Cognitive Function in Survivors of Out-of-Hospital Cardiac Arrest After Target Temperature Management at 33°C Versus 36°C

Running title: Lilja et al.; Cognitive function after cardiac arrest

Gisela Lilja, OT1,2; Niklas Nielsen, MD, PhD2,3; Hans Friberg, MD, PhD2,4; Janneke Horn, MD, PhD5; Jesper Kjaergaard, MD, DMSG6; Fredrik Nilsson, PhD7; Tommaso Pellis, MD8; Jørn Wetterslev, MD, PhD9; Matt P. Wise, MD, DPhil10; Frank Bosch, MD, PhD11; John Bro-Jeppesen, MD, PhD5; Iole Brunetti, MD12; Azul Forti Buratti, MD13; Christian Hassager, MD, DMSG9; Caisa Hofgren, PhD14; Angelo Insorsi, MD12; Michael Kuiper, MD, PhD5,15; Alice Martini, MS8; Nicki Palmer, RN10; Malin Rundgren, MD, PhD2,4; Christian Rylander, MD, PhD16; Annelou van der Veen, RN5; Michael Wanscher, MD, PhD17; Helen Watkins, DClinPsy10; Tobias Cronberg, MD, PhD1,2

1Dept of Neurology and Rehabilitation Medicine, Skåne University Hospital, Lund, Sweden; 2Dept of Clinical Sciences, Lund University, Lund, Sweden; 3Dept of Anesthesiology and Intensive Care, Helsingborg Hospital, Helsingborg, Sweden; 4Dept of Intensive and Perioperative Care, Skåne University Hospital, Lund, Sweden; 5Dept of Intensive Care, Academic Medical Center, Amsterdam, Netherlands; 6Dept of Cardiology, The Heart Centre, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark; 7Research and Development Centre, Unit for Medical Statistics and Epidemiology, Skåne University Hospital, Lund, Sweden; 8Dept of Anaesthesia, Intensive Care and Emergency Medical Service, Santa Maria degli Angeli Hospital, Pordenone, Italy; 9Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark; 10Adult Critical Care, University Hospital of Wales, Cardiff, United Kingdom; 11Dept of Intensive Care, Rijnstate Hospital, Arnhem, Netherlands; 12Dept of Anaesthesia and Intensive Care, IRCSS San Martino IST, University of Genoa, Genoa, Italy; 13Academic Unit of Child and Adolescent Psychiatry, Imperial College, London, United Kingdom; 14Institute of Neuroscience and Physiology, Section of Clinical Neuroscience and Rehabilitation Medicine, Sahlgrenska Academy, University of Gothenburg, Sweden; 15Dept of Intensive Care, Medical Center Leeuwarden, Leeuwarden, Netherlands; 16Dept of Anesthesiology and Intensive Care, Sahlgrenska University Hospital, Gothenburg, Sweden; 17Dept of Cardiothoracic Anesthesiology, The Heart Centre, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark

Address for Correspondence:
Gisela Lilja, OT
Center for Resuscitation Science in the Oresundregion
Skane University Hospital, Lund
Kampradhuset, Barngatan 2 B, 4th floor
S-221 85, Lund, Sweden
Tel: 46 46 176084
Fax: 46 46 176094
E-mail: gisela.lilja@med.lu.se

Abstract

Background—Target temperature management is recommended as a neuro-protective strategy after out-of-hospital cardiac arrest. Potential effects of different target temperatures on cognitive impairment commonly described in survivors are not sufficiently investigated. The primary aim of this study was to evaluate whether a target temperature of 33°C compared to 36°C was favourable for cognitive function, and secondary to describe cognitive impairment in cardiac arrest survivors in general.

Methods and Results—Study-sites included 652 cardiac arrest survivors originally randomized and stratified for site to temperature control at 33°C or 36°C within the Target Temperature Management trial. Survival until 180 days after the arrest was 52% (33°C n=178/328 36°C n=164/324). Survivors were invited to a face-to-face follow-up and 287 cardiac arrest survivors (33°C n=148/36°C n=139) were assessed with tests for memory (Rivermead Behavioural Memory Test), executive functions (Frontal Assessment Battery) and attention/mental speed (Symbol Digit Modalities Test). A control-group of 119 matched patients hospitalized for acute ST-elevation myocardial infarction (STEMI) without cardiac arrest performed the same assessments. Half of the cardiac arrest survivors had cognitive impairment, which was mostly mild. Cognitive outcome did not differ (p >0.30) between the two temperature groups (33°C/36°C). Compared to STEMI-controls attention/mental speed was more affected among cardiac arrest patients, but results for memory and executive functioning were similar.

Conclusions—Cognitive function was comparable in survivors of out-of-hospital cardiac arrest when targeting a temperature of 33°C and 36°C. Cognitive impairment detected in cardiac arrest survivors was also common in matched STEMI-controls not having had a cardiac arrest.

Clinical Trial Registration Information—ClinicalTrials.gov. Identifier: NCT01946932.

Key words: heart arrest, resuscitation, myocardial infarction, brain, follow-up study, out-of-hospital cardiac arrest, hypothermia, induced, cardiovascular diseases, cognition, brain injuries
Brain injury is the major cause of death after hospital admission in patients who are admitted following successful resuscitation from an out-of-hospital cardiac arrest (OHCA). Mild induced hypothermia to 32-34°C is recommended as a neuro-protective strategy for patients who remain comatose after hospital admission. Recently, the Target Temperature Management after out-of-hospital cardiac arrest (TTM)-trial found no benefit for survival or crude neurological function when targeting a temperature of 33°C compared to 36°C during an intervention period of 36 hours.

Considering the impact of brain injury on survival after cardiac arrest, severe neurological impairment is rare among survivors, with as many as 90% achieving good long-term neurological outcome according to the commonly used Cerebral Performance Categories (CPC) scale. Despite a good outcome according to CPC, cognitive difficulties may nevertheless be prevalent as reported in several smaller studies using neuropsychological tests. In a recent review, 30-50% of survivors from cardiac arrest were reported to suffer from cognitive impairment. The generalizability of previous studies is poor due to small sample sizes, missing data and patient selection excluding those with a poor outcome, including only patients with severe symptoms or absence of a non-arrest control group.

Optimally OHCA-survivors should be evaluated for the cognitive functions known to be most affected; memory, attention and executive functions. One small study, within the Hypothermia after Cardiac Arrest-trial evaluated the effects of induced hypothermia against no temperature management and reported no statistically significant differences between the two intervention groups, but a tendency towards more favourable results for hypothermia-treated patients.

In this study we hypothesized primarily that, due to possible neuro-protective effects,
cognitive impairment would be less pronounced in patients treated with 33°C compared to those treated with 36°C, and secondarily that both groups (33°C and 36°C) of OHCA-survivors would have more cognitive impairment than a group of control patients matched for important risk-factors.

Methods

Study design

The protocol for this pre-defined study in the TTM-trial (ClinicalTrials.gov: NCT01020916) was published\textsuperscript{16} and registered at ClinicalTrials.gov: NCT01946932. Patients were randomized, stratified for site, to targeted temperature management of 33°C or 36°C after cardiac arrest with a total intervention period of 36 hours.\textsuperscript{5, 17} Patients surviving to hospital discharge were invited to a face-to-face follow-up at approximately 180 days post-arrest to complete the neurological outcome assessments of the main trial.\textsuperscript{16-18} At these follow-up visits patients at 20 out of 36 sites in five European countries (Sweden, Denmark, the Netherlands, Italy, and United Kingdom) participated in this study. Matched control-patients completed the same assessments as the OHCA-survivors. Examiners were blinded for the targeted temperature management allocation but not whether the patient was a control. The follow-up meetings were performed from June 2011 to September 2013. All participating centres had ethical approval for the TTM-trial with additional approval for this study. Written informed consent was obtained before follow-up.

Setting

The face-to-face follow-up was primarily performed at the participating institutions. If a patient was unable to visit the institution, the follow-up was performed in the patient’s home/nursing home. Examiners were an occupational therapist, a psychologist, a research nurse or a physician.
The tests were administered in a defined order, pre-specified in a written study manual. Examiners attended training and follow-up meetings. The study coordinator performed regular monitoring and provided support.

**Study population**

Within the TTM-trial⁵ unconscious patients 18 years or older with OHCA of a presumed cardiac origin irrespective of initial rhythm were randomized at hospital arrival to targeted temperature management at either 33°C or 36°C. The randomisation and inclusion process has been described previously.⁵, ¹⁶, ¹⁷ For the present study, control patients were recruited with an intended 2:1 ratio where every second OHCA patient was matched to a control with a pre-specified estimation of 120 patients in each group. The control population was recruited at one site in each country from a cohort of ST-elevation myocardial infarction patients (STEMI) treated with percutaneous coronary intervention, matched for age, gender, country and time-point of hospitalization (±two weeks). Socio-demographical and medical background variables were collected.¹⁶

**Outcome Assessment**

Following the neurological tests of the main trial¹⁷, ¹⁸ patients from the 33°C-group, the 36°C-group and the STEMI-control group performed cognitive tests¹⁶ selected to assess the most commonly affected cognitive domains after OHCA: memory, attention, and executive function.¹¹ In addition potential differences in psychological stress between the groups were tested.

Rivermead Behavioural Memory Test (RBMT)¹⁹ evaluates memory functions needed in everyday life. The profile-score has pre-defined cut-off levels to grade the memory performance into normal (22-24) mild (17-21), moderate (10-16) or severe (0-9) impairment.¹⁹

Frontal Assessment Battery²⁰ is a screening battery for executive impairments. Scores
range from 0-18 (lower scores indicates poorer performance).\textsuperscript{20} A cut-off at 14 has been found to accurately separate normal from impaired function.\textsuperscript{21}

Symbol Digit Modalities Test (SDMT)\textsuperscript{22} assesses the ability to maintain attention and mental speed. Raw scores are transformed into age and education adjusted z-scores.\textsuperscript{22} Scores below one standard deviation (SD) are considered low and 2 SD very low. A cut-off used to indicate possible cerebral dysfunction is 1.5 standard deviation below the mean.\textsuperscript{22}

Hospital Anxiety and Depression rating Scale (HADS)\textsuperscript{23} is a questionnaire evaluating psychological stress with separate subscales for anxiety and depression, each containing 7 items with an individual score of 0-3 (lower is better). Subscale sum scores <8 are considered normal.\textsuperscript{23}

**Statistical Analysis**

Statistical analyses were performed on three levels. Level 1 embraces all randomized patients in the TTM-trial at the centres participating in this study (33°C and 36°C) and includes the deceased to avoid survival bias. Level 2 includes all patients surviving to follow up at the study centres. In the third exploratory level (level 3) only survivors that actually participated in the follow-up were analysed. STEMI-controls were included in the third level of analysis only.

Analysis level 1 (*Figure 1*): Differences in cognitive impairment between the two treatment groups measured by FAB, RBMT and SDMT were analysed with scores as a continuous variable using the non-parametric Mann-Whitney-Wilcoxon test, and the Bonferroni-Holm method to correct for multiple testing. Deceased patients were assigned a lower rank than the lowest rank of those observed, and multiple imputations (online-only Data Supplement) were performed for alive non-responders (not participating in the testing) and for missing data. A stratified analysis was performed to explore influences of country using the Kruskal-Wallis test.
Analysis level 2: The same analyses as in level 1 were repeated with exclusion of the deceased patients, as sensitivity analyses.

Analysis level 3: The third exploratory analysis included only those patients who participated in the follow-up and the matched STEMI-controls. Since baseline imbalance was likely at this level socio-demographical and medical background variables are shown if present in ≥10% of the patients in any of the groups and potential between-group differences were analysed by Fisher’s test for binary/categorical data or Kruskal-Wallis/Mann-Whitney-Wilcoxon test for continuous data. The categorical results of the assessments (RBMT, FAB, SDMT) based on pre-specified cut-off values (e.g. normal-mild-moderate-severe impairment) are only reported descriptively as percentage of cases at each level, with the controls presented as a substitute for lack of baseline data. Continuous scores and multiple imputations for missing values were used to identify statistically significant differences between the three groups. Analyses were performed both unadjusted (Kruskal-Wallis test) and adjusted for covariates using ordinal regression (FAB, RBMT) or a univariate general linear model (SDMT). Sex and country were used as covariates in all adjusted models. Additionally, the adjusted model for FAB and RBMT included age and education as covariates, already adjusted for in the SDMT by conversion to z-scores. Post-hoc analyses, with the false discovery rate to correct for multiplicity, was performed only if the overall test had a p-value <0.05. Descriptive data for the tests are presented for complete and imputed cases. An a priori sample size calculation showed >80% power to detect a 10% difference between the groups based on the RBMT profile score.\textsuperscript{13} Statistical analyses were performed using SPSS 22.0 and R 3.10.\textsuperscript{24}
Results

At the 20 participating sites 652 OHCA-patients were included from the TTM-trial with 328 randomized to the 33°C-group and 324 to the 36°C-group. All patients at each site were included. In the 33°C-group 150 patients died within the first 180 days, compared to 160 in the 36°C-group. Of survivors 287 (90% of patients alive and eligible to include, 84% of alive) participated in the face-to-face follow-up (148 in the 33°C-group and 139 in the 36°C-group) and were matched to 119 STEMI-control patients. The flowchart for inclusion in this study is shown in Figure 1. Of all eligible patients 10% had a CPC 3-4, equal in both groups (Figure 1) and 42% of these denied or were unable to participate in the follow-up. Consequently, a higher percentage of missing patients were severely impaired (42%) than participants (7%). Of STEMI-patients identified as possible controls (n=192), we were unable to contact 14% to ask for participation and an additional 24% declined. In total 38% of eligible controls were missing and most common reasons for not participating were: not interested, already participating in several studies or no time (e.g. working full-time).

Socio-demographic and medical background variables are presented for OHCA patients and the controls in Table 1 and 2 and were representative of the whole TTM-population (Supplemental Table 1). Among patients included in the level 3 analysis, individuals in the 33°C-group were slightly older, had less years of education, received less bystander cardiopulmonary resuscitation and more often had a history of ischemic heart disease and/or arrhythmia. All other pre-hospital variables were similar

Levels of depressive and anxiety symptoms according to the HADS (Table 2) did not differ between the three groups (p>0.30). Among patients that worked before the event, 46% of the OHCA-patients in both groups had returned to their previous level of occupation at the time
of follow-up vs. 72% of the controls (p=0.008), while 69% of the OHCA-patients versus 80% of the controls had returned to work in some degree (p=0.23). Among patients working at the time of the event 5% (n=7) of OHCA-patients vs. 10% (n=5) of STEMI-controls had retired.

In the primary analysis including dead and imputed patients (Figure 1, level 1) the three tests; RBMT, FAB and SDMT were descriptively similar (Table 3) and p-values indicated no statistically significant differences between the two temperature interventions with all test having a p-value > 0.30 (Supplemental Table 2), both when including and excluding deceased patients. Stratification by country did not change these results.

In the exploratory comparisons of participants in the face-to-face follow up and controls (Figure 1, level 3) approximately half of the OHCA-patients and controls obtained a normal score at the memory assessment (RBMT) (Figure 2). Less than 10% of the OHCA survivors had scores compatible with a severe memory disturbance, but almost none of the controls. When the comparison was expanded to include patients with moderate impairment 20% of OHCA-patients had moderate-severe memory impairment as compared to 17% of the controls. The mean RBMT-scores were similar for OHCA-patients and STEMI-controls (Table 3). No statistically significant group differences were found overall (unadjusted p=0.46/ adjusted p=0.06).

Executive dysfunction was detected by the FAB in 20-23% of OHCA-patients participating in the follow-up (Figure 3) compared to 13% of the controls. The analysis of the continuous FAB-score did not show any statistically significant difference between the three groups (unadjusted p=0.22). However, including the specified covariates there was a statistically significant difference (adjusted p=0.008). An interaction between group and country (p=0.017) was found and further post-hoc analyses showed a statistical significant difference between all cardiac arrest patients and STEMI-controls in Italy (Italy: 33°C /STEMI-controls p=0.01 and
36°C/STEMI-controls p=0.003) but no statistical significant difference between the two temperature groups (Italy; 33°C /36°C p=0.59). There were no significant differences found between any of the three groups in the other countries (p >0.30).

The two groups of OHCA-patients performed similarly but worse than STEMI-controls on the SDMT assessing mental speed and attention (Table 3), and more than half of the OHCA population in Level 3 had low z-scores (<-1) (Figure 4). The overall analysis of the SDMT detected a statistically significant difference between the three groups (unadjusted p<0.001). Unadjusted post-hoc analyses showed a difference between the OHCA groups compared to the controls (33°C/STEMI-controls p=0.007, 36°C/STEMI-controls p<0.001) but no statistical significant difference between the two temperature groups (33°C/36°C p=0.65) Also the covariate-adjusted analysis revealed a statistically significant result (adjusted p=0.02). The additional adjusted post-hoc analysis did not show any difference between the two treatment groups (33°C/36°C p=0.94) but statistically significant differences between the STEMI-controls and the 33°C and 36°C groups respectively (33°C/STEMI-controls p <0.001, 36°C/STEMI-controls p <0.001). Supplemental Table 3 shows estimated means (SDMT z-scores) for the adjusted analysis.

Education and age but not gender had a significant effect on cognitive outcome in all adjusted analyses (FAB, RBMT). The patients in the 33°C-group were older and had a lower education level but adjustment for these small differences in baseline variables did not significantly alter the results of the comparisons between the two temperature groups. Both unadjusted and adjusted analyses showed very similar results with no significant differences between the two temperature groups.
Discussion

This study, performed within a large clinical trial of temperature management for cardiac arrest, included the majority of high recruiting centres in five countries and two-thirds of the patients randomized in the trial. We add to the results of the main trial\textsuperscript{5,18} that the two intervention groups behave similarly. Although we detected no differences between survivors allocated to 33°C or 36°C we could confirm the results of previous smaller and less controlled studies that cognitive impairment is common among OHCA-survivors. Impairment was typically mild-moderate with only a minority showing signs of severe brain injury. Importantly, our control group of disease matched STEMI-patients had cognitive difficulties resembling those of the cardiac arrest patients, except in the test of attention and processing speed (SDMT), where cardiac arrest survivors performed significantly poorer. This is a novel finding suggesting that other factors than the brain injury related to the cardiac arrest may be of major importance to explain cognitive impairment in OHCA-survivors.

Cognitive impairment at similar levels as for the OHCA-population has been reported for ICU-treated patients suffering critical illness without primary brain injury\textsuperscript{25-27} Potential causal factors include age and disease-severity at baseline, use of sedatives and analgesics in the ICU, neuro-inflammatory processes, systemic factors (e.g. hypotension, hypo/hyper glycaemia) and psychological morbidity (e.g. anxiety, depression and posttraumatic stress).\textsuperscript{26,27} The duration of delirium seems to play an important role for post-ICU cognitive impairment\textsuperscript{25} but the causality remains unexplained. Most studies of cognition in critically ill patients are hampered by similar methodological weaknesses as most OHCA-studies, including lack of objectively measured baseline-data and matched controls.

Due to the unexpected nature of a cardiac arrest, baseline cognitive performance is
difficult to assess. Assigning all cognitive impairment in OHCA-survivors to the brain injury related to the cardiac arrest can be misleading since cognitive impairment may be present prior to the arrest due to age and/or cardiovascular risk factors. A control group addressing this important confounder was included in only a minority of previous studies. These investigations all reported more cognitive problems in the OHCA-group but milder cognitive impairment was detected among 18-37% of control patients. We used a control group well matched regarding known risk factors for cognitive decline. When comparing the cardiac arrest patients with the STEMI-controls the residual cognitive impairment attributable to the OHCA was less than previously reported. Impaired memory was almost equally common for STEMI-controls and less than 50% of the detected executive dysfunction may be related to the OHCA.

Correspondingly, for many years a substantial cognitive decline following coronary by-pass-grafting (CABG) was reported. However, as investigators included adequately disease-matched controls without CABG a similar decline was found. CABG patients have resembling comorbidities as OHCA-patients and it is reasonable to assume that cognitive decline in these groups may be more influenced by age and underlying vascular disease rather than the consequence of a specific intervention or event. Diabetes and hypertension are associated with cognitive decline in late-middle age and to disregard these co-morbidities may lead to an overestimation of cognitive impairment associated with any cardiac disease. However, the lack of a healthy control group limits our conclusions regarding the possible contribution of the STEMI to cognitive disability in our control population, something that needs to be addressed in future studies.

There are an extensive number of cognitive tests available and to select the most accurate tests to evaluate patients surviving an OHCA is challenging as no gold standard tests or
combination of tests currently exists. We chose instruments with acceptable levels of reliability and validity, translated to the languages of the participating countries and without too specific demands on the examiner or patients in order to enhance inclusion and target the cognitive functions known to be the most commonly affected after OHCA.\textsuperscript{11} Although translated, a limitation is that most assessments we use lack further cross-validation studies.

RBMT is a sensitive test to evaluate mild cognitive impairment.\textsuperscript{34,35} Criticisms that it may be insensitive for very mild impairment have led to the updated RBMT-3 version, which was not available when the current study was commenced. The mean RBMT-score for the OHCA-survivors in our study was better than previously reported (17.4-18.1)\textsuperscript{13,36} but lower compared to a healthy sample (22.2).\textsuperscript{19} A normal memory score was obtained by 50\% of the patients in our study compared to the previously described 20\% for OHCA survivors.\textsuperscript{13,36} Although this might be an effect of improvements in care\textsuperscript{37,38} it may also reflect the much larger sample size in our study. Moreover, it is unlikely that the 14 (4\%) missing eligible patients with a poor outcome would affect this results if included together with the 19 (6\%) missing patients with a good outcome.

Frontal/executive impairment has been described as one of the most common findings in OHCA-survivors, particularly in the severely brain injured patients.\textsuperscript{39} Executive functions such as planning, flexibility and abstract thinking are important factors for the ability to learn strategies and adjust to new circumstances, which may be crucial for the patient’s recovery and ability to return to work. In our study executive dysfunction was less common than memory problems and diminished processing speed although 20\% of the OHCA-patients had a low score. As a limitation, we recognize that the prevalence of frontal impairment in our study may have been underestimated since we used only a short screening battery (FAB). Several validation
studies have shown that the FAB is sensitive to detect frontal executive impairment when compared with more extensive neuropsychological tests. However, most of these studies were performed on dementia patients\textsuperscript{20,40,41} and the FAB has not been validated in an OHCA-population.

Although reduction in processing speed was not uncommon among the STEMI-controls it was much more prevalent among the OHCA-patients measured with the SDMT-test. A decreased processing speed and attention deficit was found in more than 50\% of the OHCA-patients and may affect the patient’s ability to learn and focus on new information and slow the retrieval of stored memories. These functions are the most sensitive to brain injury of any cause.\textsuperscript{22} However, when testing memory function with the RBMT, OHCA-patients and STEMI-controls performed similarly, indicating that the consequences of a lower process speed for everyday life remains uncertain and that decreased processing speed may be compensated for by e.g. staying focused and spending more time on the task. This may explain why subjective memory complaints are more common among younger OHCA-survivors\textsuperscript{14} with higher levels of activities and demands. Lower processing speed is closely associated with fatigue, which is an important limitation for return to work and participation in leisure activities.\textsuperscript{42}

In our adjusted analyses there was a tendency towards worse cognitive outcome for Italian OHCA-patients with a larger difference to the controls in this country. At 180 days five of the Italian patients (13\% of Italian survivors) were in a vegetative state (CPC 4), an outcome not found in the other countries and 29\% of the Italian OHCA-survivors had a poor outcome (CPC 3-4). This has not been investigated, but possible explanatory factors, except for random effects, may be different traditions in practise of life support.

Most previous trials of cognitive impairment following cardiac arrest had high rates of
missing data describing only a selected sample of survivors\textsuperscript{7, 8, 10, 13, 14, 43, 44}. Among the strengths of the current study is the high inclusion ratio, but also that we were able to obtain information on patients who chose not to participate in the study but consented to the main trial. These data were used to perform multiple imputations. The fact that the imputed data set consisted of patients with worse outcome than the complete cases emphasizes the importance of this statistical approach.

As a limitation we recognize as a potential source of bias that STEMI-controls may have been more prone to participation if they experienced subjective cognitive complaints, or conversely that patients eligible with more severe problems may have declined to a higher extent.

Only a small group of OHCA survivors (<10\%) will survive with a severe brain injury and much of the milder cognitive impairment described are likely not attributable to the OHCA alone. The cognitive impairment must be understood not only in a context of the increased risk for ischemic brain injury due to the cardiac arrest, but also in relation to age, previous cardiovascular disease and factors of suffering a critical-illness and prolonged ICU-care.

**Conclusion**

We found no differences in cognitive outcome between out-of-hospital cardiac arrest survivors managed with targeted temperature management at 33°C or 36°C. Half of the cardiac arrest patients had cognitive impairment that was mostly mild and more often affected attention and processing speed. Although cognitive impairment was common among cardiac arrest survivors the impact of brain injury related to the cardiac arrest may have been overestimated as disease matched STEMI-control patients were found to have similar levels of impairment.
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**Conflict of Interest Disclosures:** Drs. Friberg, Nielsen, Pellis and Wise report lecture fees from Bard Medical.

**References:**


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Table 1. Socio-demographical and medical background variables for all patients in the study.

<table>
<thead>
<tr>
<th></th>
<th>Level 1 (All cardiac arrest including dead)</th>
<th>Level 2 (All cardiac arrest excluding dead)</th>
<th>Level 3 (Follow-up participants cardiac arrest and STEMI-controls)</th>
<th>Controls (n=119)</th>
<th>p-values (level 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age -median (IQR)</td>
<td>33°C (n=328)</td>
<td>33°C (n=178)</td>
<td>33°C (n=148)</td>
<td>64 (57-71)</td>
<td>0.04</td>
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<tr>
<td>Male gender -no. (%)</td>
<td>65 (58-72) (83)</td>
<td>65 (55-73) (85)</td>
<td>63 (55-69) (87)</td>
<td>102 (86)</td>
<td>0.86</td>
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<tr>
<td>Co-morbidities</td>
<td></td>
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<td></td>
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<td>Previous myocardial infarction -no. (%)</td>
<td>78 (24)</td>
<td>57 (18)</td>
<td>38 (21) (13)</td>
<td>19 (14)</td>
<td>0.15</td>
</tr>
<tr>
<td>Previous ischemic heart disease -no. (%)</td>
<td>98 (30)</td>
<td>78 (24)</td>
<td>49 (28) (19)</td>
<td>26 (19)</td>
<td>0.01</td>
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<tr>
<td>Previous cardiac arrhythmia -no. (%)</td>
<td>65 (20)</td>
<td>50 (15)</td>
<td>29 (16) (10)</td>
<td>16 (12)</td>
<td>0.03</td>
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<tr>
<td>Previous arterial hypertension -no. (%)</td>
<td>133 (40)</td>
<td>124 (38)</td>
<td>75 (42) (32)</td>
<td>44 (32)</td>
<td>0.13</td>
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<td>Previous diabetes mellitus -no. (%)</td>
<td>41 (12)</td>
<td>59 (18)</td>
<td>19 (11) (15)</td>
<td>23 (16)</td>
<td>0.36</td>
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<td>Pre-hospital variables</td>
<td></td>
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<tr>
<td>Location of cardiac arrest at home -no. (%)</td>
<td>179 (55)</td>
<td>192 (59)</td>
<td>80 (45) (55)</td>
<td>78 (56)</td>
<td>0.30</td>
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<td>Bystander witnessed arrest -no. (%)</td>
<td>291 (89)</td>
<td>291 (90)</td>
<td>167 (94) (93)</td>
<td>130 (94)</td>
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<td>Bystander cardiopulmonary resuscitation (CPR) -no. (%)</td>
<td>231 (70)</td>
<td>239 (74)</td>
<td>131 (74) (85)</td>
<td>117 (84)</td>
<td>0.03</td>
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<td>Bystander defibrillation -no. (%)</td>
<td>34 (10)</td>
<td>34 (10)</td>
<td>24 (14) (14)</td>
<td>19 (14)</td>
<td>0.60</td>
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<td>First monitored rhythm shock able -no. (%)</td>
<td>270 (82)</td>
<td>263 (81)</td>
<td>165 (93) (95)</td>
<td>133 (96)</td>
<td>0.32</td>
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<tr>
<td>Time (minutes) from arrest to ROSC -median(IQR)</td>
<td>25 (17-40)</td>
<td>25 (15-40)</td>
<td>20 (15-30) (13-30)</td>
<td>20 (15-30)</td>
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</tbody>
</table>

*Binary variables are presented with no.= numbers (and percentage) and analysis on level 3 calculated with Fishers test using 2 sided significance. Continuous variables are presented with median and interquartile range (IQR). Level 3 p-values calculated with Mann-Whitney-Wilcoxon test/or Kruskal-Wallis test. Exact values or Monte Carlo (99%) have been used and P<0.05 indicate statistical significant differences between the three groups.

†ROSC = Return of Spontaneous Circulation
Table 2. 180 days background information for patients participating in the follow-up (level 3).

<table>
<thead>
<tr>
<th></th>
<th>33°C n=148</th>
<th>36°C n=139</th>
<th>STEMI-controls n=119</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days at hospital -median (IQR)</td>
<td>14 (7-22)</td>
<td>13 (7-22)</td>
<td>4 (3-5)</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>Cardiac Interventions (&lt;180 days)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percutaneous Coronary Intervention (PCI) -no. (%)</td>
<td>77 (52)</td>
<td>86 (62)</td>
<td>118 (99)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Coronary bypass grafting (CABG) -no. (%)</td>
<td>17 (12)</td>
<td>9 (6)</td>
<td>8 (7)</td>
<td>0.27</td>
</tr>
<tr>
<td>Implantable cardioverter defibrillator (ICD) -no. (%)</td>
<td>49 (33)</td>
<td>39 (28)</td>
<td>1 (1)</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>At time for the follow-up</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days from CA/MI until follow-up -median (IQR)</td>
<td>183 (177-196)</td>
<td>185 (177-195)</td>
<td>225 (194-261)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Less than 12 years of education -no. (%)</td>
<td>93 (64)</td>
<td>64 (46)</td>
<td>60 (50)</td>
<td>0.01</td>
</tr>
<tr>
<td>HADS depression -median (IQR)</td>
<td>2 (1-6)</td>
<td>2 (1-4)</td>
<td>2 (1-5)</td>
<td>0.99</td>
</tr>
<tr>
<td>HADS anxiety -median (IQR)</td>
<td>3 (1-8)</td>
<td>4 (1-7)</td>
<td>3 (1-7)</td>
<td>0.89</td>
</tr>
<tr>
<td><strong>Employment status pre-arrest/at time for follow-up</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.49/0.11</td>
</tr>
<tr>
<td>Working full-time -no. (%)</td>
<td>58 (39)/27 (18)</td>
<td>63 (45)/29 (21)</td>
<td>40 (34)/29 (24)</td>
<td></td>
</tr>
<tr>
<td>Working part-time -no. (%)</td>
<td>11 (7)/18 (12)</td>
<td>10 (7)/24 (17)</td>
<td>10 (8)/11 (9)</td>
<td></td>
</tr>
<tr>
<td>Unemployed -no. (%)</td>
<td>7 (5)/7 (5)</td>
<td>2 (1)/3 (2)</td>
<td>3 (2)/6 (5)</td>
<td></td>
</tr>
<tr>
<td>Retired -no. (%)</td>
<td>65 (44)/70 (47)</td>
<td>57 (41)/59 (42)</td>
<td>59 (50)/64 (54)</td>
<td></td>
</tr>
<tr>
<td>On sick leave -no. (%)</td>
<td>6 (4)/25 (17)</td>
<td>4 (3)/21 (15)</td>
<td>7 (6)/9 (8)</td>
<td></td>
</tr>
<tr>
<td><strong>mRS score at 180 days -no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.0001</td>
</tr>
<tr>
<td>0</td>
<td>56 (38)</td>
<td>49 (35)</td>
<td>81 (68)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>49 (33)</td>
<td>54 (39)</td>
<td>25 (21)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>28 (19)</td>
<td>18 (13)</td>
<td>11 (9)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6 (4)</td>
<td>10 (7)</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>6 (4)</td>
<td>4 (3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3 (2)</td>
<td>4 (3)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*aBinary variables are presented with numbers (and percentage) and p-values calculated with Fishers test using 2-sided significance. Continuous variables are presented with median and interquartile range (IQR) and p-values calculated with Mann-Whitney-Wilcoxon test /or Kruskal-Wallis test. Exact values or Monte Carlo (99%) have been used and P<0.05 indicating statistical significant differences between the three groups.

†HADS= Hospital Anxiety and Depression rating Scale; mRS= modified Rankin Scale
Table 3. Continuous values for the cognitive outcome measures.

<table>
<thead>
<tr>
<th>Level 2</th>
<th>RBMT</th>
<th>RBMT</th>
<th>FAB</th>
<th>FAB</th>
<th>SDMT</th>
<th>SDMT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=178</td>
<td>(21) 16-23</td>
<td>n=178</td>
<td>(16) 14-18</td>
<td>n=178</td>
<td>-1.4±1.4</td>
</tr>
<tr>
<td>33°C ALL excluding dead*</td>
<td>17.9±6.9</td>
<td>15±3.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=164</td>
<td>(20) 16-23</td>
<td>n=164</td>
<td>(16) 15-18</td>
<td>n=164</td>
<td>-1.4±1.5</td>
</tr>
<tr>
<td>36°C ALL excluding dead*</td>
<td>18±7.2</td>
<td>14.8±4.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

95% confidence intervals for median difference

33°C versus 36°C

<table>
<thead>
<tr>
<th>Level 3</th>
<th>RBMT</th>
<th>RBMT</th>
<th>FAB</th>
<th>FAB</th>
<th>SDMT</th>
<th>SDMT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=148</td>
<td>(21) 18-23</td>
<td>n=148</td>
<td>(16) 15-18</td>
<td>n=148</td>
<td>-1.2±1.3</td>
</tr>
<tr>
<td>33°C study participants*</td>
<td>19±5.9</td>
<td>15.4±3.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=139</td>
<td>(21) 18-24</td>
<td>n=139</td>
<td>(17) 15-18</td>
<td>n=139</td>
<td>-1.3±1.4</td>
</tr>
<tr>
<td>36 °C study participants*</td>
<td>18.9±6.4</td>
<td>15.3±3.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=119</td>
<td>(21) 19-23</td>
<td>n=119</td>
<td>(17) 15-18</td>
<td>n=119</td>
<td>-0.7±1</td>
</tr>
<tr>
<td>STEMI-control study participants*</td>
<td>20.3±3.7</td>
<td>16.3±2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Follow-up participants with complete test results

<table>
<thead>
<tr>
<th>Level 3</th>
<th>RBMT</th>
<th>RBMT</th>
<th>FAB</th>
<th>FAB</th>
<th>SDMT</th>
<th>SDMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>33°C complete cases</td>
<td>n=138</td>
<td>(21) 18-23</td>
<td>n=143</td>
<td>(16) 15-18</td>
<td>n=138</td>
<td>-1.1±1.2</td>
</tr>
<tr>
<td>19.7±4.8</td>
<td>15.6±3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36°C complete cases</td>
<td>n=134</td>
<td>(21.5) 18-24</td>
<td>n=136</td>
<td>(17) 15-18</td>
<td>n=132</td>
<td>-1.2±1.4</td>
</tr>
<tr>
<td>19.3±5.9</td>
<td>15.5±3.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI-control complete cases</td>
<td>n=118</td>
<td>(21) 19-23</td>
<td>n=119</td>
<td>(17) 15-18</td>
<td>n=117</td>
<td>-0.7±1</td>
</tr>
<tr>
<td>20.3±3.7</td>
<td>16.3±2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Data including multiple imputations for non-responders. Confidence intervals for the difference in median between the two intervention groups in Level 2 was established using bootstrapping.
† Data presented with mean ±SD and (median) Inter Quartile Range (IQR).
‡RBMT=Rivermead Behavioural Memory Test; FAB=Frontal Assessment Battery; SDMT= Symbol Digit Modalities Test
Figure Legends:

**Figure 1.** Flow-chart for inclusion. Statistical analyses were performed on three different levels. TTM= the Target Temperature Management trial; UK= United Kingdom; CPC= Cerebral Performance Category; STEMI= ST-elevation myocardial infarction.

**Figure 2.** Categorical outcome for the Rivermead Behavioural Memory Test (RBMT). Presented for all cardiac arrest patients (Level 1; 33°C n=328/36°C n=324) and for included patients (*Level 3; 33°C n=148/36°C n=139/STEMI-controls n=119). Includes imputed cases. Categorized scores: Normal function (22-24)/memory impairment: mild (17-21), moderate (10-16), severe (0-9).

**Figure 3.** Categorical outcome for the Frontal Assessment Battery (FAB). Presented for all cardiac arrest patients (Level 1; 33°C n=328/36°C n=324) and for included patients (*Level 3; 33°C n=148/36°C n=139/STEMI-controls n=119). Includes imputed cases. Categorized scores: normal function (15-18)/impaired (≤14).

**Figure 4.** Categorical outcome for the Symbol Digit Modalities test (SDMT). Presented for all cardiac arrest survivors (Level 1; 33°C n=328/36°C n=324 and for included patients (*Level 3; 33°C n=148/36°C n=139/STEMI-controls n=119). Includes imputed cases. Categorized z-scores: normal function (>1 SD)/ borderline impairment (<1 SD)/ impaired (<1.5 SD).
Cardiac Arrest patients at study sites  
$n=652$  
(67% of the original TTM-trial)

**Intervention 33°C**  
$n=328$ (50%)

Alive at 180 days  
$n=178$ (54%)

**Intervention 36°C**  
$n=324$ (50%)

Alive at 180 days  
$n=164$ (51%)

### Analysis level 1

**Eligible patients to include**  
$n=164$ (50%)

**Included in the study**  
$n=148$  
CPC 1 $n=130$ (88%)  
CPC 2 $n=8$ (5%)  
CPC 3+4 $n=8+1$ (7%)

### Analysis level 2

**Eligible patients to include**  
$n=156$ (48%)

**Included in the study**  
$n=139$  
CPC 1 $n=114$ (82%)  
CPC 2 $n=16$ (11.5%)  
CPC 3+4 $n=8+1$ (6.5%)

### Analysis level 3

**Included in the study**  
$n=139$  
CPC 1 $n=114$ (82%)  
CPC 2 $n=16$ (11.5%)  
CPC 3+4 $n=8+1$ (6.5%)

**STEMI-controls**  
$n=119$  
CPC 1 $n=116$ (97.5%)  
CPC 2 $n=2$ (1.7%)  
CPC 3+4 $n=1$ (0.8%)

**Eligible patients to include**  
$n=164$ (50%)

**Included in the study**  
$n=148$  
CPC 1 $n=130$ (88%)  
CPC 2 $n=8$ (5%)  
CPC 3+4 $n=8+1$ (7%)

**Completely lost from TTM-trial**  
$n=3$

**Before UK ethical approval**  
$n=5$

**Not full-filling inclusion criteria**  
$n=6$

**Missing**  
$n=16$

CPC 1 $n=9$ (56%)

CPC 2 $n=0$ (0%)

CPC 3+4 $n=6+1$ (44%)

**Eligible patients to include**  
$n=156$ (48%)

**Included in the study**  
$n=139$  
CPC 1 $n=114$ (82%)  
CPC 2 $n=16$ (11.5%)  
CPC 3+4 $n=8+1$ (6.5%)

**Completely lost from TTM-trial**  
$n=1$

**Before UK ethical approval**  
$n=4$

**Not full-filling inclusion criteria**  
$n=3$

**Missing**  
$n=17$

CPC 1 $n=8$ (47%)

CPC 2 $n=2$ (12%)

CPC 3+4 $n=6+1$ (41%)

Figure 1
Figure 2

Bar chart illustrating the distribution of outcomes for cardiac arrest at 33°C and 36°C.

- Cardiac arrest 33°C ALL
  - Normal: 21
  - Mild: 19
  - Moderate: 7
  - Severe: 7
  - Dead: 46

- Cardiac arrest 36°C ALL
  - Normal: 23
  - Mild: 14
  - Moderate: 6
  - Severe: 7
  - Dead: 49

- Cardiac arrest 33°C
  - Normal: 42
  - Mild: 36
  - Moderate: 13
  - Severe: 8

- Cardiac arrest 36°C
  - Normal: 49
  - Mild: 29
  - Moderate: 12
  - Severe: 10

- STEMI-controls
  - Normal: 48
  - Mild: 35
  - Moderate: 16
  - Severe: 0
Figure 3
Cognitive Function in Survivors of Out-of-Hospital Cardiac Arrest After Target Temperature Management at 33°C Versus 36°C


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Data Supplement (unedited) at:
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Supplemental Material

Supplemental Methods

Report of the multiple imputation process

Since severely impaired patients being more likely to have absent test results (MAR assumption) imputations were considered important in the analysis. To exclude influences of survival bias the primary analysis also included deceased patients by assigning them a lower rank than the lowest rank of the included using non-parametric test statistics for analysis. The variables used for the multiple imputations included information from the original TTM database with 93% of survivors participating in a structured follow-up 180 days after the arrest and assessed with the MiniMental Status Examination (MMSE), Informant Questionnaire on Cognitive Decline (IQCODE), Two Simple Questions (TSQ), Cerebral Performance category (CPC) and modified Rankin Scale (mRS).

- The imputations were separated for cases and controls to avoid contamination.
- Variables used for multiple imputations for cardiac arrest patients were: age, sex, education, randomization code, country, previous arterial hypertension, known diabetes, previous ischemic heart disease, previous acute myocardial infarction, previous arrhythmia, known neurological disease, cardiac arrest location, bystander witnessed arrest, bystander cardio-pulmonary resuscitation, bystander defibrillation, use of automatic compression/decompression, number of defibrillations, pre-hospital intubation, time to ROSC (return of spontaneous circulation), days at hospital, days from event to follow-up, intervention with CABG, MMSE sum score, CPC at 180 days, mRS at 180 days, HADS anxiety sum scores, HADS depression sum scores,
IQCODE sum scores, Two Simple Questions 1,1b,2, , FAB sum score, RBMT profile sum score, SDMT z-score.

- Variables used for multiple imputations for controls with incomplete test results: age, sex, education, , country, previous arterial hypertension, known diabetes, previous ischemic heart disease, previous acute myocardial infarction, previous arrhythmia, known neurological disease, days at hospital, days from event to follow-up, intervention with CABG, MMSE sum score, CPC at 180 days, mRS at 180 days, HADS anxiety sum scores, HADS depression sum scores, IQCODE sum scores, Two Simple Questions 1,1b,2, , FAB sum score, RBMT profile sum score, SDMT z-score.

- Non-normally distributed imputation variables were prevented by using predictive mean matching.

- Ten imputed datasets were created. A total run length of 20 iterations was used to obtain convergence.

- Multiple imputations were performed in the R statistical software 3.1.0 using the mice 2.21 package.¹
<table>
<thead>
<tr>
<th>Suppl al Results</th>
<th>Complete TTM sample</th>
<th>Level 1: Cognitive outcome study-sites</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All cardiac arrest</td>
<td>All cardiac arrest including dead</td>
</tr>
<tr>
<td></td>
<td>33°C n=473</td>
<td>36°C n=466</td>
</tr>
<tr>
<td>------------------</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td>Age -median (IQR)</td>
<td>65 (57-73)</td>
<td>65 (56-73)</td>
</tr>
<tr>
<td>Male gender -no. (%)</td>
<td>393 (83)</td>
<td>368 (79)</td>
</tr>
</tbody>
</table>

**Co-morbidities**

**Previous myocardial infarction**

| -no. (%) | 107 (23) | 86 (18)   | 78 (24)    | 57 (18)    |

**Previous ischemic heart disease**

<p>| -no. (%) | 145 (31) | 115 (25) | 98 (30)   | 78 (24)   |</p>
<table>
<thead>
<tr>
<th>Previous cardiac arrhythmia</th>
<th>87 (18)</th>
<th>79 (17)</th>
<th>65 (20)</th>
<th>50 (15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous arterial hypertension</td>
<td>193 (41)</td>
<td>181 (39)</td>
<td>133 (40)</td>
<td>124 (38)</td>
</tr>
<tr>
<td>Previous diabetes mellitus</td>
<td>61 (13)</td>
<td>80 (17)</td>
<td>41 (12)</td>
<td>59 (18)</td>
</tr>
<tr>
<td><strong>Pre-hospital variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location of cardiac arrest at home</td>
<td>245 (52)</td>
<td>255 (55)</td>
<td>179 (55)</td>
<td>192 (59)</td>
</tr>
<tr>
<td>Bystander witnessed</td>
<td>arrest</td>
<td>Bystander</td>
<td>cardiopulmonary resuscitation (CPR)</td>
<td>Bystander defibrillation</td>
</tr>
<tr>
<td>---------------------</td>
<td>--------</td>
<td>-----------</td>
<td>-------------------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td></td>
<td>no. (%)</td>
<td></td>
<td>no. (%)</td>
<td></td>
</tr>
<tr>
<td>arrest</td>
<td>420 (89) 418 (90)</td>
<td>291 (89) 291 (90)</td>
<td>344 (73) 339 (73)</td>
<td>231 (70) 239 (74)</td>
</tr>
<tr>
<td>-no. (%)</td>
<td></td>
<td></td>
<td>(%)</td>
<td>(%)</td>
</tr>
</tbody>
</table>
Supplemental Table 1

Socio-demographical and medical background variables for patients included in the study compared to the patient included in the main Target Temperature Management (TTM) trial

*Binary variables are presented with no.= numbers (and percentage). Continuous variables are presented with median and interquartile range (IQR).
†ROSC = Return of Spontaneous Circulation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study Patients (Median, IQR)</th>
<th>Main TTM Patients (Median, IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-median(IQR)</td>
<td>25 (18-40)</td>
<td>25 (16-40)</td>
</tr>
<tr>
<td></td>
<td>Level 1</td>
<td>Level 2</td>
</tr>
<tr>
<td>----------------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td></td>
<td>33°C/36°C all including dead</td>
<td>33°C/36°C all excluding dead</td>
</tr>
<tr>
<td>RBMT</td>
<td>0.56</td>
<td>0.52</td>
</tr>
<tr>
<td>FAB</td>
<td>0.43</td>
<td>0.83</td>
</tr>
<tr>
<td>SDMT</td>
<td>0.31</td>
<td>0.67</td>
</tr>
</tbody>
</table>

**Supplemental Table 2**

*P-value results from analyses of the whole intervention group treated with 33°C or 36°C target temperature and STEMI-controls (only level 3).

†Level 1 and 2: Statistical test method Wilcoxon-Mann-Whitney with a critical p-value of <0.017 used to identify statistical significant differences between the two groups. Level 3: Statistical test method for the unadjusted analysis is the Kruskal-Wallis test and for adjusted analysis ordinal regression (RBMT, FAB) or a univariate general linear model (SDMT).

‡RBMT= Rivermead Behavioural Memory Test; FAB= Frontal Assessment battery; SDMT= Symbol Digit Modalities Test
<table>
<thead>
<tr>
<th>Country</th>
<th>33°C (± SD)</th>
<th>36°C (± SD)</th>
<th>STEMI-Controls (± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denmark</td>
<td>-1.32 (± 0.36)</td>
<td>-1.52 (± 0.34)</td>
<td>-1.14 (± 0.43)</td>
</tr>
<tr>
<td>Italy</td>
<td>-1.85 (± 0.53)</td>
<td>-1.76 (± 0.66)</td>
<td>-0.25 (± 0.56)</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>-1.19 (± 0.47)</td>
<td>-1.29 (± 0.48)</td>
<td>-0.53 (± 0.69)</td>
</tr>
<tr>
<td>Sweden</td>
<td>-0.88 (± 0.39)</td>
<td>-1.09 (± 0.45)</td>
<td>-0.36 (± 0.44)</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>-1.72 (± 0.47)</td>
<td>-0.88 (± 0.48)</td>
<td>-0.91 (± 0.66)</td>
</tr>
</tbody>
</table>

Supplemental Table 3. Estimated means for the Symbol Digit Modalities Test (SDMT)

*Estimated means (± 95% confidence interval) are presented from the analysis of SDMT including covariates (gender, country).

†Estimated mean scores are presented as z-scores (age and education adjusted) with pre-specified levels of impairment defined as: < -1 SD = low score, < -1.5 SD used as a cut-off for possible cerebral dysfunction and < -2 very low scores.

‡Overall p-values from post-hoc analyses: 33°C vs. 36°C p=0.94, 33°C vs. controls p=0.001 and 36°C vs. controls p=0.001. R-square (adjusted, including intercept) =8.2%.
Supplemental References