiac arrest	88	54	73	22	32-34	37	Mattress & ice pack	NA	1440	3	Change in sCr and Cr clearance; need for dialysis
Qiu	2007	China	Traumatic brain injury	80	41	65	NA	34.5-36	37	Cooling blanket, and cooling cap ice pack	NA	5760	4	Not specified

Author	Year	Country	Population setting	Total number of patients	Mean age (years)	Men (%)	Mean cardiac arrest duration (min)	Hypothermia group target temperature (°C)	Normothermia group temperature (°C)	Cooling technique	Infusion type	Duration of cooling (min)	Study Quality	Definition of AKI
Boodhwani	2009	Canada	CABG-CPB	267	69	88	46	34	37	Thermal pads connected to thermal control system	NA	77.3	2	>25% increase in sCr or decrease in Cr clearance
Kamarainen	2009	Finland	Out-of-hospital cardiac arrest	43	61	95	23	33	37	Fluid infusion	Ringer' solution	37	3	Single sCr measurement (in emergency room)
Castrén	2010	European countries	Out-of-hospital cardiac arrest	200	65	75	31	34	37	Intranasal cooling	NA	32	3	Not specified
Hemmen	2010	USA	Ischemic stroke	58	66	55	NA	33	37	Intravascular cooling with thermal control system	NA	1440	3	sCr & urea nitrogen measurement at day 2 & 7

AAA denotes abdominal aortic aneurysm; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass pump; HACA, Hypothermia after Cardiac Arrest Study Group; NR, not reported; Cr, creatinine; sCr, serum creatinine;

^a renal temperature

^b temperature of solution. A study quality score of 0-1, 2-3, and 4-5 corresponds to a study of poor, fair, and good quality, respectively.