

A review of the utility of a hypothermia protocol in cardiac arrests due to non-shockable rhythms

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Abstract

Background: *Therapeutic hypothermia and targeted temperature management are considered standard of care in the management of patients following out-of-hospital cardiac arrests due to shockable rhythms to improve neurological outcomes. In those presenting out-of-hospital cardiac arrests associated with non-shockable rhythms, the benefit of hypothermia is less clear. In this review we try to clarify the utility of implementing a hypothermia protocol after cardiac arrests due to non-shockable rhythms.*

Methods: *PUBMED, Ovid, MEDLINE, EMBASE, and clinicaltrials.gov websites were searched through during October, 2016 using the terms “non shockable”, “hypothermia,” and “cardiac arrest.” Studies were excluded if they solely evaluated in-hospital cardiac arrests, shockable rhythms, and/or pediatric patients. Data was extracted by two authors.*

Results: *Forty studies were included in this review, most of which were not randomized or controlled, nor were they powered to make significant conclusions about the efficacy of hypothermia in this population. Some did evaluate specific factors that may portend to a better outcome in patients presenting with out-of-hospital cardiac arrest due to non-shockable rhythms undergoing hypothermia. Shortcomings included incorporating in-hospital cardiac arrest patients in analyses, comparing results of hypothermia in shockable versus non-shockable rhythm patients as an outcome measure, lacking standardization in cooling protocols, and short-term measures of outcomes.*

Conclusions: *It was concluded that further study is needed to characterize patients presenting non-shockable rhythms who would benefit from hypothermia to better guide its use in this population given the costs and implications of treatment and long-term care in those who survive with poor outcomes. (Cardiol J 2017; 24, 3: 324–333)*

Key words: cardiac arrest, non shockable, hypothermia, targeted temperature management

Introduction

With roughly 400,000 out-of-hospital cardiac arrests (OHCA) in the United States per year [1], therapeutic hypothermia (TH) or targeted temperature management (TTM) is now the standard of care in their management. The pathophysiology underlying the effect of body temperature on hypoxic-ischemic brain injury has been described in detail [2–4]. Improved outcomes have been demonstrated in randomized controlled trials (RCTs) in a group of post-anoxic patients who present with

OHCA due to “shockable rhythms,” ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT) [2–4].

It has been well established that more patients are presenting with cardiac arrest (CA) due to non-shockable rhythms (nSR), pulseless electrical activity (PEA) or asystole, than VT/VF [5]. This is possibly related to more aggressive cardiac interventions and better long-term medical management of coronary disease and heart failure. This may ultimately lead to fewer OHCA due to

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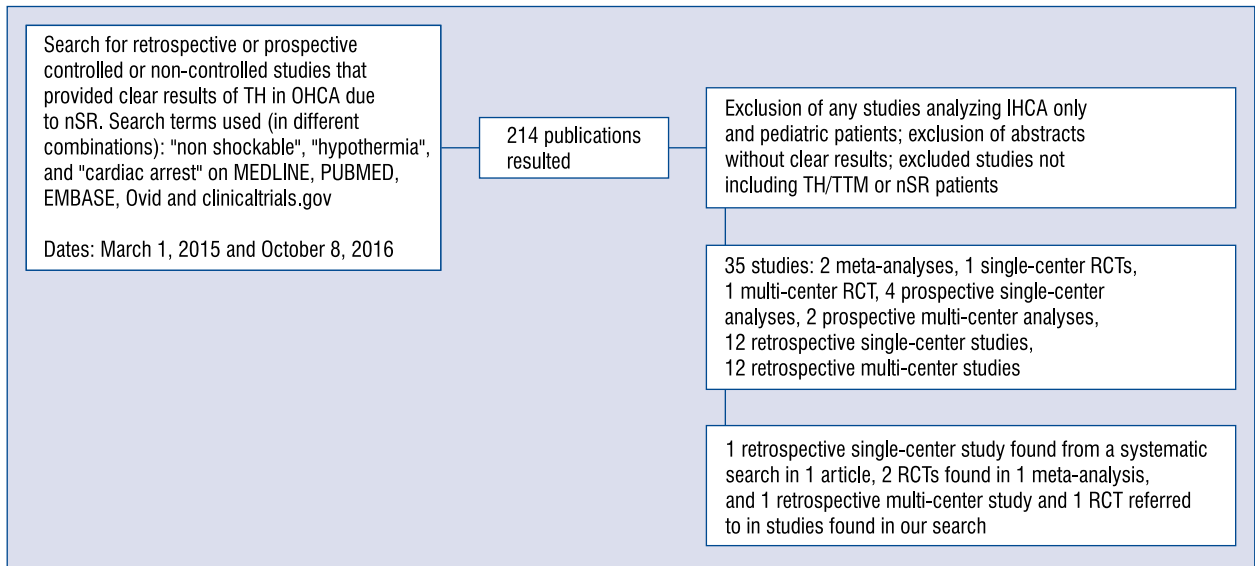


Figure 1. Literature search for studies evaluating therapeutic hypothermia (TH)/targeted temperature management (TTM) in out-of-hospital cardiac arrests (OHCA) due to non-shockable rhythm (nSR); IHCA — in-hospital cardiac arrests; RCT — randomized controlled trial.

VT/VF [5, 6]. Yet a fewer percentage of patients presenting with OHCA due to nSR receive TH/TTM than those with VT/VF [5]. The largest RCTs on TH/TTM in OHCA have excluded nSR [2, 3] or were not designed to evaluate the effects of hypothermia in nSR as a primary outcome [4]. This is likely because studies have revealed significantly worse outcomes in OHCA associated with nSR, and intervention has been assumed to have little benefit given the costs [7, 8]. However, a hypothermia protocol may be beneficial in a subgroup of patients presenting with OHCA due to nSR if certain criteria are met [8]. Though recent publications support the use of TH/TTM in cardiac arrests regardless of rhythm [9, 10], understanding the clinical variables that render patients suitable candidates for TH/TTM, especially in those presenting with nSR, is vital given that cost-benefit is a reason proposed by some institutions to withhold treatment, especially when considering the consequences of long-term care in survivors with poor outcomes.

In this article, a review the literature on TH/TTM in OHCA due to nSR is presented. We point out possible clinical features that may make certain patients presenting with OHCA due to nSR good candidates for intervention and discuss the difficulties in extrapolating the results of these studies to refute or support the benefit of TH/TTM in OHCA due to nSR.

Methods

A systematic literature search was performed using PUBMED, Ovid, MEDLINE, EMBASE, and clinicaltrials.gov websites first in March, 2015 and then again in October, 2016. The primary author (BF) performed the search. Both authors (BF, PK) decided which studies would be included or excluded. The terms “non shockable,” “hypothermia,” and “cardiac arrest” in different combinations were used. Studies included those which demonstrated outcomes from TH in OHCA due to nSR. Studies were excluded if it was clearly stated that they included only those with shockable rhythms, in-hospital cardiac arrests (IHCA) or pediatric patients. Many of the results were abstracts submitted to meetings and if results were unclear with respect to the efficacy of TH/TTM in nSR they were also excluded (Fig. 1).

Each study was evaluated by the quality of its data using a categorical system adapted from a previously published guideline by American Academy of Neurology (AAN) [10] which was modified by Dr. David Gloss. The quality of each study was based on a categorical rating as follows: Category I — broad spectrum prospective trial; Category II — narrow spectrum, prospective trial or broad spectrum retrospective trial; Category III — narrow spectrum, retrospective trial or case control study; Category IV — review, case series, expert opinion paper (Table 1).

Table 1. Studies evaluating therapeutic hypothermia (TH)/targeted temperature management (TTM) in out-of-hospital cardiac arrests due to non-shockable rhythm.

Study	Study type	Survival/outcome with TH/TTM	Data quality
Studies demonstrating benefit from TH/TTM			
Choi [11]	Retrospective multicenter study	OR for survival to discharge: PEA = 2.28 (95% CI 1.69–3.07), Asystole = 1.84 (95% CI 1.58–2.15); ORs for good outcome (CPC 1–2): PEA = 2.3 (95% CI 1.50–3.53), Asystole = 1.07 (CI 0.83–1.38)	Category II data
Lindner [12]	Prospective multicenter study	17% survived to discharge (p = 0.051); 14% TH vs. 9% of controls (p = 0.094) had good outcome	Category III data
Sung [13]	Retrospective multicenter study	For all nSR — OR for good outcome (CPC 1–2) = 2.9 (95% CI 1.9–4.4)	Category III data
Testori [14]	Retrospective single center analysis	Improved survival at 6 months with TH with adjusted OR 0.56 (95% CI 0.34–0.93), p = 0.025; 35% of TH-treated patients had good outcomes (CPC 1–2) adjusted OR 1.84 (95% CI 1.08–3.13), p = 0.024	Category III data
Lundbye [15]	Retrospective single center analysis	Adjusted OR for survival to discharge was 5.65 (95% CI 1.66–19.23), p = 0.06 in TH group; adjusted OR for good neurologic outcome from TH was 4.35 (95% CI 1.10–17.24), p = 0.04	Category III data
Soga [16]	Retrospective multicenter study	59% of patients survived to 30 days with TH; 32% of those undergoing TH had a favorable outcome; if ROSC < 16 min, outcomes were similar to VT/VF (p = 0.84)	Category III data
Kim [17]	Meta-analysis and systematic review including 2 RCTs, 6 prospective (2 multicenter) and 6 retrospective analyses (4 included IHCA and OHCA)	Decreased in-hospital mortality (OR 0.84, 95% CI 0.78–0.92) in the non-randomized studies in TH groups; pooled RR for 6 month mortality 0.85 (95% CI 0.65–1.11) in the 2 RCTs in those undergoing TH; trend towards less poor outcomes in those undergoing TH (OR 0.95, 95% CI 0.90–1.01) in the non-randomized studies	Category IV data
Kim [19]	Retrospective multicenter study	Unadjusted OR 2.34 (95% CI 1.08–5.05) for women and unadjusted OR 1.67 (95% CI 1.01–2.75) for men with good outcome (CPC 1–2) (under 45 years old); Unadjusted OR 1.53 (95% CI 1.09–2.14) for men with CPC 1–2 (45–65 years old)	Category II data
Yoshida [39]	Retrospective single center analysis	Significantly more patients with CPC 1–2 (p < 0.0001 at 3 months) and better survival (p < 0.0001 at 3 months) if pulmonary embolism was cause of OHCA; incidental hypothermia increased likelihood of 3-month survival (p < 0.0001) and good outcome (p < 0.0001)	Category II data
Fontanals [40]	Retrospective single center analysis	Survival at 12 months — 33.3% and CPC 1–2 — 25%	Category III data
Katz [41]	Retrospective multicenter study	No difference in outcomes or survival in patients who overdosed vs. non-overdose patients undergoing TTM despite more nSR in the overdose group	Category III data
Lee [42]	Retrospective multicenter study	Adjusted OR 2.05 (95% CI 1.51–2.79) for survival to discharge in nSR undergoing TH vs. control and OR 1.13 (95% CI 0.59–2.20) for good neurologic outcome in nSR undergoing TH vs. control	Category II data
Nair [43]	Prospective single center study	Of the 64 post-cardiac arrest patients in the hypothermia group, 16 (25%) had a CPC 1–2 (good outcome) which was associated with time down and time to CPR	Category II data
Perman [47]	Retrospective multicenter study	OR 3.1 (95% CI 1.6–5.8) for survival to discharge in those undergoing TH in the nSR group; OR 2.1 (95% CI 1.0–4.4) for good outcomes in TH in nSR group	Category III data

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Table 1 (cont.). Studies evaluating therapeutic hypothermia(TH)/targeted temperature management (TTM) in out-of-hospital cardiac arrests due to non-shockable rhythm.

Study	Study type	Survival/outcome with TH/TTM	Data quality
Studies demonstrating no benefit from TH/TTM			
Vaahersalo [5]	Prospective multicenter study	80.6% of those with nSR undergoing TH survived with CPC 3–5 (p = 0.56)	Category II data
Martinell [6]	Prospective single center study	OR 0.67 (95% CI 0.31–1.46) for survival at 30 days in group undergoing TH and OR 0.64 (95% CI 0.27–1.54) for survival at 1 year in this group despite significant increase in use of TH; CPC score among survivors was not significantly different if undergoing TH (p = 0.36)	Category II data
Frydland [18]	Multicenter RCT (sub-group analysis)	Mortality 84% in TTM33 and TTM36; 13% had a good outcome in the TTM33 group and 15% in the TTM36 group	Category II data
Lopez-de-sa [20]	Single center RCT	No survivors at 6 months (asystole only)	Category II data
Dumas [21]	Prospective single center study	16% overall survival in the TH group with a trend toward better outcomes versus controls (OR 0.71, 95% CI 0.37–1.36), p = 0.48	Category II data
Storm [22]	Prospective single center study	27.59% good outcome in TH group (p = 0.175)	Category III data
Wee [23]	Retrospective multicenter study	46/80 patients survived in the TH group; 6/80 patients had good outcome; no association of rhythm with survival (p = 0.737)	Category III data
Hoffmann [24]	Retrospective single center analysis	None of the OHCA and nSR undergoing hypothermia had favorable outcome	Category III data
Uribarri [25]	Retrospective single center analysis	3/44 in nSR group survived with CPC ≤ 2, adjusted OR 13.8 (95% CI = 3.4–56.1), p < 0.001 compared to all undergoing TH	Category III data
Kocjanic [26]	Retrospective single center analysis	9% survived with CPC 1–2 with TH (“intensified resuscitation”) (p = 0.27)	Category III data
Ganga [27]	Retrospective single center analysis	17/98 with nSR reached CPC 1–2	Category III data
Gebhardt [28]	Retrospective single center analysis	In TH cohort presence of PEA predicted poor outcome (OR 0.09, 95% CI 0.02–0.40 for good outcome, defined as disposition home/rehab)	Category III data
Schenone [29]	Meta-analysis and systematic review including 3 RCTs, 8 cohort studies evaluating shockable and non-shockable rhythms (1 RCT and 6 cohort studies included nSR)	Did not specifically evaluate effects of TH on nSR separately from a group of pooled results of nSR and VT/VF, did evaluate levels of temperature in nSR and found non-significant benefit of lower temperature vs. higher temperature in good outcome (CPC 1–2) in nSR	Category IV data
Modisett [30]	Retrospective single center analysis	11/18 patients with VT/VF and 7/30 patients with nSR survived (p = 0.01)	Category III data
Whittaker [31]	Retrospective single center analysis	OR for death 5.6 (95% CI 2.0–15.4), p = 0.018 when compared nSR to VT/VF, only 3 patients with nSR survived to discharge	Category III data



Table 1 (cont.). Studies evaluating therapeutic hypothermia (TH)/targeted temperature management (TTM) in out-of-hospital cardiac arrests due to non-shockable rhythm.

Study	Study type	Survival/outcome with TH/TTM	Data quality
Kim [32]	Retrospective multicenter study	More patients with nSR than VT/VF in the bad outcome group (CPC 3–5) and more VT/VF than nSR patients and in the good outcome group (CPC 1–2) ($p < 0.01$) — likely skewed by asystole; multivariate analysis for decreased chance of good outcome in nSR with OR 7.13 (95% CI 4.85–10.48)	Category II data
Afzal [33]	Retrospective single center study	Of those receiving TH: in the VT/VF group — 69% expired, 23% went home, and 7.7% were sent to nursing facility; in the nSR group — 89.7% expired, 7.6% went home and 2.5% went to nursing facility	Category III data
Thomsen [34]	Retrospective single center study	nSR was a significant predictor of mortality HR = 2.26 (95% CI 1.67–3.07), and having any comorbidity noted in this study was an independent predictor of mortality in nSR HR = 1.67 (95% CI 1.08–2.59)	Category III data
Lazerri [35]	Retrospective multicenter study	More nSR observed in non-survivors ($p = 0.026$) who showed a longer collapse — recovery of spontaneous circulation time ($p = 0.01$). Only 3/18 survivors had presented with nSR, 15/18 had VT/VF	Category III data
Kim [36]	Retrospective multicenter study	Outcomes in nSR associated with time down: 10.3% of nSR survived with good outcome (3/29) if downtime > 10 min but 61.5% if downtime < 10 min	Category II data
Dell’anna [37]	Retrospective multicenter study	75% of non-survivors had nSR vs. 33% of survivors ($p > 0.0001$); less nSR patients were in the group with CPC 1–2 than in the group with CPC 3–5 ($p < 0.0001$)	Category III data
Coute [38]	Retrospective multicenter study	10.6% (261 patients) of the total cohort received TH; mortality 83.9% in those receiving TH and 78.5% in nSR patients in the non-TH group (78.5%) ($p = 0.04$), though differences by rhythm category were observed; those that converted to shockable rhythm had better outcomes	Category III data
Pfeifer [44]	Retrospective single center analysis	Significantly more patients with CPC 1–2 undergoing TH had VT/VF than those with CPC 3–5; no benefit in mortality from TH in nSR ($p = 0.149$)	Category III data
Idriss-Hachimi [45]	Single center RCT	15 died in control group, 12 died in TH group (no statistical analysis); 2/16 in the TH group had CPC 1–2, 0/16 had CPC 1–2 in control	Category II data
Laurent [46]	Two center RCT	mortality 68% vs. 79% in TH and control; CPC 1–2 45% in TH and 26% in control	Category II data
Kim [48]	Single center RCT	In “non-VF” cohort 9% of field-cooled patients survived ($p = 0.13$)	Category II data

CI — confidence interval; CPC — cerebral performance category; CPR — cardiopulmonary resuscitation; HR — hazard ratio; IHCA — in-hospital cardiac arrest; nSR — non-shockable rhythm; OR — odds ratios; OHCA — out-of-hospital cardiac arrests; PEA — pulseless electrical activity; RCT — randomized controlled trial; ROSC — return of spontaneous circulation; RR — risk ratio; TH — therapeutic hypothermia; TTM — targeted temperature management; VT/VF — ventricular tachycardia/ventricular fibrillation

Results

A total of 214 publications were gathered from our search, 35 of which were included in this analysis [5, 6, 11–43]. In 1 study [18], a literature search was performed which found 12 studies, of which 1 retrospective study [44] was not found in our search or in any of the meta-analyses. This study was added to our analysis. One of the studies above was a high quality review and meta-analysis of nSR and TH [17] which included 2 RCTs [45] and

[46] that was analyzed separately, also a non-RCT [22] was found in the search. Another more recent meta-analysis [29] included 11 trials of patients undergoing TH versus a control group which included both shockable and non-shockable rhythms. Most of the trials in their analysis had already been found in this search or were included in the previous meta-analysis that had been reviewed above [17]. Three other studies noted in this meta-analysis pooled results from TH in OHCA due to nSR and VT/VF together, so specific outcomes in nSR were

not clarified and were thus excluded. After reviewing reference lists of the resulting papers above, 2 more studies not listed in prior searches [47] and [48] were discovered. 1 randomized, controlled trial currently enrolling [49] was also discovered, which focuses on hypothermia protocol in OHCA due to nSR. In total, 40 studies were included in the present analysis.

The studies are described in Table 1. The results of each study are highlighted based on survival and good outcomes. Some of the studies used cerebral performance category (CPC) scale to define good outcomes while others used post-discharge disposition. There were 14 studies that demonstrated benefit with TH/TTM [11–17, 19, 47, 39–43] while 26 studies showed unclear or no benefit from TH/TTM [5, 6, 18, 20–38, 44–46, 48]. Based on a categorical system rating the quality of data, none of the studies received a Category I rating.

Outcome variables

Some of the retrospective studies noted variables that may have negatively impacted outcomes in OHCA. These include delayed time to initiating cardiopulmonary resuscitation (CPR), less bystander CPR, poor CPR quality, longer time to return of spontaneous circulation (ROSC), non-cardiac cause for arrest, medical comorbidities, older age, female gender, higher Acute Physiology and Chronic Health Evaluation (APACHE) II scores, lactic acidosis on admission, and post-resuscitation circulatory shock [7, 12, 16, 19–21, 25, 28, 35, 36, 43, 45]. Some studies cited comparisons between nSR and VT/VF with respect to the efficacy of TH/TTM as major findings [7, 16, 18, 20, 24–28, 30–33, 35, 44]. One trial concluded that if ROSC was < 16 min, TH benefitted OHCA due to nSR similarly to VT/VF ($p = 0.84$) [16]. The effect of time down during arrest also was described in another trial with a cutoff noted at 10 min for improved outcomes [32]. Other studies also focused on variables affecting outcomes in TH/TTM-treated patients presenting with OHCA due to nSR [29, 34–36, 39].

Study design

Four of the five RCTs in this review were small, with cohort sizes ranging from 6 to 16 subjects [20, 45, 46, 48]. In the subgroup analysis of the original TTM study [4], a larger cohort was studied but the authors noted that their trial was underpowered [18]. Another issue was that the RCTs were designed with primary endpoints that did not specifically address TH/TTM in nSR. One study was designed to evaluate both the feasibility

of a helmet cooling protocol and effects of hypothermia on serum levels of S-100 β , an astroglial protein that could be a marker, or direct mediator of neuronal injury in OHCA [45]. Another RCT was a pilot study designed to obtain initial data when using different temperature targets for TH and assess TH effect on outcomes [20]. In another study, the primary endpoint was to assess different levels of hypothermia and their efficacy [18]. The two other RCTs in this study were created to evaluate hemofiltration [46] and rapid in-field cooling in OHCA [25].

With respect to comparing outcomes between PEA arrest and asystole, one trial found that patients presenting with OHCA due to PEA arrest benefitted more from TH than those with asystole [11]. Others also noted possible differences between asystolic and PEA arrest in outcomes in those undergoing TH/TTM [32, 38].

The change in the goal temperature for cooling, from TH to TTM, could confound results and analyses of these studies though they were included together in the present study. Differences in cooling protocols, other than target temperature, were noted in some trials. In 1 study there was a difference in the method of hypothermia maintenance based on the time of enrollment with roughly half of patients undergoing more modern techniques. In this same study, there were some patients who did not complete the 24-h period of hypothermia [25]. Variability in the form of maintenance hypothermia was also specifically noted in another non-RCT and could have affected outcomes [23]. In another study, different cooling methods were used in the shockable and non-shockable rhythm groups [45].

The time to outcomes measured in most of these studies was short. Other studies with longer-term follow up demonstrated good outcomes [14, 17, 40].

Though most trials focused on OHCA, some studies included IHCA in their analyses [17, 24, 27, 28, 37, 41]. Others, which only included abstracts presented at national meetings, may also have included these patients though some did not specifically address this issue in their presentation.

Discussion

In this focused review, results were outlined from randomized and non-randomized studies of TH/TTM in patients presenting with OHCA due to nSR. As noted in Table 1, there are few high quality studies on this topic. Though it is difficult to make broad conclusions from their findings, these studies do shed light on some factors that may play a role in

outcomes and could guide clinical decision-making and highlight shortcomings in design that should be kept in mind for future trials.

Outcome variables

The difficulty with measuring outcomes in OHCA due to nSR is that they are more likely to have many of these features, particularly when compared to VT/VF [7, 12, 16, 18, 24, 25, 45, 47]. Also, each clinical variable may not alter outcomes in a similar fashion in VT/VF and nSR groups [32, 34]. Considering the fundamental differences between these groups, it is not surprising that many found that OHCA due to nSR have worse outcomes when compared to those with SR with TH/TTM. To define the utility of TH/TTM in OHCA due to nSR, studies should compare treatment and control groups within this population.

Some studies specifically focused on factors affecting outcomes in those with nSR undergoing TH/TTM, as noted above. However, many that did this demonstrated baseline differences that would favor survival in the control group, which could have confounded the results and therefore one cannot make significant conclusions from their findings [11, 12, 16, 19, 21, 26, 28, 47]. Nevertheless, evaluating outcome measures in those presenting in nSR, without comparing them to those with VT/VF, should be replicated in future studies.

Study design

The highest quality studies available are RCTs but those were ones that evaluated outcomes in TH/TTM in OHCA due to nSR and were not specifically designed to address the efficacy of TH/TTM in OHCA in this subgroup. Also, though the RCTs may have been powered for their own primary end points, they were too small to determine outcomes in TH in OHCA due to nSR. These factors have likely contributed to the lack of quality data available.

Analyzing PEA and asystolic arrests together may not be ideal since it has been demonstrated that OHCA due to PEA may portend a better outcome than those due to asystole [7]. This was also demonstrated in the few studies that compared their outcomes [11, 32, 38]. Separate analyses of PEA and asystolic arrests may help elucidate those who would benefit from intervention in these groups.

There were differences in cooling methods and duration of cooling seen across the randomized and non-randomized trials which could have led to inconsistent time-to-target temperature and actual

temperature during the testing period. Optimally, cooling protocols could be more consistent in future analyses, given that this inconsistency could confound results.

Differences between nSR and VT/VF with respect to outcomes become less apparent as the length of time to follow up is longer [46]. This is thought to be due to the fact that more time is needed for full recovery after an acute illness and brain injury [6]. Most of these trials used short-term outcome measures at the time of discharge or a few months afterward but as noted above, those with longer-term follow up showed intervention to be beneficial [14, 17, 40]. Analyzing survival and neurologic function over a longer time period might shed light on the utility of TH/TTM in OHCA due to nSR as these patients may derive more benefit in the long-term.

Evaluating IHCA with OHCA poses challenges. IHCA patients are more complicated as they often have more varied underlying etiologies, which can include more non-cardiac causes and a higher rate of nSR, and they often have more active medical comorbidities which can negatively affect outcomes [24]. A recent article has questioned the efficacy of TH/TTM in IHCA [50]. Therefore, OHCA and IHCA may be evaluated better separately.

Limitations of the study

This literature review was focused and therefore it is possible that some studies had eluded this search. Also, given that a meta-analysis was not undertaken, there were a lack of high quality studies, variable outcome measures, and confounders limit the utility of this study. Substantive conclusions are also limited by the scope of the studies themselves. The RCTs lack power or an appropriate study design for our purposes. The non-RCTs are limited by inherent shortcomings, including selection bias, their varying outcome measures, confounders, and some by their small subject sizes, as well as others that we have outlined above. Also, given that abstracts included data which were presented at national meetings, we cannot definitively conclude much from them nor can we guarantee they did not include IHCA or pediatric patients.

Conclusions

In this review and analysis of the most recent data on TH/TTM in OHCA due to nSR, which includes RCTs and non-RCTs, it remained inconclusive as to whether TH/TTM has a role in post-OHCA care in nSR. Most studies are under-

powered or not primarily designed to make significant conclusions about the efficacy of TH/TTM in OHCA due to nSR. In particular, many compared the efficacy of TH/TTM in nSR to VT/VF, which is problematic due to inherent differences between the two groups. Features that may portend better results within the nSR group itself, which would be useful in defining those who could benefit from TH/TTM, were analyzed in some studies but were not comprehensive. Analyzing PEA and asystole separately, excluding IHCA, normalizing cooling protocols, and evaluating longer-term outcomes could improve future studies. Based on the results of this review, the benefit of TH/TTM in OHCA due to nSR is still unclear. An RCT devoted to studying this population is currently enrolling patients [49] and its results could help shed light on the utility of TH/TTM in OHCA due to nSR. Given the possible efficacy of TH/TTM in OHCA due to nSR, the 2015 American Heart Association guidelines are well founded [51] and advocate the use of TTM/TH in OHCA due to nSR while proposing that continued study in this field would help to better define those that could benefit from TH/TTM to avoid withholding a possible life-saving intervention while ensuring that expensive resources are not misappropriated.

Conflict of interest: None declared

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