EFFECT OF TRANS-NASAL EVAPORATIVE INTRA-ARREST COOLING ON FUNCTIONAL NEUROLOGIC OUTCOME IN OUT-OF-HOSPITAL CARDIAC ARREST: THE PRINCESS RANDOMIZED CLINICAL TRIAL

Trial Registration: ClinicalTrials.gov Identifier: NCT01400373

Title page

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Key points

Question: Does cooling of the brain, initiated prehospital during cardiopulmonary resuscitation, improve neurologic intact survival in patients with out-of-hospital cardiac arrest?

Findings: In this randomized clinical trial of 677 patients with out-of-hospital cardiac arrest, good neurologic outcome (Cerebral Performance Category 1–2) was 16.6% in the trans-nasal cooling group compared with 13.5% in the usual care group, a difference that did not reach statistical significance.

Meaning: Trans-nasal evaporative intra-arrest cooling did not result in a statistically significant improvement in neurologic intact survival.

Abstract

Importance: Therapeutic hypothermia may increase neurologic intact survival after cardiac arrest. Trans-nasal evaporative cooling is a method to induce cooling during cardiopulmonary resuscitation (i.e. intra-arrest), primarily of the brain.

Objective: To determine whether pre-hospital trans-nasal evaporative intra-arrest cooling improves neurologic intact survival compared with cooling initiated after hospital arrival.

Design, Setting, Participants: The PRINCESS trial was an investigator-initiated, randomized clinical, international multicenter study with blinded assessment of the outcome, performed by emergency medical services in seven European countries from July 2010 to January 2018, with final follow up April 30, 2018. In total, 677 patients with bystander-witnessed out-of-hospital cardiac-arrest were enrolled.

Interventions: Patients were randomly assigned to trans-nasal evaporative intra-arrest cooling (n=343) or standard care (n=334). Patients admitted to hospital in both groups received systemic therapeutic hypothermia, at 32–34 ºC, for 24 hours.

Main outcomes and Measures: Primary outcome was neurologic intact survival, Cerebral Performance Category (CPC) 1–2, at 90 days. Among secondary outcomes were: survival at 90 days; and time to reach core body temperature of <34 ºC.

Results: Among the 677 randomized patients (median age 65; 172 [25%] women) 671 completed the trial. Median time to core temperature <34 ºC was 105 min in the intervention group versus 182 min in controls, p< .001. The proportion of patients with CPC 1–2, at 90 days was 16.6% (56/337) in the intervention group versus 13.5% (45/334) in controls (difference 3.1%; 95% confidence interval [CI], -2.3% to 8.5%; relative risk [RR] 1.23 [0.86–1.72], p= .25). Survival at 90 days was 17.8% (60/337) versus 15.6% (52/334) respectively (difference 2.2%; 95% CI, -3.4% to 7.9%; RR 1.14 [0.81–1.57, p= .44). Minor nosebleed was the most

common device-related adverse event, reported in 13% of the patients in the intervention group (45/337). The adverse event rate within 7 days was similar between groups.

Conclusions and Relevance: Among patients with out-of-hospital cardiac arrest, trans-nasal evaporative intra-arrest cooling compared with usual care did not result in a statistically significant improvement in neurologic intact survival at 90 days.

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INTRODUCTION

Therapeutic hypothermia may increase survival with good neurologic outcome after out-of-hospital cardiac arrest.[1] Experimental data show that therapeutic hypothermia in cardiac arrest reduces ischemic and reperfusion brain injury, with a beneficial effect of early, intra-arrest cooling, i.e. started during cardiopulmonary resuscitation (CPR), compared with cooling initiated at a later stage.[2-4] Despite this, the majority of clinical studies have concerned the effect of therapeutic hypothermia when cooling was initiated after hospital arrival, most often at the intensive care unit (ICU), several hours after the cardiac arrest.[1,5] Currently, treatment guidelines recommend hospital use of therapeutic hypothermia or temperature control at a temperature of 32 °C to 36 °C for at least 24 hours, with the strongest indication in patients with ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT) as first rhythm.[6,7] Clinical trials assessing the effect of early, pre-hospital cooling have in general involved the use of infusions of cold fluids administered intra-arrest or early after return of spontaneous circulation (ROSC).[8-11] Cold fluids cool the patient effectively, but seem to have significant hemodynamic side effects.[11] In particular, this has been observed in patients with VF as first rhythm, where intra-arrest infusion of cold fluid decreased the rate of patients achieving ROSC.[9] Based on these findings, pre-hospital cooling using rapid infusion of cold intravenous fluid is not recommended.[6,7]

Trans-nasal evaporative cooling is a method that does not add volume to the patient. This non-invasive cooling method can be induced intra-arrest and leads to continuous cooling, primarily of the brain.[12,13] The primary objective of this study was to determine whether pre-hospital trans-nasal evaporative intra-arrest cooling improves survival with good neurologic outcome, compared with current practice where cooling is initiated after hospital arrival.

METHODS

Trial design

The PRINCESS trial was an investigator-initiated, randomized clinical trial with blinded assessment of the outcome. The study was conducted in 11 Emergency Medical Services (EMSs) in seven European countries between 07-01-2010 and 01-31-2018. The last patient was followed-up on April 29, 2018. Ethics and institutional committees in each participating country approved the study protocol and statistical analysis plan (Supplement 1) and the rationale and design of the trial have been published previously.[14] An independent Data and Safety Monitoring (DSM) committee reviewed predefined endpoints at interim analyses after recruitment of 200 and 500 randomized patients. After the interim analysis at 500 patients, further recruitment of study patients by helicopter EMSs was stopped because of prolonged times to inclusion, being regarded as a safety issue. The study was conducted according to the requirements of the Declaration of Helsinki. Written informed consent was obtained from the closest relative or a legal representative after hospital admission, and, at a later stage, from each patient who regained mental capacity. Neither EMS nor hospital personnel were blinded to treatment, because of the nature of the intervention. However, nurses/physicians performing neurological assessment of patients prior to discharge and at 90 days, as well as data managers and researchers were blinded to the patients' group assignment.

Patients

The inclusion criteria were bystander-witnessed cardiac arrests in patients of ≥18 years of age. Exclusion criteria were patients aged ≥80 years; an etiology of cardiac arrest due to trauma, head trauma, severe bleeding, drug overdose, cerebrovascular accident, drowning, smoke inhalation, electrocution, hanging; already hypothermic; an obvious anatomic barrier to

placing intra-nasal catheters; an existing do not attempt resuscitation (DNAR) order; known terminal disease; known or clinically apparent pregnancy; known coagulopathy (except therapeutically induced); need for supplemental oxygen; patients that achieved ROSC prior to randomization; EMS response time (collapse to EMS arrival) >15 minutes.

Randomization and trial intervention

Patients were screened for eligibility by the advanced life-support team after airway management (i.e. endotracheal intubation or laryngeal mask). If the study criteria were fulfilled, patients were randomly assigned (1:1 ratio) to either intra-arrest cooling or standard care, using sequentially numbered envelopes, which were provided by the Karolinska Institute to the participating study site. Randomization was generated in blocks of four without stratification. Both study groups received standard advanced life-support care according to international guidelines. In patients randomized to intervention, trans-nasal evaporative cooling was initiated intra-arrest. The cooling method delivers a mixture of air or oxygen and a liquid coolant (perfluorohexane) via nasal catheters. When the coolant evaporates, it absorbs heat from the surrounding tissue and rapidly cools the nasal cavity to about 2 °C. The method was developed primarily to cool the brain, as it takes advantage of the nasal pathways (i.e., the conchal folds and turbinates) that provide a highly vascular and large, diffuse surface area that is in close proximity to the cerebral circulation. The method has previously been described in detail.[12,14,15] If the patient achieved ROSC or was transported during CPR to hospital, trans-nasal evaporative cooling was continued until hospital arrival and whenever possible until systemic hospital cooling was initiated.

Hospital-admitted patients received post-resuscitation treatment according to current treatment guidelines, including systemic hypothermia for both study groups.[16]

Intravenous sedation, analgesia and neuromuscular blockade were used according to institutional cooling protocols. The targets for ventilation settings, mean arterial blood pressure and glucose control have been described previously.[14] The temperature was measured according to local practices in the urinary bladder, rectum, esophagus, or with intravascular probes. The target core temperature for all patients was 33 °C ± 1 °C and the duration of hypothermia was 24 hours. The re-warming rate was 0.2–0.5 °C per hour. Temperature control to avoid fever was recommended for 72 hours.

Data collection

Data on factors at resuscitation, e.g. age, bystander CPR and initial rhythm followed the template recommended by guidelines.[17] The advanced life-support team recorded pre-hospital event times and temperature measurements at ROSC. Tympanic and core temperature was measured after hospital arrival and during the first 72 hours. In-hospital measures were recorded, such as coronary angiography, intra-aortic balloon pump use and neurologic prognostic measures. Data on adverse events were collected up to and including day seven following admission. At 90 days, data on good functional recovery was collected by means of a structured interview over the phone or person-to-person, using the Pittsburgh cerebral performance category (CPC) scale,[18] where CPC 1 is good recovery (alert and has normal cerebral function), CPC 2 represents moderate disability (alert and has sufficient cerebral function to live independently and work in a sheltered environment), CPC 3, severe disability (conscious but dependent on others for daily support), CPC 4, vegetative state (any degree of coma without the presence of all brain-death criteria), and 5, dead. In addition, good functional recovery assessment according to the Modified Rankin scale was performed at 90 days (Supplement 2).

Outcomes

The primary outcome was survival with good neurologic outcome 90 days after arrest, defined as a CPC score of 1 or 2.

The secondary outcomes were (1) overall survival rate at 90 days, and (2) cooling efficacy measured as time from collapse to core temperature of <34 °C.[14]

Two secondary endpoints, "sustained ROSC" (defined in the protocol as ROSC >20 minutes) and "admitted alive to hospital" were post-hoc merged into one variable "sustained ROSC and admitted alive" as the EMS crew did not correctly report sustained ROSC according to the protocol definition. To be "admitted alive" also requires sustained ROSC.

Adverse events were reported as device-related adverse events within 24 hours and adverse events at hospital within the first seven days after randomization.

Post-hoc endpoints were proportion of patients achieving sustained ROSC and admitted alive to hospital; survival with CPC 1 at 90 days; and the full distribution of CPC scores and Modified Rankin Scale scores at 90 days.

Statistical analyses

Power calculation was based on the preceding safety and feasibility trial that showed an absolute difference of 16% (21% versus 37%) in survival with CPC 1-2 at discharge among the patients admitted alive at hospital.[12] To show this absolute difference of 16% in the primary outcome patients a sample size of 150 patients admitted alive to hospital in each study arm was required for 80% power (2-sided, alpha level of 0.05). This would require a total sample of 650 to 800 patients to be randomized pre-hospital depending on the proportion of those patients that was resuscitated and admitted to hospital.[14] After recommendations from the DSM committee, the primary outcome analyses were performed in all randomized patients instead of those who were admitted alive to hospital.

The primary analyses were performed on all randomized patients, except those allocated to intervention that did not fulfill study criteria and never received the intervention (n=6). Continuous variables that were not normally distributed are reported as medians and interquartile ranges. Categorical variables are reported as counts and percentages. Primary analysis for the efficacy endpoints was conducted with Pearson's χ^2 tests for comparison of binominal proportions. As a post-hoc analyze, generalized linear mixed-effect models with study site as a random variable was used to calculate relative differences between categorical variables. Odds ratios were converted to relative risks (RRs) with 95% confidence intervals (CIs).[19] For continuous endpoints (time to core temperature <34 °C) the Hodges–Lehmann estimator was used.

The secondary analysis was performed as a "per-protocol" analysis that was restricted to all randomized patients with adherence to the intervention (i.e. excluded those in the intervention group that did not receive intra-arrest cooling). The secondary analysis was performed in accordance with the primary analysis.

Analyzes on the primary, secondary and exploratory endpoints were performed in pre-specified subgroups: patients with VF/VT as the initial rhythm; and patients where EMSs started CPR in less than 10 minutes. Exploratory endpoints (post-hoc), i.e. CPC 1 and the distribution of neurologic scores, were analyzed as absolute differences in proportions with 95% CI.

Multiple imputations have not been performed, as we had no missing values for primary and main secondary outcome (i.e. overall survival at 90 days).

All probability values were 2-sided, with values less than .05 regarded as statistically significant. No post-hoc adjustment of the significance level was performed. Because of the potential for type 1 error due to multiple comparisons, findings for analyses of secondary endpoints should be interpreted as exploratory. Post-hoc analyses on CPC1 and the

distribution of neurologic scores should also be considered as exploratory. Statistical analyses were performed with R (version 3.4.3)

RESULTS

Patients

Among 677 randomized patients, 671 (337 intervention and 334 control) were included in the primary analysis, see Figure 1.

Baseline characteristics

Patient characteristics, factors at the scene of the arrest, resuscitation measures, and event times prior to randomization were similar in the two groups (Table 1).

Event times, prehospital and hospital factors

In patients randomly assigned to intra-arrest cooling, the median time to start of cooling was 19 minutes from collapse. Tympanic temperatures at ROSC were 35.7 versus 36.0 ºC (p=0.02). At hospital arrival at a median time of 25 minutes post-ROSC, temperatures were 34.6 versus 35.8 ºC, p<0.001(eFigure 5, Supplement 2). Characteristics and measures after hospital arrival were similar in the two groups (Table 2).

Outcome

Primary outcome

In the primary analysis, the proportion of patients who survived with good neurologic function (CPC 1–2) at 90 days was 16.6% (56/337) in the intervention group versus 13.5% (45/334) in controls (difference 3.1%; 95% CI -2.3% to 8.5%; RR 1.23 [0.86–1.72], p= .25;

Table 3, eFigure 2, Supplement 2). In the secondary, per-protocol, analysis, the rate of CPC 1–2 at 90 days was 17.1% (56/328) versus 13.5% (45/334) respectively (difference 3.6%; 95% CI -1.9% to 9.1%; RR 1.26 [0.88–1.75], p= .20; eTable 1, Supplement 2). Primary outcome analysis for those patients admitted alive to hospital is presented in eTable 2, Supplement 2.

Secondary outcomes

Overall survival at 90 days was 17.8% (60/337) in the intervention group versus 15.6% (52/334) in controls (difference 2.2%; 95% CI -3.4% to 7.9%; RR 1.14 [0.81–1.57], p= .44; Table 3). Times to target core temperature were 105 min. in the intervention group versus 182 min. in controls (p< .001). Secondary outcomes in the secondary, per protocol, analysis are presented in the eTable1, Supplement 2.

Pre-defined subgroup analyses

In patients with VF or pulseless ventricular tachycardia (VT) as first rhythm the proportions of those with CPC 1–2 at 90 days were 34.8% (48/138) in the intervention group and 25.9% (35/135) in controls (difference 8.9%; 95% CI -2.0 to 19.7%; RR 1.28 [0.90–1.72], p= .11; Table 3; eFigure 3, Supplement 2). The p-value for interaction was .31. For further subgroup analyses, see Figure 2.

Post-hoc analyses

The proportion that achieved sustained ROSC and were admitted alive to hospital was 44.2% (149/337) in the intervention group versus 42.5% (142/334) in controls (difference 1.7%; 95% CI -5.8% to 9.2%; RR 1.04 [0.87–1.22], p= .66).

The proportion of CPC 1 was 14.8% (50/337) in the intervention group versus 10.5%

(35/334) in controls (difference 4.4%; 95% CI -0.7% to 9.4%; RR 1.40 [0.95-2.01]), see Figure 3. In the subgroup with VF or pulseless VT the proportion of patients with CPC 1 was 32.6% (45/138) versus 20% (27/135) (difference 12.6%; 95% CI 2.3 to 22.9%; RR 1.54 [1.06-2.06]). The distribution of CPC categories is shown in Figure 3. Modified Rankin scale scores at 90 days are presented in eTables 6, Supplement 2.

Adverse events

Nosebleeds and nasal whitening were the most common device-related adverse events. In four patients cooling had to be stopped because of relatively severe nose bleeding. In one patient a CT scan showed pneumocephalus, which was seen as a serious device-related complication with probable intra-cerebral air leakage from the sinuses. The pneumocephalus was found to be resolved in the second CT scan after 10 days. The patient recovered and was assessed as CPC 2 at 90 days. Overall adverse events within seven days as regards bleeding that requires transfusion, pneumonia, recurrence of VF or VT, cardiogenic shock, pulmonary edema and seizures were 170/337 (50%) versus 163/334 (49 %). Detailed data on adverse events are presented in eTable 5, Supplement 2.

DISCUSSION

The main finding of this randomized clinical trial, including 677 patients with out-of-hospital cardiac arrest, was that trans-nasal intra-arrest cooling at the scene of collapse compared with standard systemic cooling at the ICU did not result in a statistically significant improvement in neurologic intact survival at 90 days.

The group that received intra-arrest cooling had significantly shorter time intervals required to reach target core-body temperature. The overall adverse event rate reported within seven days

of randomization was similar in the two treatment groups. These results were consistent across predefined subgroups.

In the light of previous studies, the safety aspects of a prehospital cooling method are important. Cold intravenous fluid decreases coronary perfusion pressure by augmenting the central venous pressure.[20] This may partly explain the lower rate of ROSC observed in a randomized clinical trial when cold fluid was used intra-arrest in patients with ventricular fibrillation[9] and the increased number of patients with re-arrest and pulmonary edema when cold fluids have been administered post-ROSC.[11] Trans-nasal evaporative cooling does not add volume to the patient and could in this trial be initiated intra-arrest without the hemodynamic adverse events seen with cold intravenous fluids.[9,11] Thus, intra-arrest cooling does not appear to have major harm when used in a prehospital setting among patients with cardiac arrest.

The differences in neurologic intact survival at 90 days were not statistically significant. There may be several reasons for this. The cooling intervention might not be effective enough to lower temperature during CPR to mitigate brain injuries secondary to the ischemia and reperfusion process. The start of cooling might have been too late to provide the benefit seen in experimental models where such cooling is immediately applied.[3,21] In this study, the cooling devices were placed in the second emergency vehicle with advanced life support capacity, which influenced the delay between start of CPR by EMS in the first vehicle and start of cooling. When comparing the results with those of the previous safety and feasibility study[12], the control group performed significantly better in terms of cooling interval (i.e. smaller difference between groups in time required to reach target core temperature), overall survival and good neurologic outcome. As power estimations were based on these findings,

this study may have been underpowered to be able to detect important clinical differences.

Patients with out-of-hospital cardiac arrest with initial rhythm of VF have the strongest recommendation for temperature management in current guidelines.[6,7] The explorative findings in this subgroup of patients may be of importance to define the study population for future hypothermia trials. Survival with complete neurologic recovery without any sequelae, e.g. only CPC 1, is the best outcome after cardiac arrest. As a post-hoc exploratory finding, there was a higher proportion of patients with CPC 1 in the intra-arrest cooling group compared with standard care.

Limitations

This study has several limitations. First, pre-hospital and hospital personnel were not blinded to treatment. Second, the study period was long and many eligible patients with cardiac arrest were not included in the trial, which may have introduced a risk of bias. Third, the study may have been underpowered to detect a clinically important difference in the primary outcome. A larger trial might have allowed detection or rejection of such a difference.

Conclusions

Among patients with out-of-hospital cardiac arrest, trans-nasal evaporative intra-arrest cooling compared with usual care did not result in a statistically significant improvement in neurologic intact survival at 90 days.

ARTICLE INFORMATION

Author contributions: Dr. Nordberg and Professor Svensson had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest disclosures:

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Figure legends.

Figure 1. Randomization, follow up and analysis of patients in the PRINCESS trial.

Figure 2. Probability of survival with neurologic intact survival, cerebral performance category (CPC) 1-2, 90 days after cardiac arrest (primary outcome).

Figure 3. Distribution of cerebral performance category (CPC) scale scores in all patients and in the subgroup of patients with shockable rhythm.

Table 1. Baseline characteristics prior to randomization.

	Intervention n=337	Control n=334
Demographic characteristics		
Age in years, median [IQR] (n)	64 [55-72] (328)	66 [56-72] (329)
Height in cm, median [IQR] (n)	177 [170-180] (306)	177 [170-180] (307)
Weight in kg, median [IQR] (n)	85 [74-95] (307)	85 [75-95] (304)
Male, no./n (%)	253/336 (75.3)	252/333 (75.7)
Female, no./n (%)	83/336 (24.7)	81/333 (24.3)
Resuscitation characteristics		
Location outside home, no./n (%)	123/300 (41.0)	108/306 (35.3)
Presumed cardiac cause, no./n (%)	260/308 (84.4)	267/311 (85.9)
Shockable rhythm, no./n (%)	138/336 (41.1)	135/334 (40.4)
Bystander CPR, no./n (%)	208/321 (64.8)	194/325 (59.7)
CPR by first responder, no./n (%)	186/306 (60.8)	205/312 (65.7)
Airway		
Intubation, no./n (%)	259/328 (79.0)	248/322 (77.0)
Laryngeal mask, no./n (%)	63/328 (19.2)	71/322 (22.0)
Laryngeal tube, no./n (%)	6/328 (1.8)	3/322 (0.9)
Medical history		
Uncertain, no./n (%)	75/259 (29.0)	72/262 (27.5)
Coronary artery disease, no./n (%)	55/259 (21.2)	65/262 (24.8)
None known, no./n (%)	56/259 (21.6)	53/262 (20.2)
Hypertension, no./n (%)	49/259 (18.9)	49/262 (18.7)
COPD, no./n (%)	13/259 (5.0)	8/262 (3.1)
Cardiac failure, no./n (%)	9/259 (3.5)	11/262 (4.2)
Pulmonary embolism, no./n (%)	2/259 (0.8)	4/262 (1.5)
Key times		
Time to CPR by EMS, median [IQR] (n)	9 [6-12] (292)	9 [7-13] (297)
Time to ALS arrival, median [IQR] (n)	13 [9-18] (287)	13 [9-18] (300)
Time to airway, median [IQR] (n)	14 [11-18] (251)	14 [11-17] (272)
Time to randomization, median [IQR] (n)	17 [13-22] (294)	16 [12-21] (299)

Abbreviations: Shockable rhythm = ventricular fibrillation or pulseless ventricular tachycardia. CPR = cardiopulmonary resuscitation. EMS = emergency medical services. ALS = advanced life support. IQR=inter quartile range.

Table 2. Post-randomization characteristics and measures.

	Intervention n=337	**Control** n=334
Prehospital characteristics		
Adrenaline, mg, median [IQR] (n)	6 [4-8] (290)	5 [3-8] (284)
Amiodarone, mg, median [IQR] (n)	300 [300-450] (112)	300 [300-450] (80)
Duration CPR by EMS, minutes, median [IQR] (n)	30 [15-40] (289)	23 [10-36] (300)
Achieved any ROSC, no./n (%)	183/333 (55.0)	152/332 (45.8)
Ongoing CPR to hospital, no./n (%)	41/333 (12.3)	55/332 (16.6)
New prehospital cardiac arrest, no./n (%)	34/202 (16.8)	25/185 (13.5)
Time to prehospital cooling, minutes, median [IQR] (n)	19 [15-25] (317)	NA
Time to ROSC, minutes, median [IQR] (n)	30 [22-40] (178)	27 [21-38] (151)
Tympanic. temperature at ROSC, ºC, median [IQR] (n)	35.8 [35.0, 36.4] (132)	36.0 [35.5, 36.5] (92)
Time to Hospital arrival, minutes median [IQR] (n)	51 [43-63] (126)	54 [40-64] (120)
Characteristics at hospital admission [a]	n=149	n=142
Tympanic. temperature at ED, ºC, median [IQR] (n)	34.8 [34.2, 35.7] (90)	35.7 [35.4, 36.0] (73)
Glasgow Coma Scale, median [IQR] (n)	3 [3-3] (110)	3 [3-4] (95)
PaO2, mmHg, median [IQR] (n)	98 [68-225] (92)	98 [68-218] (82)
PaCO2, mmHg, median [IQR] (n)	45 [53-83] (106)	45 [53-83] (97)
pH value, median [IQR (n)	7.1 [6.9, 7.2] (111)	7.1 [7.0, 7.2] (99)
Base excess, mmol/l, median [IQR] (n)	-14.0 [-19.7, -8.9] (103)	-12.2 [-15.6, -9.7] (94)
Lactate, mmol/l, median [IQR] (n)	10.2 [7.7, 14.4] (99)	10.3 [7.4, 13.9] (93)
Heart rate, min^{-1} , median [IQR] (n)	82 [72-98] (113)	87 [74-100] (99)
Systolic blood pressure, mmHg, median [IQR] (n)	117 [99-135] (89)	115 [102-130] (79)
Mean arterial pressure, mmHg, median [IQR] (n)	74 [63-93] (106)	80 [68-87] (90)
SpO2, %, median [IQR] (n)	97 [94-99] (107)	97 [93-99] (98)
EtCO2, median [IQR] (n)	43 [35-52] (29)	43 [38-55] (22)
Spontaneous breathing, no./n (%)	20/106 (18.9)	28/85 (32.9)
ST-elevation/new LBBB on ECG, no./n (%)	39/114 (34.2)	32/99 (32.3)
ST-depression >1mm on ECG, no./n (%)	26/106 (24.5)	35/93 (37.6)
Revascularization and circulatory support [a]		
Angiography, acute, no./n (%)	72/137 (52.6)	65/125 (52.0)
Angiography during ICU stay, no./n (%)	10/137 (7.3)	8/125 (6.4)
Angiography after ICU stay, no./n (%)	4/137 (2.9)	4/125 (3.2)
PCI performed, no./n (%)	50/89 (56.2)	41/80 (51.2)
CABG performed, no./n (%)	5/88 (5.7)	1/81 (1.2)
IABP performed, no./n (%)	5/130 (3.8)	6/124 (4.8)

Abbreviations: IQR=inter quartile range. ROSC=return of spontaneous circulation. SpO2=peripheral oxygen saturation. EtCO2=endtidal carbon dioxide. LBBB=left bundle branch block. PCI=percutaneous coronary intervention. CABG=coronary artery bypass graft.

[a] Only in patients that were admitted alive at hospital

Table 3. Primary and Secondary outcomes.

	Intervention	Control	Difference (95% CI)	Relative Risk (95% CI)	P Value
	n=337	n=334			
Primary outcome					
Survival with CPC 1-2 at 90 days, no./n (%)					
All patients	56/337 (16.6)	45/334 (13.5)	3.1 (-2.3 to 8.5)	1.23 (0.86 to 1.72)	.25
Patients with shockable rhythm	48/138 (34.8)	35/135 (25.9)	8.9 (-2.0 to 19.7)	1.28 (0.90 to 1.72)	.11
Patients with non-shockable rhythm	8/198 (4.0)	10/199 (5.0)	-1.0 (-5.1 to 3.1)	0.80 (0.32 to 1.97)	.64
Secondary outcomes					
Overall survival at 90 days, no./n (%)					
All patients	60/337 (17.8)	52/334 (15.6)	2.2 (-3.4 to 7.9)	1.14 (0.81 to 1.57)	.44
Patients with shockable rhythm	51/138 (37.0)	41/135 (30.4)	6.6 (-4.6 to 17.8)	1.18 (0.83 to 1.56)	.25
Patients with non-shockable rhythm	9/198 (4.5)	11/199 (5.5)	-1.0 (-5.3 to 3.3)	0.82 (0.34 to 1.91)	.65
Sustained ROSC and admitted to hospital, no./n (%)					
All patients	149/337 (44.2)	142/334 (42.5)	1.7 (-5.8 to 9.2)	1.04 (0.87 to 1.22)	.66
Patients with shockable rhythm	83/138 (60.1)	78/135 (57.8)	2.4 (-9.3 to 14.0)	1.02 (0.82 to 1.21)	.69
Patients with non-shockable rhythm	65/198 (32.8)	64/199 (32.2)	0.7 (-8.5 to 9.9)	1.03 (0.76 to 1.34)	.89
Time to core body temp. <34ºC, minutes, median [IQR] (n)					
All patients	105 [80, 183]	182 [132, 312]	-70 (-100 to -44)	0.59 (0.49 to 0.71)	<.001
Patients with shockable rhythm	110 [80, 192]	236 [158, 415]	-102 (-169 to -60)	0.52 (0.39 to 0.65)	<.001
Patients with non-shockable rhythm	99 [82, 166]	152 [125, 202]	-50 (-86 to -16)	0.66 (0.50 to 0.87)	.004

Abbreviations: Shockable rhythm = ventricular fibrillation or pulseless ventricular tachycardia. ROSC=return of spontaneous circulation. IQR=inter quartile range.