Meta-Analysis of the Usefulness of Therapeutic Hypothermia After Cardiac Arrest

Amit Rout, MD[a,*], Sahib Singh, MD[a], Sauradeep Sarkar, MD[a], Immad Munawar, MD[a], Aakash Garg, MD[b], Christopher R. D'Adamo, PhD[c], Udaya S. Tantry, PhD[d], Ashwin Dharmadhikari, MD[a], and Paul A. Gurbel, MD[a,d]

Despite current guidelines recommending therapeutic hypothermia (TH) for post cardiac arrest comatose patient, its use remains limited. Randomized controlled trials (RCTs) have also reported conflicting results on the efficacy of TH. Therefore, we conducted an updated meta-analysis to evaluate the effect of TH in post cardiac arrest patients. We searched electronic databases for RCTs comparing TH (32°C to 34°C) with controls (normothermia or temperature ≥36°C) in comatose patients who sustained cardiac arrest. Mortality and neurological outcomes were the outcomes of interest. We used random effect meta-analysis to estimate risk ratio (RR) with 95% confidence interval (CI). Eight RCTs with a total of 2,026 patients (TH n = 1,025 and control n = 1,001) were included. Irrespective of initial rhythm, TH was associated with significant reduction in poor neurological outcomes (RR 0.87, 95% CI 0.77 to 0.98; p = 0.02) without any difference in mortality (RR 0.94, 95% CI 0.85 to 1.03; p = 0.17). In patients with initial shockable rhythm compared with control, TH reduced mortality (RR 0.85, 95% CI 0.73 to 0.99; p = 0.04) and poor neurological outcomes (RR 0.81, 95% CI 0.67 to 0.99; p = 0.04). Whereas, in patients with initial nonshockable rhythm, TH was associated with decreased poor neurological outcomes after excluding one trial (RR 0.95 95% CI 0.91 to 1.00; p = 0.05). In conclusion, TH is associated with improved neurological outcomes in all patients sustaining cardiac arrest and with decreased mortality in patients with initial shockable rhythm. **(Am J Cardiol 2020;133:48−53)**

An estimated 700,000 adults have cardiac arrest every year in the United States, out of which 390,000 are out of hospital cardiac arrest (OHCA).[1,2] Although early initiation of cardiopulmonary resuscitation and defibrillation using automated external defibrillators have improved outcomes in OHCA, overall survival remains low.[3] Data from the Cardiac Arrest Registry to Enhance Survival (CARES) registry showed that approximately 10.4% patients with cardiac arrest survived to hospital discharge.[4] Randomized controlled trials (RCTs) in the early 2000s reported that use of therapeutic hypothermia (TH) was associated with improved mortality and neurological outcomes.[5,6] The 2010 American Heart Association guidelines recommended hypothermia (32˚C to 34˚C) as a part of postcardiac arrest care in resuscitated patients.[7] In 2013, the targeted temperature management (TTM) trial showed no difference in outcomes between 33˚C and 36˚C hypothermia.[8] Accordingly, the 2015 American Heart Association/International Liaison Committee on Resuscitation guidelines recommend hypothermia (32˚C to 36˚C) as a part of post cardiac arrest care in resuscitated comatose patients.[9,10] Recently, the Cardiac Arrest Registry to Enhance Survival surveillance group reported a declining trend in use of TH between late 2013 and 2016. Following the publication of the TTM trial, the use of TH decreased despite being supported by guidelines.[11] Recently the HYPERION trial (TTM for Cardiac Arrest with Nonshockable Rhythm) showed an improvement in neurological outcomes in patients assigned to TH when compared with normothermia.[12] In this study, we conducted an updated meta-analysis to compare the efficacy of TH in post cardiac arrest patients, including the HYPERION trial.

Methods

We searched MEDLINE, EMBASE, and Cochrane databases for RCTs published since inception through January 31st, 2020. We used search terms like "TTM," "cardiac arrest," "comatose," "TH," "normothermia," "out of hospital cardiac arrest (OHCA)," "in-hospital cardiac arrest (IHCA)," "shockable rhythm," and "nonshockable rhythm" in different combinations.

Studies were included if they met the following criteria: RCTs of adult human subjects reporting clinical outcomes in patients with OHCA or IHCA who were treated with TH versus a control arm; minimum temperature for the control arm was set ≥36˚C; and reporting at least one clinical end point based on treatment approach. The main exclusion

[a]Department of Medicine, Sinai Hospital of Baltimore, Baltimore, Maryland; [b]Division of Cardiology, Newark Beth Israel Medical Center, Newark, New Jersey; [c]Departments of Family and Community Medicine and Epidemiology and Public Health, Center for Integrative Medicine, University of Maryland School of Medicine, Baltimore, Maryland; and [d]Sinai Center for Thrombosis Research, Sinai Hospital of Baltimore, Baltimore, Maryland. Manuscript received April 14, 2020; revised manuscript received and accepted July 20, 2020.

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*Corresponding author: Tel: +1-4107108761.

E-mail address: amitrout90@gmail.com (A. Rout).

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criteria were: nonrandomized study design; and comparison between out of hospital or in hospital initiation of hypothermia only.

Two reviewers (SS and IM) independently screened study reports for eligibility, assessed risk of bias and collected data from each eligible study. Any differences between the 2 reviewers were resolved with consensus after discussion with the third reviewer (AR). From eligible RCTs, data on study characteristics like study design, year of publication, inclusion and exclusion criteria, sample size, follow-up period, baseline patient characteristics, treatment data including temperatures in both groups and clinical outcomes at the longest available follow-up were obtained. When available, individual end points based on shockable (pulseless ventricular tachycardia or ventricular fibrillation) or nonshockable initial rhythms (asystole or pulseless electrical activity) were also obtained. Individual study outcomes regarding mortality and poor neurological outcomes were obtained. Neurological outcomes were based on individual study definition.

This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[13] We used Cochrane Review Manager, version 5.3 for study analysis.[14] For each clinical outcome, pooled risk ratio (RR) and 95% confidence interval (CI) were calculated using random-effects models with Mantel-Haenszel method. A p value of 0.05 or less was assigned as the measure of statistical significance. The consistency and heterogeneity were assessed by calculating I squared statistic (I^2), heterogeneity was considered significant in the case of I^2 >50%. Forest plots were generated to demonstrate the relative effect size of hypothermia versus control arm for individual clinical end points.

Results

The initial study search yielded 6,903 studies out of which 8 RCTs were identified.[5,6,8,12,15-18] Supplementary Figure 1 shows the search strategy. A total of 2,026 patients with 1,025 in the TH arm and 1,001 patients in the control arm were included in the final analysis (Table 1). Data for one of the trials was accessed using an abstract and previous meta-analysis.[18-21] The duration of follow-up was from 14 days to 180 days or until hospital discharge. Baseline patient characteristics are included in Table 2. The mean age was 64 years and 72% of the study population were men. Approximately 40% of patients had a nonshockable rhythm at initial presentation. OHCA patients were included in all trials except for the HYPERION trial.[12] The duration of cooling in the hypothermia group was 24 hours in 4 trials (Table 2). The temperature in the TH group was maintained between 32˚C and 34˚C, with trials using several different cooling techniques (Table 2). Hemofiltration was used to achieve hypothermia in the trial by Laurent et al.[17] The temperature goal for the control arm trials was normothermia except for the TTM trial, where it was 36˚C.[8] Given this heterogeneity in the control arm, the analysis was divided between subgroups of hypothermia versus normothermia group and 33˚C versus 36˚C.

Poor neurological outcome was reported in all studies. Cerebral performance category scale was used in most studies where a score of 3 to 5 was considered poor neurological outcome (Table 1). TH was significantly associated with a decreased risk of poor neurological outcome (RR 0.87, 95% CI 0.77 to 0.98; p = 0.02) but with significant heterogeneity (I^2 = 64%) when compared with the control arm. There was a significant difference in results between TH versus normothermia and 33˚C versus 36˚C subgroups

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

Study (year)	N patients	Temperature (˚C)	Follow-up	Major inclusion criteria	Major exclusion criteria	Poor neurological outcomes definition
Mori (2000)	TH: 36 C: 18	32 - 34 NA	30 days	VF/VT or PEA/Asystole	NA	Glasgow outcome scale
Hachimi-idrissi (2001)	TH: 16 C: 14	34 NT	Discharge	PEA/Asystole	NA	Death + overall performance category 3
Bernard (2002)	TH: 43 C: 34	33 37	Discharge	VF/VT	Cardiogenic shock; drug overdose, head trauma, CVA	Death or discharge to long term nursing facility
HACA (2002)	TH: 137 C: 138	32 -34 NT	6 months	VF/VT	Coma due to drugs given during arrest; cardiac arrest after EMS arrived; coagulopathy	CPC 3, 4 & 5
Laurent (2005)	TH: 22 C: 20	32 37	6 months	VF/VT or PEA/Asystole	Response to verbal commands after ROSC	CPC 3, 4 & 5
Hachimi-idrissi (2005)	TH: 14 C: 14	33 NT	6 months	VF/VT	Cardiac arrest from intoxication or trauma; preexisting coagulopathy	CPC 3, 4 & 5
TTM (2013)	TH: 473 C: 466	33 36	180 days	VF/VT or PEA/Asystole	Unwitnessed arrest with asystole; stroke; coagulopathy	CPC 3, 4 & 5
HYPERION (2019)	TH: 284 C: 297	33 36.5−37.5	90 days	PEA/Asystole	Hemodynamic instability	CPC 3, 4 & 5

C = control group; CPC = cerebral performance category; CPR = cardiopulmonary resuscitation; CVA = cerebrovascular accident; EMS = emergency medical services; GCS = Glasgow coma scale; HACA = hypothermia after cardiac arrest; HYPERION = therapeutic hypothermia after cardiac arrest in nonshockable rhythm; therapeutic hypothermia group; NT = normothermia; OHCA = out of hospital cardiac arrests; ROSC = return of spontaneous circulation; TTM = targeted temperature management; VF = ventricular fibrillation; VT = pulseless ventricular tachycardia.

Table 2
Baseline characteristics of the patients and cooling method included in the trial

Study	Age (y) with range	Male (%)	H/o cardiac disease (n/N total)	Cooling method	Cooling duration (hours)	Rewarming
Mori	NA	NA	NA	NA	72	NA
Hachimi-idrissi	TH: 76.5 (52−95) C: 74 (59-91)	56 64	NA	External (Helmet)	4	Passive over 8 hours
Bernard	TH: 66.8 (49−89) C: 65.0 (41−85)	58 79	NA	External (Ice packs)	12	Active rewarming over 6 hours starting at 18 hours
HACA	TH: 59 (51−69) C: 59 (49−67)	76 77	43/135 59/138	External (cooling device, ice packs)	24	Passive over 8 hours
Laurent	TH: 56 (50−70) C: 52 (47−59)	82 80	3/22 6/20	Internal (cooled hemofiltration fluid), External (surface)	24	Passive
Hachimi-idrissi	TH: 61.3 (59.3−63.3) C: 62.7 (59.7−65.7)	85 78	NA	External (air mattress)	24	Passive over 8 hours
TTM	TH: 64 (52−76) C: 64 (51−77)	83 79	371/473 309/466	Internal and external (ice-cold fluids, ice packs, and intravascular or surface temperature-management devices)	28	Gradual rewarming to 37˚C after 28 hours
HYPERION	TH: 67.1 (56.9−76.3) C: 67.2 (57.8−76.1)	65 63	162/284 180/297	Internal (intravascular cooling catheter), External (surface)	24	Slow rewarming (0.25 to 0.50˚C per hour) to 36.5-37.5˚C

C = control; n = number of patients with cardiac disease; N = total number of patients; HACA = hypothermia after cardiac arrest; HYPERION = therapeutic hypothermia after cardiac arrest in nonshockable rhythm; TH = therapeutic hypothermia; TTM = targeted temperature management.

(p = 0.04; Figure 1). Additional sensitivity analysis was performed by excluding each trial (Supplementary Table 1). A nonsignificant difference in poor neurological outcomes were noted after removing the HACA trial and the trial by Mori et al.

Mortality was reported in 7 trials, 1,167 deaths were reported in 1,972 patients. There was a nonsignificant increase in the incidence of mortality in the control arm (RR 0.94, 95% CI 0.85 to 1.03; p = 0.17, I^2 = 28%) compared with TH. Exclusion of TTM trial resulted in a similar mortality risk (RR 0.89, 95% CI 0.77 to 1.03; p = 0.12; Figure 2).

Four trials with a total of 1,132 patients reported both mortality and poor neurological outcomes in patients with initial shockable rhythm. Compared with the control arm, the hypothermia arm was associated with decreased risk for mortality (RR 0.85, 95% CI 0.73 to 0.99; I^2 = 16%). Similarly, the risk of poor neurological outcome was lower in the hypothermia arm compared with the control arm (RR 0.81, 95% CI 0.67 to 0.99; p = 0.04, I^2 = 49%; Figure 3).

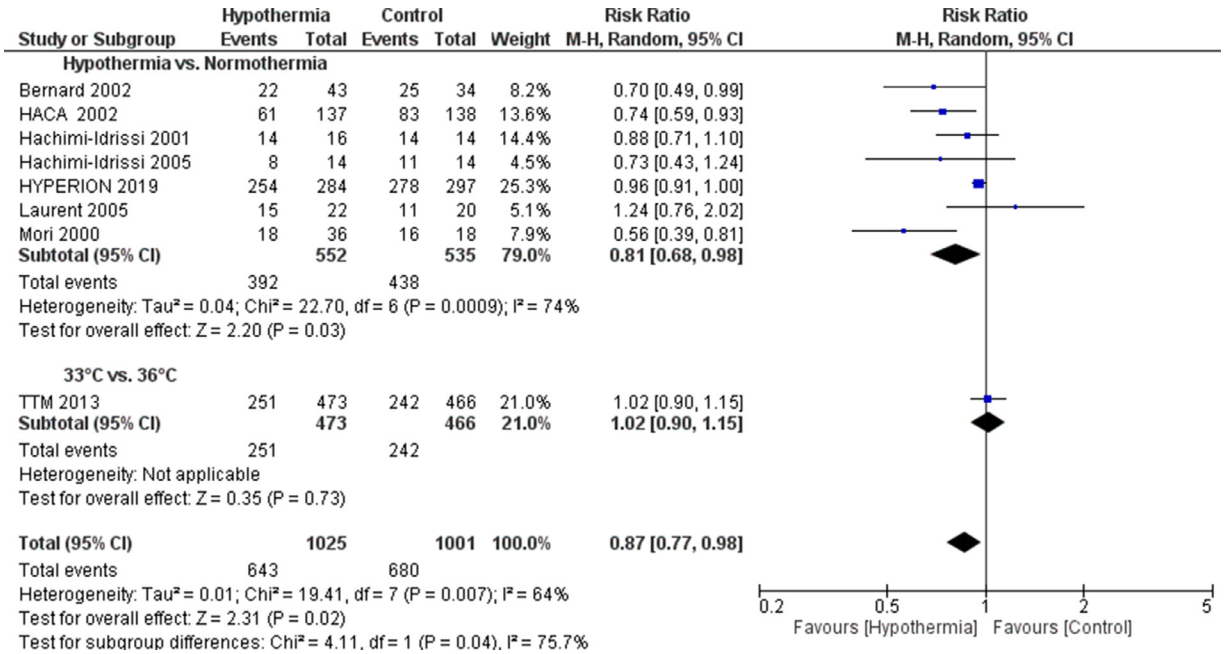

Figure 1. Forest plot showing risk ratio of poor neurological outcomes in all patients.

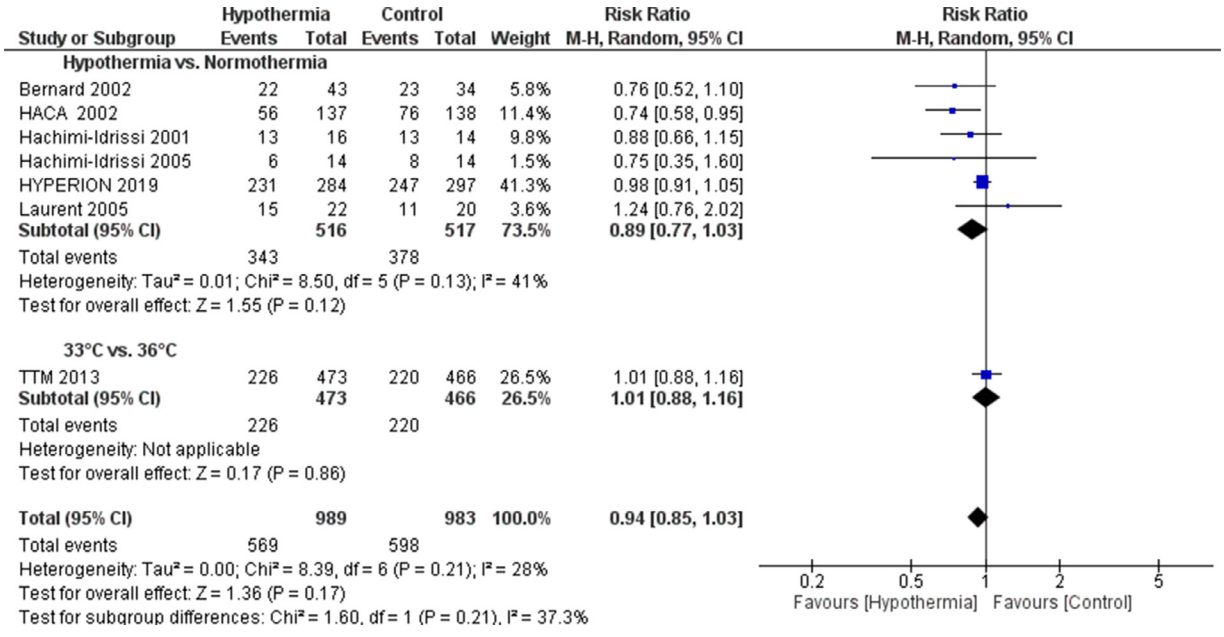

Figure 2. Forest plot showing risk ratio of mortality in all patients.

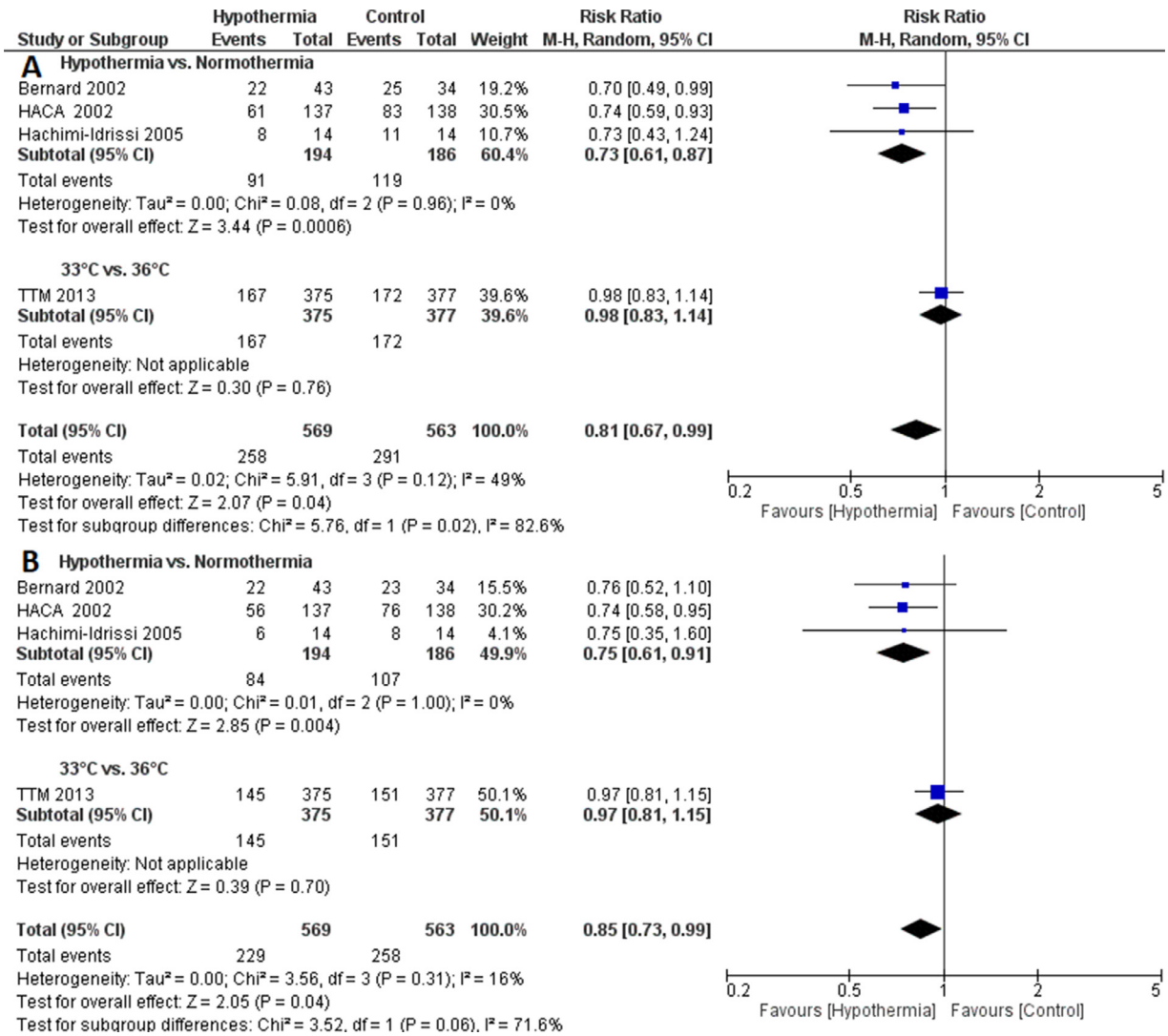

Figure 3. Forest plot showing risk ratio of (*A*) poor neurological outcome and (*B*) mortality in patients with initial shockable rhythm.

Additional sensitivity analysis for poor neurological outcomes and mortality by excluding each trial shows nonsignificant difference between TH and control after removing individual trials except for TTM trial (Supplementary Table 1).

Initial nonshockable rhythm was reported in 3 trials with a total of 789 patients. Both TH and control arms were associated with similar risks for mortality (RR 0.98, 95% CI 0.92 to 1.04; p = 0.50) and poor neurological outcomes (RR 0.97, 95% CI 0.92 to 1.01; p = 0.15). In the subgroup analysis, TH compared with normothermia (after excluding TTM) was associated with decreased risk of poor neurological outcomes (RR 0.95, 95% CI 0.91 to 1.00; p = 0.05).

Discussion

This updated meta-analysis of 2,026 comatose post cardiac arrest patients demonstrated that TH improved neurological outcomes irrespective of initial rhythm. In the subgroup of patients with initial shockable rhythm, significant improvement in mortality was also observed, whereas such a benefit was not noticed in patients with initial nonshockable rhythm.

Current guidelines recommend using TH between 32˚C and 36˚C in all postcardiac arrest patients.[9,10] Despite this, recent study suggests TH utilization in only 46% of patients after OHCA.[11] In a retrospective study by Chan et al, the investigators reported that use of TH after IHCA was associated with no benefits in terms of mortality and neurological survival.[22] Their study included only IHCA patients and had some limitations, including possibility of residual confounding and the temperature data field being optional, leading to missing data for most patients.[22,23] Our meta-analysis is the largest to date including both shockable and nonshockable cardiac arrest patients. The results confirm improved neurological outcomes noted in other RCTs of TH thus further supporting the current guidelines. Further, we found improved survival in patients with arrest due to a shockable rhythm. These findings are consistent with an earlier RCT that showed survival benefit of TH in such patients.[5] On the contrary, we did not observe any survival benefit in patients with nonshockable rhythm cardiac arrest. Similarly, the HYPERION trial did not find improved survival with TH compared with normothermia in patients with nonshockable rhythms. Cardiac arrest patients with nonshockable rhythms represent a heterogeneous group, often with noncardiac etiologies for the arrest. Additionally, survival and neurological outcomes of such patients resuscitated postarrest are poorer compared with those with shockable rhythms.

Previous meta-analysis in similar patient population had reported conflicting results with respect to mortality.[19-21,24-26] However, the difference in improvement in neurological outcomes was observed in most studies.[19-21,24-26] A meta-analysis of RCTs published in 2019 reported improvement in mortality and neurological outcomes irrespective of initial rhythm.[26] There were some important limitations in that meta-analysis, such as inclusion of non-RCTs and a secondary study of the HACA trial despite including the original HACA trial.[26] Our results are similar to some of the previous meta-analysis but those meta-analysis failed to show benefit in the hypothermia group with the inclusion of TTM trial.[20,21,24] In addition, we included the recently published HYPERION trial which evaluated use of targeted hypothermia in patients with initial nonshockable rhythm.[12]

Our study has a few limitations. First, the present study is a trial level analysis and thus some heterogeneity was noted in the different studies. Specifically, the studies differed in terms of targeted temperature used in the TH arm, cooling techniques, duration of cooling and difference in time from resuscitation to initiation of hypothermia. Second, only half of the studies in our analysis have a low risk for bias, and therefore the result should be interpreted with caution. As noted in the sensitivity analysis, removal of some trials can offset the benefits in outcomes, though this can be countered by removal of the TTM trial which compared 33˚C versus 36˚C. The TTM trial was a large multicenter trial and despite its limitation, excluding this trial from analysis is not completely appropriate.[8] Third, the ideal targeted temperature for TH protocols is still unclear. Interestingly, in a retrospective study published recently, the authors compared TTM of 33˚C versus 36˚C and found improvement in neurological outcomes without any difference in mortality.[27] All other trials reported a TH of 32˚C to 34˚C compared with normothermia. Given these disparities, newer RCTs are ongoing to improve the quality of evidence. One such large trial currently undergoing is the TTM 2 (targeted hypothermia versus targeted normothermia after OHCA) trial.[28] This multicenter, international randomized controlled, and superiority trial will evaluate hypothermia of 33˚C with normothermia. The trial aims to enroll 1,900 patients and the primary end point is mortality and secondary end point is poor neurological outcomes.[28,29]

In conclusion, this updated meta-analysis shows that TH (32˚C to 34˚C) after cardiac arrest was associated with improved neurological outcomes in patients with both shockable and nonshockable rhythms. In patients with initial shockable rhythm, use of TH might be associated with survival benefit.

Authors' Contributions

Amit Rout: Conceptualization, Methodology, Software, Writing;

Sahib Singh: Data curation, Writing- Original draft preparation;

Sauradeep Sarkar: Data curation, Writing;

Immad Munawar: Data curation;

Aakash Garg: Methodology, Writing;

Christopher R. D'Adamo: Methodology, Software;

Udaya S. Tantry: Writing- Reviewing and Editing;

Ashwin Dharmadhikari: Reviewing and Editing;

Paul A. Gurbel: Reviewing and Editing.

Disclosures

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.07.038.

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