Intensive Care Med
https://doi.org/10.1007/s00134-025-07883-4

ORIGINAL

Intravascular vs. surface cooling in out-of-hospital cardiac arrest patients receiving hypothermia after hospital arrival: a post hoc analysis of the TTM2 trial

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Abstract

Purpose: To compare the performance of targeted temperature management (TTM) at 33 °C using intravascular (IC) vs. surface-cooling (SFC) devices after out-of-hospital cardiac arrest (OHCA).

Methods: A post hoc analysis including OHCA patients randomized to hypothermia in the TTM2-trial (NCT02908308) comparing hypothermia with normothermia. The main outcome was cooling performance, defined as the proportion of patients reaching target temperature < 33.5 °C within 4 h, time outside temperature ranges during maintenance, rewarming rate and post-TTM fever. Exploratory outcomes included survival and good functional outcome, defined as modified Rankin Scale (mRS) scores of 0–3 at 6 months, analyzed using Inverse Probability Treatment Weighting (IPTW).

Results: Among 930 patients randomized to hypothermia, 876 were treated with a cooling device and included in this study. Of those, 27.3% received IC devices, while 72.7% received SFC devices. The proportion reaching target temperature within 4 h was higher with IC (IC: 69.6% vs. SFC: 49.2%; $p < 0.001$). Temperature outside ranges during the cooling period and post-TTM fever were lower with IC compared to SFC (17.2% vs. 39.6%; $p < 0.001$ and 0% vs. 6.3%; $p < 0.001$, respectively). In the exploratory IPTW analysis, 6-month survival rates were 55.2% in the IC group and 50.2% in the SFC group (OR 1.22, 95% CI 0.89–1.68) and survival with good functional outcome at 6 months was 51.1% patients in the IC group and 44.9% in the SFC (OR 1.28, 95% CI 0.93–1.77).

Conclusions: Among OHCA patients randomized to hypothermia in the TTM2 study, intravascular cooling, compared with surface cooling, was associated with better cooling performance.

Keywords: Out-of-hospital cardiac arrest, Hypothermia, Intravascular cooling, Surface cooling

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Introduction

Recently revised international guidelines recommend normothermia with fever prevention in comatose patients for 72 h after cardiac arrest, although targeting temperatures between 32 °C and 36 °C may be considered for selected patients [1]. The broad temperature interval reflects the heterogeneity in evidence from clinical trials during the last two decades [2]. The more recent TTM trial (comparing 33 °C vs. 36 °C) and the subsequent TTM2 trial (comparing 33 °C vs. controlled normothermia) did not demonstrate any difference in survival or functional outcome [3, 4] between these strategies when targeted temperature management (TTM) was applied after arrival to the intensive care unit (ICU). However, in the HYPERION trial, including both in-hospital and out-of-hospital cardiac arrests with non-shockable rhythm, more patients in the hypothermia group (33 °C) survived with good neurological outcome [5].

Despite this change in guidelines, several important questions still need to be addressed. One of these is whether the choice of cooling method influences the performance of TTM and if this, subsequently, can affect the outcomes. There are a number of different cooling methods, some of which are relatively non-invasive or easy to use (e.g., exposure, cooling blankets or cold intravenous fluids), while others are more invasive [e.g., use of intravascular cooling (IC) or surface cooling (SFC) devices]. In general, IC and SFC are temperature-feedback systems that use closed-loop technology to guide the intervention [6–9].

Studies have shown that IC and SFC devices achieve target temperature faster, lead to less overcooling, less rebound fever and are associated with better neurological outcomes compared with non invasive systems or easy-to-use interventions, whick lack the temperature-feedback adjustment [10–13]. Although both IC and SFC devices are very effective, they work in fundamentally different ways [12, 14–18]. The IC device consists of a heat-exchanger catheter in direct contact with the blood, with cold solution flowing within the catether, causing internal/convective cooling. The SFC device, on the other hand, relies more on peripheral perfusion being in contact with external cooling and are based on thermal conductivity. There are several types of SFC with different types of extern cooling techniques (e.g., water circulating cooling blankets and adhesive surface pads [19]).

Whether IC or SFC should be preferred is unclear. SFC may increase the risk for skin injuries, while IC seems to increase the risk for cathether-related bleeding, infection and thrombosis [20, 21]. In several studies, IC has been associated with less temperature variability compared with SFC [22–25]. Meta-analyses have suggested that IC is associated with better neurological outcomes in resuscitated OHCA patients, but this is based on low-certainty evidence [13, 20, 26, 27].

Take-home message

Intravascular cooling, compared to surface cooling, after out-of-hospital cardiac arrest, was associated with better cooling performance (faster, holds a more stable temperature and less fever). In the explorative analysis, there was a non-significant difference in 6-month survival and 6-month survival with good functional outcome (defined as modified Rankin Scale 0-3) favoring the intravascular cooling group.

The aim of this study was to compare the cooling performance of IC and SFC in achieving and maintaining a target temperature of 33 °C after OHCA, and to explore their association with patient outcomes.

Methods

Setting

This is a post hoc analysis of data from the Hypothermia vs. Normothermia after Out-of-Hospital Cardiac Arrest trial (TTM2-trial; NCT02908308) [4]. The TTM2-trial was an investigator-initiated multicenter randomized controlled trial in which targeted temperature management to 33 °C was compared with controlled normothermia (e.g., body temperature < 37.8 °C) in OHCA patients. A total of 1900 patients were recruited and the trial demonstrated no difference in the primary outcome of survival at 6 months.

Study population and interventions

Adult patients with OHCA of a presumed cardiac or unknown cause, who achieved sustained return of spontaneous circulation (ROSC) and were admitted to the hospital unconscious, were included in the TTM2 trial. Patients were eligible for inclusion within 180 min from ROSC.

The patients were randomized 1:1 to hypothermia or normothermia. The intervention period was 40 h and started at the time of inclusion. All patients were sedated and mechanically ventilated during the intervention period. In the hypothermia group, the protocol urged the use of a cooling device with temperature feedback, but whether to use IC or SFC was left to the discretion of each participating centre. Each hospital stated in the individual case reports 1) whether a cooling device was used, 2) which device was used, and 3) when the device was started. In addition to IC or SFC, cooling induction could be combined with less invasive methods such as administration of intravenous cold fluids, intranasal cooling, ice-packs, cooling pads or complete exposure of the patient.

Core temperature was measured hourly, primarily via a urinary bladder thermometer. If bladder recording was unavailable, alternative temperature measurements were taken via an intravascular or esophageal probe. In patients randomized to hypothermia, cooling was started as soon as possible using either IC or SFC to a target temperature of 33 °C. This temperature was maintained for 28 h after inclusion, followed by 12 h of slow rewarming (0.3 °C per hour) targeting 37 °C (Supplemental Fig. 1). After rewarming, the aim was to avoid fever (< 37.8 °C) in all patients during the first 72 h after inclusion. Details of the trial interventions have been described previously [4, 28].

In this post hoc analysis, the group randomized to TTM at 33 °C was analyzed. The intervention was divided into two phases: cooling and rewarming. The cooling phase was defined as the period from randomization until 28-h post-randomization, and the rewarming phase as 28–40 h after randomization.

All patients in the TTM2 trial who were randomized to TTM at 33 °C and underwent cooling with a device were eligible for this study. Exclusion criteria were: (1) if the device type was not recorded; (2) if the patient underwent both IC and SFC; (3) if the patient was rewarmed or died during the intervention period (excluded from the cooling performance analysis but included in the outcome analysis); and (4) if the outcome at 6 months was unknown (excluded from the outcome analysis but included in the cooling performance analysis).

Outcomes and outcome asssessments

Cooling performance

The main outcome in this study was cooling performance assessed by (1) the proportion of patients reaching the targeted temperature of ≤ 33.5 °C (a pragmatically chosen cutoff point) within 4 h after randomization, (2) the median time from randomization to achieving a temperature ≤ 33.5 °C, (3) the proportion of patients that were overcooled (defined as ≤ 32.5 °C), and (4) cumulative deviation (magnitude × duration of deviation) of temperatures of more than ± 0.5 °C from 33 °C. Furthermore, the number of patients with post-TTM fever (defined as at least one temperature > 38.0 °C after 28-h post-randomization) was assessed.

Explorative outcomes

As exploratory outcomes, we analyzed the patient-centred outcomes survival and survival with good functional outcome (defined as a modified Rankin Scale (mRS) score of 0–3) at 6 months.

Serious adverse events and shivering

We analyzed the same serious adverse events (SAE) as in the main TTM2-trial. Shivering was assessed according to the Bedside shivering assessment scale (BSAS) 0–3, where 0 is no shivering, 1 is mild shivering, 2 is moderate shivering and 3 is severe shivering.

Statistical analysis

Categorial variables are presented as counts and proportions, normally distributed continuous variables are presented as means and standard deviations, and non-normally distributed continuous variables are presented as medians and quartiles. Differences in baseline characteristics were assessed using standardized mean differences (SMDs). To adjust for potential confounders between IC and SFC group, we used Inverse Probability Treatment Weighting (IPTW) based on the propensity sore. The inverse of the propensity score are used as weights in to balance the treatment groups. The choice of IPTW was to estimate the average treatment effect (ATE). Variables included in the propensity score calculations were age, sex, initial rhythm, frailty score, time to ROSC, witnessed status, bystander CPR, location of cardiac arrest (i.e., at home or outside home), the Charlson comorbidity index, time from cardiac arrest to randomization and coronary angiography within 2 h from randomization. Furthermore, we performed an supplemental IPTW analysis also including the bilateral pupillary reflex as a variable. The matched data were analysed using a conditional logistic regression.

Supplementary analyses using both frequentist and Bayesian multilevel logistic regression were performed with the same variables as above, with the addition of study site as a random effect. Furthermore, when comparing outcomes of IC vs. SFC, cooled patients in hospitals with access to both cooling methods were analyzed. For the Bayesian analyses a normal distribution [Normal(0,1)] was used as prior distribution (log-odds scale). The Bayesian regression analyses used a normal prior distribution with a mean of 0, and a standard deviation of 1 on the log odds scale. 10,000 iterations were used, where 1000 of them were used as warm-up. Data are presented as odds ratios (ORs) and 95% confidence/credible intervals (CIs/CrIs). All analyses were performed using R version 4.2.2 (R foundation for Statistical Computing, Vienna, Austria).

Furthermore, we analyzed outcomes for IC and SFC patients, respectively, in the hypothermia group that are IPTW matched with normothermia patients from the same hospital using the same variables listed above.

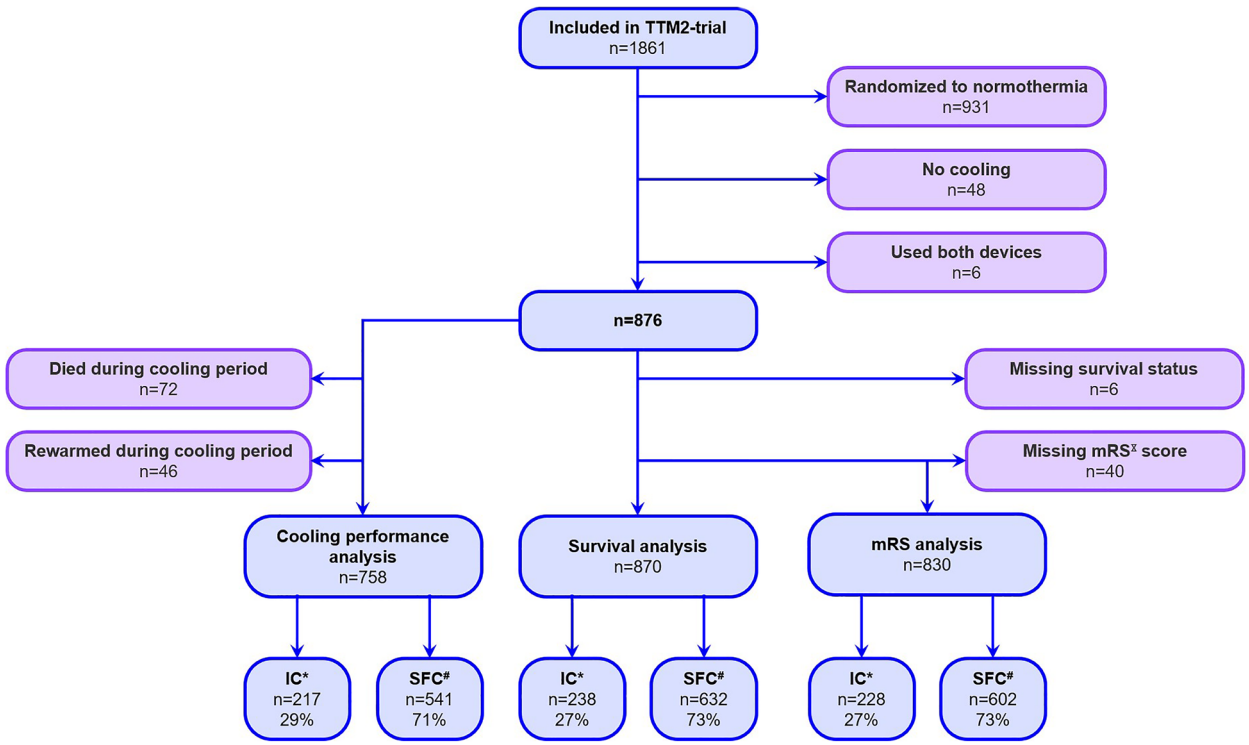

Fig. 1 Flow of patients. ⁵Modified Rankin scale. *Intravascular cooling.#Surface cooling

Results

Study population

Among 930 patients randomized to TTM 33°C2, 876 (94.2%) were included in this study. Of these, 239 patients (27.3%) underwent IC and 637 (72.7%) underwent SFC. Of 60 centers, the majority ($n=47$, 78.3%) primarily used SFC. When including those that had used SFC in at least one patient the number increased to 53 (88.3%). Fewer sites ($n=13$, 21.7%) used IC as their primarily choice, but 23 centers (38.3%) had used IC at least once. Most centres that had access to both methods had a clear tendency to use one or the other (Supplemental Table 1). All IC centres used the same type of device, while SFC centers used various surface devices.

Out of the 876 included patients, 118 died or were rewarmed during the cooling phase, excluding them from the analysis of cooling performance ($n=758$) and 6 patients lacked survival data excluding them from the survival analysis ($n=870$) (Fig. 1). Baseline characteristics of the patients before the IPTW are presented in Table 1. Overall, the variables were balanced, with SMD < 0.1 for all covariates used in propensity scoring.

Cooling performance

Cooling performance in the IC and SFC groups is presented in Table 2 and Figs. 2 and 3. A larger proportion of the IC group reached target temperature within 4 h of randomization (69.6% vs. 49.2%, $p<0.001$) and within 8 h (93.5% vs. 87.1%, $p=0.02$). The median time to reach the target temperature of ≤33.5 °C was approximately 3 h in the IC group and approximately 4 h in the SFC group (Fig. 3). Fewer patients in the IC group had at least one episode of overcooling (17.5% vs. 74.5%, $p<0.001$). Temperature variability was significantly lower in the IC group (Table 2 and Fig. 2). Furthermore, no patient in the IC group had any measured episode of post TTM-fever vs. 6.3% of patients in the SFC group ($p<0.001$).

Exploratory outcomes

Outcomes regarding survival and functional status are presented in Table 2, Supplemental Figs 2,3, 4 and Supplemental Table 3, 4.

Unadjusted 6-month survival rates were 138 of 238 (58.0%) patients in the IC group vs. 309 of 632 (48.9%) patients in the SFC group. After IPTW, the 6-month survival rates were 55.2.0% in the IC group and 50.2% in the SFC group (OR 1.22, 95% CI 0.89–1.68, $p=0.2$).

Table 1 Baseline characteristics of patients before and after Inverse Probability of Treatment Weighting (IPTW)

	Intravascular cooling (*n* = 239)	Surface device cooling (*n* = 637)	Missing (%)	SMD# (unadjusted)	Intravascular cooling Ω	Surface device cooling Ω	SMD# (adjusted)
Demographic characteristics							
Age—mean yr (SD*)	64 ± 13	64 ± 13	0	0.02	64	64	0.01
Male sex—no (%)	195 (82)	510 (80)	0	0.04	81%	80%	< 0.01
Medical history							
Hypertension—no (%)	85 (37)	241 (39)	4.2	0.04	–	–	–
Diabetes—no (%)	44 (18)	120 (19)	0	0.01	–	–	–
Myocardial infarction—no (%)	38 (17)	94 (15)	4.2	0.04	–	–	–
PCI—no (%)	37 (16)	85 (14)	4.2	0.07	–	–	–
Coronary artery bypass graft—no (%)	18 (8)	52 (9)	4.2	0.02	–	–	–
Heart failure—no (%)	15 (7)	69 (11)	4.2	0.16	–	–	–
Charlson comorbity index, mean (SD)	2.9 (2.1)	3.1 (2.1)	0	0.11	3.1	3.0	< 0.01
Frailty score**—mean (SD)	2.6 (1.3)	2.7 (1.4)	0	0.12	2.7	2.7	< 0.01
Characteristics of the cardiac arrest							
Initial shockable rhythm—no (%)	187 (78)	457 (72)	0	0.15	74%	74%	< 0.01
Location at home—no (%)	124 (52)	334 (52)	0	0.01	52%	52%	0.01
Bystander-witnessed cardiac arrest—no (%)	211 (88)	593 (93)	0	0.17	92%	92%	< 0.01
Bystander CPR—no (%)	190 (79)	526 (83)	0	0.08	82%	81%	0.02
Mean time from cardiac arrest to sustained ROSC—min (SD)	30 (19)	31 (20)	0	0.03	30	30	0.03
Mean time from cardiac arrest to randomization—min (SD)	133 (42)	139 (46)	0	0.03	137	137	< 0.01
Clinical characteristics on admission							
Tympanic temperature—mean °C (SD)	35.2 (1.1)	35.3 (1.1)	29	0.07	–	–	–
Bilateral pupillary reflex present—no (%)	171 (81)	342 (67)	17.5	0.32	–	–	–
Arterial pH—mean (SD)	7.20 (0.1)	7.18 (0.2)	1.6	0.07	–	–	–
Arterial lactate level—mean mmol/L (SD)	5.9 (5.0)	5.8 (4.1)	3.4	0.02	–	–	–
Shock—no (%)	62 (26)	177 (28)	0	0.04	–	–	–
ST-segment elevation myocardial infarction—no (%)	110 (47)	254 (40)	1.1	0.13	–	–	–
Coronary angiography < 2 h from randomization—no (%)	198 (83)	423 (66)	0	0.38	71%	71%	< 0.01

Ω Average weighting for variables included in the IPTW analysis *Standard deviation (SD) **Level of fitness, 1–9 (1 = very fit, 9 = terminally ill)

At 6 months, 122 of 228 (53.5%) patients in the IC group and 262 of 602 (43.5%) patients in the SFC group were alive with good functional outcome corresponding to an mRS scores of 0–3. After IPTW, 51.1% of the patients in the IC group and 44.9% of the patients in the SFC group were alive with mRS scores of 0–3 (OR 1.28, 95% CI 0.93–1.77, $p = 0.13$).

The adjusted Bayesian analyses showed similar results and are presented in Supplementary Fig. 2.

Adverse events and shivering

There was no significant difference between the groups in the incidence of prespecified serious adverse events. One case of thromboembolism was reported in the IC group. The IC group had statistically significant more shivering at day 1 and higher occurrence of severe shivering (defined as BSAS grade 3) at day 3. Adverse events and shivering are presented in Supplemental Table 2.

Table 2 Cooling precision and outcomes for intravascular versus surface devices

	Intravascular cooling	Surface device cooling	p value
Cooling performance			
Number of patients reaching target temperature within 4 h of randomization (%)	111 (69.6)	266 (49.2)	< 0.001
Number of patients reaching target temperature within 8 h of randomization (%)	203 (93.5)	471 (87.1)	0.02
Number of patients with at least one episode of overcooling (%)	38 (17.5)	403 (74.5)	< 0.001
Proportion of temperature measurements out of range (%)	17.2	39.6	< 0.001
Mean temperature deviation among measurements out of range (^{0}C)	0.9	1.0	< 0.001
Cumulative temperature deviation (proportion × mean deviation)	15.4	39.6	< 0.001
Number of patients with at least one episode of post-TTM fever (%)	0 (0)	34 (6.3)	< 0.001
Patient centred outcomes			
Unadjusted survival at 180 days	57.7%	48.9%	0.02
Survival at 180 days after IPTW matching[#]	55.2% OR 1.22 (95% CI 0.89–1.68)	50.2%	0.2
Unadjusted survival with mRS^ 0–3 at 180 days	53.5%	43.5%	0.01
Survival with mRS^ 0–3 at 180 days after IPTW matching[#]	51.1% OR 1.28 (95% CI 0.93–1.77)	44.9%	0.13

^Modified Rankin Scale 0–3

[#] The Invserse Probability Treatment Weighting (IPTW) matching included age, sex, initial rhythm, frailty score, time to ROSC, witnessed status, bystander CPR, location, Charlson comorbidity score, coronary angiography within 2 h

Discussion

In this post hoc analysis of OHCA patients randomized to hypothermia in the TTM2 trial, we found that IC demonstrated better cooling performance compared with SFC. IC had shorter time to target temperature after cooling initiation and better adherence to the set temperature target during the maintenance and rewarming period.

Hypothermia after cardiac arrest is divided into different phases: induction, maintenance and rewarming. An ideal cooling method should be easy to use, induce hypothermia fast (without overcooling), maintain a stable target temperature during the maintenance phase, achieve slow and controlled rewarming, avoid rebound fever and have few adverse effects [29, 30]. Although IC requires insertion of a large-gauge catheter into a central vein, which may be associated with risks and could be time-consuming, it may thereafter, compared with SFC, deliver a more high-quality cooling [11].

In the latest European Resuscitation Council guidelines, no specific cooling method is recommended over another [1]. This is based on a meta-analysis which included only RCTs [31]. There are only three RCTs comparing IC and SFC, of which one [17] concerned IC with basic surface cooling (e.g., antipyretic drugs, fans, homemade tents and ice-packs) and two are small feasibility studies not powered to detect a difference in clinical outcomes [24, 25]. In several observational studies comparing cooling performance, IC has been associated with less temperature variability and less overcooling [13, 27]. Three other meta-analyses, which included observational studies, suggest that IC, compared with SFC, is associated with better neurological outcomes [13, 26, 27]. In these meta-analyses, as in this study, no significant difference was seen as regards overall survival.

In a post hoc analysis of the TTM trial ($n = 934$), IC was not associated with faster cooling speed but was associated with less temperature variability [22]. The IC group had a 3.7% higher crude survival rate and a 5.3% higher rate of survival with good functional outcome, but these differences were not statistically significant [22]. In a post hoc analysis of the TTH48 trial ($n = 352$), comparing hypothermia to 33 °C for either 24 or 48 h, IC was associated with less temperature variability, had a 3% higher survival rate and a 6% higher rate of survival with good neurological outcome, but the outcome differences were also not statistically significant [23]. In an observational study ($n = 803$), more patients in the IC group survived with good neurological status, but this difference was no longer significant after propensity score matching [18].

This study showed similar tendencies as in previous studies that IC was associated with better functional outcome than SFC. Since most hospitals used either IC or SFC, there is a risk of selection bias and different case mixes, which could explain some of the differences seen in clinical outcomes. For example, large referral centres with percutaneous coronary intervention (PCI) facilities might have a greater tendency to use IC. Although this was considered in the adjusted model, more patients in the IC group received coronary angiography within 2 h

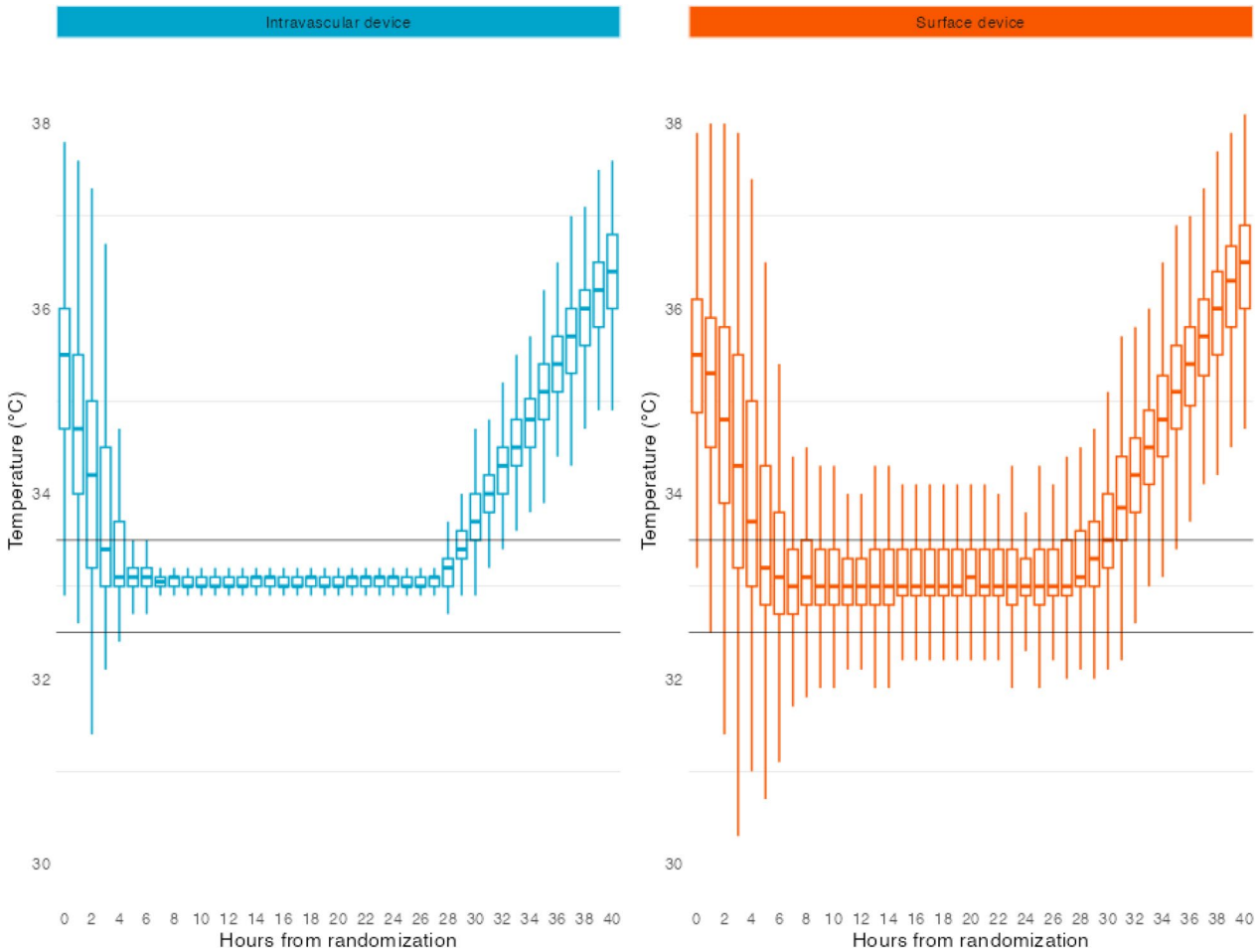

Fig. 2 Patient temperatures over the intervention period. Hours from randomization on x-axis. Median and interquartile temperatures in intravascular (blue) and surface (red) cooling groups during the intervention period

(79% vs. 67%, see Table 1) and the risk of a "site effect" or selection bias with regard to cardiac causes of arrest, cannot be eliminated. On the other hand, the fact that IC demonstrated better cooling performance from several points of view could be a possible explanation and ought to be explored in future studies. In this study IC was associated with a shorter time to target temperature, less overcooling, less temperature variability and fewer episodes of post-TTM fever. Although these are reasonable explanations from a physiological perspective, the evidence for a causal relationship between these parameters and clinical outcome is weak [13, 32, 33]. In two observational studies, temperature variability was not associated with neurological outcome [34, 35]. Time to goal temperature, and post-TTM fever have been associated with neurological outcome, but there are no RCTs that have demonstrated any causal relationship [32, 36].

One important aspect that may have influenced the results is that in the SFC group several different SFC devices were used, based on different methods (e.g., hydrogel pads or cooling blankets) with different capacities to cool, different feedback loops and cooling capacities. Although the study protocol recommended the use of feedback-loop devices, we did not have patient-level data on which type of device was used, and we cannot assume that different devices performed equally well.

This study has several strengths and adds novel information to this research question. This is one of the largest studies to date, where it has been possible to compare IC and SFC in patients targeted to 33 °C. Although being an observational post hoc analysis, the data was prospectively and systematically collected as part of an RTC. We have granular patient data on temperature and other patient-related parameters. The study was investigator-led and was not supported by any industry or commercial funds.

This study has several limitations. First, as mentioned above, the risk of selection bias cannot be excluded. Second, in centres with both IC and SFC, we do not know if there

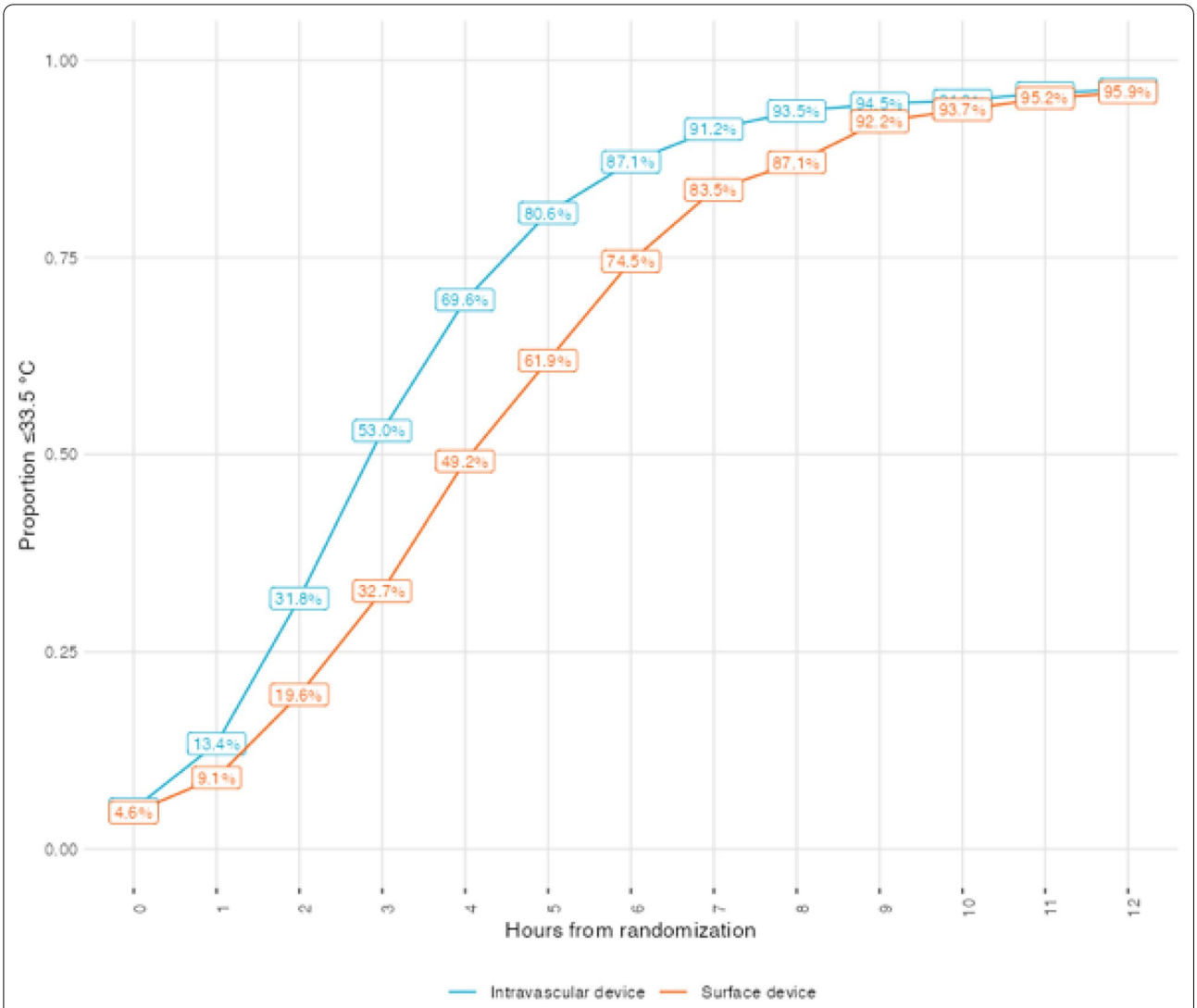

Fig. 3 Proportion of patients reaching targeted temperature within 12 h in the intravascular versus the surface-device group

were patient-related factors that affected the choice of one method over the other. Third, as in all observational studies, there is always a risk of residual confounding. Fourth, we did not have information on whether or not IC/SFC was combined with less invasive cooling methods (e.g., intravenous cold fluids or ice-packs), which could have affected cooling performance and clinical outcomes. Fifth, we lack patient-level data on which type of SFC device was used. Sixth, this was a post-hoc analysis without a predetermined protocol.

Conclusions

Among patient in the TTM2 study treated with TTM to 33°C after OHCA, intravascular cooling, compared with surface cooling, was associated with more rapid cooling, less temperature variability and less post TTM fever.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1007/s00134-025-07883-4.

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Authors contributions
AA, PN, MJ, JD and NN are responsible for the study design. AA wrote the first draft of the manuscript, PN funded and supervised. MJ and AA are responsible for the statistical analysis. All authors were involved in patient recruitment, data collection, interpretation of the results, editing, critical review and approval of the final manuscript.

Funding
Open access funding provided by Karolinska Institute. Hjärt-Lungfonden, 20210394, Per Nordberg

Declarations

Conflicts of interest
P.N. has received funding from BD and the Swedish Heart Lund Fundation. F.S.T. has received lecture fees from BD and Zoll. The rest of the authors declare no conflicts of interest.

Publisher's Note

Received: 4 December 2024 Accepted: 25 March 2025
Published online: 28 April 2025

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