Original Investigation | CLINICAL TRIAL

Neurologic Function and Health-Related Quality of Life in Patients Following Targeted Temperature Management at 33°C vs 36°C After Out-of-Hospital Cardiac Arrest
A Randomized Clinical Trial

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IMPORTANCE Brain injury affects neurologic function and quality of life in survivors after cardiac arrest.

OBJECTIVE To compare the effects of 2 target temperature regimens on long-term cognitive function and quality of life after cardiac arrest.

DESIGN, SETTING, AND PARTICIPANTS In this multicenter, international, parallel group, assessor-masked randomized clinical trial performed from November 11, 2010, through January 10, 2013, we enrolled 950 unconscious adults with cardiac arrest of presumed cardiac cause from 36 intensive care units in Europe and Australia. Eleven patients were excluded from analysis for a total sample size of 939.

INTERVENTIONS Targeted temperature management at 33°C vs 36°C.

MAIN OUTCOMES AND MEASURES Cognitive function was measured by the Mini-Mental State Examination (MMSE) and assessed by observers through the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). Patients reported their activities in daily life and mental recovery through Two Simple Questions and their quality of life through the Medical Outcomes Study 36-Item Short Form Health Survey, version 2.

RESULTS In the modified intent-to-treat population, including nonsurvivors, the median MMSE score was 14 in the 33°C group (interquartile range [IQR], 0-28) vs 17 in the 36°C group (IQR, 0-29) (P = .77), and the IQCODE score was 115 (IQR, 79-130) vs 115 (IQR, 80-130) (P = .57) in the 33°C and 36°C groups, respectively. The median MMSE score for survivors was within the reference range and similar (33°C group median, 28; IQR, 26-30; vs 36°C group median, 28; IQR, 25-30; P = .61). The median IQCODE score was within the minor deficit range (33°C group median, 79.5; IQR, 78.0-85.9; vs 36°C group median, 80.7; IQR, 78.0-86.9; P = .04). A total of 18.8% vs 17.5% of survivors reported needing help with everyday activities (P = .71), and 66.5% in the 33°C group vs 61.8% in the 36°C group reported that they thought they had made a complete mental recovery (P = .32). The mean (SD) mental component summary score was 49.1 (12.5) vs 49.0 (12.2) (P = .79), and the mean (SD) physical component summary score was 46.8 (13.8) and 47.5 (13.8) (P = .45), comparable to the population norm.

CONCLUSIONS AND RELEVANCE Quality of life was good and similar in patients with cardiac arrest receiving targeted temperature management at 33°C or 36°C. Cognitive function was similar in both intervention groups, but many patients and observers reported impairment not detected previously by standard outcome scales.

TRIAL REGISTRATION ClinicalTrials.gov NCT01020916

JAMA Neurol. doi:10.1001/jamaneurol.2015.0169
Published online April 6, 2015.

Editorial

Supplemental content at jamaneurology.com

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Section Editor: Ira Shoulson, MD.

Brain injury is the primary cause of death for patients treated in an intensive care unit after out-of-hospital cardiac arrest (CA).[1,2] Severe neurologic impairment in long-term survivors is, however, rare, and most appear to have little or no disability when assessed with recommended outcome measures, such as the Cerebral Performance Category (CPC) and modified Rankin scale (mRS).[3] Good quality of life in survivors after CA has been reported[4] to be similar to that of the general population.[5,6] This finding notwithstanding, cognitive impairment has been detected in as many as half the survivors when assessed by more detailed neuropsychological investigations,[7] suggesting reduced quality of life[8] and increased caregiver strain.[9]

Targeted temperature management (TTM) has been implemented as a neuroprotective treatment for comatose CA survivors after reports of improved survival[10] and neurologic function.[10,11] The TTM trial compared 2 temperature management regimens, 33°C and 36°C, after out-of-hospital CA of presumed cardiac cause in adults. It found no differences in mortality or the composite outcome of death and poor neurologic function at 6 months. No difference was found in the distribution of CPC and mRS scores between the 2 intervention groups.[12] This report is an exploratory analysis of cognitive function and quality of life in the CA population included in the TTM trial using performance, observer-reported, and patient-reported measures.

Methods

Trial Design

The TTM trial was a parallel group randomized clinical trial performed in 36 intensive care units in Europe and Australia. The trial rationale, design, statistical analysis plan, background characteristics of patients, intervention performance, and main outcomes have been previously published.[12-14] Ethics committees in all countries approved the protocol. The trial protocol is reproduced in Supplement 1.

Patients

We consecutively screened unconscious (Glasgow Coma Scale score <8) adults (≥18 years of age) admitted to the hospital after out-of-hospital CA of presumed cardiac cause with sustained return of spontaneous circulation. The main exclusion criteria were an interval from return of spontaneous circulation to screening of more than 240 minutes, unwitnessed CA with asystole as the initial rhythm, suspected or known acute intracranial hemorrhage or stroke, and body temperature less than 30°C (for all exclusion criteria see the eAppendix in Supplement 2). Waived and delayed and/or written informed consent from a legal surrogate and written consent from each patient regaining mental capacity were obtained according to national requirements.

Randomization, Masking, and Intervention

Eligible patients were randomly assigned 1:1 to TTM at either 33°C or 36°C.[12] Health care professionals caring for trial patients were not masked to the intervention assignment because of inherent problems with masking of body temperature. However, they were instructed not to discuss allocation temperature with the patients' relatives, although body temperature measurements were not actively concealed. Physicians performing neurologic prognostication and assessors of outcomes were masked. For details of the intervention, see the eAppendix in Supplement 2.

Clinical Outcome Assessment

Patients alive after discharge from hospital and their relatives were invited to a structured follow-up assessment 6 months after the CA. Patients and relatives not able to attend were invited to be tested in their residence. If absolutely required, interviews were conducted by telephone. A central coordinator (G.L.) continuously monitored follow-up and maintained contacts.

Outcome was assessed from 4 perspectives: clinician-reported measures, performance measures, observer-reported measures, and patient-reported outcome measures. Clinician-reported measures were the previously used[12] ordinal scales for neurologic (CPC)[15] and overall outcome (mRS).[16,17] Performance measures were the Mini-Mental State Examination[18] (MMSE) for cognitive function and the MMSE Adult Lifestyles and Function Interview (ALFI) for patients assessed over the telephone.[19] The observer-reported measure of cognitive function was the Informant Questionnaire of Cognitive Decline in the Elderly (IQCODE).[20] The patients reported their level of daily function and mental recovery through Two Simple Questions[21] and their health-related quality of life with the Medical Outcomes Study 36-Item Short Form Health Survey, version 2 (SF-36v2).[22] For details of the tests, see eTable 1 in Supplement 2.

The MMSE scores general cognitive function on a scale of 1 to 30, with higher being better. The MMSE-ALFI was adapted for telephone interview and has a maximum score of 22. The MMSE scores of patients tested with the MMSE-ALFI were estimated by multiple imputation (see below) and this score included in the analyses. Although not validated in this specific patient population, the MMSE has been used in studies[23,24] of survivors of CA. The MMSE can detect moderate to severe cognitive decline of any cause but is less sensitive for mild cognitive impairment.[23] The serial 7's task, primarily used in our study, increased this sensitivity.[24]

To our knowledge, the IQCODE, a questionnaire for a patient's relative or close acquaintance, has not been used previously in CA studies. The IQCODE is validated for testing for dementia. The informant is classically asked to compare the patient's current status with that of 10 years before, but some studies[20,25] have used a shorter time frame. The scale ranges from 26 to 130, with lower scores indicating better function and a score of 78 suggesting no change. We adapted the IQCODE by asking informants to compare the present status of the patient with that before CA.

The Two Simple Questions have been previously adapted for use in studies of survivors of cardiac arrest from original research on the effects of stroke and correlates well with more extensive tests.[21] If the answer to question 1, "In the last 2 weeks did you require help from another person for your everyday activities?" is yes, another question, "Is this a new situation

following your heart arrest?" is posed. If the answer to the additional question is no, patients are grouped with those who answered no to the original question. Question 2 is "Do you feel that you have made a complete mental recovery after your heart arrest?"

The SF-36v2 is an extensively used broad generic health status assessment. The SF-36v2 scores are calculated using the Quality Metrics Health Outcomes Scoring Software, version 4.5 (QualityMetric Inc) and presented as norm-based T scores. T scores from the 8 domains are used to calculate 2 overall measures of health: the mental component summary (MCS) scores and the physical component summary (PCS). Prespecified continuous, binary, and categorical values for the assessments are presented in detail in eTable 1 in Supplement 2.

In the primary analyses that included all patients (modified intent-to-treat population), nonsurvivors are assigned the worst possible score for the performance and observer-reported measure: 0 for the MMSE and 130 for the IQCODE. Patient-reported outcomes are only analyzed for survivors.

Statistical Analysis

The detailed statistical analysis plan of this study is available at www.ctu.dk. The TTM trial included 950 patients, achieving the required sample size estimation performed for the primary outcome of survival until the end of the trial. Eleven patients were excluded from analysis for a total sample size of 939. The outcomes presented in this article were not part of the original power calculations and therefore defined as exploratory and hypothesis-generating.[14] Post hoc power calculations were performed to describe the minimally detectable differences for each test (eAppendix in Supplement 2). The primary analyses in this material were performed on a modified intent-to-treat population, defined as all patients randomized except those for whom consent was withdrawn for use of all trial data and those not fulfilling inclusion criteria and never receiving the intervention.[14]

Proportions are reported as number (percentage), normally distributed continuous data as mean (SD), and nonnormally distributed data as median (interquartile range [IQR]). Continuous, binary, and ordinal quantities are compared between the intervention groups using the Wilcoxon-Mann-Whitney test, χ^2 test, and Cochrane-Armitage test for trend, respectively. Missing data for MMSE, IQCODE, Two Simple Questions, PCS, and MCS were imputed using 10-fold multiple imputation, including the variables age, sex, time to return of spontaneous circulation, initial rhythm (shockable or not), circulatory shock on admission (or not), randomization code, CPC score at hospital discharge, CPC score at follow-up, mRS score at follow-up, IQCODE score, MMSE score, MMSE-ALFI score, Two Simple Questions 1 and 2 responses, MCS score, PCS score, and site category. Category 1 comprises the 2 sites enrolling the largest number of patients, and category 2 comprises the rest. All analyses and results in this article are from the imputed data set (eTable 2 in Supplement 2). SAS statistical software, version 9.3 (SAS Institute Inc), and SPSS statistical software, versions 17.1 and 22 (SPSS Inc), were used for all analyses. All tests are 2-sided, and $P < .05$ is considered to identify possible hypotheses to be tested prospectively.

Results

Patients

A total of 950 patients were enrolled from November 11, 2010, through January 10, 2013. The last follow-up was performed July 13, 2013. Eleven patients were excluded from analysis for a total sample size of 939. The modified intent-to-treat group consisted of 473 patients assigned to 33°C and 466 assigned to 36°C (**Figure**).[12]

At follow-up, 245 were alive in the 33°C group and 246 in the 36°C group, with 229 (93.5%) and 226 (91.9%), respectively, participating in the structured examination. Twelve patients in the 33°C group and 18 in the 36°C group were unable or refused to participate, and 4 and 2 patients, respectively, were lost to follow-up (Figure).

The patients alive at follow-up were similar in known prognostic baseline variables, occupational status, and place of stay, but more patients in the 33°C group had less than 12 years in school ($P = .002$) (**Table 1**). A total of 90.3% of survivors had returned to their home, but the fraction of patients working full or part time had decreased from 50.8% before arrest to 31.6% at 6 months after the CA, similar between groups (Table 1).

Outcomes

Median time from CA to follow-up was 186 days (IQR, 179-200 days). Follow-ups were performed face-to-face in 92.1% and by telephone in 7.9%. The Two Simple Questions and SF-36v2 were completed by 92.3% and 91.0% of survivors, respectively, and by proxies in 7.7% and 7.1%. The IQCODE, MMSE, and MMSE-ALFI were completed for 88.6%, 86.2%, and 6.1% of survivors. For the IQCODE, 74.8% of the observers were living with the patient at follow-up (eTable 3 in Supplement 2). Of those not living together, 73.0% met the patient at least once a week. Factors that potentially influenced neurologic assessments included neurologic disease, prearrest memory problems, dyslexia, and problems with hearing, vision, or speech without difference between the 2 intervention groups (eTable 4 in Supplement 2).

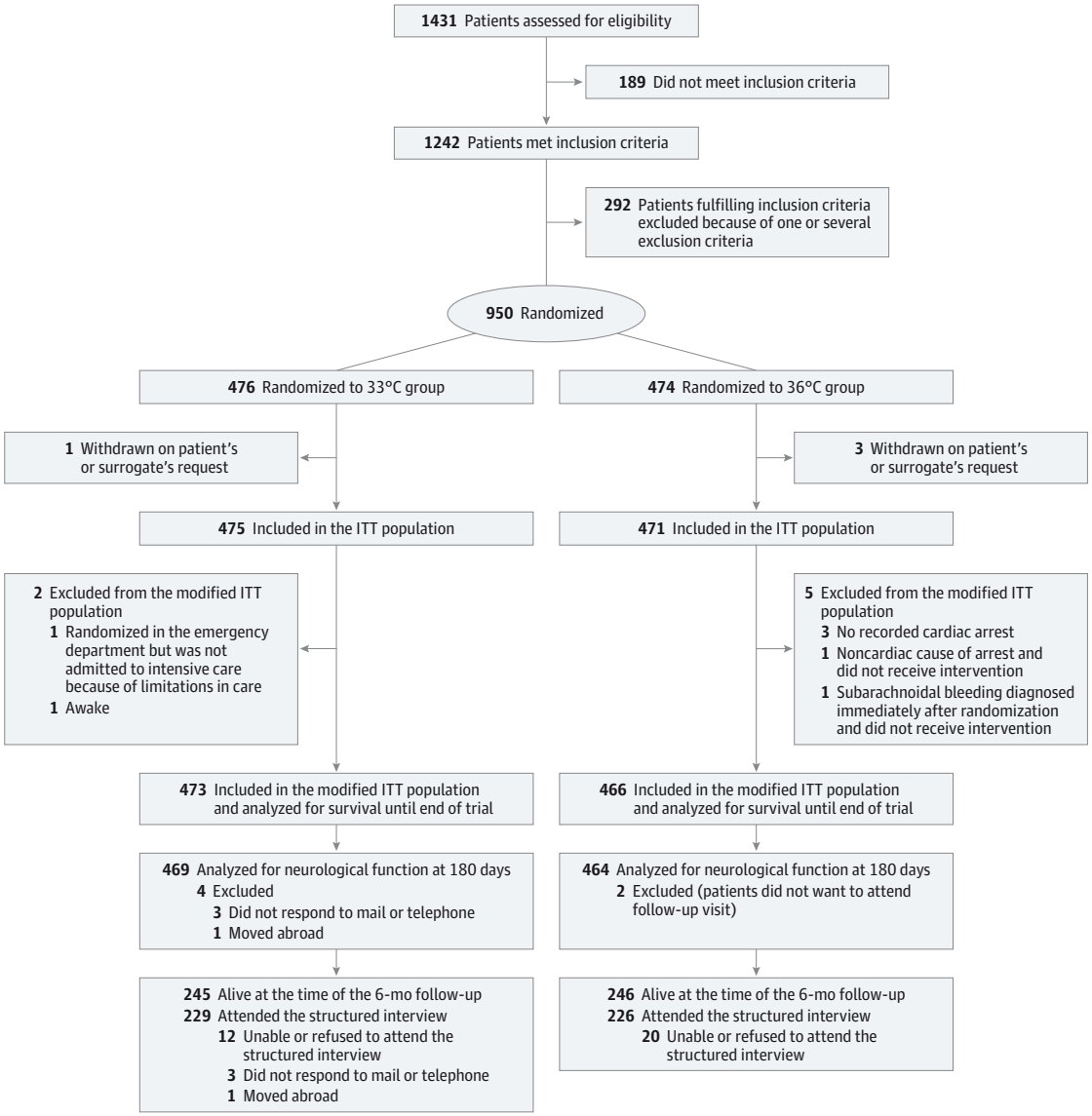
Performance Measures

For all patients, including nonsurvivors, the median MMSE score was 14 (IQR, 0-28) and 17 (IQR, 0-29) in the 33°C and the 36°C groups ($P = .77$), respectively. The median MMSE score for survivors was within the reference range and similar in the 33°C and 36°C groups (median, 28; IQR, 26-30; and median, 28; IQR, 25-30; $P = .61$). In an analysis of MMSE scores by category, no difference was found between the 33°C and 36°C groups ($P = .94$).

Observer-Reported Measures

The median IQCODE score for all patients, including nonsurvivors, was 115 (IQR, 79-130) and 115 (IQR, 80-130) ($P = .57$), respectively. The median IQCODE score for survivors was within the minor decline range in both groups: 79.5 (IQR, 78.0-85.9) in the 33°C compared with 80.7 (IQR, 78.0-86.9) in the 36°C group ($P = .04$) (**Table 2**). In an analysis of IQCODE scores by category, no difference was found between the 33°C and 36°C groups ($P = .32$) (**Table 3**).

Figure. CONSORT Flowchart



Assessment, randomization, and analysis populations (intention-to-treat [ITT] and modified ITT) and follow-up of the patients in the Target Temperature Management trial with reasons for exclusions.

Patient-Reported Measures

When patients were asked the first of the Two Simple Questions, no difference was found in the percentage of patients with an increased need for help in activities of daily living, with 46 (18.8%) of 245 and 43 (17.5%) of 246 in the 33°C and the 36°C groups, respectively (P = .71). When asked the second of the Two Simple Questions, 164 (66.9%) of 245 and 152 (61.8%) of 246 in the 33°C and the 36°C groups, respectively, thought they had made a complete mental recovery (P = .32).

The mean (SD) mental component summary score of the SF-36v2 was 49.1 (12.5) for survivors in the 33°C group compared with 49.0 (12.2) in the 36°C group, with no between-group difference (P = .77). The mean (SD) PCS scores were 46.8 (13.8) and 47.5 (13.8) in the 33°C and 36°C groups, respectively (P = .44). The mean MCS and PCS scores were within or very close to the reference range of the general population norm (score, ≥47). Complete case analyses and post hoc power calculations for the minimal detectable differences per outcome are available in the eAppendix and eTables 5 and 6 in Supplement 2.

Discussion

Using a structured long-term follow-up of performance, observer-reported, and patient-reported outcome measures in the TTM trial, we found no differences between patients receiving TTM at 33°C vs 36°C. Cognitive function measured

Table 1. Baseline and Background Characteristics of Survivors at Time of Follow-up[a]

Characteristic	33°C Group (n = 473)	36°C Group (n = 466)
Survivors at time of follow-up	245/473 (51.8)	246/466 (52.8)
Baseline characteristics at time of randomization		
Age, mean (SD), y	61/473 (12.9)	59/466 (12.7)
Male sex	210/245 (85.7)	203/246 (82.5)
First monitored rhythm		
Ventricular fibrillation, ventricular tachycardia, or otherwise responsive to direct current shock	228/245 (93.1)	232/246 (94.3)
Asystole	7/245 (2.9)	10/246 (4.1)
Pulseless electrical activity	9/245 (3.7)	3/246 (1.2)
Time from CA to return of spontaneous circulation, median (IQR), min[b]	20 (15-27)	20 (14-30)
Shock on admission[c]	19/245 (7.8)	24/246 (9.8)
Performed follow-up interview	229/245 (93.5)	226/246 (91.9)
Education of <12 years	136/229 (59.4)	102/226 (45.1)
Occupational status before cardiac arrest		
Working full time	95/229 (41.5)	101/226 (44.7)
Working part time	18/229 (7.9)	17/226 (7.5)
Unemployed	12/229 (5.2)	8/226 (3.5)
Retired	95/229 (41.5)	92/226 (40.7)
On sick leave	6/229 (2.6)	6/226 (2.7)
Occupational status at time of follow-up		
Working full time	39/229 (17.0)	38/226 (16.8)
Working part time	30/229 (13.1)	37/226 (16.4)
Unemployed	12/229 (5.2)	10/226 (4.4)
Retired	103/229 (45.0)	98/226 (43.4)
On sick leave	40/229 (17.5)	41/226 (18.1)
Place of stay at time of follow-up		
Home	206/229 (90.0)	205/226 (90.7)
Hospital	9/229 (3.9)	5/226 (2.2)
Rehabilitation center	5/229 (2.2)	4/226 (1.8)
Nursing home	4/229 (1.7)	6/226 (2.7)

Abbreviations: CA, cardiac arrest; IQR, interquartile range.

[a] Data are presented as number (percentage) of patients unless otherwise indicated. $P > .05$ in all comparisons except educational level (<12 years of education), which had $P < .002$.

[b] For unwitnessed CAs, intervals were calculated from emergency call to event.

[c] Defined as a systolic blood pressure less than 90 mm Hg for more than 30 minutes or end-organ hypoperfusion (cool extremities, urine output <30 mL/h, and heart rate <60 /min).

by MMSE and IQCODE was similar, and in accordance, the proportion of survivors who needed help with their activities of daily living and who considered themselves mentally recovered were also similar. Self-rated quality of life using the SF-36v2 was almost identical in the 2 groups. These findings are concordant with our previous report using 2 recommended clinician-reported discriminators, CPC and mRS.[12]

Despite survival rates after CA more than doubling between early neuroprotective trials of thiopentone[26] or calcium channel blockade[27] and later studies using hypothermia,[10,11] most survivors in these trials consistently made a good recovery as defined by CPC. Thus, improved survival has not been accompanied by an increase in survivors with severe neurologic deficits. However, the observation that good outcome defined by CPC is almost identical to survival might call for tests and scales that can improve the discrimination of the degree of neurologic recovery. The mRS has a higher resolution than the CPC, and it is evident from our previous report that many patients in the highest CPC (good cerebral performance) still have degrees of disability and dependence by their mRS score.[12] The patient description provided by the CPC and mRS may be improved further by neuropsychological testing,[28] and a meta-analysis[7] of several small detailed studies, using such tests, indicates that as many as half of the survivors of CA have measurable cognitive deficits. However, no neuropsychological test battery is generally accepted for survivors of CA because of their complexity and the availability of trained neuropsychologists.

As an alternative to neuropsychological testing, we used a novel approach for clinical outcome assessment in the TTM trial[29] and combined a performance outcome measure (MMSE) with information reported by a clinician (CPC and mRS), the patient (Two Simple Questions and SF-36v2), and an observer (IQCODE). From the clinician's perspective, outcome was good in 9 of 10 survivors.[12] The MMSE results of this study convey the same message, with a median score of 28, similar to an age-matched control group.[30] Most survivors reported that they were independent in their daily activities, but one-third stated that they had not made a complete mental recovery after their CA. This finding was supported by the report of a relative or close acquaintance, observing a minor decline by IQCODE in half of the survivors and a moderate or severe decline in a quar-

Table 2. Outcomes of Cognitive Function and Health-Related Quality of Life at Follow-up[a]

Outcome	33°C Group (n = 473)	36°C Group (n = 466)	*P* Value
Survivors at follow-up, No. (%)[b]	245 (51.8)	246 (52.8)	.76[c]
Performance measures			
MMSE score (all patients)			
Median (IQR)	14 (0-28)	17 (0-29)	.77[d]
Mean (SD)	13.8 (13.8)	14 (13.8)	
MMSE score (of survivors at follow-up)			
Median (IQR)	28 (26-30)	28 (25-30)	.61[d]
Mean (SD)	26.7 (4.3)	26.5 (4.8)	
Observer-reported measures			
IQCODE score (all patients)			
Median (IQR)	115 (79-130)	115 (80-130)	.57[d]
Mean (SD)	106 (24.2)	106 (25.1)	
IQCODE score (of survivors at follow-up)			
Median (IQR)	79.5 (78.0-85.9)	80.7 (78.0-86.9)	.04[d]
Mean (SD)	83.2 (12.3)	85.4 (13.2)	
Patient-reported measures			
TSQ1: "In the last 2 weeks did you require help from another person for your everyday activities?," No. (%) of yes responses[d,e]	46/245 (18.8)	42/246 (17.1)	.71[c]
TSQ2: "Do you feel that you have made a complete mental recovery after the cardiac arrest?," No. (%) of yes responses	163/245 (66.5)	152/246 (61.8)	.32[c]
SF-36v2 MCS (of survivors at follow-up)			
Median (IQR)	51.3 (40.8-58.3)	51.2 (40.5-58.0)	.79[d]
Mean (SD)	48.4 (12.7)	48.3 (13.4)	
SF-36v2 PCS (of survivors at follow-up)			
Median (IQR)	46.9 (38.5-54.4)	48.3 (39.1-55.2)	.45[d]
Mean (SD)	45.8 (10.5)	46.3 (11.3)	

Abbreviations: IQCODE, Informant Questionnaire of Cognitive Decline for the Elderly; IQR, interquartile range; MCS, mental component summary; MMSE, Mini-Mental State Examination; PCS, physical component summary. SF-36v2, Medical Outcomes Study 36-Item Short Form Health Survey, version 2; TSQ, Two Simple Questions.

[a] All analyses were performed on the imputed data set. Complete case analyses are available in the eAppendix in Supplement 2.

[b] Includes 6 patients lost to follow-up for evaluation of neurologic function and quality of life who were alive at time of follow-up.

[c] *P* values obtained by the χ^2 test.

[d] *P* values obtained by the Wilcoxon-Mann-Whitney test.

[e] The number excludes patients who did need help for everyday activities but when this situation was not new after the cardiac arrest.

Table 3. Analysis of MMSE and IQCODE per Category[a]

Test	33°C Group (n = 473)	36°C Group (n = 466)	*P* Value
MMSE			
Normal impairment (reference range, 27-30)	173 (36.6)	167 (35.8)	.94
Mild impairment (reference range, 21-26)	50 (10.6)	52 (11.2)	
Moderate impairment (reference range, 11-20)	19 (4.0)	23 (4.9)	
Major impairment (reference range, 0-11)	3 (0.6)	4 (0.9)	
Dead	228 (48.2)	220 (47.2)	
IQCODE			
No decline (reference range, 26-78)	107 (22.6)	82 (17.6)	.32
Minor decline (reference range, 79-83)	65 (13.7)	78 (16.7)	
Moderate decline (reference range, 84-86)	16 (3.4)	21 (4.5)	
Major decline (reference range, 87-130)	57 (12.1)	65 (13.9)	
Dead	228 (48.2)	220 (47.2)	

Abbreviations: IQCODE, Informant Questionnaire of Cognitive Decline for the Elderly; MMSE, Mini-Mental State Examination.

[a] All analyses were performed on the imputed data set. Complete case analyses are available in the eAppendix in Supplement 2. *P* values obtained by Cochran-Armitage trend test.

ter. In agreement with more detailed neuropsychological investigations,[7] it appears that subtle cognitive dysfunction may be missed by the standard follow-up instruments CPC and mRS and provide a possible explanation for the observation that less than half of the patients in both intervention groups had returned to their previous level of employment. However, reasons for prolonged sick leave are complex. We note that the PCS score of our CA survivors was comparatively more reduced than their MCS score. An Australian report[6] also observed this disparity. Of interest, despite its grounding in describing physical capability, the PCS score of the SF-36v2 correlates with cognitive ability.[8] The association among cognitive deficits, physical disabilities, and participation in society warrants further explanation and studies.

The MMSE has a low sensitivity to detect mild cognitive impairment, which is consistent with our results.[31] The scores were similar in the intervention groups, in both the primary analysis that included nonsurvivors and an analysis of survi-

vors only. The IQCODE is developed for dementia screening[20] and has been used as a sensitive method to detect cognitive decline in patients with stroke.[32] To our knowledge, it has not been used previously for describing patients after CA and requires further validation. Still, we propose that this questionnaire, directed to someone who has continuously followed up a patient's daily activities before and after their CA, may be more sensitive to subtle cognitive change than a categorical outcome scale or a screening test. In the primary analysis, including nonsurvivors, the IQCODE was identical in the intervention groups. However, there was a statistically significant median difference of 1.2 IQCODE points in favor of the 33°C regimen when analyzing survivors (P = .04). This statistical outcome must be interpreted cautiously because we did not correct P values for multiple analyses of trial outcomes, and our post hoc power calculation indicates insufficient power to detect a difference of less than 4.6 points in the IQCODE. In addition, a point estimate in the main outcome survival, indicating more deaths in the 33°C group,[12] makes between-group comparisons restricted to survivors prone to survival bias.

We note that more patients in the 33°C group had less than 12 years of education. This random bias may have affected the IQCODE results because informants of disproportionately highly educated patients might have recognized decline more easily. We therefore emphasize the uncertainty of any conjecture based on these results. Nevertheless, it is plausible that subgroups of patients with CA would benefit from temperature management at either 33°C or 36°C. A future challenge will be to identify these potential groups and perhaps allow for tailored therapies.[33]

To our knowledge, this is the largest prospective study of cognitive outcome and quality of life to date in patients after out-of-hospital CA. The TTM trial included 4 of 5 patients admitted to the participating centers, and the results should therefore be considered generalizable.

The high rate of face-to-face follow-up reflected a priority given to cognitive testing as part of the trial. However, the optimum timing of patient assessment remains to be determined. Although survival and crude neurologic outcome might have reached steady state at 6 months, cognitive ability, quality of life, and capacity to return to work might change after a longer observation period.

We recognize the risk of bias in our results if informants noted the allocated temperature at the bedside during the intervention. They could have passed this information to our patients. Therefore, uncertain influences based on the knowledge of their treatment could have affected answers to the Two Simple Questions, the IQCODE, and the SF-36v2.

Conclusions

Quality of life was good and similar in patients with CA receiving TTM at 33°C or 36°C. Cognitive function was similar in both intervention groups, but many patients and observers reported impairment not detected previously by standard outcome scales.

ARTICLE INFORMATION

Accepted for Publication: February 10, 2015.

Published Online: April 6, 2015. doi:10.1001/jamaneurol.2015.0169.

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Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Cronberg, Lilja, Winkel, Wetterslev, Nielsen.
Obtained funding: Cronberg, Erlinge, Friberg, Wanscher, Nielsen.
Administrative, technical, or material support: Cronberg, Lilja, Nielsen.
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Conflict of Interest Disclosures: Dr Erlinge reported receiving speaker fees from Philips and Zoll. Drs Friberg, Nielsen, Pellis, and Wise reported receiving lecture fees from Bard Medical. No other disclosures were reported.

Funding/Support: The TTM trial was funded by independent research grants from the following nonprofit or governmental agencies: grants 20090275 and 20120491 from the Swedish Heart Lung Foundation, grant 100001 from the Arbetsmarknadens Försäkringsaktiebolag Insurance Foundation, grant 2013-3572 from the Swedish Research Council, regional research support, grants 134281 and 286321 from Region Skåne, grants 209851, 295281, 296211, and 353301 from governmental funding of clinical research within the Swedish National Health Services, Thelma Zoega Foundation, Krapperup Foundation, Thure Carlsson Foundation, Hans-Gabriel and Alice Trolle-Wachtmeister Foundation for Medical Research, Skåne University Hospital (all from Sweden), grant 7-12-0454 from TrygFonden (Denmark), and the European Clinical Research Infrastructures Network.

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication.

Group Information: The TIM Investigators are listed in Supplement 1.

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