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Clinical paper

Functional outcomes associated with varying levels of targeted temperature management after out-of-hospital cardiac arrest — An INTCAR2 registry analysis

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Abstract

Introduction: Targeted temperature management (TTM) after out-of-hospital cardiac arrest (OHCA) has been recommended in international guidelines since 2005. The TTM-trial published in 2013 showed no difference in survival or neurological outcome for patients randomised to 33 °C or 36 °C, and many hospitals have changed practice. The optimal utilization of TTM is still debated. This study aimed to analyse if a difference in temperature goal was associated with outcome in an unselected international registry population.

Methods: This is a retrospective observational study based on a prospective registry — the International Cardiac Arrest Registry 2. Patients were categorized as receiving TTM in the lower range at 32–34 °C (TTM-low) or at 35–37 °C (TTM-high). Primary outcome was good functional status defined as cerebral performance category (CPC) of 1–2 at hospital discharge and secondary outcome was adverse events related to TTM. A logistic

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regression model was created to evaluate the independent effect of temperature by correcting for clinical and demographic factors associated with outcome.

Results: Of 1710 patients included, 1242 (72,6%) received TTM-low and 468 (27,4%) TTM-high. In patients receiving TTM-low, 31.3% survived with good outcome compared to 28.8% in the TTM-high group. There was no significant association between temperature and outcome ($p = 0.352$). In analyses adjusted for baseline differences the OR for a good outcome with TTM-low was 1.27, 95% CI (0.94−1.73). Haemodynamic instability leading to discontinuation of TTM was more common in TTM-low.

Conclusions: No significant difference in functional outcome at hospital discharge was found in patients receiving lower- versus higher targeted temperature management.

Keywords: Cardiac arrest, Out-of-hospital, Outcome, Targeted temperature management, TTM

Introduction

The use of targeted temperature management (TTM) as an intervention to mitigate secondary neurologic injury in comatose survivors of cardiac arrest has been widely adopted during the last 15 years despite low to very-low overall quality of evidence.[1,2] The TTM-trial published in 2013 compared a target temperature of 33 °C−36 °C in out-of-hospital cardiac arrest (OHCA) patients and did not demonstrate a benefit regarding survival or neurological outcome.[3] This trial was, however, different compared to earlier trials in that both intervention groups were tightly temperature controlled and kept at temperature below normal, avoiding the natural temperature trajectory for cardiac arrest patients; hence the trial compared mild hypothermia to very mild hypothermia.[4,5] Additional subgroup analyses and observational data support the neutral result of the TTM-trial[6−10] and since 2013 many centers have changed their standard practice treatment strategy aiming for a target temperature of 36 °C.

Some centers have continued to use traditional induced hypothermia (32−34 °C) whereas some do not use, or have abandoned TTM, despite the updated European Resuscitation Council (ERC)- and American Heart Association (AHA)-guidelines from 2015, strongly recommending TTM at 32−36 °C for adult survivors of OHCA with an initial shockable rhythm who remain unresponsive after return of spontaneous circulation (ROSC).[1,2] Thus, there is a substantial international variation of clinical practice with different approaches to TTM.[11,12] Recently, results from large intensive care databases have confirmed a change in the use of TTM after OHCA; fewer patients receive TTM and more patients experience fever during the intensive care stay.[12,13] However, any impact on overall survival or neurological function has been difficult to distinguish. Tendencies towards worse outcome have been reported with these changes, though inconsistently linked to changes in TTM practices.[13]

In this study we aimed to see if differences in target temperature affected functional outcomes in an international observational registry of OHCA-patients where baseline variables allow for adjusted analyses.

Methods

The International Cardiac Arrest Registry 2

INTCAR2 is a multinational, internet-based registry of cardiac arrest patients treated in an intensive care unit (ICU) setting. INTCAR2 received data from 25 centers in the United States, Sweden, Norway and Luxembourg. The registry was started as a continuation of INTCAR1 and the Hypothermia Network Registry.[14]

It predominantly encompasses a prospectively registered sample of consecutive patients most of whom were treated with temperature management, and includes details about presumed causes, treatment and outcomes for patients after cardiac arrest at all locations admitted to intensive care.

Patients

The patients in our study were OHCA-patients treated at centers reporting to INTCAR2 between 2008 and 2017 (start and end dates of INTCAR2). Patients registered before 2013 were excluded to minimize treatment bias due to the change in treatment strategy of OHCA patients following publication of the TTM-trial.[3]

Inclusion criteria were OHCA-arrest patients of any cause of arrest, ≥18 years of age, stable ROSC, not responding to verbal commands at admission and being treated in an ICU-setting with temperature management. Exclusion criteria were arrest in the ED or location missing, missing outcome data or missing temperature allocation.

Each participating center treated patients according to local protocols, including choice of cooling devices and cooling methods.

The ethical review board in Lund, Sweden approved the registry (272/2007) and local ethical approval was granted as per regulations of each participating hospital. Information about the study was provided to patients who regained consciousness or to next of kin, if required by legal statute in each country.

Data

INTCAR2-data were derived from ambulance charts, admission journals, ICU observation charts and medical records from hospitals and rehabilitation centers. Pre-hospital data were defined according to the Utstein guidelines[15] and in-hospital data according to the extended Utstein guidelines for reporting post-resuscitation care.[16]

Comorbidities were registered if they were pharmacologically or previously surgically treated, or subject to continuous monitoring at the time of the cardiac arrest. Time to ROSC was defined as time from collapse until return of spontaneous circulation, leading to stable circulation without the need for cardiopulmonary resuscitation (CPR) for at least 20 min. Temperature management was defined as an active attempt to keep the patient's body temperature within a prescribed target range. TTM at 32−34 °C was defined as TTM-low and TTM at 35−37 °C as TTM-high. Adverse events during ICU care were recorded according to a predefined protocol.

Outcome

Primary outcome was survival with good neurological function at hospital discharge, using the Cerebral Performance Category (CPC)

scale where CPC 1 = good cerebral performance with normal function or minor disability; CPC 2 = moderate cerebral disability, independent in activities of daily life; CPC 3 = severe cerebral disability and dependent on others for daily activities; CPC 4 = a patient in coma or a vegetative state; and CPC 5 = dead.[17] The CPC scale was dichotomized into good (CPC 1 and 2) and poor (CPC 3–5) outcome according to the Utstein guidelines.[18,19]

In a subset of patients, no outcome data were registered at hospital discharge but had long term (180 days) follow-up data. In these cases, we used the follow-up outcome as a hospital discharge outcome-substitute in the analysis (last observation carried backwards). The primary outcome was reported for all patients according to TTM-group. We also performed subgroup analysis using the prespecified subgroups defined in the TTM-trial: age (above/below 65 years), sex (male/female), initial rhythm shockable (yes/no), time to ROSC (above/below 25 min) and circulatory shock on arrival in hospital (yes/no).[20]

The secondary outcome was adverse events related to TTM during ICU care: pneumonia (defined as three of the following four criteria: progressive or new infiltrates on chest X-ray (mandatory), fever above 38 °C in the first 72 h of admission, leukocytosis and purulent mucus in endotracheal tube; major bleeding (defined as cerebral bleeding or bleeding requiring transfusion); haemodynamic instability leading to discontinuation of TTM; severe sepsis and septic shock defined according to the criteria of the American College of Chest Physicians and Society of Critical Care Medicine[21] leading to discontinuation of TTM; and seizures based on clinical detection and diagnosis during TTM.

Statistical analysis

Continuous variables are presented as mean ± one standard deviation if normally distributed and as median and interquartile range if non-normally distributed.

Binary and categorical variables are presented as numbers and percentages. Categorical data were compared using Chi-Square test, continuous normally distributed data were compared using Student's *t*-test and non-normally distributed data by the Wilcoxon–Mann–Whitney test. A univariate logistic regression was performed and presented as odds ratios (OR) with 95% confidence intervals (CI) indicating the association of the variable with a good outcome and OR-values >1 indicating a favourable association.

A multivariate analysis was also performed using logistic regression with adjustment for important covariables with a potential to influence outcome after cardiac arrest including age, sex, comorbidities, bystander-CPR, arrest characteristics, circulatory shock on admission and urgent angiography prior to hospital discharge. Some of these variables were not complete in the dataset but due to an overall low number of missing values (<5%) no imputation was performed.[22]

A forest plot was created assessing interaction of age (above or below 65 years), sex, time to ROSC (above or below 25 min), initial rhythm (shockable or non-shockable) and circulatory shock on admission to investigate whether any of these groups would signal a positive association to either TTM-high or TTM-low. Finally, adverse events during the patients' ICU stay were compared between the two temperature groups. A *p*-value <0.05 was considered statistically significant and all tests were two-tailed. R was used for statistical analysis (R Core Team, 2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL (http://www.R-project.org/).

Results

Between October 2008 and November 2017, 3252 cardiac arrest patients were registered in the INTCAR2 database. Of these, 1710 were eligible for the final analysis after excluding patients with age <18 years (*n* = 23), arrest in-hospital, in the ED or unknown (*n* = 868), missing data on outcome or targeted temperature (*n* = 177) and registered before 2013 (*n* = 474). Of the 1710 patients, 1059 (61,9%) was registered in the United States, 427 (24,9%) in Sweden, 142 (8,3%) in Norway and 82 (4,8%) in Luxembourg (Fig. 1). The patients were grouped according to prescribed temperature treatment, including 1242 (72.6%) patients treated with TTM-low and 468 (27.4%) with TTM-high. The distribution of TTM-low vs. TTM-high patients was not evenly distributed between participating countries. Patients in the TTM-low group were predominately entered from the United States and Norway, while patients in the TTM-high group were from Sweden and Luxembourg (Fig. 1).

Baseline characteristics for the two treatment groups are shown in Table 1. There were more male patients in TTM-high (*n* = 358, 76.5%) compared to TTM-low (*n* = 829, 66.7%) and patients in the low temperature group were younger with a mean age of 59.2 (±15.8)

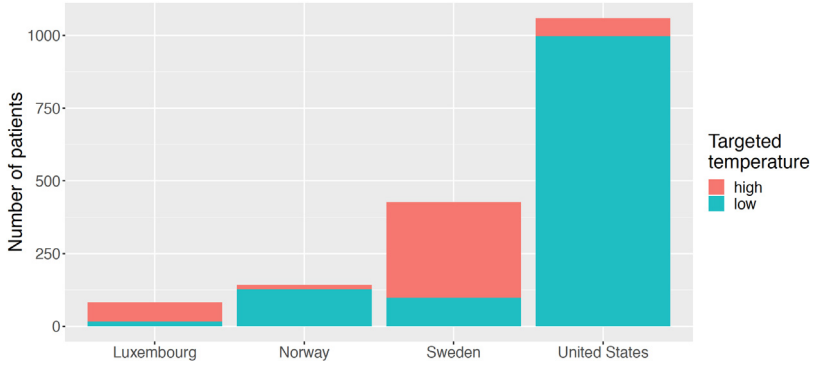

Fig. 1 – Targeted temperature by country.
The majority of patients receiving TTM-high did so in Sweden, with Luxembourg contributing some patients. The United States almost exclusively uses TTM-low. TTM-low denotes 32–34 °C and TTM-high denotes 35–37 °C. TTM: targeted temperature management.

Table 1 – Baseline characteristics stratified into in high- and low targeted temperature groups.

	TTM-low[a] ($n=1242$)	TTM-high[b] ($n=468$)	p-value
Age (years) mean ± SD	59.5 ± 15.8	63.7 ± 14.5	<0.001
Male sex (%)	829 (66.7)	358 (76.5)	<0.001
Previous chronic heart failure (%)	198 (15.9)	89 (19.0)	0.149
Previous myocardial infarction (%)	233 (18.8)	71 (15.2)	0.097
Previous hypertenison (%)	589 (47.4)	173 (37.0)	<0.001
Previous insulin dependent diabetes (%)	142 (11.4)	51 (10.9)	0.821
Previous non-insulin dependent diabetes (%)	170 (13.7)	45 (9.6)	0.029
Previous COPD (%)	215 (17.3)	53 (11.3)	0.003
Previous dementia or cognitive impairment (%)	51 (4.1)	13 (2.8)	0.251
Witnessed cardiac arrest (%)	928 (75.6)	364 (79.8)	0.077
Bystander CPR (%)			0.001
- Yes (%)	645 (52.4)	278 (60.4)	
- No (%)	411 (33.4)	144 (31.3)	
- Arrest with EMS present (%)	174 (14.1)	38 (8.3)	
VT/VF or AED-advised shockable rhythm (%)	618 (50.0)	248 (53.6)	0.210
Time to ROSC in minutes (IQR)[c]	29 (19–48)	34 (24–53)	0.006
Urgent Angiography (%)	431 (37.5)	231 (50.5)	<0.001
Shock on admission (%)[d]	562 (48.4)	180 (39.1)	0.001
ICU length of stay in days (IQR)	5 (3.00–9.00)	4 (2.00–7.75)	<0.001
Hospital length of stay in days (IQR)	7 (3.00–13.00)	7 (3.00–16.00)	0.15

Data are presented as mean (± SD), n (%) or median (IQR). n denotes the number of cases with valid data. A p-value of <0.05 was considered significant. SD: standard deviation; IQR: interquartile range; TTM: targeted temperature management; COPD: chronic obstructive pulmonary disease; CPR: cardio-pulmonary resuscitation; EMS: Emergency Medical Service; VT: ventricular tachycardia; VF: ventricular fibrillation; AED: automated external defibrillator; ROSC: return of spontaneous circulation; ICU: intensive care unit.

[a] TTM-low denotes 32–34 °C.

[b] TTM-high denotes 35–37 °C.

[c] If unwitnessed, time is calculated from emergency call.

[d] Shock on admission is defined as systolic blood pressure of less than 90 mm Hg for more than 30 min or end-organ hypoperfusion unless vasoactives are administered.

compared to 63.7 (±14.5) years. Patients in TTM-low had more comorbidities in general compared to TTM-high. There was no significant difference regarding frequency of witnessed arrest between the two temperature groups whereas bystander-CPR was more common in the TTM-high ($n=278$, 60.4% vs. $n=645$, 52.4%). Arrest with Emergency Medical Service (EMS) present was more common in TTM-low ($n=174$, 14.1% vs. $n=38$, 8.3%). The percentage of patients with a shockable rhythm did not differ significantly between groups whereas time to ROSC was significantly longer in TTM-high (34 min [IQR 24–53] vs. 29 min [IQR 19–48]). More urgent angiography was performed in the TTM-high group ($n=231$, 51% vs. $n=431$, 38%) and post-arrest shock on admission was more common in TTM-low ($n=562$, 48.4% vs. $n=180$, 39.1%). The ICU length of stay was shorter for the TTM-high group (4 days [IQR 2.00–7.75] vs. 5 days [IQR 3.00–9.00], $p<0.001$) whereas hospital length of stay did not differ significantly between groups (7 days [IQR 3.00–16.00] for TTM-high vs. 7 days [IQR 3.00–13.00] for TTM-low, $p=0.15$.

Outcome

Primary outcome

The number of patients with good functional outcome (CPC1-2) was 389 of 1242 (31,3%) in TTM-low and 135 of 468 (28,8%) in TTM-high. Mortality (CPC 5) was also similar, 59.2% (735 of 1242) in TTM-low and 61.8% in TTM-high (289 of 468) (Fig. 2). A Chi-square test for temperature vs. outcome had a p-value of 0.352.

The univariate analysis showed no statistically significant association between a low temperature and a good functional outcome (OR = 1.12, 95% CI 0.89–1.42, $p=0.32$), confirmed in the multivariate analysis (OR =1.27, 95% CI 0.94–1.73, $p=0.11$) (Table 2). Among covariables, the presence of a shockable rhythm had the strongest multivariate association with a good outcome (OR = 4.39, 95% CI 3.23–6.01, $p<0.001$).

For the predefined subgroup analyses, in patients with female sex and presence of circulatory shock on hospital admission, TTM-high was associated with a good outcome (Fig. 3).

Secondary outcome

Regarding adverse events during the ICU stay, haemodynamic instability leading to discontinued TTM was more common in TTM-low ($n=58$, 4.9% vs. $n=8$, 1.7%, $p<0.001$) and pneumonia was similarly common in both groups ($n=435$, 38,4% in TTM-low and $n=170$, 37.1% in TTM-high, $p=0.67$) (Table 3). There were no statistically significant differences in the frequency of adverse events regarding major bleeding ($n=88$, 7.8% in TTM-low vs. $n=30$, 6.6% in TTM-high, $p=0.47$), sepsis ($n=3$, 0.3% in TTM-low vs. $n=0$, 0% in TTM-high, $p=0.66$) or seizures ($n=98$, 8.5% in TTM-low vs. $n=39$, 8.4% in TTM-low, $p=1.00$).

Discussion

In this large retrospective, observational registry study we investigated whether the results from the TTM-trial could be demonstrated in

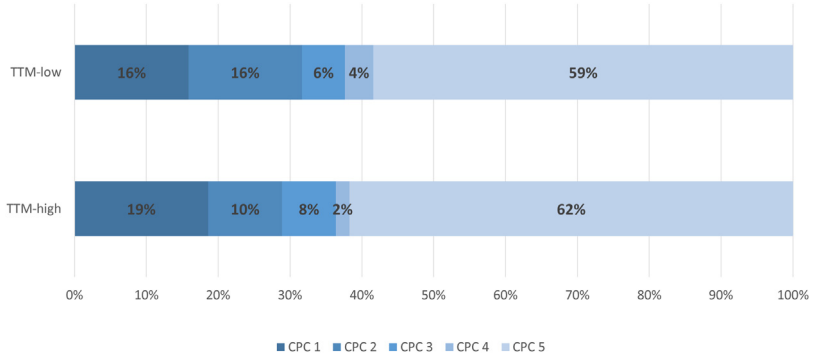

Fig. 2 – CPC distribution and comparison between the low- and high targeted temperature groups. Values are percentages of the total amount of patients in that group. CPC: cerebral performance category; CPC 1, good cerebral performance, might have mild neurological or psychological deficit. CPC 2, moderate cerebral disability. Able to work in sheltered environment and enough function for independent activities of daily life. CPC 3, severe cerebral disability, conscious, dependant on other people for daily support (a wide spectrum of cerebral function). CPC 4, coma or vegetative state. CPC 5, brain dead. TTM-low denotes 32–34 °C and TTM-high denotes 35–37 °C. TTM: targeted temperature management.

Table 2 – Univariate and multivariate logistic regression analysis of baseline factors and their association with outcome.

	Univariate analysis Odds Ratio (95% CI)	*p*-Value	Multivariate analysis Odds Ratio (95% CI)	*p*-Value
TTM-low[a]	1.12 (0.89–1.42)	0.32	1.27 (0.94–1.73)	0.11
Age (per year)	0.97 (0.97–0.98)	<0.001	0.97 (0.96–0.98)	<0.001
Male sex	1.98 (1.56–2.53)	<0.001	1.33 (0.97–1.83)	0.08
Previous chronic heart failure	0.67 (0.50–0.90)	0.008	1.01 (0.68–1.47)	0.97
Previous myocardial infarction	1.00 (0.76–1.30)	0.983	1.10 (0.76–1.59)	0.60
Previous hypertenison	0.61 (0.49–0.75)	<0.001	0.78 (0.58–1.04)	0.09
Previous insulin dependent diabetes	0.35 (0.23–0.52)	<0.001	0.45 (0.26–0.75)	<0.001
Previous non-insulin dependent diabetes	0.67 (0.48–0.93)	0.019	0.88 (0.57–1.36)	0.57
Previous COPD	0.30 (0.21–0.43)	<0.001	0.46 (0.27–0.74)	<0.001
Previous dementia or cognitive impairment	0.18 (0.06–0.42)	<0.001	0.23 (0.07–0.64)	0.01
Witnessed cardiac arrest	1.96 (1.50–2.58)	<0.001	1.80 (1.26–2.58)	<0.001
VT/VF or AED-advised shockable rhythm	6.31 (4.96–8.08)	<0.001	4.39 (3.23–6.01)	<0.001
Time to ROSC (per minute)[b]	0.98 (0.98–0.99)	<0.001	0.99 (0.98–0.99)	<0.001
Urgent angiography	2.74 (2.20–3.41)	<0.001	1.60 (1.21–2.13)	<0.001
Shock on admission[c]	0.45 (0.36–0.56)	<0.001	0.51 (0.39–0.67)	<0.001
Bystander CPR				
- No	Ref	Ref	Ref	Ref
- Yes	2.20 (1.73–2.82)	<0.001	1.43 (1.05–1.95)	0.02
- Arrest with EMS present	1.06 (0.72–1.54)	1.000	1.47 (0.90–2.37)	0.12

Odds ratios for good neurological outcome for the group in entirety where a value of >1 indicates each factor's beneficial influence on outcome. A *p*-value of <0.05 was considered significant. In the multivariate model adjustment for potential confounding factors previously known to influence outcome after out-of-hospital cardiac arrest (OHCA) such as age, gender, co-morbidities, arrest characteristics, angiography and shock on admission was made. CI: confidence Interval; TTM: targeted temperature management; COPD: chronic obstructive pulmonary disease; VT: ventricular tachycardia; VF: ventricular fibrillation; AED: automated external defibrillator; ROSC: return of spontaneous circulation; CPR: cardiopulmonary resuscitation; EMS: Emergency Medical Service.

[a] TTM-low denotes 32–34 °C.

[b] If unwitnessed arrest, time is calculated from emergency call.

[c] Shock on admission is defined as a systolic blood pressure of less than 90 mmHg for more than 30 min or end-organ hypoperfusion unless vasoactives are administered.

OHCA patients included in the INTCAR2-registry containing cardiac arrest data where baseline variables allow for adjusted analyses. Our analyses showed no statistically significant difference in functional outcome at hospital discharge between patients treated with TTM-low (32–34 °C) or TTM-high (35–37 °C) in either unadjusted or adjusted analyses.

Although the crude numbers for good outcome between the TTM-groups were strikingly similar, the multivariable analysis revealed a

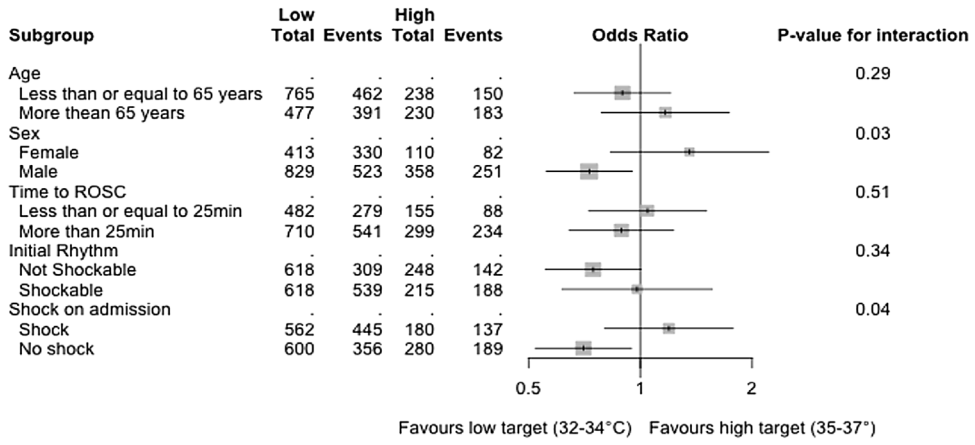

Fig. 3 – Odds ratio of outcome according to subgroups.
The forest plot shows the odds ratio for five predefined subgroups in regard to whether these subgroups were favoured by a low- or a high targeted temperature at hospital discharge. The horizontal bars represent 95% confidence intervals (CI). *p*-values are for the tests of subgroup heterogeneity (tests of interactions) and a *p*-value of <0.05 was considered significant. For unwitnessed cardiac arrests the time to ROSC was calculated from time of emergency call. Shock on admission is defined as a systolic blood pressure of less than 90 mmHg for more than 30 min or end-organ hypoperfusion unless vasoactives are administered. Low targeted denotes 32–34 °C (TTM-low) and High targeted denotes 35–37 °C (TTM-high).

Table 3 – Adverse events for total sample dichotomized in low- and high targeted temperature groups.

	n	TTM-low[a] (%)	TTM-high[b] (%)	*p*-Value
Signs of seizure during TTM	1616	98 (8.5)	39 (8.4)	1.00
Pneumonia Clinical or Microbial diagnosis[c]	1590	435 (38.4)	170 (37.1)	0.67
Major bleeding[d]	1591	88 (7.8)	30 (6.6)	0.47
TTM discontinued - Haemodynamic instability	1649	58 (4.9)	8 (1.7)	<0.001
TTM discontinued - Severe sepsis/septic shock[e]	1649	3 (0.3)	0 (0)	0.66

Secondary outcome in the study was adverse events during the ICU stay. Data are presented as *n* (%) and *n* denotes the number of cases with valid data. The events were compared using Chi-square and a *p*-value of <0.05 was considered significant. TTM: targeted temperature management.
[a] TTM-low denotes 32–34 °C.
[b] TTM-high denotes 35–37 °C.
[c] Pneumonia is defined as 3 of the following criteria: progressive or new infiltrates on chest X-ray (mandatory), fever above 38 °C, leucocytosis and purulent mucus in tube.
[d] Major bleeding is defined as cerebral bleeding or bleeding requiring transfusion.
[e] Severe sepsis/septic shock is defined according to the criteria of the American College of Chest Physician and Society of Critical Care Medicine.

tendency towards a more favourable outcome in TTM-low after adjustment for potential confounding factors previously known to be associated with outcome.[23–25] Similar concerns were raised in prior observational studies.[12,13] Although complex mediation analysis of data from 45 935 patients in a study from Bradley et al.[13] suggested inconsistency regarding the role of target temperature in theses outcomes, the lack of randomisation and high potential for bias and confounding suggests great caution when interpreting these results.[26] Similarly, our results must be interpreted with caution, and potential benefit of TTM-low may be worth exploring in further randomised clinical trials.

The overall incidence of adverse events was low in both groups, however pneumonia was the more common and occurred with similar frequency in both temperature groups. The high incidence of pneumonia during post-cardiac arrest care is described in other OHCA cohorts.[3,27,28] More TTM-low patients had TTM discontinued due to hemodynamic instability, and the rate of TTM discontinuation in our study was higher than reported in the TTM-trial.[3] This might reflect a greater tendency to abort temperature treatment in unstable and deteriorating patients if not being part of a research trial protocol. Interestingly, the signal from the TTM-trial that patients in circulatory shock on hospital arrival tended to have a better outcome when treated with TTM at 36 °C, as suggested by Annborn et al.,[6] was also evident in our cohort. Additionally, subgroup analysis suggests an association between a good outcome and women treated with TTM-high, which was not seen in the TTM-trial, though the point estimate was in the same direction.[3]

Our treatment groups differed in baseline characteristics such as age, sex, comorbidities, arrest characteristics, pre-hospital circumstances, cardiac interventions and shock on admission, all variables significantly associated with outcome after cardiac arrest. These differences may reflect geographic, demographic and policy-related or patient-selection factors specific to treating physicians. In Sweden, the mean age at arrest is higher, male patients suffering cardiac arrest outnumber female patients, shockable rhythms are more common and the frequency of bystander-CPR is much higher compared to the

United States.[29,30] The marked difference in baseline variables between the United States and Europe might indicate the presence of other unidentified and unmeasured factors that differ, resulting in considerable residual confounding. A validated cardiac arrest-specific severity scoring model could facilitate the comparison between groups with different baseline characteristics.

There are a number of limitations to this study. This was a retrospective study of prospectively collected registry data and the sample size was determined by convenience. No audit or formal quality control was performed, making erroneous data and misinterpreted entries in the INTCAR2 database possible. The generalizability of our findings may be limited, as our results reflect standards in highly specialized OHCA-centers using TTM. Hospital characteristics are associated with OHCA outcome, favoring centers with 24-h cardiac interventional services.[31,32] Recent studies have shown that the variation in outcome after cardiac arrest may be influenced by variations in withdrawal of life sustaining therapy (WLST) strategies and in-hospital management differences.[33,34]

Hospital discharge may not be an ideal outcome assessment time point, since functional outcome may evolve after cardiac arrest, and time of discharge varied considerably.[35] The TTM-trial, however, showed that the difference in neurological function between hospital survival and 180-day survival was limited.[3]

Our sample-size differed between TTM-low and TTM-high (Table 1) due to the fact that the majority of INTCAR2-patients were registered in the United States where treatment at 33 °C was more common in the participating sites. The reverse situation was present for patients included in Sweden (Fig. 1) where temperature control at 36 °C has become standard care after the TTM-trial. This difference in treatment strategies in different countries might represent a bias when analysing data from an international multicenter registry. Therefore, patients registered before 2013 were excluded to minimize any treatment bias following the publication of the TTM-trial.

During the five-year inclusion period, changes may have occurred in cardiac arrest care, including standardized intensive care bundles and more early cardiac intervention. Advanced pre-hospital care has also evolved and both availability of public defibrillators and layperson awareness of cardiac arrest and bystander-CPR may have increased. In addition, fewer patients presented with shockable rhythms.[36] Finally, the lack of international standardized processes for prognostication and WLST in cardiac arrest patients may have influenced outcome in these patients.

Strengths include a large multinational perspective, a prospective registry, well established cardiac arrest centers, well defined covariables important for adjustment of treatment effects and consecutively entered patients which may better reflect real-world practices than clinical trials do.

While the overall mortality from cardiac arrest remains high, the prognosis for unconscious OHCA patients with initial shockable rhythms and ROSC admitted to the ICU are improving, as more than half will survive with a good functional outcome.[8]

Controlling body temperature is a potential treatment that may prevent secondary brain damage but the precise mechanisms are still unknown. Optimal post-cardiac arrest care remains controversial, including which temperature to target, how long to deliver temperature control, the optimal way of rewarming and whether different target temperatures are appropriate for different patients.[37–39] Overall quality of evidence for this therapy is low or very low, and further studies are necessary to determine benefits and risks related to temperature management.[1] The TTM2-trial (NCT02908308) is an ongoing international, multicenter, parallel group, investigator initiated, superiority trial in which 1900 OHCA patients will be randomised to a targeted temperature of 33 °C or to normothermia with early treatment of fever (≥37.8 °C).[40]

Conclusions

This large international registry study of OHCA patients revealed no significant difference in outcome between patients treated with TTM-low or TTM-high, supporting the findings from the TTM-trial. When adjusting for confounding factors, the multivariate analysis indicated a non-significant tendency towards better functional outcome with TTM-low. This was, however, associated with more hemodynamic instability and discontinuation of TTM therapy. Limitations in the current evidence support larger randomised trials to better establish the potential benefits and harms of specific approaches to TTM after OHCA.

Conflict of interest

The authors declare that they have no conflict of interest with the contents of this article.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.10.020.

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