Aims: Guidelines recommend mild therapeutic hypothermia (MTH) for survivors of out-of-hospital cardiac arrest (OHCA). However, there is little literature demonstrating a survival benefit. We performed a meta-analysis of randomized controlled trials (RCTs) assessing the efficacy of MTH in patients successfully resuscitated from OHCA.

Materials and Methods: Electronic databases were searched for RCT involving MTH in survivors of OHCA, and the results were put through a meta-analysis. The primary endpoint was all-cause mortality, and the secondary endpoint was favorable neurological function. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed using the Mantel–Haenszel method. A fixed-effect model was used and, if heterogeneity ($I^2$) was >40, effects were analyzed using a random model.

Results: Six RCT ($n = 1400$ patients) were included. Overall survival was 50.7%, and favorable neurological recovery was 45.5%. Pooled data demonstrated no significant all-cause mortality (OR, 0.81; 95% CI 0.55–1.21) or neurological recovery (OR, 0.77; 95% CI 0.47–1.24). No evidence of publication bias was observed.

Conclusion: This meta-analysis demonstrated that MTH did not confer benefit on overall survival rate and neurological recovery in patients resuscitated from OHCA.

Key words: Cardiac arrest; Meta-analysis; Therapeutic hypothermia

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) is a significant problem worldwide, with an estimated rate of 36–128/100,000 patients and a mortality rate of approximately 65–95%. In the United States alone, approximately, 424,000 people utilize emergency medical service assessment for OHCA each year. Most of these patients are at high risk for death and poor neurological function.

In 2002, two landmark randomized controlled trials (RCTs) were published that demonstrated the efficacy of mild therapeutic hypothermia (MTH) in comatose survivors after OHCA by decreasing mortality and improving neurologic outcomes. Since then, numerous studies, mostly meta-analyses and retrospectives...
reviews, supported MTH. The 2015 American Heart Association (AHA) Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care and the International Liaison Committee on Resuscitation (ILCOR) recommend using MTH. They propose a core temperature goal of 32–34°C for unconscious adult patients with return of spontaneous circulation (ROSC) after witnessed out-of-hospital ventricular fibrillation arrest (strong recommendation, low-quality evidence) and nonventricular fibrillation and in-hospital cardiac arrest (CA) (weak recommendation, very low-quality evidence), for at least 24 h (strong recommendation, moderate-quality evidence).

Despite these recommendations, some investigators argue that the evidence of the early randomized trials has revealed conflicting results, have low power and limited methodology; moreover, a recent publication by Nielsen et al. challenged the role of MTH in OHCA, demonstrating that normothermia (36°C) results in similar outcomes to MTH. With this new information and the potentially unfavorable side effects reported with hypothermia, further analyses are warranted assessing the efficacy of MTH therapy on post-CA mortality and neurological outcome. With this in mind, we conducted a systematic review of literature and subsequent meta-analysis investigating the efficacy of MTH.

**MATERIALS AND METHODS**

**Search strategy**

A computerized literature search of all publications in PubMed, CENTRAL, EMBASE, The Cochrane Central Register of Controlled Trials, the ClinicalTrials.gov website, and Google Scholar databases was performed. We also utilized manual searches of the article reference lists and conference proceedings. This was last assessed as up-to-date: June 30, 2015.

Search terms keywords included: Hypothermia, therapeutic hypothermia, mild hypothermia protocol, CA, heart arrest, OHCA, anoxic brain injury, cardiopulmonary resuscitation, RCTs. No language restrictions were enforced. Only human trials were included.

**Inclusion criteria**

The PRISMA statement for reporting systematic reviews and meta-analyses of RCTs was applied to the methods for this study. Only human studies were included for analysis.

Included studies met the following specifications: (1) RCT design, (2) evaluation of patients with OHCA defined as any nonperfusing cardiac rhythm, including shockable rhythms (ventricular fibrillation or ventricular tachycardia) and nonshockable rhythms (pulseless electrical activity and asystole) occurring in a patient not already in or admitted to a hospital with age more than 18 years old, (3) patient who successfully had ROSC but comatose after CA, (4) studies which provided data on patients who received MTH on neurological outcome and mortality, (5) MTH at a targeted temperature between 32°C and 34°C either prehospital or hospital initiation (any method of cooling was accepted), and (6) control group intervention treated with standard intensive unit care or maintained patients normothermic at a target temperature ≥36°C.

Exclusion criteria were patients who are (1) pregnant, (2) did not meet the above-mentioned criteria, (3) age <18 years or patients who were hypotensive and did not achieve ROSC, and (4) control group cooled with MTH at a targeted temperature between 32°C and 34°C.

Two reviewers (PV and DB) independently extracted data from identified RCTs. Disagreements were resolved by consensus or, if necessary, by a third party (MM-EE).

**Study endpoints**

The primary outcome was all-cause mortality. We considered mortality to hospital discharge or longest follow-up postarrest. The secondary outcome was a favorable neurological function. Neurological function was evaluated according to cerebral performance category (CPC) where CPC 1 and 2 was defined as a good neurological outcome. We also considered a favorable neurological function to hospital discharge or longest postarrest follow-up. If one of these validated metrics were not reported, reasonably defined favorable neurologic outcome by the individual study authors was accepted. If outcomes were reported at more than one follow-up period, we used data from the longest follow-up for each trial.

**Statistical analysis**

Data were summarized across treatment arms using the Mantel–Haenszel odds ratio (OR) fixed-effects model. We evaluated heterogeneity of effects using the Higgins $F$ statistic. In cases of heterogeneity (defined as $F > 40\%$), random effects models were used. To address publication bias, we used four methods: Funnel plots, Begg–Mazumdar test, Egger test, and the
Duval and Tweedie’s test. Sensitivity analyses were performed using the one-study-out method, addressing the influence of each study by testing whether deleting each individual would significantly change the pooled results of the meta-analysis on the final effect and its precision. Finally, chronological cumulative analyses were used to test if the effect size and precision shifts based on the technical advancement of MHT seen over time. The statistical analysis was performed by the Comprehensive Meta-Analysis version 2.0 software (Biostat, Inc., New Jersey, USA).

**Individual study quality appraisal**

Two authors (PV, MM) independently assessed the risk of bias of included trials using standard criteria defined in the Cochrane Handbook for Systematic Reviews of Interventions. This validated instrument for appraising randomized trials measures risk of bias in seven categories: (1) Adequate random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective reporting, and (7) other bias. Each trial is described as having a high, low, or unclear risk of bias in each of the seven domains. Discrepancies were resolved by discussion or adjudication by a third author (DB).

**RESULTS**

**Study selection and characteristics**

The flow diagram of study identification through the review is shown in Figure 1. The search strategy identified a total of 2352 potential articles. After removing duplicates and articles not meeting inclusion criteria, we screened 266 titles and abstracts. Of these, 14 were selected for further review of eligibility. Finally, 6 RCTs satisfied inclusion criteria, all of which were published in English.

Baseline characteristics are presented in Table 1. Overall, the 6 RCTs enrolled a total of 1400 patients who were successfully resuscitated from OHCA. Numerous cooling methods were used in these included studies, including surface and invasive cooling. In all the studies, the target temperature of cooling range was between 32°C and 34°C, with a duration time of 12–24 h. Duration of follow-up ranged from hospital discharge up to 6 months.

**Quantitative data synthesis**

**Endpoints**

There were a total of 710 deaths reported in all patients that suffered OHCA: 49.7% (352/710) in MTH group and 51.9% (358/690) in the control group. There was no significant difference in all-cause mortality between the two groups (OR, 0.81; 95% confidence interval (CI) 0.55–1.21) [Figure 2].

Among patients with OHCA, 633 had an overall favorable neurological outcome after OHCA. As indicated in Figure 3, using a random model, no significant difference was observed in favorable neurological outcome in patients who received MTH 46.9% (331/705 patients) versus control 44.1% (302/687 patients) (OR, 0.77; 95% CI 0.47–1.24).

**Sensitivity analysis**

Sensitivity analysis involving the removal of each of the RCT’s one at a time did not demonstrate difference or any changes in the overall outcomes, even when the Nielsen et al. trial was removed; all-cause mortality (OR, 0.68; 95% CI 0.41–1.14) and favorable neurological outcome (OR, 0.64; 95% CI 0.36–1.17) [Figure 1 in the Supplemental Material].

**Cumulative analysis**

Chronological cumulative analysis for each outcome did not find any significant change in the final effect outcomes; however, when the analysis was performed addressing all-cause mortality and favorable neurological outcomes, we observed transient changes in the final effect favoring the hypothermia group when the Bernard et al. study was included. Subsequent accumulated analysis did not experience changes in the
### Table 1: Baseline characteristics of trials

| Study name       | Total number of patients ($n$) | Event place | Intervention place | Rhythm | Intervention | Selection criteria | Follow up duration for primary and secondary endpoints | All Case Mortality $n$=t total number of deaths | Favorable Neurological outcomes |
|------------------|--------------------------------|-------------|--------------------|--------|--------------|--------------------|--------------------------------------------------------|--------------------------------|---------------------------------|
| Hachimi-Idrissi et al.\[26\] | 30 | Out of hospital | In hospital | Asystole or PEA | Helmet device to achieve a target temperature of 34°C. When temperature of 34°C achieved or 4h hours after initiation elapsed then passive rewarming for 8 hours | IV acetaminophen for temperature $>$38°C, otherwise standard ICU care | >18 years, temp $>$30°C, GCS $<$7 | Pregnancy, coagulopathy, other causes of coma (drugs, etc.), cardiogenic shock (MAP $<$60), GCS $\geq$7 | 14 days | 13 13 2 0 |
| Holzer et al.\[5\] | 275 | Out of hospital | In hospital | VF, VT | Air Cooling to a target temperature of 32°C to 34°C with the use of an external cooling device, and ice packs for 24 hours then passive rewarming for 8 hrs | No intervention for Temperature control, Standard ICU protocol care | Witnessed OHCA of cardiac origin, age 18-75 years, 5-15 minutes from collapse to CPR and, $<$60 minutes to ROSC | Temp $<$30°C, coma because of drugs before CA, pregnancy, response to verbal command, MAP $<$60 for $>$30 minutes, hypoxemia $>$15 minutes, terminal illness, factors making follow-up unlikely, coagulopathy, other study, CA after arrival of medical personnel | 6 months | 56 76 75 54 |
| Bernard et al.\[4\] | 77 | Out of hospital | Pre hospital | VF | Ice packs, target temperature 33°C for 12 hours then active rewarming for 6 hrs | No intervention for coma after Temperature control, Standard ICU protocol care | Persistent intervention for coma after ROSC Age $<$18 years for men, $<$50 years for women, cardiogenic shock, other causes of coma than CA (drugs, etc.), no available ICU bed | Till hospital discharge | 22 23 21 9 |

Contd...
Table 1: Contd...

| Study name  | Total number of patients (n) | Event place | Intervention place | Rhythm | Intervention | Selection criteria | Follow up duration for primary and secondary endpoints | Outcomes | All Case Mortality n= | Favorable Neurological outcomes |
|-------------|-------------------------------|-------------|-------------------|--------|--------------|-------------------|-----------------------------------------------------|----------|-------------------|---------------------------------|
| Laurent et al. [28] | 42 | Out of hospital | In hospital | VF or asystole | CVVH for 8 h to target temp of 32-33°C then external cooling to maintain temp for 16 hours then passive rewarming (rewarming duration not mentioned) | CVVH for 8 h to maintain temp of 37 thereafter no further temp control | Age 18-75 years, <10 min to start of CPR, <50 min to ROSC | 6 months | 15 | 11 | 7 | 9 |
| Kamarainen et al. [27] | 37 | Out of hospital | Pre hospital | VF, PEA, asystole | IV fluid (ringer lactate), to achieve a target temperature of 33°C, then discontinuing, or at Physician disclosure, no mention on rewarming time | No intervention for Temperature control, Standard ICU protocol care | OHCA in >18 year old regardless of initial rhythm, GSC <5 for >9 min after ROSC | Till hospital discharge | 11 | 10 | 8 | 8 |
| Nielsen et al. [11] | 939 | Out of hospital | In hospital | VF, PEA, asystole | Ice packs, IV fluids, to target temperature of 33°C for 28hrs then rewarming for 8 hours (hourly increment of 0.5 °C) | Ice packs, IV fluids, to target temperature of 36°C for 28hrs then rewarming for 1 hours (hourly increment of 0.5 °C) | OHCA in >18 year old regardless of initial rhythm, GSC <8 for >20 min after ROSC | 6 months | 235 | 225 | 218 | 222 |

CA: Cardiac arrest, C: Celsius, CVVH: Continuous veno venous filtration, CPR: Cardiopulmonary resuscitation, GSC: Glasgow comma scale, ICU: Intensive care unit, IV: Intravenous, MAP: Mean arterial pressure, OHCA: Out of hospital cardiac arrest, PEA: Pulseless electrical activity, ROSC: Return to spontaneous circulation, SBP: Systolic blood pressure, VF: Ventricular fibrillation, VT: Ventricular tachycardia
overall effect when the last two RCTs were added\cite{11,27} [Figure 2 in the Supplemental Material].

**Bias**

Funnel plot did not show asymmetry suggesting bias for all-cause mortality outcomes except for favorable neurological outcomes [Figure 4]. However, after quantifying the observed bias with other methods (Begg–Mazumdar, Egger and Duval, and Tweedie’s trim and fill test), no evidence of publication bias was observed [Figure 3 in the Supplemental Material]. The individual study quality appraisal and the risk of bias for the 6 included RCTs are summarized in Table 2.

**DISCUSSION**

This meta-analysis provides a comprehensive update of RCTs assessing the effect of mild MTH on patients successfully resuscitated post-OHCA. To our knowledge, this comprises the largest sample in the literature assessing the role of MTH in patients post-OHCA at the time of submission. This includes two trials not previously cited in meta-analysis,\cite{29,30} including the latest trial published by Nielsen et al.\cite{11} Our meta-analysis did not find a benefit of MTH on mortality or neurological outcome as reported in earlier analyses.\cite{4,6,29,30} These results not only correlate with the finding in the strongest powered study to date,\cite{11} but also correlate with “real world” observational studies following OHCA showing similar poor outcomes,\cite{33} and with multicenter trials in children who were the evidence of MTH effect was not substantially different from adults,\cite{34} regardless of the presenting rhythm.

We believe that the outcome differences in our analysis compared to some earlier trials by Holzer\cite{5} and Bernard et al.\cite{4} are a reflection not only of tight temperature control but also close monitoring and optimization of other parameters over the past 15 years. This includes, but is not limited to, improved patient monitoring of hemodynamics and metabolic control. In addition, advancements in circulatory support and early coronary interventions may have had an effect on the reported outcome, resulting in improved survival.\cite{35} Early referral of postarrest patients to tertiary care centers was a vital contributor to improved outcomes, virtually doubling the likelihood that patient will survive to discharge.\cite{36}

Along with the initial published RCTs and observational data,\cite{27} current guidelines have influenced many centers to adopt a mandatory protocol utilizing MTH in patients presenting with OHCA.\cite{37,38} MTH should be done with the awareness of all the physiological changes in the circulatory and metabolic systems causes by hypothermia.\cite{39} Potential complications and side effects reported with MTH include but are not limited to coagulopathies, increased rates of infections, cardiovascular complications, hyperglycemia, and electrolyte disorders.\cite{12-15,40-42} The financial burden of MTH is not to be overlooked. A cost-effectiveness analysis of MTH after OHCA showed that patients treated with MTH had an incremental cost of $31,254 compared to those treated conventionally.\cite{43} While neurological recovery or survival cannot be predicted among survivors of CA, it is important to consider the additional cost of this intervention.

Many factors are tentative contributors to the potential improvement of CA patients, and the role for MTH should be further investigated. Review of the literature suggests a potential role for simply avoiding hyperthermia and specific means of cooling survivors of OHCA. As described by Zeiner et al.,\cite{44} patients with hyperpyrexia after CA have worse neurologic outcomes that increase
for each degree Celsius higher, with an OR of 2.26. In this same study, patients with favorable neurologic recovery showed a higher lowest temperature and a lower highest temperature during the first 48 h after the restoration of spontaneous circulation. The majority of patients in the control groups included in our analysis were not treated actively for fever to keep them normothermic, allowing natural temperature course. This raises the possibility that the effect seen in early RCTs favoring MTH is due to an increased temperature in the control group. Nielsen et al. [11] attempted to answer this question comparing MTH with the control group temperature close to normothermia and found no significant differences between the two groups. These findings could be a key point to address future management of OHCA patients. Perhaps avoidance of fever, rather than hypothermia, is actually the most important element of temperature management after CA. Even Bernard et al., the author of one of the early trials that favored MHT, [4] has changed his own institution guidelines to a target temperature of 36°C [45]. In addition to the limited therapeutic resources to mitigate the postanoxic injury in OHCA, arguments against changes on the target temperature set for MTH (32–34°C) are the lack of differences of adverse events seen with MTH compared to normothermia, and that there might be subgroups of patients, based on the severity of neurologic injury that may require more individualized degrees of hypothermia to achieve the best outcome. Two RCTs are currently recruiting patients to evaluated differences in target temperature; The Centre Hospitalier Departemental Vendee is randomizing patient with OHCA to a targeted temperature between 32.5°C and 33.5°C and the control group between 36.5°C and 37.5°C testing the potential improvement of neurological outcome with these two target temperatures. The other group from the University of Ottawa Heart Institute is being even more aggressive and is determining whether neurologic outcomes at 6 months are improved with moderate (31°C) versus mild (34°C) therapeutic hypothermia following ROSC in patients suffering OHCA. [46]

Other key point is the duration of MHT; the RCTs included in this meta-analysis utilized different durations of targeted temperature management after OHCA ranging from 12 to 28 h. There are no data that can be used to compare different durations of targeted temperature; however, we know that regardless of the target temperature chosen, temperature in postarrest patients should be tightly controlled and monitored. This important point was recognized in the new guidelines that updated the cooling time duration

**Table 2: Risk of bias across individual randomized control trials**

| Study name          | Sequence generation | Allocation concealment | Blinding | Incomplete outcome data | Selective reporting | Baseline reporting | Source of funding bias | Academic bias |
|---------------------|---------------------|------------------------|----------|-------------------------|---------------------|--------------------|------------------------|--------------|
| Holzer et al. [5]   | Low                 | Low                    | Uncertain| Low                     | Low                 | High               | Low                    | Low          |
| Bernard et al. [4]  | High                | High                   | Low      | High                    | Low                 | High               | Low                    | Low          |
| Hachimi-Idrissi et al. [26] | Uncertain          | Uncertain              | Uncertain| Low                     | Low                 | Uncertain          | Low                    | Low          |
| Kamarainen et al. [28] | Low                | Low                    | Uncertain| Low                     | Low                 | Low                | Low                    | Low          |
| Nielsen et al. [12] | High                | High                   | Low      | High                    | Low                 | High               | Low                    | Low          |
| Laurent et al. [29] | Low                 | Low                    | Uncertain| Uncertain               | Low                 | Uncertain          | Low                    | Low          |
from 12 to 24 h to at least 24 h.[10] The TTH48 trial was recently completed and is examined prolonged MTH (32–34°C) in 24 versus 48 h with the primary outcome CPC after 6 months in OHCA patients.[47] Hopefully, we will have more answer on what is the optimal duration of MHT.

Though the new surface and endovascular (invasive) cooling methods are the most commonly used methods to both induce and maintain hypothermia. Optimal means of cooling have not yet been determined, but both randomized and observational studies suggest that endovascular cooling maintains target temperatures better than conventional surface cooling. Endovascular cooling also has less temperature fluctuation and has fewer complications associated with it than surface cooling.[48,49] Current guidelines do not specify which method to use but this may be a valuable consideration.

It has been discussed that a delay of several hours from resuscitation until the target temperature had been reached can impact neurologic outcomes. Some of the trials included in our meta-analysis started prehospital cooling as compared to hospital cooling, postulating earlier cooling results would improve neurologic recovery. This hypothesis was tested in the Hypothermia Network Registry[50] and some RCTs with adult patients after OHCA.[51,52] No differences in outcomes were observed. In fact, the intervention group was more likely to have re-arrest in the field.[52,53] The new hypothermia guidelines recommend against prehospital cooling with rapid infusion of large volumes of cold intravenous fluid (strong recommendation, moderate-quality evidence).[10]

We are not suggesting intensivists abandon temperature management after CA; however, the questions that remain are whether we should cool our postarrest patients to 36°C or continue with the old target temperatures. Regardless of the target temperature chosen, the temperature in postarrest patients should be tightly controlled and monitored. While 36°C may be a sufficient temperature goal, with no temperature control, many postarrest patients may become febrile with detrimental effects on mortality and neurologic function.

The benefit of MTH after in-patient CA has not been tested in RCTs. However, retrospective studies have shown no difference in neurological outcome at discharge among patients treated with MTH compared to control group.[54] The largest published cohort of patient included 8316 patients with complete data, of whom 214 (2.6%) had hypothermia induced, and 2521 (30%) survived to discharge. Only 40% were documented as achieving a temperature between 32°C and 34°C. Induced hypothermia was not associated with favorable neurological outcomes or improved survival. The lack of benefit in this population may reflect lack of effect, inefficient application of the intervention.[55] The new ILCOR and AHA, we suggest targeted temperature management as opposed to no targeted temperature management for adults with in-hospital CA (weak recommendation, very low-quality evidence) with any initial rhythm who remain unresponsive after ROSC.

In the perioperative setting, there are no specific guidelines to guide post-CA treatment. CA occurs in 0.7–2.9% of cardiac surgical patients.[56,57] The uncommon event of patient requiring MTH needing cardiac surgery can pose significant challenges to the perioperative physician. In terms of anesthetic management, the key goals relate to maintenance of normal hemodynamics (preservation of the myocardial oxygen demand/supply balance, judicious fluid management guided by appropriate intravascular monitoring and transesophageal echocardiographic and satisfactory pain management. Temperature management in the operating room and Intensive Care Unit can be difficult owing to the multiple factors that affect core body temperature in the perioperative period. To date, there is little specific data reporting safety or efficacy of TH in cardiac surgery patients who experience unintentional CA. Only a few published case series experience have been reported with a safe and successful use of MTH after unintentional perioperative CA in 3 cardiac surgery patients. The target temperature range between 32°C and 34°C and was maintained through the use of intermittent fanning for a period of 24 h, followed by passive rewarming.[54] High-quality controlled studies are required to better characterize the effect of induced hypothermia in this population.

LIMITATIONS

This systematic review and meta-analysis have several important limitations that should be acknowledged. First, this is a meta-analysis performed on study-level data. Second, the studies included in the meta-analysis enrolled heterogeneous populations and were characterized by different study protocols and defined endpoints differently. Third, none of the studies were
blinded for the intervention assignments, though some of the latest trials tried to decrease the bias by
blinding statisticians. Fourth, there were differences
in the target temperature for control groups; the
results of our review come from mixed-up analyses
that did not separate each hypothermic temperature
level between 32°C and 34°C and for most studies
included, it stated merely the body temperature level
of hypothermia as 32–34°C. Finally, several of the
trials we analyzed had premature patient withdrawal
that may affect overall neurologic recovery. Most of
the trials did not specify whether the decision on
withdrawal of intensive care was made and if the
assessor of the prognostication was blinded, except
for the Nielsen et al.'s trial that had a strict protocol
for neurologic prognostication and withdrawal of
life-sustaining therapies. Short-term follow-up may be
troublesome since the neurological status for survivors
can evolve over the first 6 months after the arrest.[58]
All these limitations may explain some of the observed
heterogeneity of the end points.

Interestingly, considering that none of the included
studies were blinded for the intervention assignments,
the open nature of the studies might, in theory, slightly
favor the MTH intervention group.[59] This, and the
consistency of the magnitude, direction, and the
stability of summary effects after the sensitivity and
cumulative analyses, further supports the results of
this meta-analysis, but results should be interpreted
cautiously.

CONCLUSIONS

The results of our meta-analysis did not confer benefit
of MTH on overall survival rate or neurological recovery
in survivors of OHCA. Overall survival rate and
neurological recovery are very limited in these patients.
Further studies are needed to determine the optimal
temperature level of hypothermia therapy.

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Conflicts of interest
There are no conflicts of interest.

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