Hypothermia versus Normothermia after Out-of-hospital Cardiac Arrest

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ABSTRACT

BACKGROUND

Targeted temperature management (TTM) is recommended after cardiac arrest, but the evidence is of low certainty.

METHODS

In an open-label, blinded outcome-assessor trial we randomly assigned 1900 comatose adults after out-of-hospital cardiac arrest of a presumed cardiac or unknown cause, either to targeted hypothermia at 33°C followed by controlled rewarming or to targeted normothermia with early treatment of fever (body temperature ≥37.8°C). The primary outcome was six-month all-cause mortality. Secondary outcomes included six-month functional outcome (modified Rankin Scale [mRS]). Predefined subgroup-analyses were sex, age, initial rhythm, time to return of spontaneous circulation, and circulatory shock. Predefined adverse events were pneumonia, sepsis, bleeding, arrhythmia with hemodynamic compromise, and TTM-device-related skin complications.

RESULTS

In total, 1850 participants were eligible for analysis. At six months 465 of 925 (50%) of the participants in the hypothermia group had died, compared with 446 of 925 (48%) in the normothermia group (relative risk with hypothermia 1.04; 95% confidence interval [CI], 0.94 to 1.14; P=0.37). Functional outcome was assessed in 1747 participants. 488 of 881 (55%) in the hypothermia group had moderately severe disability or worse (mRS≥4), compared with 479 of 866 (55%) in the normothermia group (relative risk with hypothermia 1.00; 95% CI, 0.92 to 1.09). Outcomes were consistent in predefined subgroups. Arrhythmia with

hemodynamic compromise was more common in the hypothermia group (24 versus 17%, P<0.001). There were no significant differences in other adverse events.

CONCLUSIONS

Targeted hypothermia did not decrease six-month mortality compared with targeted normothermia in comatose patients after out-of-hospital cardiac arrest.

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Introduction

International guidelines recommend targeted temperature management (TTM) to prevent hypoxic-ischemic brain damage in patients comatose after cardiac arrest.[1,2] The evidence behind these recommendations originates from trials in patients resuscitated from an out-of-hospital cardiac arrest of a presumed cardiac cause and shockable initial rhythms.[3,4] These trials suggested improved survival and neurological outcome with hypothermia at 33°C. A recent trial including patients with cardiac arrest of non-shockable origin reported better neurological outcome when targeting hypothermia at 33°C compared with targeting normothermia at 37°C.[5] The dose of TTM has been investigated in trials comparing the level of TTM (33°C versus 36°C) and duration of TTM (24h versus 48h), both indicating no dose-effect.[6,7]

While guidelines offer strong recommendations to use TTM, selecting a constant target between 32°C and 36°C, they also state that the overall evidence is of low certainty. Systematic review with meta-analysis and trial sequential analysis assessed the available trials as having high risks of bias and random errors.[8]

Fever has been proposed as a risk factor for an unfavorable neurologic outcome after cardiac arrest although it is unknown if there is a causal and modifiable relationship.[9] Accordingly, we conducted a randomized trial to assess the beneficial and harmful effects of post-cardiac arrest hypothermia compared to normothermia with early treatment of fever. Our hypothesis was that hypothermia compared with normothermia would decrease six-month mortality.

Methods

Trial Design

We conducted an international, investigator-initiated, randomized, clinical trial. The rationale for and design of the trial, as well as the statistical analysis plan, have been published previously.[10,11] The protocol was approved by the ethics committees in each participating country. Written informed consent was waived, deferred, or obtained from a legal surrogate, depending on the circumstances, and was obtained from each participant who regained mental capacity. An independent data safety monitoring committee reviewed the data and performed one prespecified, blinded interim analysis. Additional details on trial design, including investigator responsibilities, are described in the Supplementary Appendix.

Participants

We consecutively screened patients ≥18 years who were unconscious (not being able to obey verbal commands (Full Outline of UnResponsiveness (FOUR)-score[12] motor response of <4) and no verbal response to pain) on admission to hospital after out-of-hospital cardiac arrest of a presumed cardiac or unknown cause, irrespective of the initial rhythm. Eligible patients had more than 20 consecutive minutes of spontaneous circulation after resuscitation.[13] The main exclusion criteria were an interval from return of spontaneous circulation to screening of more than 180 minutes, unwitnessed arrest with asystole as the initial rhythm, and limitations in care. Detailed inclusion and exclusion criteria are provided in the Supplementary Appendix.

Randomization and Blinding

After eligibility screening, participants were randomly assigned 1:1 to *hypothermia* or *normothermia*. Randomization was performed with using a web-based system involving permuted blocks of varying size and was stratified according to site and co- enrollment in the

Targeted Mild Hypercapnia versus Targeted Normocapnia after Cardiac Arrest (TAME)-trial (NCT03114033).[10]

Healthcare professionals caring for the trial participants were aware of the intervention assignments because of inherent problems with blinding body temperature. Physicians performing neurologic prognostication, assessors of functional outcome, and study administrators were unaware of the intervention assignments. During the analysis phase statisticians and authors were unaware of group assignments, which were identified as Y and Z. A manuscript was written for each scenario before the randomization code was broken (Y=hypothermia/Z=normothermia and vice versa).[14]

Trial Intervention

The intervention period of 40 hours commenced at randomization. Participants allocated to hypothermia were immediately cooled using a surface or intravascular temperature management device and a target temperature of 33°C. This target was maintained until 28 hours after randomization followed by rewarming to 37°C in hourly increments of 1/3°C. In the normothermia group the aim was to maintain a temperature ≤37.5°C. If conservative and pharmacological measures were insufficient and the body temperature reached 37.8°C, cooling with a surface or intravascular temperature management device was initiated with a target temperature of 37.5°C. There was no active warming or cooling for participants in the normothermia group with a spontaneous body temperature below <37.8°C. Sedation was mandated in both groups until the end of the intervention period. After the intervention period, a normothermic target (36.5-37.7°C) was kept until 72h after randomization in participants who remained sedated or comatose. Details of the trial interventions are provided in the Supplementary Appendix.

Assessment of neurological prognosis

At 96 hours after randomization or later a physician, blinded to intervention assignments, performed a neurologic assessment for participants who remained in the ICU and assessed whether the criteria for a likely poor neurological outcome (Supplementary Appendix), were present.

Withdrawal of life-support.

All decisions on withdrawal of life-support were at the discretion of the treating physician, guided by the protocol. Following protocolized neurologic prognostication, withdrawal of life-sustaining therapies due to a presumed poor neurological prognosis was allowed (Supplementary Appendix).

Follow-up and outcomes

The primary outcome was all-cause mortality at six months. The main secondary outcome was a poor functional outcome at six months, defined as a score of 4-6 using the modified Rankin Scale (mRS).[15,16] mRS scores range from 0 to 6, with 0 representing no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. mRS-scoring was performed using a structured questionnaire by a trained outcome assessor. The mRS-score was based on face-to-face follow-up or telephone interviews with participants, relatives and healthcare providers.[17]

If a structured assessment could not be completed a binary assessment based on all available data (including medical records) was performed; functional outcome was classed as “good” or “poor” based on a dichotomized mRS-scale (mRS 0-3 versus 4-6). This post-hoc approach was employed as a consequence of the Covid-19-pandemic.

Other secondary outcomes were number of days alive outside hospital until day 180, survival assessed as time-to-death and health-related quality of life assessed using the EQ-5D-5L-Visual Analogue Scale (VAS) (range: 0-100, higher scores indicate better self-assessed health).[15] Verification of trial data and outcome measures are described in the Supplementary Appendix.

Adverse events

Predefined adverse events were pneumonia, sepsis, bleeding, arrhythmia with hemodynamic compromise, and TTM-device-related skin complications. For definitions see the Supplementary Appendix.

Statistical Analysis

We estimated that a sample size of 1862 participants would provide a 90% power to detect a 15% relative reduction in the risk of death in the hypothermia group compared with the normothermia group, at a two-sided alpha level of 0.05 (absolute risk reduction of 7.5%). The estimated relative risk is based on results from earlier trials on hypothermia for cardiac arrest.[10] To allow for loss to follow-up and withdrawn consent, a sample size of 1900 was chosen.

The principal trial analyses were performed in the intention-to-treat population, defined as all randomly assigned participants except those withdrawing consent. Dichotomous outcomes, including the primary analysis, were assessed using a mixed-effects generalized linear model with a logit link with adjustment for stratification variables and reported as population-level (marginal) relative risks derived by G-computation. Analysis of survival data was performed using Cox regression. For all regression analyses we tested for an interaction effect between group allocation and allocation in the TAME-trial. We made no assumptions regarding the

pattern of missing data. Missing data were handled according to the statistical analysis plan.[11,18] A P-value of <0.05 was considered significant for the primary outcome. Secondary outcomes are presented using 95% confidence intervals and were not adjusted for multiplicity. All analyses were performed using R: A Language and Environment for Statistical Computing.[19]

Results

Participants

A total of 1900 participants were enrolled between November 2017 and January 2020. Thirty-nine participants withdrew consent resulting in an intention-to-treat population of 1861, of whom 931 were assigned to the hypothermia group and 930 to the normothermia group. (Figure S1 in the Supplementary Appendix). Baseline characteristics are reported in Table 1. Drugs, interventions, neuroprognostication, withdrawal of life-sustaining therapy, length-of-stay, and TAME-co-enrollment data are reported in Tables S1-6 and Figures S2-3 of the Supplementary Appendix.

Temperature Intervention

The temperature curves are depicted in Figure 1. In the hypothermia group the median time from start of the intervention to reaching 34°C was 3 hours. In the hypothermia group 53 (5.7%) participants were rewarmed before 40 hours after randomization, as allowed by the protocol, primarily due to cardiovascular instability and arrhythmias. (Table S7 in the Supplementary Appendix). A total of 882 of 930 participants (95%) in the hypothermia group and 428 of 929 participants (46%) in the normothermia group received cooling with a device. Among participants who received cooling the types of devices used by treatment group were similar (70% surface and 30% intravascular versus 69% surface and 31% intravascular, in the hypothermia and normothermia groups respectively). In the hypothermia group the reasons for not receiving a device were intracranial hemorrhage, early death, early awakening, hemodynamic instability and referral for cardiac surgery, while the main reason in the normothermia group was not reaching the threshold for fever. Additional data regarding temperatures and shivering are available in the Supplementary Appendix Figures S4-7, Table S8.

Follow-up and Outcomes

Data on the primary outcome were missing for 11 (0.6%) participants (6 in the hypothermia group and 5 in the normothermia group). At six months, 465 of 925 (50%) of the participants in the hypothermia group and 446 of 925 (48%%) of the participants in the normothermia group (48%) had died (relative risk with hypothermia, 1.04; 95% confidence interval (CI), 0.94 to 1.14; P=0.37). Best-worst and worst-best analyses indicated that missing data did not have the potential to affect the results of the primary analysis (Supplementary Appendix Table S9). The effect of the intervention on mortality was consistent across prespecified subgroups (Figure 2a) and when assessed as time-to-event (hazard ratio in the hypothermia group 1.08 (95% CI, 0.95-1.23) (Figure 3).

Structured mRS-scoring was performed in 1747 participants (94%) (Supplementary Appendix Figure S8). A structured assessment was performed face-to-face (72%), by phone (23%), or by proxy interview (5%). Additionally, functional outcome was classified only as "good" or "poor" based on telephone interviews with relatives and healthcare providers, and medical records in 37 of 931 (4%) and 45 of 930 (5%) participants in the hypothermia and normothermia groups respectively. In total functional outcome was assessed in 1829 of 1861 (98%) participants.

At six months 488 of 881 (55%) in the hypothermia group and 479 of 866 (55%) in the normothermia group had a mRS-score of 4-6 (relative risk with hypothermia, 1.00; 95% CI, 0.92 to 1.09). In the binary assessment of functional outcome 495 of 918 (54%) in the hypothermia group and 495 of 911 (54%) in the normothermia group participants had a poor functional outcome (relative risk in the hypothermia group, 1.00; 95% CI, 0.91 to 1.08). Best-worst and worst-best analyses indicated that missing data did not have the potential to affect

the results of the primary analysis (Supplementary Appendix Table S9). The effect of the intervention on functional outcome was consistent across prespecified subgroups (Figure 2b).

Sensitivity analyses for the primary and secondary outcome are reported in the Supplementary Appendix Table S10 a and b.

Health-related quality of life assessed using the EQ5D-5L-VAS scale was similar in the hypothermia and normothermia groups, regardless of whether participants who died were included (and set to 0), or if only survivors were analyzed (mean difference for survivors: minus 0.8 points in the hypothermia group, 95% CI: -3.6 - 2.0 points) (Supplementary Appendix, Table S11). Days alive and outside of hospital were similar in both groups. (Supplementary Appendix, Figure S9).

There were no significant interactions between group allocation and allocation in the TAME-trial for any of the outcomes ($P_{interaction}$ range 0.58-0.94) (Supplementary Appendix Table S12.

Adverse events

The frequencies of pre-defined adverse events are reported in Table 2. Arrhythmias resulting in hemodynamic compromise were more common in the hypothermia group compared with the normothermia group (24 versus 17%, P<0.001). There were no significant differences in other prespecified adverse events. There were two unexpected serious, possibly intervention-related adverse events in each group: an intravascular device-related thrombosis in one hypothermia and two normothermia group participants; bradycardia with worsening hemodynamics in one hypothermia group participant (Supplementary Appendix).

Discussion

In this randomized trial, we compared hypothermia with normothermia in comatose patients resuscitated after out-of-hospital cardiac arrest of a presumed cardiac or unknown cause. There was no significant difference between the two groups in mortality and poor functional outcome at six months. The distribution of modified Rankin scores between groups were similar, as was health-related quality of life. The results were consistent in survival analysis and in predefined subgroups.

Our results contrast to those of the practice-changing trials published in 2002 where a benefit of hypothermia was reported.[3,4] There have been changes in intensive care standards since then, which may have influenced intervention effects.[20,21] Other explanations would be a lower risk of bias in the current trial[22] and a lower risk of random error with a sample size five times greater than the combined sample of the earlier trials.[23,24] While the patient population we studied differed somewhat from the prior trials, our subgroup analyses indicate that different eligibility criteria are unlikely to explain the discordance.

Our findings accord with a recent trial where hypothermia at 33°C was not shown to reduce mortality compared to normothermia at 37°C in patients with non-shockable rhythms.[5] In that trial, it was reported that hypothermia may improve functional outcomes, but this finding was based on a small number of events and was not replicated in the group of patients with initial non-shockable rhythm in our trial.

The results of the current trial are broadly consistent with the results of our previous Target Temperature Management (TTM)-trial comparing 33°C and 36°C.[6] The combined results of the TTM-trial and our current trial imply a low likelihood of any meaningful clinical improvement with hypothermia compared to normothermia, as 36°C may be considered the lower boundary of normothermia.

It is physiologically plausible that time to hypothermia is related to potential benefits of the intervention, and this is supported by experiments in animals.[25] In our trial participants were cooled at a similar or faster rate than in most previous trials.[3,5–7] As all participating sites in our trial had previous experience of using hypothermia and a large proportion of participants were included at cardiac arrest centers, faster in-hospital cooling rates are likely not feasible in current clinical practice.

Hypothermia did not increase the frequency of pneumonia, sepsis or bleeding, but arrhythmias causing hemodynamic compromise were more common than in the normothermia group. Possible reasons for this include electrolyte disturbances, fluid status and a temperature effect on cardiac myocytes.[26]

Our trial has several limitations. First, to isolate the effect of hypothermia both trial groups were treated similarly, except for the temperature intervention. Elements of standard ICU care, such as sedation, paralysis and mechanical ventilation, were therefore protocolized in a form not necessarily representing clinical practice. It is unclear what influence these elements had on the outcomes. The trial also included a conservative protocol for neuroprognostication and guidance for withdrawal of life support which may have influenced outcomes. Second, ICU staff were aware of the assigned target temperature during the ICU-stay. We aimed to minimize this problem by using robust outcomes, blinded outcome-assessors, and a conservative protocol for neurologic prognostication and withdrawal of life supporting therapies. During the analysis and writing process the investigators, statisticians and authors were unaware of temperature group allocation and writing of the manuscript was performed in duplicate with the groups interchanged. Third, since the intervention aiming for normothermia and early treatment of fever has not been previously studied and since we did not include a control group without temperature management, this trial leaves a knowledge gap regarding whether any temperature management is better than no temperature

management. Nonetheless, actual temperatures in the normothermia group were broadly similar to those recorded in the control group of the Hypothermia after Cardiac Arrest (HACA) trial where no temperature management was used.[3] Contrary to the HACA-trial, in the current trial about half of the participants in the normothermia group were cooled with a device. Whether this type of fever-control is of benefit must be addressed in a separate trial. Fourth, concomitant care, except for sedation and prognostication, were not protocolized and left to the discretion of participating hospitals. However, sites were instructed to treat the groups similarly and the stratification for participating hospitals should balance inter-site differences. Fifth, the trial is limited to out-of-hospital cardiac arrest of a presumed cardiac or unknown cause and is therefore not fully applicable to other presentations of cardiac arrest. However, lack of cerebral perfusion is the primary cause of hypoxic-ischemic encephalopathy regardless of the location (in or out-of-hospital) or the cause of arrest. Finally, one fifth of the participants were also enrolled in the TAME-trial. We did not anticipate any interaction effect and our analyses supported this, although these analyses were likely underpowered.

Our results were consistent across the objective outcome mortality, the clinician-reported functional outcome (mRS) and patient-reported health-related quality of life (EQ-VAS). The large sample size, broad eligibility criteria, numerous hospitals and countries represented in this trial increase the generalizability.

In conclusion, targeted hypothermia did not decrease six-month mortality compared with targeted normothermia in comatose patients after out-of-hospital cardiac arrest.

Author Disclosures
Disclosure forms provided by the authors are available with the full text of this article at NEJM.org

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Figure 1. Body temperature during the intervention period

Body temperature curves in the hypothermia and normothermia groups for the patients in whom bladder temperature was recorded. The median number of temperature recordings was 38 in both the hypothermia and normothermia group, out of 41 possible recordings. The temperature curves display the means, and I-bars indicate ±2 standard deviations (95% of the observations are within the bars). The median time from cardiac arrest to randomization in the trial was 135 minutes. Temperatures up to 72 hours after randomization are available in the Supplementary Appendix (Table S4).

Figure 2. Risk ratios at six months for the primary end point of death (a) and the secondary end point of a modified Rankin Score of 4-6 in pre-specified subgroups (b)

Risk ratio for (a) death at six months and (b) modified Rankin Score score of 4-6 at six months, according to subgroup. Risk ratios are derived from a stratified generalized linear model with site as a random intercept. The forest plot shows the risk ratios for five predefined subgroups. The horizontal bars represent 95% confidence intervals. The events are the total events six months after randomization. ROSC denotes return of spontaneous circulation. For unwitnessed cardiac arrests the time to ROSC was calculated from time of emergency call. Shock at admission was defined as a systolic blood pressure <90mmHg for >30min or end-organ hypoperfusion (cool extremities, urine output <30mm/hour, heart rate <60 beats/minute)

Figure 3 Probability of survival until 180 days after randomization.

Shown are Kaplan-Meier estimates of the probability of survival for patients assigned to hypothermia or normothermia until 180 days after randomization based on the 1850 participants with data on mortality, among which there was no missing data on time of death. Censoring was performed on the day of follow-up.

Figure 1

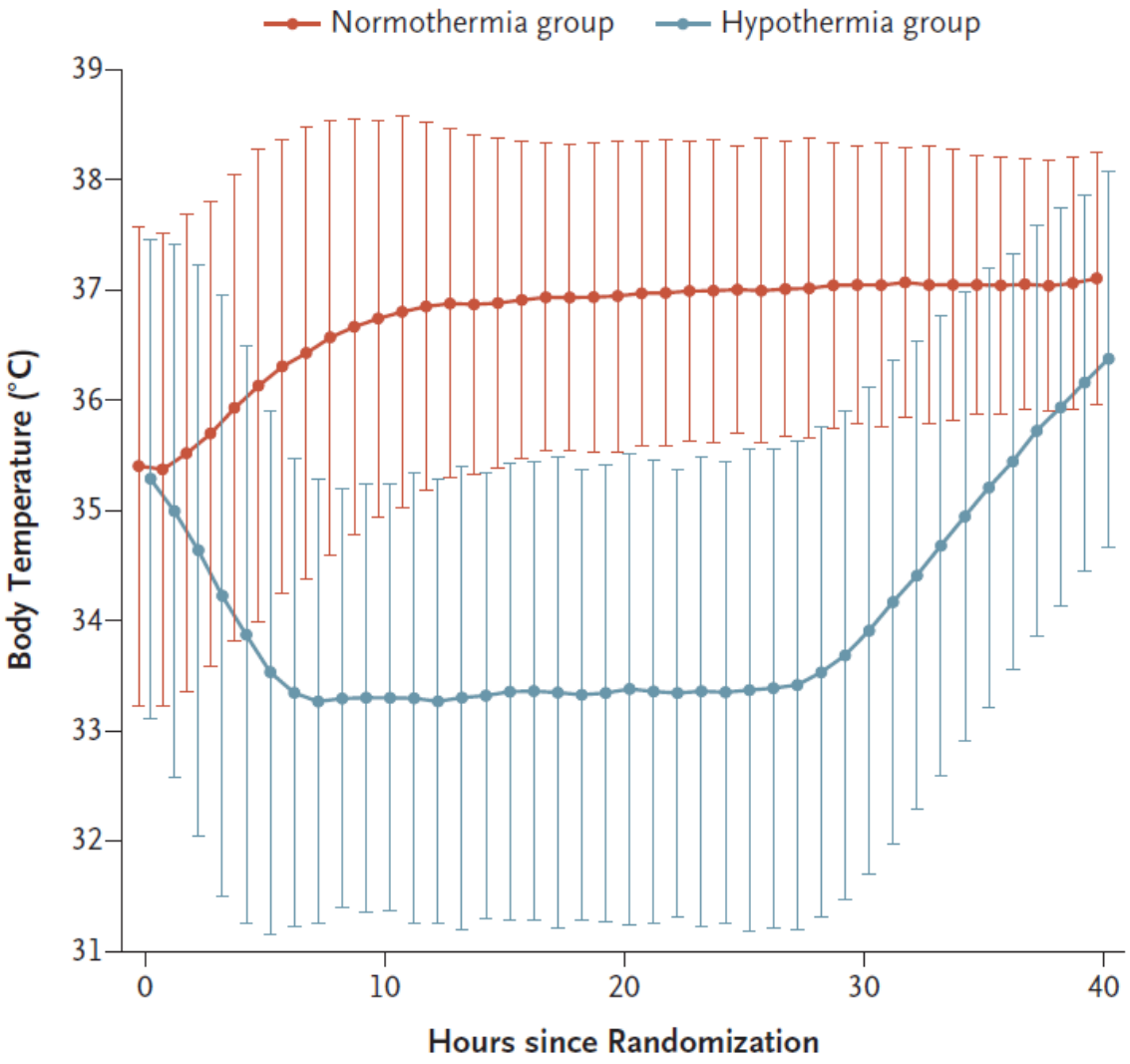

Normothermia group
Hypothermia group
Body Temperature (°C)
39
38
37
36
35
34
33
32
31
0
10
20
30
40
Hours since Randomization

Figure 2

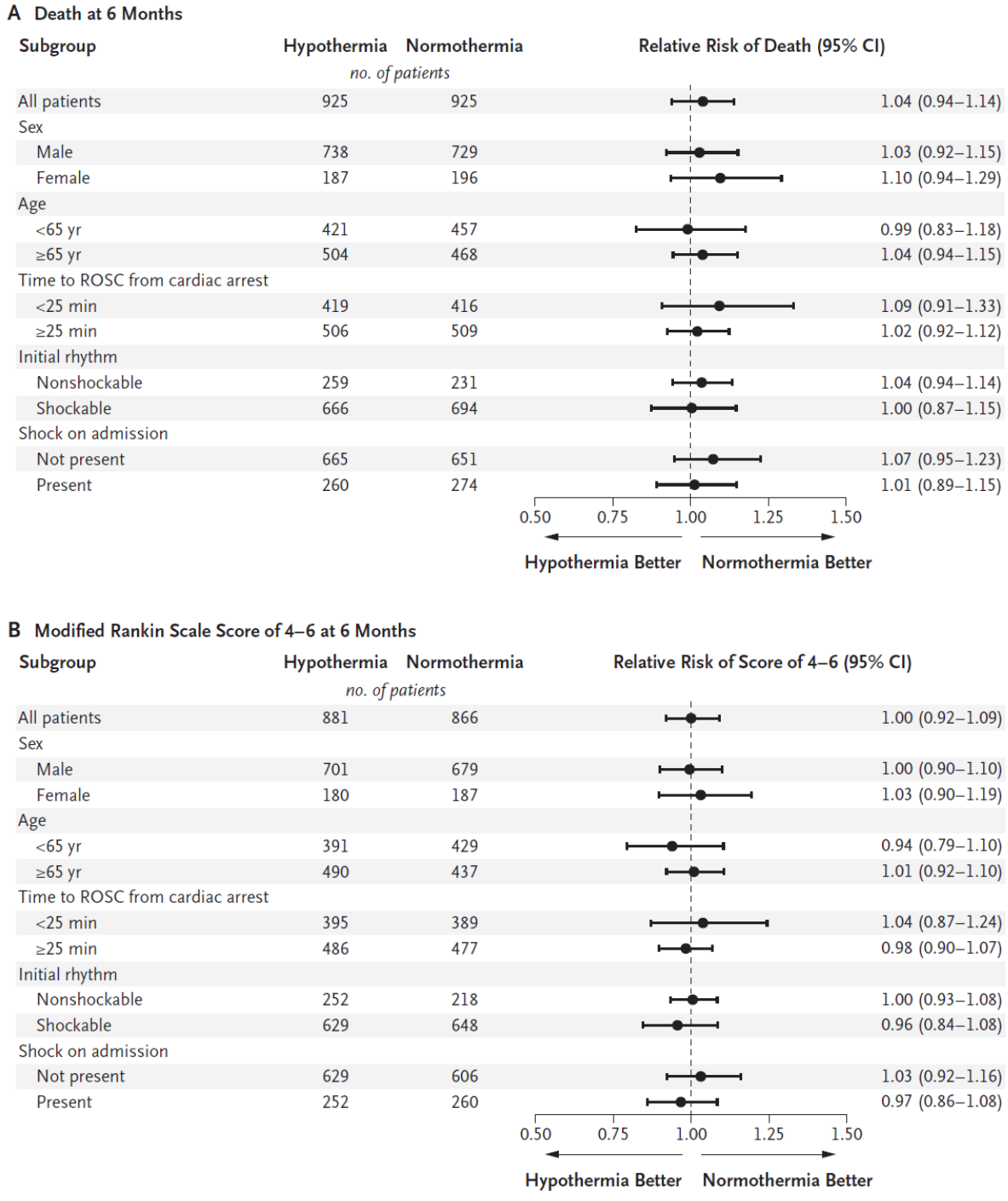
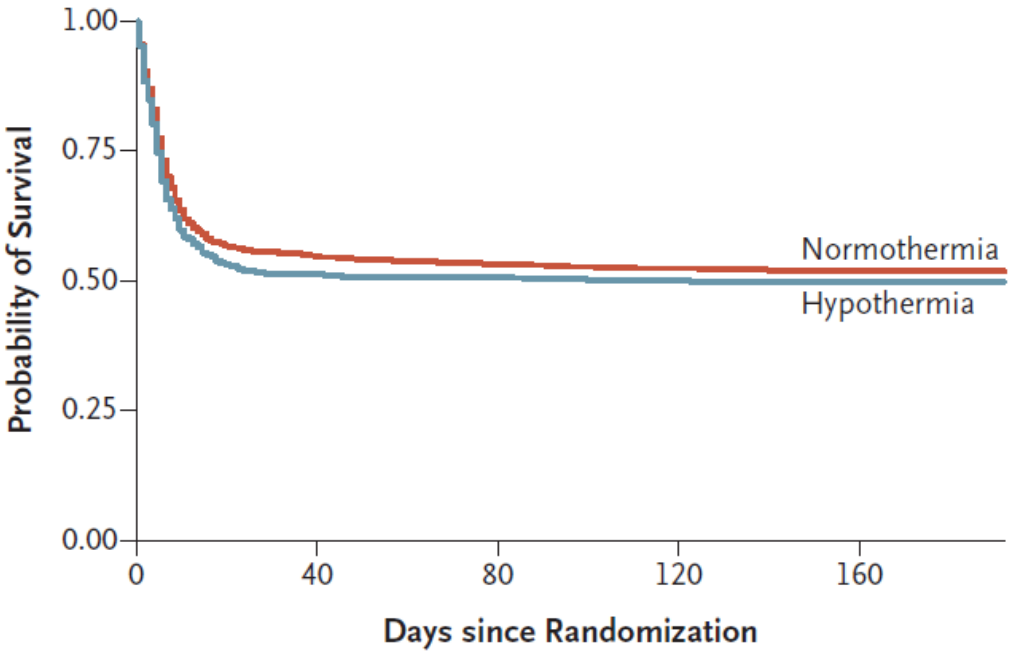

A Death at 6 Months
Subgroup
Hypothermia
Normothermia
no. of patients
Relative Risk of Death (95% CI)
All patients 925 925 1.04 (0.94–1.14)
Sex
Male 738 729 1.03 (0.92–1.15)
Female 187 196 1.10 (0.94–1.29)
Age
<65 yr 421 457 0.99 (0.83–1.18)
≥65 yr 504 468 1.04 (0.94–1.15)
Time to ROSC from cardiac arrest
<25 min 419 416 1.09 (0.91–1.33)
≥25 min 506 509 1.02 (0.92–1.12)
Initial rhythm
Nonshockable 259 231 1.04 (0.94–1.14)
Shockable 666 694 1.00 (0.87–1.15)
Shock on admission
Not present 665 651 1.07 (0.95–1.23)
Present 260 274 1.01 (0.89–1.15)
0.50 0.75 1.00 1.25 1.50
Hypothermia Better
Normothermia Better
B Modified Rankin Scale Score of 4–6 at 6 Months
Subgroup
Hypothermia
Normothermia
no. of patients
Relative Risk of Score of 4–6 (95% CI)
All patients 881 866 1.00 (0.92–1.09)
Sex
Male 701 679 1.00 (0.90–1.10)
Female 180 187 1.03 (0.90–1.19)
Age
<65 yr 391 429 0.94 (0.79–1.10)
≥65 yr 490 437 1.01 (0.92–1.10)
Time to ROSC from cardiac arrest
<25 min 395 389 1.04 (0.87–1.24)
≥25 min 486 477 0.98 (0.90–1.07)
Initial rhythm
Nonshockable 252 218 1.00 (0.93–1.08)
Shockable 629 648 0.96 (0.84–1.08)
Shock on admission
Not present 629 606 1.03 (0.92–1.16)
Present 252 260 0.97 (0.86–1.08)
0.50 0.75 1.00 1.25 1.50
Hypothermia Better
Normothermia Better

Figure 3



No. at Risk					
Normothermia	925	506	491	484	480
Hypothermia	925	474	468	462	461

Table 1. Characteristics of the intention to treat population at randomization

Characteristic	Hypothermia (n=930)	Normothermia (n=931)
Age – years mean (SD)	64 (13)	63 (14)
Male sex – no. (%)	742 (80)	735 (79)
Medical History		
Previous hypertension - no. (%)	345 (37)	298 (32)
Previous diabetes - no. (%)	173 (19)	167 (18)
Previous myocardial Infarction - no. (%)	139 (15)	154 (17)
Previous PCI – no. (%)	130 (14)	140 (15)
Previous coronary artery bypass grafting – no. (%)	73 (8)	76 (8)
Previous heart failure - no. (%)	90 (10)	93 (10)
- NYHA III or IV – no. (%)*	20 (2)	23 (3)
Charlson Comorbidity index – median (IQR)	3 (2, 4)	3 (1, 4)
Characteristics of the cardiac arrest		
Location of arrest		
- Home – no. (%)	487 (52)	491 (53)
- Public place – no. (%)	338 (36)	320 (34)
- Other – no. (%)	105 (11)	120 (13)
Bystander witnessed arrest – no. (%)	850 (91)	852 (92)
Bystander CPR performed – no. (%)	759 (82)	728 (78)
First monitored rhythm		
Shockable rhythm – no. (%)	671 (72)	700 (75)
- Ventricular fibrillation no. (%)	576 (62)	585 (63)
- Non-perfusing ventricular tachycardia no. (%)	31 (3)	29 (3)
- ROSC after bystander defibrillation no. (%)	24 (3)	41 (4)
- Unknown rhythm – shock administered no. (%)	40 (4)	45 (5)
Non-shockable rhythm	259 (28)	231 (25)
- Pulseless electrical activity - no. (%)	117 (13)	113 (12)
- Asystole no. - (%)	124 (13)	100 (11)
- Unknown – no shock administered - no. (%)	18 (2)	18 (2)
Time from cardiac arrest to sustained ROSC[&] – minutes median (IQR)	25 (16, 40)	25 (17, 40)
Time from arrest to randomization – minutes median (IQR)	136 (103, 170)	133 (99, 173)
Clinical characteristics on admission		
Tympanic temperature - °C mean (SD) [†]	35.3 (1.1)	35.4 (1.1)
FOUR motor score – median (IQR) [‡]	0 (0, 0)	0 (0, 0)
Corneal reflexes bilaterally present - no. (%)	168/511 (33)	194/537 (36)
Pupillary reflexes bilaterally present - no. (%)	535/761 (70)	529/776 (68)
Arterial pH – pH mean (SD)[§]	7.2 (0.2)	7.2 (0.2)
Serum lactate - mmol/L mean (SD) [¶]	5.9 (4.4)	5.8 (4.2)
Shock on admission - no. (%)	261 (28)	275 (30)
ST-elevation myocardial infarction - no. (%)	379/918 (41)	370/921 (40)

PCI denotes Percutaneous coronary intervention, NYHA New York Heart Associated Heart Failure class, CPR Cardiopulmonary resuscitation, ROSC Return of spontaneous circulation,

FOUR Full Outline of UnResponsiveness score for assessment of motor function (range 0-4), a higher score indicates better motor function. Shock at admission was defined as a systolic blood pressure <90mmHg for >30min or end-organ hypoperfusion (cool extremities, urine output <30mm/hour, heart rate <60 beats/minute). *NYHA Class was not assessed in 51 participants with previous heart failure. & For unwitnessed cardiac arrests the time to ROSC was calculated from time of emergency call. †Tympanic temperature was assessed in 1559 participants. ‡FOUR motor score was assessed in 1696 participants, §Arterial pH was measured in 1829 participants, ¶Arterial lactate was measured in 1781 participants.

Table 2. Outcomes and Adverse Events*

	Hypothermia	Normothermia	Risk Ratio†	P Value
	no./total no. (%)		*(95%CI)*	
Primary outcome:				
All-Cause Mortality at 6 months	465/925 (50%)	446/925 (48%)	1.04 (0.94 to 1.14)	0.37
Main secondary outcome:				
mRS 4-6 at 6-month follow-up‡	488/881 (55%)	479/866 (55%)	1.00 (0.92 to 1.09)	
Poor functional outcome§ at 6-months	495/918 (54%)	493/911 (54%)	1.00 (0.91 to 1.08)	
mRS-score at 6-month follow-up‡				
- mRS 0	140 (16%)	148 /17%		
- mRS 1	87 (10%)	80 (9%)		
- mRS 2	132 (15%)	127 (15%)		
- mRS 3	34 (4%)	32 (4%)		
- mRS 4	16 (2%)	20 (2%)		
- mRS 5	7 (1%)	13 (2%)		
- mRS 6	465 (53%)	446 (52%)		
Serious adverse events:				
- Arrhythmia resulting in hemodynamic compromise	222/927 (24%)	152/921 (17%)	1.45 (1.21 to 1.75)	<0.001
- Bleeding	44/927 (9%)	46/922 (9%)	0.95 (0.63 to 1.42)	0.81
- Device-related skin complication	10/927 (1%)	5/922 (1%)	1.99 (0.71 to 6.37)	0.21
- Pneumonia	330/927 (36%)	322/921 (35%)	1.02 (0.90 to 1.15)	0.75
- Sepsis	99/926 (11%)	83/922 (9%)	1.19 (0.90 to 1.57)	0.23

∗CI denotes confidence interval and mRS denotes modified Rankin Scale. The mRS-score ranges from 0 to 6. Higher scores indicate more severe disability and 6 indicates death. The widths of the confidence intervals have not been adjusted for multiple testing, so the intervals should not be used to infer definitive differences between the groups.

†The risk ratios for all-cause mortality, mRS 4-6 and poor neurological function at 6 months are adjusted for the stratification variables (participating site and co-enrolment status (not co-enrolled, co-enrolled TAME group A, co-enrolled TAME group B) in the Targeted Mild Hypercapnia versus Targeted Normocapnia after Cardiac Arrest (TAME)-trial). Risk ratios

for serious adverse events were adjusted for co-enrollment status (as above) in the TAME trial, but not for site. The risk ratio for device-related skin complication was unadjusted. ‡Based on data from a structured interview. §Based on all available data.