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Targeted Temperature Management in Out-of-Hospital Cardiac Arrest With Shockable Rhythm: A Post Hoc Analysis of the Coronary Angiography After Cardiac Arrest Trial

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OBJECTIVES: The optimal targeted temperature in patients with shockable rhythm is unclear, and current guidelines recommend targeted temperature management with a correspondingly wide range between 32°C and 36°C. Our aim was to study survival and neurologic outcome associated with targeted temperature management strategy in postarrest patients with initial shockable rhythm.

DESIGN: Observational substudy of the Coronary Angiography after Cardiac Arrest without ST-segment Elevation trial.

SETTING: Nineteen hospitals in The Netherlands.

PATIENTS: The Coronary Angiography after Cardiac Arrest trial randomized successfully resuscitated patients with shockable rhythm and absence of ST-segment elevation to a strategy of immediate or delayed coronary angiography. In this substudy, 459 patients treated with mild therapeutic hypothermia (32.0–34.0°C) or targeted normothermia (36.0–37.0°C) were included. Allocation to targeted temperature management strategy was at the discretion of the physician.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: After 90 days, 171 patients (63.6%) in the mild therapeutic hypothermia group and 129 (67.9%) in the targeted normothermia group were alive (hazard ratio, 0.86 [95% CI, 0.62–1.18]; log-rank $p = 0.35$; adjusted odds ratio, 0.89; 95% CI, 0.45–1.72). Patients in the mild therapeutic hypothermia group had longer ICU stay (4 d [3–7 d] vs 3 d [2–5 d]; ratio of geometric means, 1.32; 95% CI, 1.15–1.51), lower blood pressures, higher lactate levels, and increased need for inotropic support. Cerebral Performance Category scores at ICU discharge and 90-day follow-up and patient-reported Mental and Physical Health Scores at 1 year were similar in the two groups.

CONCLUSIONS: In the context of out-of-hospital cardiac arrest with shockable rhythm and no ST-elevation, treatment with mild therapeutic hypothermia was not associated with improved 90-day survival compared with targeted normothermia. Neurologic outcomes at 90 days as well as patient-reported Mental and Physical Health Scores at 1 year did not differ between the groups.

KEY WORDS: cardiac arrest; shockable rhythm; targeted temperature management

Survival rates of patients who are successfully resuscitated after out-of-hospital cardiac arrest (OHCA) have increased in recent years but remain low (1). Postcardiac arrest syndrome, including whole body ischemia and reperfusion damage, is the main reason for death after return of spontaneous circulation (ROSC) in patients after cardiac arrest (2, 3). It is well known that pyrexia, which is common at an early stage after resuscitation, is associated

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with deleterious neurologic outcomes (4–6). Reducing core body temperature has been suggested to decrease cerebral metabolic rate for oxygen and the production of free radicals, which can lead to lower amounts of cell death and improved survival and neurologic outcomes (7–9). Based on two landmark studies among patients with an initial shockable rhythm, the use of targeted temperature management (TTM) in postarrest patients is advocated in the European Society of Cardiology and International Liaison Committee on Resuscitation guidelines (3, 10–12).

The TTM trial, encompassing a study population with 80% of patients who had initial shockable rhythm, was the first study to compare a targeted temperature of 33–36°C and was neutral on both survival and favorable neurologic outcomes (13). Since the publication of TTM trial, a decrease in the use of TTM and target temperature was observed, resulting in concerns about an observed decrease in survival in the same period (14–16). A recently published study among patients with nonshockable rhythms found a higher percentage of survival with good neurologic outcome in patients treated with 33°C compared with 37°C, suggesting that cardiac arrest characteristics may influence TTM effects. Furthermore, since the publication of the landmark trials, postcardiac arrest care has markedly improved. Since the optimal targeted temperature is still unclear and current guidelines recommend TTM in postarrest patients with a correspondingly wide range of temperatures between 32°C and 36°C (3), further data on the optimal targeted temperature in a modern postarrest care setting are needed. In this observational subanalysis of the Coronary Angiography after Cardiac Arrest (COACT) trial (17, 18), our objective was to compare mild therapeutic hypothermia (32–34°C) with targeted normothermia (36–37°C) on survival and neurologic outcome in a modern postcardiac care setting of patients with initial shockable rhythm and absence of ST-segment elevation myocardial infarction (STEMI).

MATERIALS AND METHODS

Study Design and Study Population

This is an observational post hoc analysis of the COACT trial. A total of 552 patients successfully resuscitated after OHCA with an initial shockable rhythm were enrolled during the time period from January 2015 to July 2018 (17). The COACT trial included comatose (i.e., Glasgow Coma Scale score < 8) patients who were successfully resuscitated after OHCA with a shockable rhythm in absence of STEMI and 1:1 randomized these patients to an immediate coronary angiography strategy (i.e., within 2 hr after randomization) or a delayed strategy (i.e., until after neurologic recovery) (17). This study found no difference with respect to 90-day survival and at 1 year (17, 18). Furthermore, it was found that patients assigned to the immediate angiography reached their targeted temperature later than patients assigned to the delayed arm. It was therefore argued that this might have attenuated any potential benefit gained from immediate coronary angiography (17). The main exclusion criteria were signs of STEMI on the postarrest electrocardiogram, shock, or an obvious noncoronary cause of the arrest. Further inclusion and exclusion criteria are reported in the **Supplementary Material** (http://links.lww.com/CCM/G697). We compared a

targeted mild therapeutic hypothermia (MTH) (32.0–34.0°C) with targeted normothermia (36.0–37.0°C) in successfully resuscitated patients with initial shockable rhythm and in absence of ST-segment elevation. All patients of the COACT trial who were treated with a target temperature of 32.0–34.0°C or 36.0–37.0°C were included in the analysis. Although each center had its own TTM protocol, the final decision was at the discretion of treating physician. Informed consent was obtained from all enrolled patients. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for reporting of observational studies (19). The trial design of the main COACT trial was reviewed and approved by the Vrije Universiteit Medisch Centrum ethics committee and is registered at The Netherlands Trial Register, number NTR4973.

Outcome Assessment and Follow-Up

Follow-up data were obtained via a telephone interview conducted at 90 days and at 1 year after randomization with the patient, a family member, or patient's general physician. Neurologic outcomes were scored at ICU discharge and at 90-day follow-up using Cerebral Performance Categories (CPCs). The CPC is a five-point scale to assess neurologic outcome with higher scores indicating worse prognosis. A good cerebral performance score was defined as CPC 1 or 2. At 1 year, patients were asked to complete a 36-Item Short Form Survey (SF-36). This is a widely used quality of life questionnaire (20). It yields eight domains to calculate the Physical Component Score (PCS) and Mental Component Score (MCS) (20). All items are summed into scale scores and subsequently transformed to a 100-point scale score. A higher score denotes a more favorable health state.

In this study, the primary point of interest was 90-day survival. Secondary points of interest were neurologic outcome using CPC scores at ICU discharge and at 90-day follow-up and quality of life at 1-year follow-up using the SF-36-Item Health Survey. Furthermore, we assessed whether duration until TTM was reached in immediate or delayed coronary angiography strategy was associated with survival or neurologic outcomes. As this was a substudy of a larger trial, no a priori sample size calculations were performed for comparison of MTH with targeted normothermia.

Statistical Analysis

Continuous variables were summarized as mean ± SD or median and interquartile ranges (IQRs, 25–75%), depending on normality of the distribution. Categorical variables were summarized as numbers and percentages. We compared groups using independent *t* test, Mann-Whitney *U* test, and chi-square or Fishers exact test, when applicable. Effect sizes were reported as odds ratios (ORs), mean differences, or ratio of geometric means with 95% CIs, where appropriate. Survival curves were constructed using Kaplan-Meier method and compared using the log-rank test. Hazard ratios with associated 95% CIs were derived using Cox proportional hazards model. Effect modification on the relation between TTM, neurologic outcomes, and survival by arrest characteristics was assessed by testing the two-way interaction of TTM group and arrest characteristics by means of a two-way interaction. The two-way interaction was tested using logistic regression after dichotomizing neurologic outcome at 90 days as good (CPC = 1 or 2) or poor (CPC = 3–5). Confounding for patient-and center-specific factors on the endpoints survival and neurologic outcome were explored using logistic regression (**Fig. S6**, http://links.lww.com/CCM/G697). Proportions of patients surviving 90 days and proportions of patients with good neurologic outcomes adjusted for in-hospital management were obtained as estimated means from a mixed logistic regression model where center was included as fixed effect together with variables related to in-hospital management. Adjustment for confounding factors was done by adding witnessed arrest, time to ROSC, academic/nonacademic center, extracorporeal membrane oxygenation (ECMO)/non-ECMO center, ICU capacity, and patient characteristics to a logistic regression with TTM group as main determinant. Causal mediation analysis was performed to assess the mediating effect of time until TTM on the relation between treatment strategy (immediate/delayed) and outcomes. Results of causal mediation analysis are reported as average causal direct and indirect effects, with their 95% CIs and *p* values determined using a nonparametric bootstrap with 10,000 replications. A two-tailed *p* value of 0.05 or less was regarded as statistically significant. Statistical analysis was performed with IBM SPSS Statistics, Version 26 (IBM, Armonk, NY). Causal mediation analysis was performed using the "mediation" package in R (version 3.6.1; R Foundation for Computing, Vienna, Austria).

RESULTS

Patients

After exclusion of 14 patients who retroactively withdrew informed consent, 38 patients in whom TTM was not initiated, and 41 patients who were treated with targeted temperature outside the study's definition range (i.e., < 32°C and 35°C), a total of 459 patients were eligible for this analysis (**Fig. S1**, http://links.lww.com/CCM/G697). The mean age was 65 ± 13 years, and 78.6% of patients were men (**Table 1**). Predictors for neurologic outcome, such as time to basic life support (MTH 2 min [1–5 min] vs targeted normothermia 2 min [1–5 min]), time to ROSC (15 min [8–20 min] vs 15 min [8–22 min]), or lactate (4.9 mol/L [2.6–8.5 mol/L] vs 5.3 mol/L [3.5–8.6 mol/L]), were similar in the MTH and targeted normothermia groups. In patients eligible for analysis, proportions randomized to immediate or delayed coronary angiography were similar in the two groups; 50.9% of patients who received MTH was randomized to the immediate arm, versus 50.5% of patients in the targeted normothermia group.

Temperature Management and Intensive Care Support

In total, 269 patients (58.6%) were treated with MTH and 190 (41.4%) with targeted normothermia (**Table S1**, http://links.lww.com/CCM/G697) (**Table 2**). Twelve centers applied hypothermia, and seven centers applied targeted normothermia. A few patients deviated to a different strategy (**Table S2**, http://links.lww.com/CCM/G697). The median targeted temperature in the MTH group was 33.0°C (32.0–33.0°C) (Table S1, http://links.lww.com/CCM/G697). In the targeted normothermia group, almost all patients (89.5%) were treated with a goal temperature of 36.0°C (**Fig. S2**, http://links.lww.com/CCM/G697). Seven patients were treated with a goal temperature of 37.0°C. Cooling was achieved using body surface cooling (88.8% in the MTH group and 57.9% in the targeted normothermia group) or an intravascular cooling device (11.2% and 42.1%) (Table S1, http://links.lww.com/CCM/G697). The median time to targeted temperature was 6.0 hours (4.0–8.6 hr) in the MTH group and 3.4 hours (1.8–6.8 hr) in the targeted normothermia group.

Hemodynamics

There were substantial differences with respect to hemodynamics and intensive care support between the two groups. Lactate was higher, and mean arterial pressures were lower in the MTH group, as measured during the first 4 days of intensive care treatment (Table 2). Furthermore, in the MTH group, the duration of midazolam and opioid administration was longer. The administration of noradrenaline was longer (44.7 hr [28.6–64.3 hr] vs 33.0 hr [21.6–59.2 hr]; ratio of geometric means, 1.27; 95% CI, 1.03–1.57) and higher dosed (0.20 mmol/L [0.10–0.46 mmol/L] vs 0.15 mmol/L [0.08–0.26 mmol/L]; ratio of geometric means, 1.42; 95% CI, 1.04–1.95) in the MTH group. Furthermore, maximum levels of troponin (0.553 µg/L [0.223–1.555 µg/L] vs 0.513 µg/L [0.184–1.024 µg/L]; ratio of geometric means, 1.41; 95% CI, 1.02–1.96) and creatinine kinase myocardial binding (38.4 µg/L [16.4–132.8 µg/L] vs 25.6 µg/L [14.4–66.5 µg/L]; ratio of geometric means, 1.44; 95% CI, 1.07–1.94) were higher in this group, which was not the case for CK (935 U/L [411–2,552 U/L] vs 731 U/L [356–1,592 U/L]; ratio of geometric means, 1.44; 95% CI, 1.07–1.94). Patients who were treated with MTH were longer admitted on the ICU (4 d [3–7 d] vs 3 d [2–5 d]; ratio of geometric means, 1.32; 95% CI, 1.15–1.51) (Table 2). **Table S3** (http://links.lww.com/CCM/G697) reports the use of medications, renal replacement therapy, and assist devices stratified by cooling strategy centers.

Neurologic Outcomes and Survival

Glasgow Coma Scale scores during the first 72 hours of admission are depicted in **Table S4** (http://links.lww.com/CCM/G697). After 90 days, 300 patients (65.4%) were alive, 171 (63.6%) patients in the MTH group and 129 (67.9%) in the targeted normothermia group (hazard ratio, 0.86 [95% CI, 0.62–1.18]; log-rank p = 0.35) (**Fig. 1** and **Table 3**). In addition, OR for 90-day survival (adjusted OR, 0.89; 95% CI, 0.45–1.73) and good neurologic outcome (adjusted OR, 0.80; 95% CI, 0.41–1.55) were similar when adjusted for potential center-specific confounders and patient characteristics (**Table 4**). After exclusion of the seven patients who were treated with a goal temperature of 37°C, the hazard ratio (95% CI) for 90-day survival was 0.90 (0.65–1.24; log-rank p = 0.51). CPC scores at 90-day follow-up did not differ between the groups.

TABLE 1.
Patient Demographics

Characteristic	All Patients (*N* = 459)	Mild Therapeutic Hypothermia (32–34°C) (*N* = 269)	Normothermia (36–37°C) (*N* = 190)	*p*
Sex, male, *n* (%)	361 (78.6)	208 (77.3)	153 (80.5)	0.41
Age, mean ± SD	65 ± 13	65 ± 12	65 ± 14	0.64
Medical history				
Coronary artery disease, *n* (%)	162 (35.3)	101 (37.5)	61 (32.1)	0.23
Myocardial infarction, *n* (%)	127 (27.7)	76 (28.3)	51 (26.8)	0.74
Percutaneous coronary intervention, *n*/*N* (%)	85/457 (18.6)	53 (19.7)	32/188 (17.0)	0.47
Coronary artery bypass grafting, *n*/*N* (%)	56/458 (12.2)	37 (13.8)	19/189 (10.1)	0.23
Hypertension, *n*/*N* (%)	218/256 (47.8)	121/268 (45.1)	97/188 (51.6)	0.18
Diabetes mellitus, *n*/*N* (%)	81/458 (17.7)	43 (16.0)	38/189 (20.1)	0.26
Hypercholesterolemia, *n*/*N* (%)	121/456 (26.5)	70/267 (26.2)	51/189 (27.0)	0.86
Cerebrovascular accident, *n*/*N* (%)	28/458 (6.1)	17 (6.3)	11/189 (5.8)	0.83
Peripheral artery disease, *n*/*N* (%)	32/458 (7.0)	20 (7.4)	12/189 (6.3)	0.65
Smoker, *n*/*N* (%)	100/424 (23.6)	60/253 (23.7)	40/171 (23.4)	0.94
Prehospital settings				
Arrest witnessed, *n* (%)	357 (77.8)	202 (75.1)	155 (81.6)	0.10
Time arrest to basic life support (min), median (interquartile range)	2 (1–5)	2 (1–5)	2 (1–5)	0.99
Time arrest to return of spontaneous circulation (min), median (interquartile range)	15 (8–20)	15 (8–20)	15 (8–22)	0.44
Signs of ischemia on electrocardiogram[a]	287/436 (65.8)	172/256 (67.2)	115/180 (63.9)	0.48
Laboratory findings				
Serum pH, mean ± SD	7.22 ± 0.14	7.22 ± 0.14	7.21 ± 0.13	0.62
Partial pressure of O_2 (kPa), median (interquartile range)	14.8 (9.4–27.3)	14.4 (9.8–26.7)	15.5 (8.9–30.0)	0.72
Bicarbonate (mmol/L), mean ± SD	19.2 ± 4.4	19.0 ± 4.4	19.6 ± 4.2	0.16
Base excess, mean ± SD	–7.7 ± 6.0	–7.5 ± 6.2	–7.9 ± 5.7	0.42
Lactic acid (mmol/L), median (interquartile range)	5.0 (2.9–8.5)	4.9 (2.6–8.5)	5.3 (3.5–8.6)	0.13
Troponin T (µg/L), median (interquartile range)	0.050 (0.028–0.093)	0.050 (0.028–0.114)	0.047 (0.028–0.085)	0.25
Creatinine kinase myocardial binding (µmol/L), median (interquartile range)	6.4 (3.9–22.8)	6.3 (3.9–14.0)	6.5 (3.9–39.0)	0.24
Creatinine kinase (U/L), median (interquartile range)	166 (118–252)	174 (118–264)	150 (118–224)	0.07
Creatinine (µmol/L), median (interquartile range)	101 (87–116)	100 (85–116)	103 (90–116)	0.16

(*Continued*)

TABLE 1. (*Continued*).
Patient Demographics

Characteristic	All Patients (*N* = 459)	Mild Therapeutic Hypothermia (32–34°C) (*N* = 269)	Normothermia (36–37°C) (*N* = 190)	*p*
Glasgow Coma Scale at admission, median (interquartile range)	3 (3–3)	3 (3–3)	3 (3–3)	0.77
Randomization to coronary angiography strategy, *n* (%)				0.93
Immediate coronary angiography	233 (50.8)	137 (50.9)	96 (50.5)	
Delayed coronary angiography	226 (49.2)	132 (49.1)	94 (49.5)	
Urgent coronary angiography due to deterioration (in the delayed group)[b], *n* (%)	33 (7.2)	21 (7.8)	12 (6.3)	0.54

[a]Signs of ischemia on electrocardiogram meaning ST-segment depression of 1 mm or more in two contiguous leads and/or T wave inversion in two contiguous leads.
[b]Thirty-six patients who were randomized to delayed coronary angiography strategy (i.e., coronary angiography until after neurologic recovery) underwent urgent coronary angiography due to cardiac deterioration.
Glasgow Coma Scale (scoring system ranging from 3 to 15, low score indicates reduced level of consciousness).

TABLE 2.
Targeted Temperature Management Characteristics, Hemodynamics, and Biomarkers

Characteristic	Mild Therapeutic Hypothermia (32–34°C) (*N* = 269)	Targeted Normothermia (36–37°C) (*N* = 190)	Effect Size (+95% CI)[a]
Treatment characteristics			
Median targeted temperature, median (interquartile range)	33 (32–33)	36 (36–36)	
Geometric mean (95% CI)	33 (33–33)	36 (36–36)	0.91 (0.91–0.91)
Lowest temperature, median (interquartile range)	32.6 (31.9–33.1)	35.2 (34.6–35.7)	
Geometric mean (95% CI)	32.6 (32.5–32.8)	35.1 (34.9–35.2)	0.93 (0.93–0.94)
Time from arrest to TTM, hr, median (interquartile range)	6.0 (4.0–8.6)	3.4 (1.8–6.8)	
Geometric mean (95% CI)	5.7 (5.2–6.2)	3.6 (3.0–4.3)	1.41 (1.21–1.64)
Time from TTM to 36°C, hr, median (interquartile range)	31.0 (22.0–34.8)	0.0 (0.0–0.0)	
Mean ± SD	27.03 ± 11.20	0.57 ± 5.83	26.46 (24.81–28.12)[b]
Hemodynamics			
Noradrenaline administration, *n* (%)	252 (93.7)	159 (83.7)	OR 2.89 (1.55–5.39)
Highest dose (µg/kg/min)[c], median (interquartile range)	0.20 (0.10–0.46)	0.15 (0.08–0.26)	
Geometric mean (95% CI)	0.22 (0.18–0.27)	0.16 (0.13–0.20)	1.42 (1.04–1.95)
Duration, hr, median (interquartile range)	44.7 (28.6–64.3)	33.0 (21.6–59.2)	
Geometric mean (95% CI)	39.0 (34.3–44.4)	32.6 (27.8–38.1)	1.27 (1.03–1.57)

(*Continued*)

TABLE 2. (*Continued*).

Targeted Temperature Management Characteristics, Hemodynamics, and Biomarkers

Characteristic	Mild Therapeutic Hypothermia (32–34°C) (*N* = 269)	Targeted Normothermia (36–37°C) (*N* = 190)	Effect Size (+95% CI)[a]
Dobutamine administration, *n* (%)	89 (33.1)	44 (23.2)	OR 1.64 (1.08–2.50)
Highest dose (μg/kg/min)[c], median (interquartile range)	3.5 (2.1–5.2)	3.0 (2.0–4.7)	
Geometric mean (95% CI)	3.0 (1.9–4.8)	2.3 (1.4–3.7)	1.31 (0.65–2.62)
Duration, hr, median (interquartile range)	29.8 (18.3–39.0)	36.0 (19.0–54.3)	
Geometric mean (95% CI)	26.9 (22.8–31.9)	28.5 (21.4–38.0)	0.89 (0.62–1.19)
Phosphodiesterase inhibitor administration, *n* (%)	26 (9.7)	12 (6.3)	OR 1.59 (0.78–3.23)
Duration, hr, median (interquartile range)	50.6 (27.8–71.8)	36.0 (17.5–74.7)	
Geometric mean (95% CI)	38.5 (23.3–64.0)	37.2 (20.1–68.6)	1.04 (0.45–2.38)
Propofol administration, *n* (%)	248 (92.2)	183 (96.3)	OR 0.45 (0.19–1.09)
Duration, hr, median (interquartile range)	58.0 (40.0–77.0)	50.0 (36.0–73.0)	
Geometric mean (95% CI)	59.8 (51.3–69.8)	58.4 (46.8–72.8)	1.05 (0.93–1.32)
Midalozam administration, *n* (%)	98 (36.4)	47 (24.7)	OR 1.74 (1.15–2.63)
Duration, hr, median (interquartile range)	23.3 (11.1–40.0)	13.8 (4.3–26.4)	
Geometric mean (95% CI)	23.4 (17.5–31.4)	10.6 (7.1–15.7)	1.95 (1.26–3.03)
Opioids administration, *n* (%)	214 (79.6)	154 (81.1)	OR 0.91 (0.57–1.45)
Duration, hr, median (interquartile range)	51.5 (38.5–79.1)	40.0 (24.0–74.0)	
Geometric mean (95% CI)	59.2 (51.3–68.2)	39.4 (32.7–47.5)	1.50 (1.19–1.90)
Duration mechanical ventilation, hr, median (interquartile range)	64 (44–119)	42 (28–71)	
Geometric mean (95% CI)	67.4 (60.3–75.4)	45.2 (39.1–52.1)	1.49 (1.27–1.79)
Circulatory assist device, *n* (%)	6 (2.2)	3 (1.6)	OR 0.70 (0.17–2.85)
Recurrence of ventricular tachycardia of ventricular fibrillation[d], *n* (%)	17 (6.3)	16 (8.4)	OR 1.36 (0.67–2.77)
Renal replacement therapy, *n* (%)	12 (4.5)	5 (2.6)	OR 0.58 (0.20–1.67)
Lowest MAP on day 1, mean ± SD	61 ± 12	63 ± 13	1.97 (−0.40 to 4.34)[f]
Lowest MAP on day 2, mean ± SD	58 ± 9	67 ± 13	9.16 (6.84–11.49)[f]
Lowest MAP on day 3, mean ± SD	63 ± 12	73 ± 18	10.03 (6.64–13.42)[f]
Lowest MAP on day 4, mean ± SD	69 ± 15	79 ± 20	9.87 (5.57–14.18)[f]
Laboratory values			
Lowest pH, median (interquartile range)	7.23 (7.15–7.29)	7.25 (7.17–7.30)	
Geometric mean (95% CI)	7.20 (7.18–7.22)	7.20 (7.18–7.23)	1.00 (0.99–1.00)
Maximum value lactate, median (interquartile range)	4.9 (2.8–8.4)	4.8 (3.0–8.1)	
Geometric mean (95% CI)	4.9 (4.3–5.5)	5.3 (4.7–5.8)	1.01 (0.89–1.15)
Peak value creatinine kinase, median (interquartile range)	935 (411–2,552)	731 (356–1,592)	
Geometric mean (95% CI)	1,087 (891–1,325)	780 (634–960)	1.25 (1.02–1.55)

(*Continued*)

TABLE 2. (*Continued*).
Targeted Temperature Management Characteristics, Hemodynamics, and Biomarkers

Characteristic	Mild Therapeutic Hypothermia (32–34°C) (*N* = 269)	Targeted Normothermia (36–37°C) (*N* = 190)	Effect Size (+95% CI)[a]
Peak value creatinine kinase myocardial binding, median (interquartile range)	38.4 (16.4–132.8)	25.6 (14.4–66.5)	
Geometric mean (95% CI)	47.2 (37.8–59.1)	32.4 (26.0–40.3)	1.44 (1.07–1.94)
Peak value troponin T, median (interquartile range)	0.553 (0.223–1.555)	0.513 (0.184–1.024)	
Geometric mean (95% CI)	0.816 (0.589–1.129)	0.617 (0.447–0.852)	1.41 (1.02–1.96)
Lactate			
6 hr, median (interquartile range)	1.5 (1.2–2.7)	1.4 (1.0–2.2)	
Geometric mean (95% CI)	1.8 (1.6–1.9)	1.4 (1.2–1.7)	1.19 (1.04–1.35)
12 hr, median (interquartile range)	1.5 (1.1–2.6)	1.4 (0.9–1.8)	
Geometric mean (95% CI)	1.6 (1.5–1.8)	1.4 (1.1–1.6)	1.30 (1.15–1.48)
24 hr, median (interquartile range)	1.5 (1.1–2.3)	1.2 (0.9–1.6)	
Geometric mean (95% CI)	1.6 (1.5–1.8)	1.3 (1.1–1.6)	1.38 (1.23–1.55)
48 hr, median (interquartile range)	1.5 (1.1–2.0)	1.1 (0.9–1.4)	
Geometric mean (95% CI)	1.5 (1.4–1.7)	1.1 (1.0–1.3)	1.41 (1.27–1.56)
72 hr, median (interquartile range)	1.1 (0.9–1.5)	1.1 (0.8–1.3)	
Geometric mean (95% CI)	1.2 (1.1–1.3)	1.1 (0.9–1.3)	1.13 (0.99–1.28)
Imaging			
Left ventricular ejection fraction[e], mean ± SD	47 ± 14	46 ± 13	0.79 (–3.27 to 4.85)[f]
Length of admission at ICU, d, median (interquartile range)	4 (3–7)	3 (2–5)	
Geometric mean (95% CI)	5 (4–5)	3 (3–4)	1.32 (1.15–1.51)
Duration of hospitalization, d, median (interquartile range)	13 (6–22)	13 (6–20)	
Geometric mean (95% CI)	11 (10–13)	11 (10–13)	1.00 (0.84–1.20)

MAP = mean arterial pressure, OR = odds ratio, TTM = targeted temperature management.
[a]The effect size is the ratio of geometric means unless otherwise noticed. For mean differences, the targeted normothermia was the reference group.
[b]Mean difference was reported as effect size as ratio of geometric means could not be calculated.
[c]Highest dose that was administered during the first 4 d of hospitalization.
[d]Recurrence of ventricular tachycardia of ventricular fibrillation needing defibrillation.
[e]Left ventricular ejection fraction was assessed in 191 patients who underwent echocardiography or MRI during hospitalization.
[f]The effect size is the mean difference between the mild therapeutic hypothermia group and the targeted normothermia group.

At 1 year, 155 of 259 (59.8%) in the MTH group were alive compared with 124 of 187 (66.3%) in the targeted normothermia group (hazard ratio, 0.81 [95% CI, 0.59–1.11]; log-rank $p = 0.18$). The Mann-Whitney *U* test showed that CPC scores did not differ between the MTH and targeted normothermia groups, both at ICU discharge ($p = 0.053$) and at 90-day follow-up ($p = 0.26$) (**Fig. S3**, http://links.lww.com/CCM/G697) (Table 3). In both groups, neurologic hypoxic brain injury was the main cause of death (**Table S5**, http://links.lww.com/CCM/G697). Causal mediation analysis did not show that the time until TTM was reached acted as mediator for the relation between treatment (immediate/delayed) and outcome (**Table S6**, http://links.lww.com/CCM/G697). To assess the quality of life, 200 of 459 patients (43.6%) completed the quality of life Health Assessment Questionnaire at 1-year follow-up (Table 3). Median PCSs were 49.9 in the MTH

TABLE 3.
Primary and Secondary Endpoints

Endpoint	Mild Therapeutic Hypothermia (32–34°C) (*N* = 269)	Normothermia (36–37°C) (*N* = 190)	Effect Size (+95% CI)[a]
Survival until 90 d	171/269 (63.6)	129/190 (67.9)	0.86 (0.62–1.18)
Survival until 1 yr	155/259 (59.8)	124/187 (66.3)	0.81 (0.59–1.11)
CPC at ICU discharge			
1	62/261 (23.8)	67/173 (38.7)	Reference
2	67/261 (25.7)	32/173 (18.5)	2.26 (1.31–3.90)
3	43/261 (16.5)	18/173 (10.4)	2.58 (1.35–4.94)
4	11/261 (4.2)	2/173 (1.2)	5.94 (1.27–27.88)
5	78/261 (29.9)	54/173 (31.2)	1.56 (0.96–2.55)
CPC at 90 d follow-up			
1	150/269 (55.8)	115/188 (61.2)	Reference
2	12/269 (4.5)	11/188 (5.9)	0.84 (0.36–1.96)
3	7/269 (2.6)	1/188 (0.5)	5.37 (0.65–44.24)
4	2/269 (0.7)	0/188 (0.0)	Not applicable
5	98/269 (36.4)	61/188 (32.4)	1.23 (0.82–1.84)
Quality of life questionnaire (36-Item Short Form Survey)[b]			
Physical Component Score	49.9 (42.9–55.0)	50.9 (43.3–55.0)	
Geometric mean (+95% CI)	46.2 (44.3–48.3)	47.7 (45.3–50.2)	0.97 (0.91–1.04)
Mental Component Score	50.2 (42.2–56.3)	51.3 (42.8–56.2)	
Geometric mean (+95% CI)	46.9 (44.9–48.9)	47.3 (44.9–49.8)	0.99 (0.93–1.06)

CPC = cerebral performance category.
[a]Effect sizes are expressed in hazard ratio's for survival, odds ratios for neurologic outcomes, and ratio of geometric means with 95% CIs for physical and mental component scores.
[b]One hundred twenty-five patients in the mild therapeutic hypothermia group and 75 patients in the normothermia group completed the 36-Item Short Form Survey Health Survey Questionnaire at 1 yr follow-up.
Data are expressed in *n* (%).

group and 50.9 in the targeted normothermia group and did not differ between groups (ratio of geometric means, 0.97; 95% CI, 0.91–1.04). Median MCSs were 50.2 in the MTH group and 51.3 in the targeted normothermia group, respectively (ratio of geometric means, 0.99; 95% CI, 0.93–1.06). Furthermore, a subanalysis restricted to arrest characteristics showed that TTM strategy did not affect survival or neurologic outcome at 90 days (**Fig. S4**, http://links.lww.com/CCM/G697). Proportions of patients surviving 90 days and proportions of patients with good neurologic outcomes adjusted for in-hospital management are reported in **Figure S5** (http://links.lww.com/CCM/G697).

DISCUSSION

In this post hoc analysis of the COACT trial, treatment with MTH was not associated with improved 90-day and 1-year survival, compared with treatment with targeted normothermia. Groups were not found to differ on CPC scores at ICU discharge and 90 days and on patient-reported MCS and PCS after 1 year. Furthermore, no associations were found on cardiac arrest characteristics and the relation between TTM strategy and survival or neurologic outcome. This is the first study in a modern postcardiac care setting to compare TTM strategies in OHCA patients with shockable rhythm and no STEMI.

TABLE 4.
Logistic Regression on 90-Day Survival and Good Neurologic Outcome Adjusted for Center-Specific Factors

	Survival				Good Neurologic Outcome			
	Univariate Analysis, OR (95% CI)	*p*	Multivariable Analysis, OR (95% CI)	*p*	Univariate Analysis, OR (95% CI)	*p*	Multivariable Analysis, OR (95% CI)	*p*
Targeted temperature management strategy[a]	0.83 (0.56–1.22)	0.34	0.89 (0.45–1.73)	0.72	0.75 (0.50–1.10)	0.14	0.80 (0.41–1.55)	0.50

OR = odds ratio.

[a]Reference category = normothermia.

The association of targeted temperature management strategy and 90-day survival and neurologic outcome (defined as a Cerebral Performance Category score of 1 or 2) at 90 d adjusted for potential center-specific confounders (arrest-specific factors (i.e., witnessed arrest, time to return of spontaneous circulation [ROSC]), center-specific factors (i.e., academic center, extracorporeal membrane oxygenation center, ICU capacity), and patient characteristics (i.e., age, sex, history of coronary artery disease, hypertension, diabetes mellitus, cerebrovascular incident). Patients who had no information available on time to ROSC (per minute) could not be incorporated in the analysis ($n = 93$).

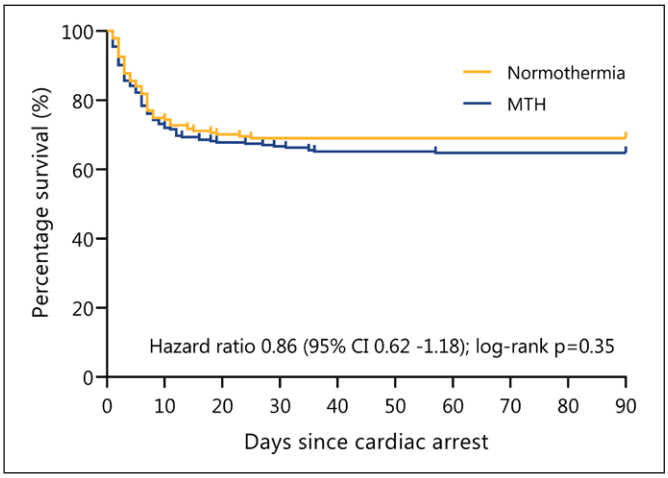

Figure 1. Kaplan-Meier estimates on survival until 90 d.
MTH = mild therapeutic hypothermia.

Survival and Neurologic Outcomes

Our results are in line with the TTM trial. The TTM trial compared a target temperature of 33°C with 36°C and also found no difference in survival or neurologic outcomes. Survival in the TTM study was around 50% in both groups (13). However, that trial included all initial rhythms, containing a mixed bag of cardiac arrest etiologies. In patients with nonshockable rhythm, a recently published randomized trial by Lascarrou et al (21) found improved survival with neurologic function in patients treated with deeper cooling. Although to date there are no strong data available supporting goal temperature based on the severity of illness, the results of Lascarrou et al (21) might imply that cardiac arrest characteristics may influence the effect of TTM and that patients with worse cardiac arrest characteristics, such as those with an nonshockable rhythm, might benefit more from deeper cooling. In these two trials, the amount of witnessed arrest and time to basic life support were comparable with our results (13, 21). However, Lascarrou et al (21) reported cardiogenic shock in 60% of the patients compared with only 15% in the TTM trial, and this indicates a worse hemodynamic profile in nonshockable cardiac arrest patients (13). In our study, we found that cardiac arrest characteristics (e.g., witnessed arrest, time to BLS) were not associated with survival and neurologic outcome stratified by TTM strategy. This is furthermore in line with a substudy of the TTM, which did not show that deeper cooling results in better outcomes in patients with hemodynamic instability (22). Further research is needed into cardiac arrest characteristics and the effect of TTM.

In our study, we found high rates of favorable neurologic outcomes, defined as a CPC score 1 or 2. Only one study that compared duration of 24 with 48 hours of TTM with 33°C found similar results (23). The most likely explanation for these favorable scores is that all patients included in the COACT trial had initial shockable rhythm, which itself is associated with improved survival outcomes compared with nonshockable

rhythms. Furthermore, the time delay from arrest to basic life support was relatively short. This may be the result of the efficient emergency medical services infrastructure in The Netherlands, leading to a shorter period of no-flow time and subsequently improved neurologic outcomes. However, the relatively favorable cardiac arrest characteristics may have attenuated potential effects of deeper cooling.

Patients in the MTH group of our study suffered from a number of adverse effects. Compared with patients in the targeted normothermia group, admission duration at the ICU was longer. Additionally, patients treated with MTH had lower blood pressures, had higher lactate rates, and needed more inotropic support during the first 4 days of admission, suggesting a worse hemodynamic profile. These results are in line with a post hoc analysis of the TTM trial, which found that patients in the 33°C group had higher Sequential Organ Failure Assessment scores, indicating the severity of organ dysfunction (22, 24). This effect on hemodynamics might be the result of increased use of sedative drugs. Despite the higher need for inotropes and dobutamine, we did not find that patients treated with MTH were at higher arrhythmogenic risk compared with patients who received targeted normothermia. Furthermore, neurologic function was comparable at 90-day follow-up.

Immediate Coronary Angiography

Patients in the COACT trial were randomized to an immediate coronary angiography strategy or a delayed strategy. Early initiation of TTM was recommended, and earlier studies have shown that inducing TTM during PCI is feasible and safe (25, 26). However in the COACT trial, patients assigned to the immediate coronary angiography group reached their targeted temperature later than patients assigned to the delayed coronary angiography strategy (median 5.4 hr [IQR, 2.9–8.6 hr] vs 4.7 hr [IQR, 2.6–7.5 hr]; ratio of geometric means, 1.19; 95% CI, 1.04–1.36). It has therefore been argued that a later achievement of target temperature might have attenuated any potential benefit gained from immediate coronary angiography (17). In the current study, we found that duration until TTM was reached did not act as a mediator for the relation between immediate or delayed angiography treatment strategy on 90-day survival, suggesting that a potential benefit of early angiography was not affected by the delay time to TTM.

Quality of Life

Neurologic injury secondary to cardiac arrest is related to quality of life outcomes (27, 28). Patients in the COACT trial reported similar outcome measures on PCS and MCS in both TTM strategies. This was also found in a study using comparable health questionnaires in patients assigned to target temperatures of either 33°C or 36°C, with means around 49 and 47 in both groups, numbers that were close to the reference range of the general population norm (29).

Cardiac Biomarkers

It has been suggested that hypothermia might have a cardioprotective effect on myocardial injury (30). We found a greater extent of cardiac biomarkers troponin and CK-MB in the MTH group. Higher CK-MB levels were also found in patients who were treated with prolonged TTM at 33°C (30). These results may suggest that deeper cooling may not be cardioprotective and might even harm cardiac function. However, echocardiography or MRI performed in 191 of the patients showed no difference in left ventricular function between the groups. Additionally, a study in patients who presented with STEMI and who were not resuscitated also found no effect of hypothermia on infarct size as measured by MRI (26).

Febrile Ranges

In contrast to previous observations, which have shown a decrease in the use of TTM since the publication of the TTM trial, we found that MTH was still widely practiced in Dutch centers (14–16).

Whether the possible benefit of TTM is caused by lowering body core temperature or by prevention of pyrexia remains debated. Nevertheless, in patients who receive targeted normothermia, temperature should be strictly maintained as they are more likely to digress into febrile ranges when the temperature rises above target. In line with the TTM-2 trial that compared hypothermia targeted at 33°C with early treatment of fever (37.6°C), we included seven patients who were treated with a goal temperature of 37.0°C although

this is currently not recommended in the European postresuscitation guidelines. Similarly, TTM-2 trial found no difference in overall survival or functional outcome at 6 months (31).

Limitations

We acknowledge a number of limitations to this study. First, this is a post hoc analysis of a prospective randomized trial comparing an immediate coronary angiography with a delayed coronary angiography strategy, and therefore, patients were not randomized by TTM strategy. Results of this substudy should therefore be considered exploratory and hypothesis generating. Second, each center had its own TTM and duration, in compliance of the European postresuscitation guidelines. Although we adjusted our primary analysis for center-specific characteristics as much as possible, some residual confounding of effect sizes by center-specific factors that were not recorded may still be present. Third, although patients with a prearrest CPC score of 3 or 4 were excluded in the COACT trial, we did not have detailed information on neurologic function prior to admission. Finally, 38 patients were not treated with TTM, and 41 patients who were treated with a target temperature outside the study's definition were not included in this substudy.

CONCLUSIONS

In the context of OHCA with shockable rhythm and no ST-elevation, treatment with MTH was not associated with improved 90-day survival compared with targeted normothermia. In addition, neurologic outcomes at ICU discharge and 90 days did not differ between groups, as well as patient-reported MCS and PCS after 1 year.

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