ORIGINAL ARTICLE

Hypothermic versus Normothermic Temperature Control after Cardiac Arrest

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Abstract

BACKGROUND The evidence for temperature control for comatose survivors of cardiac arrest is inconclusive. Controversy exists as to whether the effects of hypothermia differ per the circumstances of the cardiac arrest or patient characteristics.

METHODS An individual patient data meta-analysis of the Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest (TTM) and Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest (TTM2) trials was conducted. The intervention was hypothermia at 33°C and the comparator was normothermia. The primary outcome was all-cause mortality at 6 months. Secondary outcomes included poor functional outcome (modified Rankin scale score of 4 to 6) at 6 months. Predefined subgroups based on the design variables in the original trials were tested for interaction with the intervention as follows: age (older or younger than the median), sex (female or male), initial cardiac rhythm (shockable or nonshockable), time to return of spontaneous circulation (above or below the median), and circulatory shock on admission (presence or absence).

RESULTS The primary analyses included 2800 patients, with 1403 assigned to hypothermia and 1397 to normothermia. Death occurred for 691 of 1398 participants (49.4%) in the hypothermia group and 666 of 1391 participants (47.9%) in the normothermia group (relative risk with hypothermia, 1.03; 95% confidence interval [CI], 0.96 to 1.11; P=0.41). A poor functional outcome occurred for 733 of 1350 participants (54.3%) in the hypothermia group

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and 718 of 1330 participants (54.0%) in the normothermia group (relative risk with hypothermia, 1.01; 95% CI, 0.94 to 1.08; P=0.88). Outcomes were consistent in the predefined subgroups.

CONCLUSIONS Hypothermia at 33°C did not decrease 6-month mortality compared with normothermia after out-of-hospital cardiac arrest. (Funded by Vetenskapsrådet; ClinicalTrials.gov numbers NCT02908308 and NCT01020916.)

Introduction

Temperature control has been one of the cornerstones in the treatment and prevention of brain injury and associated death or disability for comatose resuscitated patients with out-of-hospital cardiac arrest.[1,2] Hypothermic temperature control was included in guidelines based on two trials published in 2002 that included a total of 359 patients with out-of-hospital cardiac arrest with a presumed cardiac cause of arrest and an initial shockable cardiac rhythm.[1,3,4] Results of these trials suggested that temperature control at 33°C had a beneficial effect on neurologic function, but both trials had limited power to assess plausible intervention effects and were at high risk of bias.[5] Since the introduction of hypothermia after cardiac arrest in guidelines, three major trials have been conducted comparing hypothermia to normothermia.[6-8]

The HYPERION trial was published in 2019. HYPERION randomly assigned 584 patients with both in- and out-of-hospital cardiac arrest with an initial nonshockable rhythm exclusively.[7] In line with the original investigations that led to the widespread introduction of hypothermic temperature control after out-of-hospital cardiac arrest, the trial investigators found a higher percentage of participants surviving with a favorable neurologic outcome compared with targeted normothermia, but there was no significant difference in mortality.[7]

In contrast, the Target Temperature Management at 33°C versus 36°C after Out-of-Hospital Cardiac Arrest (TTM) trial compared the hypothermic target temperature of 33°C with 36°C. The investigators found no benefit of temperature control at 33°C compared with 36°C.[6] The clinical applicability of these findings was challenged by perceived limitations, including that both trial groups received mandatory temperature control. To address this, the Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest (TTM2) trial compared a target temperature of 33°C with normothermia in participants with out-of-hospital cardiac arrest.[8] Normothermia was defined as a temperature of 37.8°C or lower, and a temperature above this triggered the use of a temperature management device to target a temperature of 37.5°C. The TTM2 trial investigators concluded that there was no benefit on survival or neurologic outcome of 33°C compared with normothermia.

Building on the expanded evidence base,[9] recently updated guidelines on temperature control after cardiac arrest no longer specifically recommend use of temperature control at 32 to 36°C for comatose resuscitated patients with out-of-hospital cardiac arrest; as an alternative treatment option, they introduce a strategy of normothermia and fever prevention.[10] Despite a lack of evidence of benefit from hypothermia in the meta-analysis that informed the guidelines, hypothermic temperature control was retained as a treatment option. This decision acknowledged a hypothetical beneficial effect of hypothermia in certain circumstances,[10] including in patients with nonshockable initial rhythm and for those with more severe hypoxic-ischemic injury.[11-13]

For both the TTM and TTM2 trials, the intervention was hypothermia at 33°C; furthermore, the comparators in both trials were within the normothermic range.[6,8,14,15] The trials had similar methodology with protocols emphasizing strict neuroprognostication, withdrawal of life support, and a structured face-to-face follow-up.[6,8] In this report we provide an individual patient data meta-analysis of the results of the TTM and TTM2 trials by combining the two intervention groups and the two comparator groups, thereby providing greater statistical power than the individual trials. Accordingly, we evaluated the overall evidence on the effect of hypothermia after out-of-hospital cardiac arrest and investigated whether certain subgroups might benefit from hypothermic temperature control.

Methods

The design and results of the TTM and TTM2 trials were published previously.[16,17] The populations in both trials were adults who experienced an out-of-hospital cardiac arrest of a presumed cardiac or unknown cause with return of spontaneous circulation. Patients were eligible for enrollment if they met all inclusion criteria and no exclusion criteria (Table S1 in the Supplementary Appendix). The intervention was 33°C for both the TTM and TTM2 trials. Similarly, a normothermic strategy was a applied as the comparator in

both trials: a target temperature of 36°C was used as the control intervention in the TTM trial, and the control intervention was maintenance of normothermia with treatment of fever (≥37.8°C) in the TTM2 trial.[6,8]

STUDY DESIGN

This individual patient data meta-analysis was conducted in accordance with a protocol that was registered before analysis, and any deviations are reported.[18] We included individual patient data from the TTM and TTM2 trials. Separate ethics approval for this study was not required, as each trial was approved by ethics committees and authorities in each participating country.

OUTCOMES

The primary outcome was all-cause mortality. Secondary outcomes were poor functional outcome (modified Rankin scale score of 4 to 6), pneumonia, sepsis, and severe bleeding. Exploratory outcomes were time to death (survival data), functional outcome (modified Rankin scale score, ordinal outcome), and observed functional outcome stratified by a low, intermediate, or high admission MIRACLE2 score (defined as a score of 0 to 2, 3 to 4, or ≥5, respectively, where higher scores denote higher risk of poor neurologic outcome).[19] Our assessment time point for mortality and functional outcome was at 6 months after randomization for each participant. The secondary outcomes of pneumonia, sepsis, and serious bleeding were assessed until day 7 of the indexed intensive care unit admission for each participant.

RISKS OF BIAS

For each outcome of interest, an external collaborator at McMaster University assessed the likelihood that confounding, selection, measurement, and reporting biases have affected the trials' estimates, following the Cochrane Risk-of-Bias Tool.[20]

STATISTICAL ANALYSES

Analyses included the modified intention-to-treat population from the TTM trial[6] and the intention-to-treat population from the TTM2 trial.[17] We assessed whether the thresholds for statistical significance and clinical significance were crossed, including Bayes factor calculations.[21] The Bayes factor indicates whether the obtained results are most likely under the null hypothesis or the alternative hypothesis (anticipated intervention effect). A value greater than 1 indicates support for the null hypothesis, whereas a value less than 1 indicates support for the alternative hypothesis.[22] Assessment of clinical significance was based on the anticipated intervention effects used in the sample size/power estimations in the TTM2 trial, set at 55% risk of mortality in the normothermia group and an absolute risk reduction of 7.5% by hypothermia corresponding to a relative risk reduction of 13.6% (the same estimated risk and risk reduction was applied for poor functional outcome).[17,23] Our primary conclusion was based on one primary outcome, and all tests of statistical significance (including subgroup analyses) were two sided with a type I error risk of 5%.[21] Because the secondary outcome results and subgroup analyses were only hypothesis generating, we made no corrections for multiplicity. Regression analyses for the primary and secondary outcomes were adjusted for site. We systematically assessed whether the underlying statistical assumptions behind the statistical analyses were violated.[24]

We performed analyses of an interaction between the intervention and the subgroups first presenting cardiac rhythm (nonshockable compared with shockable initial rhythm), time to return of spontaneous circulation (at or above the median compared with below the median), presence of circulatory shock on admission (circulatory shock not present on admission compared with circulatory shock present on admission), sex (male compared with female), and age (at or above the median compared with below the median). As a post hoc analysis, we also performed a test of interaction for observed functional outcome stratified by a low, intermediate, or high admission MIRACLE2 score, which has previously been validated as a means for assessment of severity and risk for a poor outcome after out-of-hospital cardiac arrest. We used the same categorization as the original MIRACLE2 publication (low, intermediate, and high risk groups defined as a score of 0 to 2, 3 to 4, or ≥5, respectively).[19] For a description of this analysis, see the analysis of severity discussion in the Supplementary Appendix. Post hoc, we also added the subgroups, time to advanced life support (at or above the median compared with below the median), presence or absence of bystander resuscitation, and whether the cardiac arrest was witnessed.

Dichotomous outcomes were analyzed by mixed-effects generalized linear models using a logit link function with site as random intercept using an unstructured covariance matrix (an exchangeable covariance matrix was planned but not feasible). Sites that participated in both the TTM and TTM2 trials were assigned separate site identities. An interaction term was added to the mixed-effects model when comparing subgroups. Results are presented as proportions of participants in each group with the event as well as risk ratios with 95% confidence intervals (CIs).

Risk ratios were calculated based on odds ratios using the G-computation. Modified Rankin scale score (ordinal) was analyzed using a Mann-Whitney U test. Missing data were handled according to Jakobsen et al.[25] Because missingness was rare, complete case analyses were performed for all predefined analyses.

To control the risk of random errors, we performed trial sequential analysis on all primary and secondary outcomes. Required information sizes were calculated for the meta-analyses (i.e., the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) and relevant trial sequential monitoring boundaries (boundary for benefit, harm, and futility).[21,26-33] For dichotomous outcomes, we estimated the required information sizes based on the observed proportion of participants with an outcome in the control group, an alpha of 5%, and a beta of 10%.[31] We estimated the lowest effect estimate that could be rejected using trial sequential analysis.

STATISTICAL ANALYSIS

Data on all outcomes were analyzed in duplicate and independently (by S.U. and J.D.).[24] Two independent statistical reports were sent to the chief principal investigator and were shared with the steering and author groups. Discrepancies between the two primary statistical reports were identified and the steering group decided which was the most correct result. A final statistical report was prepared. Statistical reports are available in the Supplementary Appendix.[24]

Results

PARTICIPANTS AND INTERVENTION

From November 2010 to January 2013 for TTM and from November 2017 to January 2020 for TTM2, the two trials randomly assigned 2850 patients with out-of-hospital cardiac arrest at 65 hospitals in Australia, Austria, Belgium, the Czech Republic, Denmark, France, Germany, Italy, Luxembourg, the Netherlands, New Zealand, Norway, Sweden, Switzerland, the United Kingdom, and the United States. The primary analysis included 2800 participants (98.2%), of whom 1403 were assigned to the hypothermia group and 1397 were assigned to the normothermia group (Table 1). Patient characteristics and delivered medical care were similar at baseline (Table 1). Temperature curves are displayed in Figure S1A and S1B.

RISK OF BIAS

Both the TTM and TTM2 trials were externally assessed to be at low risk of bias (Table S2).

PRIMARY OUTCOME

In total, data on mortality were missing for 11 of 2800 participants (0.4%) (Table S3). Death occurred for 691 of 1398 participants (49.4%) in the hypothermia group and 666 of 1391 participants (47.9%) in the normothermia group (relative risk with hypothermia, 1.03; 95% CI, 0.96 to 1.11; P=0.41) (Fig. 1). The Bayes factor demonstrated that this result was over 25,000 times more likely under the assumption of the null hypothesis than under the assumption of a hypothesis that hypothermia reduces the relative risk of death by 13.6% (see Fig. S2 for a graphical presentation of the Bayes factor as a function of relative risk reduction of 0% to 20%). Trial sequential analysis showed that we could reject the hypothesis that hypothermia reduces or increases the relative risk of death by 10% (Fig. S3A). None of the pre-planned tests of interaction for subgroups, including initial shockable compared with nonshockable cardiac rhythm, showed evidence of a difference (Fig. 1). In a post hoc analysis of subgroups, patients with bystander resuscitation had higher mortality with hypothermia (Fig. 1).
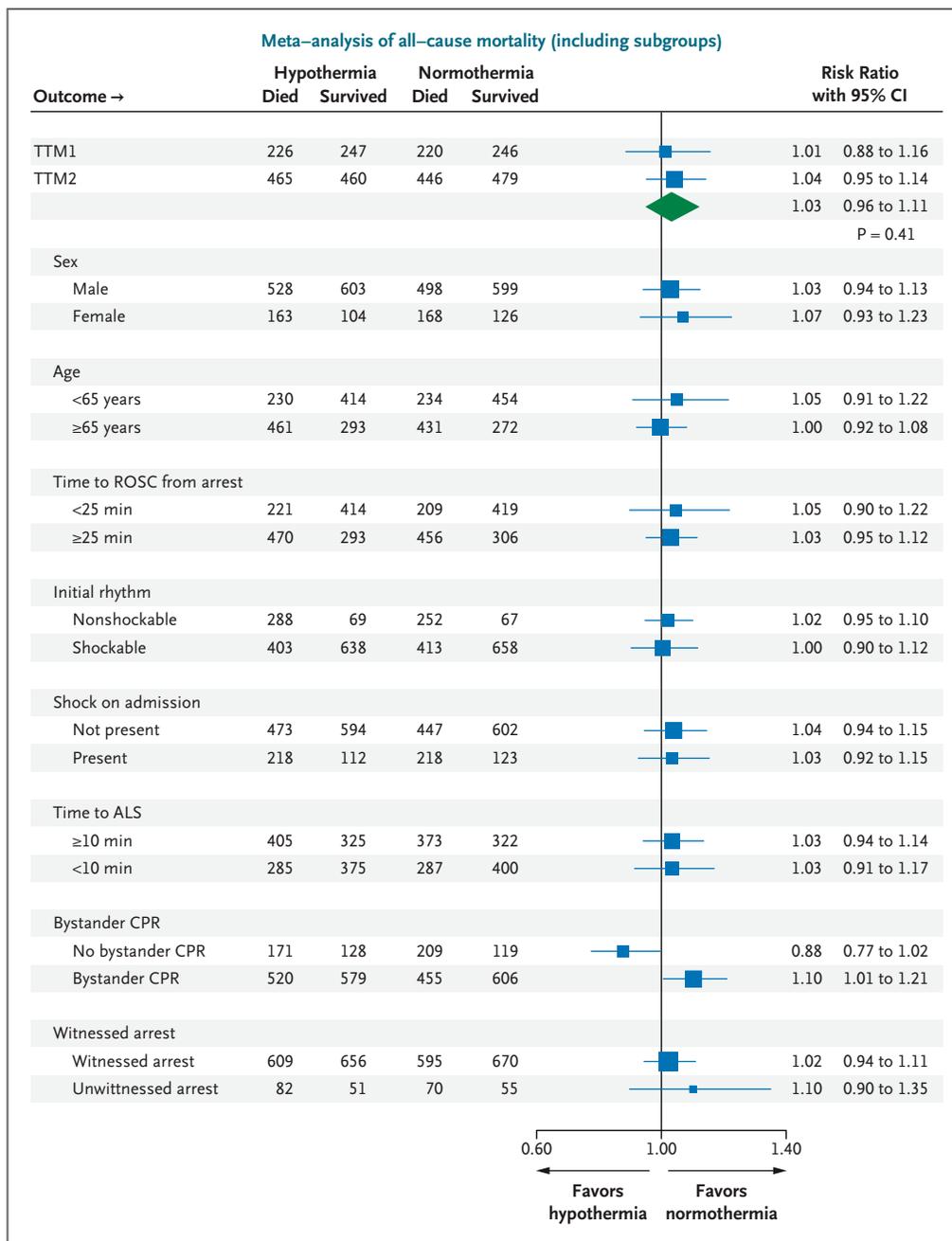
SECONDARY OUTCOMES

Data on functional outcome were missing for 120 of 2800 participants (4.3%) (Table S3). At 6 months, 733 of 1350 participants (54.3%) in the hypothermia group and 718 of 1330 participants (54.0%) in the normothermia group had a poor functional outcome (relative risk with hypothermia, 1.01; 95% CI, 0.94 to 1.08; P=0.88) (Fig. 2). The Bayes factor demonstrated that this result was over 9000 times more likely under the assumption of the null hypothesis than under the assumption of a hypothesis that hypothermia reduces the relative risk of a poor functional outcome by 13.6% (Fig. S2). Trial sequential analysis showed that we could reject the hypothesis that hypothermia reduces or increases the relative risk of a poor functional outcome by 8% (Fig. S3B). None of the predefined tests of interaction for subgroups, including initial shockable compared with non-shockable cardiac rhythm, showed evidence of a difference (Fig. 2). In a post hoc analysis of subgroups, patients without bystander resuscitation had better functional outcome with hypothermia (Fig. 2) while there was no differentiated effect in MIRACLE2 severity classes. The remaining post hoc subgroup analyses showed no evidence of a difference.

Table 1. Patient Characteristics.*

Characteristic	Normothermia (n=1397)	Hypothermia (n=1403)
mean (SD) — yr	63.4 (13.5)	64.4 (12.8)
Male sex — No. (%)	1103 (79.0)	1135 (80.9)
Medical history (known/previous) — No. (%)		
Heart failure	122 (8.7)	122 (8.7)
Unknown	52 (3.7)	41 (2.9)
Acute myocardial infarction	240 (17.2)	246 (17.5)
Unknown	52 (3.7)	40 (2.9)
Coronary-artery bypass grafting	118 (8.4)	120 (8.6)
Unknown	54 (3.9)	40 (2.9)
PCI	190 (13.6)	188 (13.4)
Unknown	54 (3.9)	40 (2.9)
Hypertension	479 (34.3)	538 (38.3)
Unknown	54 (3.9)	40 (2.9)
Cardiac arrest — No. (%)		
First monitored rhythm		
Ventricular fibrillation	941 (67.4)	925 (65.9)
Nonperfusing VT	41 (2.9)	43 (3.1)
Asystole	154 (11.0)	183 (13.0)
PEA	141 (10.1)	154 (11.0)
Unknown, no shock administered	24 (1.7)	20 (1.4)
Unknown, shock administered	50 (3.6)	45 (3.2)
ROSC after bystander defibrillation	45 (3.2)	33 (2.4)
Unknown	1 (0.1)	0 (0.0)
Time to ALS — median (IQR) — min	10 (6, 14)	10 (6, 15)
Time to ROSC — median (IQR) — min	25 (17, 40)	25 (17, 40)
Clinical characteristics on admission		
Initial temperature — mean (SD) — °C	35.4 (1.1)	35.3 (1.2)
Corneal reflex present — No. (%)	451 (32.3)	431 (30.7)
Unknown	470 (33.6)	486 (34.6)
Pupillary reflex present — No. (%)	890 (63.7)	878 (62.6)
Unknown	165 (11.8)	183 (13.0)
pH — mean (SD)	7.19 (0.15)	7.19 (0.16)
Lactate — mean (SD)	6.12 (4.28)	6.17 (4.46)
Circulatory shock — No. (%)	342 (24.5)	331 (23.6)
Unknown	1 (0.1)	1 (0.1)
ST-segment elevation myocardial infarction — No. (%)	564 (40.4)	569 (40.6)
Unknown	14 (1.0)	19 (1.4)

* ALS denotes advanced life support; IQR, interquartile range; min, minutes; PCI, percutaneous coronary intervention; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; VT, ventricular tachycardia.
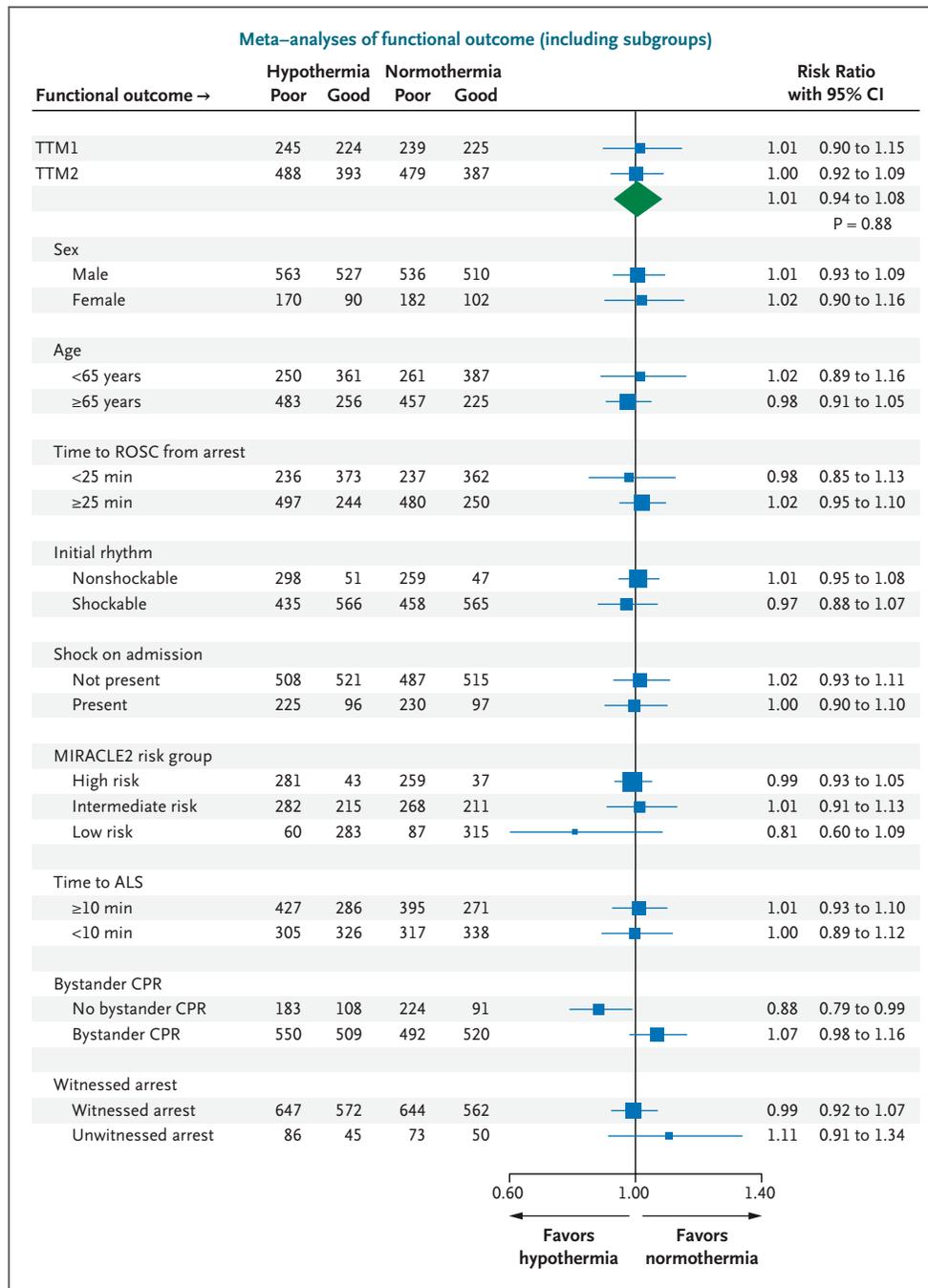
There were no intervention-related significant differences in the occurrence of the prespecified adverse events of pneumonia (relative risk with hypothermia, 1.06; 95% CI, 0.97 to 1.15; P=0.19), sepsis (relative risk with hypothermia, 1.14; 95% CI, 0.91 to 1.42; P=0.25), or severe bleeding (relative risk with hypothermia, 0.95; 95% CI, 0.69 to 1.28; P=0.74) (Table S3). Trial sequential analyses showed that we could reject that hypothermia reduces or increases the relative risk of pneumonia by 13%, sepsis by 28%, and severe bleeding by 32% compared with normothermia. Forest plots and trial sequential analyses are reported in Figures S4 through S9.

Meta-analysis of all-cause mortality (including subgroups)

Outcome →	Hypothermia Died	Hypothermia Survived	Normothermia Died	Normothermia Survived		Risk Ratio with 95% CI	
TTM1	226	247	220	246		1.01	0.88 to 1.16
TTM2	465	460	446	479		1.04	0.95 to 1.14
						1.03	0.96 to 1.11
							P = 0.41
Sex							
Male	528	603	498	599		1.03	0.94 to 1.13
Female	163	104	168	126		1.07	0.93 to 1.23
Age							
<65 years	230	414	234	454		1.05	0.91 to 1.22
≥65 years	461	293	431	272		1.00	0.92 to 1.08
Time to ROSC from arrest							
<25 min	221	414	209	419		1.05	0.90 to 1.22
≥25 min	470	293	456	306		1.03	0.95 to 1.12
Initial rhythm							
Nonshockable	288	69	252	67		1.02	0.95 to 1.10
Shockable	403	638	413	658		1.00	0.90 to 1.12
Shock on admission							
Not present	473	594	447	602		1.04	0.94 to 1.15
Present	218	112	218	123		1.03	0.92 to 1.15
Time to ALS							
≥10 min	405	325	373	322		1.03	0.94 to 1.14
<10 min	285	375	287	400		1.03	0.91 to 1.17
Bystander CPR							
No bystander CPR	171	128	209	119		0.88	0.77 to 1.02
Bystander CPR	520	579	455	606		1.10	1.01 to 1.21
Witnessed arrest							
Witnessed arrest	609	656	595	670		1.02	0.94 to 1.11
Unwittnessed arrest	82	51	70	55		1.10	0.90 to 1.35

0.60   1.00   1.40

Favors hypothermia — Favors normothermia

Figure 1. Fixed-Effects Meta-Analysis of Overall All-Cause Mortality at 6 months and Stratified by Subgroup.

All-cause mortality at 6 months, both overall and stratified by subgroup. For all-cause mortality, a fixed-effects meta-analysis was performed. Fixed-effects meta-analysis showed no evidence of a difference between hypothermia and normothermia on the risk of death (risk ratio, 1.03; 95% CI, 0.96 to 1.11; P=0.41). ALS denotes advanced life support; CI, confidence interval; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; TTM1, Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest; and TTM2, Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest.

Meta–analyses of functional outcome (including subgroups)

Functional outcome →	Hypothermia Poor	Good	Normothermia Poor	Good		Risk Ratio	with 95% CI
TTM1	245	224	239	225		1.01	0.90 to 1.15
TTM2	488	393	479	387		1.00	0.92 to 1.09
						1.01	0.94 to 1.08
							P = 0.88
Sex							
Male	563	527	536	510		1.01	0.93 to 1.09
Female	170	90	182	102		1.02	0.90 to 1.16
Age							
<65 years	250	361	261	387		1.02	0.89 to 1.16
≥65 years	483	256	457	225		0.98	0.91 to 1.05
Time to ROSC from arrest							
<25 min	236	373	237	362		0.98	0.85 to 1.13
≥25 min	497	244	480	250		1.02	0.95 to 1.10
Initial rhythm							
Nonshockable	298	51	259	47		1.01	0.95 to 1.08
Shockable	435	566	458	565		0.97	0.88 to 1.07
Shock on admission							
Not present	508	521	487	515		1.02	0.93 to 1.11
Present	225	96	230	97		1.00	0.90 to 1.10
MIRACLE2 risk group							
High risk	281	43	259	37		0.99	0.93 to 1.05
Intermediate risk	282	215	268	211		1.01	0.91 to 1.13
Low risk	60	283	87	315		0.81	0.60 to 1.09
Time to ALS							
≥10 min	427	286	395	271		1.01	0.93 to 1.10
<10 min	305	326	317	338		1.00	0.89 to 1.12
Bystander CPR							
No bystander CPR	183	108	224	91		0.88	0.79 to 0.99
Bystander CPR	550	509	492	520		1.07	0.98 to 1.16
Witnessed arrest							
Witnessed arrest	647	572	644	562		0.99	0.92 to 1.07
Unwitnessed arrest	86	45	73	50		1.11	0.91 to 1.34

Axis: 0.60 — 1.00 — 1.40

Favors hypothermia ← → Favors normothermia

Figure 2. Random-Effects Meta-Analysis of Overall Poor Functional Outcome at 6 months and Stratified by Subgroup.

Poor functional outcome at 6 months, both overall and stratified by subgroup. For poor functional outcome, a random-effects meta-analysis was performed. A poor functional outcome was defined as a modified Rankin scale score of 4 to 6. Random-effects meta-analysis showed no evidence of a difference between hypothermia and normothermia on the risk of a poor functional outcome (risk ratio, 1.01; 95% CI, 0.94 to 1.08; P=0.88). MIRACLE2 risk groups indicate severity and worse prognosis at admission, and the groups are defined as low risk for a score of 0 to 2, medium for 3 to 5, and high for 6 to 10.[19] ALS denotes advanced life support; CI, confidence interval; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; TTM1, Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest; and TTM2, Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest.
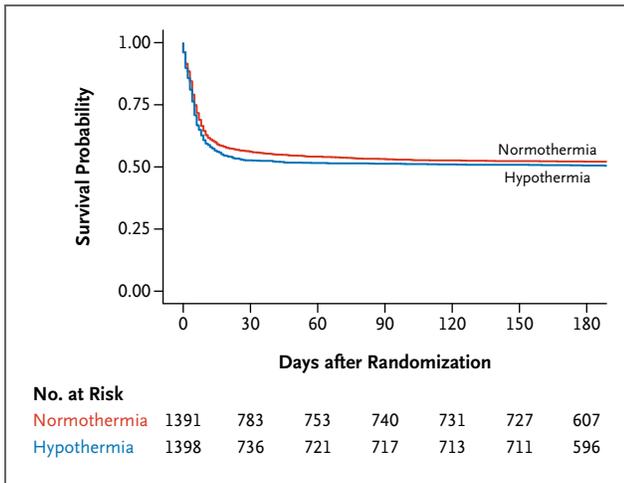
Figure 3. Survival Probability at 180 Days.

Kaplan–Meier plot showing estimates of the probability of survival and number at risk until 180 days after randomization for participants randomly assigned to either hypothermia or normothermia (explorative outcome).

EXPLORATORY OUTCOMES

Time to death was similar in both the hypothermia and normothermia groups (hazard ratio with hypothermia, 1.08; 95% CI, 0.97 to 1.20; P=0.15), and the complementary log-rank test also showed no difference (P=0.16) (Fig. 3).

Modified Rankin scale scores (ordinal data) showed no difference between the hypothermia and normothermia groups (P=0.44) (Fig. 4).

For a presentation of functional outcome according to MIRACLE2 scores as observed for the cohort as a whole and dispersion of the study population over the risk scores, see Figure 5A. We found no evidence of interaction (P=0.42) when stratifying patients based on low, intermediate, or high MIRACLE2 risk groups (Fig. 5B). This was performed as a post hoc analysis.

Discussion

In this individual patient data meta-analysis of the TTM and TTM2 trials, we found that there was no benefit of hypothermia at 33°C compared with normothermia on survival or functional outcome at 6 months among adult patients surviving out-of-hospital cardiac arrest attributed to a cardiac etiology. We found no signs of heterogeneity between the two trials. These findings are confirmatory of the results of the individual trials.[6,8] Furthermore, there was no benefit of hypothermia on mortality or functional outcome in any of the prespecified subgroups representing certain conditions of the cardiac arrest or patient characteristics, including for nonshockable compared with shockable initial rhythm of the cardiac arrest. Finally, post hoc analysis suggested higher mortality in patients with bystander resuscitation treated
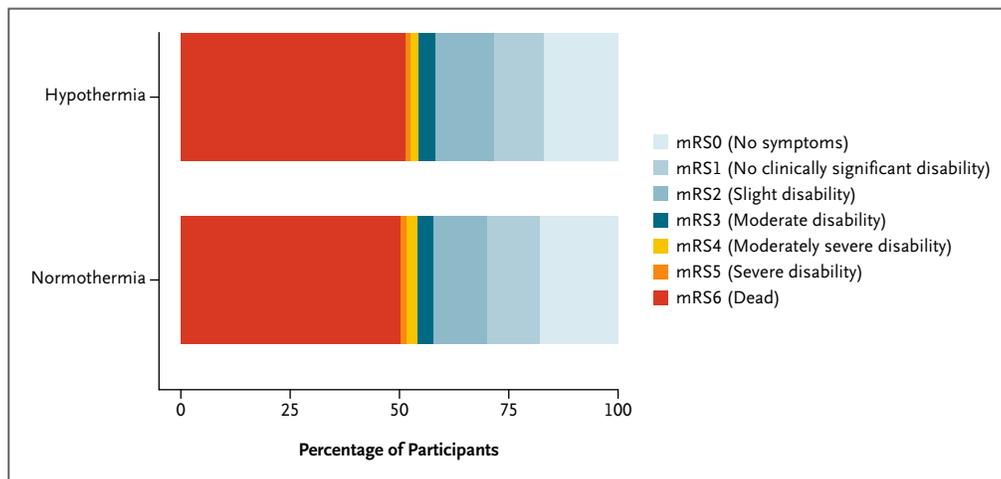
Figure 4. Modified Rankin Scale Score at 180 Days.

Modified Rankin scale (mRS) score at 180 days of follow-up. Shown are the distributions of participants based on their mRS score and assignment to either hypothermia or normothermia (exploratory outcome).
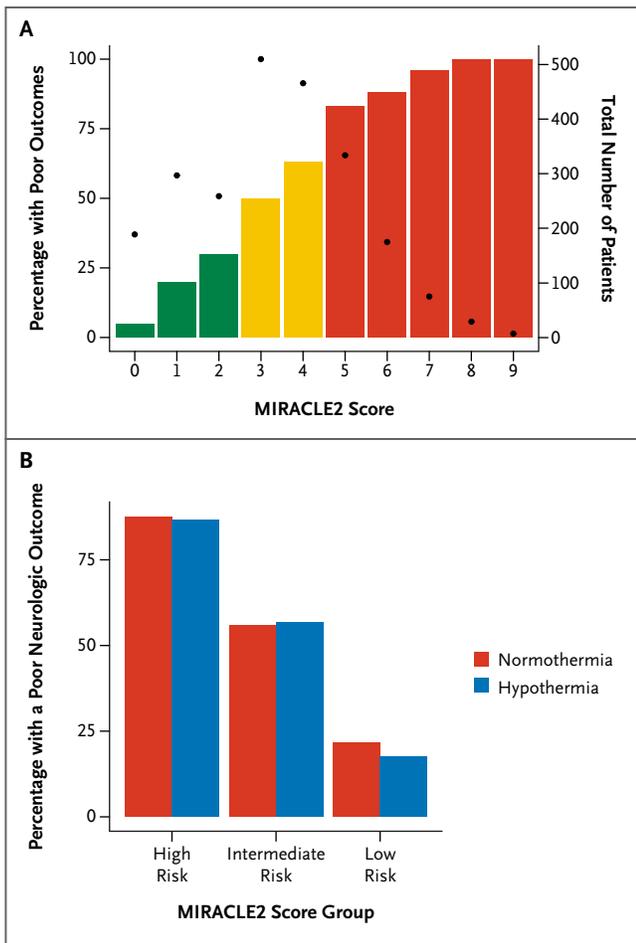
Figure 5. Assessment of Severity by Applying the MIRACLE2 Score.

Panel A shows the observed functional outcome as a function of MIRACLE2 score on an ordinal scale and indicates the number of patients assigned to each score (not stratified by treatment group). Bars denote the percentage of poor outcomes, whereas dots indicate the total number of patients. Panel B shows the observed functional outcome stratified by low, medium, or high MIRACLE2 risk group and assignment to the hypothermia or normothermia group. This was performed as a post hoc analysis. MIRACLE2 is a validated score that can be applied at hospital admission for assessing the risk of a poor neurologic outcome. The score ranges from 1 to 10 (a higher score indicates worse prognosis) and includes the following: Missed (unwitnessed arrest), Initial rhythm (not shockable), Reactive pupils (no pupillary reflex), Age (older than 60 or older than 80 years of age), Changing rhythms (any two of ventricular fibrillation, pulseless electrical activity, or asystole), Low pH (pH<7.2) and Epinephrine given (adrenaline given). MIRACLE2 risk groups indicate severity and worse prognosis at admission and the groups are defined as low risk for a score of 0 to 2, medium for 3 to 5, and high for 6 to10.[19] For a further description, please see the analysis of severity discussion in the Supplementary Appendix.

with hypothermia, whereas patients without bystander resuscitation had better functional outcome with hypothermia. We did not find evidence of interaction when stratifying patients based on low, intermediate, or high MIRACLE2 risk groups, suggesting that the treatment effect of hypothermia is not dependent on the overall severity of the insult.

The type of temperature control to induce and maintain hypothermia that has been investigated in clinical trials and utilized clinically the last two decades does not, according to our results as well as recent systematic reviews with traditional meta-analysis,[9,34] appear to provide the intended benefit. Of note, our present results relate to the potential effect of two different temperature control strategies — namely, hypothermia at 33°C and targeted normothermia (36 to 37.8°C) — delivered during a 36- to 40-hour period, and we thus did not investigate the potential effects of duration,[35] speed of achieving hypothermia,[36] or modality of temperature control (e.g., surface cooling, intravascular cooling, or other method of achieving cooling).[36,37] If future trials in hypothermia after cardiac arrest are to be conducted, the design of such should be informed by updated experimental data, as systematic review with meta-analyses of animal studies points to quality issues and knowledge gaps in the existing evidence.[38,39]

Trial sequential analyses, a method of estimating the number of participants needed to detect or reject a certain effect size, were performed to determine at what level we could rule out an effect of hypothermia compared with normothermia. This analysis revealed that we can reject the hypotheses of a relative risk benefit of hypothermia as subtle as 10% for mortality and 8% for poor functional outcome. Smaller yet clinically relevant effect sizes are still plausible. Bayes factor calculations for both all-cause mortality and poor functional outcome show that it would be far more likely to find no benefit of targeted hypothermia than benefit. Furthermore, the potential costs accompanying treatment with hypothermia, as well as the substantial number of participants needed to investigate smaller intervention effects, should also be taken into account when considering further trials.

The HYPERION trial is the only other major trial besides the TTM and TTM2 trials on temperature control after out-of-hospital cardiac arrest since 2002. Our findings contrast the main finding of the HYPERION trial of an

apparent benefit of hypothermia on functional outcome.[7] This difference might reflect the statistical fragility of the smaller HYPERION trial but may also result from differences in the enrolled patients and implementation of temperature control. The present individual patient data meta-analysis included both patients with initial shockable and nonshockable cardiac rhythms, while the HYPERION trial only included patients with nonshockable rhythms. However, our results do not indicate a differentiated treatment response to targeted hypothermia per initial cardiac rhythm, and the test of interaction in the present study is based on a larger sample size and more events than the HYPERION trial. Furthermore, the HYPERION trial included patients with cardiac arrest from all etiologies and a mix of patients with in- and out-of-hospital cardiac arrest, and the suggested effect was mainly in the in-hospital group.[7] The TTM and TTM2 trials excluded patients with noncardiac causes of the cardiac arrest and included only patients with out-of-hospital cardiac arrest.[6,8]

Based on observational studies and from theoretical extrapolation, it has been put forward that specific phenotypes of cardiac arrests might benefit from hypothermia.[10-13] Surrogate markers of the severity of hypoxic-ischemic encephalopathy such as duration of the cardiac arrest and bystander cardiopulmonary resuscitation have been suggested to modify the effect of hypothermia. In addition, based on the overall magnitude of the cardiac arrest ischemia, defined by risk classes, both patients with high and medium risk of a poor outcome have been suggested to benefit from hypothermia at 33°C.[12,13] Our subgroup analyses are based on randomized data and have more statistical power than any previous material to date. In the predefined subgroups based on the design variables in the TTM and TTM2 trials, there were no signals of a differentiated effect between hypothermia and normothermia.[6,8] However, in a post hoc analysis, we found a signal of potential harm with hypothermia in patients who had received bystander cardiopulmonary resuscitation, as hypothermic temperature control was associated with increased mortality compared with normothermic temperature control. We found a signal of benefit with hypothermia in patients who had not received bystander cardiopulmonary resuscitation, as hypothermic temperature control was associated with a higher incidence of a good functional outcome compared with normothermic temperature control. These post hoc subgroup analyses should be interpreted with great caution, owing to problems with multiplicity,[40] no clear pattern in relation to other subgroups, and lack of supporting data tying a treatment effect of hypothermia to

the severity of the ischemic insult, as our analysis using the validated MIRACLE2 severity classification did not indicate a difference in outcome. Two thirds of patients in the combined TTM and TTM2 population were defined as have a medium or high risk, suggesting a severely injured population included in the trials.

The main limitation with the TTM trials and with their interpretation in regard to effects of temperature control and fever prevention is that the control groups were designed with the prevailing notion that hypothermia and fever management is of benefit, even if that notion was based on low certainty evidence and observational data. Therefore, the 36°C arm of the TTM trial was the highest possible target temperature within the range of normothermia that was accepted by the research and clinical community in 2010. In 2017, with the neutral results of the TTM trial present, it was acceptable to stretch the highest possible target to strict normothermia avoiding fever using a conservative definition of 37.8°C or higher. Both control arms thus represent active intervention (100% had a temperature device in the control group of the TTM trial and 46% in the TTM2 trial). Hence, the interpretation of the TTM trials and this current independent data meta-analysis is complicated by the fact that there was no control group in which temperature control using a temperature device was not allowed. It is therefore uncertain whether the neutral effect of the trials and this meta-analysis is attributable to both temperature interventions being beneficial, ineffective, or even harmful. A large trial of fever management with temperature devices to target normothermia compared with no use of temperature devices is necessary to answer this question.

The results of this individual patient data meta-analysis are informative but do not directly relate to the treatment of patients with noncardiac causes of cardiac arrest, in-hospital cardiac arrests, or for different strategies of achieving hypothermic temperature control. There is, however, at least one randomized trial registered at ClinicalTrials.gov for the in-hospital cardiac arrest group, which is reported as completed but still not published (HACAinhospital, NCT00457431), and there is an ongoing large trial of different durations of hypothermia delivered within 4 hours after out-of-hospital cardiac arrest (ICECAP, NCT04217551).

In conclusion, this individual patient data analysis found no benefit of hypothermia compared with normothermia

with respect to mortality for patients with out-of-hospital cardiac arrest.

Disclosures

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