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Time to intra-arrest therapeutic hypothermia in out-of-hospital cardiac arrest patients and its association with neurologic outcome: a propensity matched sub-analysis of the PRINCESS trial

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Abstract

Purpose: To study the association between early initiation of intra-arrest therapeutic hypothermia and neurologic outcome in out-of-hospital cardiac arrest.

Methods: A prespecified sub-analysis of the PRINCESS trial (NCT01400373) that randomized 677 bystander-witnessed cardiac arrests to transnasal evaporative intra-arrest cooling initiated by emergency medical services or cooling started after hospital arrival. Early cooling (intervention) was defined as intra-arrest cooling initiated < 20 min from collapse (i.e., \leq median time to cooling in PRINCESS). Propensity score matching established comparable control patients. Primary outcome was favorable neurologic outcome, Cerebral Performance Category (CPC) 1–2 at 90 days. Complete recovery (CPC 1) was among secondary outcomes.

Results: In total, 300 patients were analyzed and the proportion with CPC 1–2 at 90 days was 35/150 (23.3%) in the intervention group versus 24/150 (16%) in the control group, odds ratio (OR) 1.92, 95% confidence interval (CI) 0.95–3.85, $p = .07$. In patients with shockable rhythm, CPC 1–2 was 29/57 (50.9%) versus 17/57 (29.8%), OR 3.25, 95% CI 1.06–9.97, $p = .04$. The proportion with CPC 1 at 90 days was 31/150 (20.7%) in the intervention group and 17/150 (11.3%) in controls, OR 2.27, 95% CI 1.12–4.62, $p = .02$. In patients with shockable rhythms, the proportion with CPC 1 was 27/57 (47.4%) versus 12/57 (21.1%), OR 5.33, 95% CI 1.55–18.3, $p = .008$.

Conclusions: In the whole study population, intra-arrest cooling initiated < 20 min from collapse compared to cooling initiated at hospital was not associated with improved favorable neurologic outcome. In the subgroup with shockable rhythms, early cooling was associated with improved favorable outcome and complete recovery.

Keywords: Intra-arrest, Therapeutic hypothermia, Out-of-hospital cardiac arrest, Neurological outcome, Transnasal cooling

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Introduction

Severe brain injury remains the primary cause of death in resuscitated cardiac arrest patients, while the strategies currently available to improve neurologic outcome are limited [1–5]. Therapeutic hypothermia reduces ischemia–reperfusion brain injury after cardiac arrest by a number of mechanisms in experimental models [6]. This is especially true when early intra-arrest hypothermia [i.e., cooling initiated during cardiopulmonary resuscitation (CPR)] is compared to delayed cooling initiated after return of spontaneous circulation (ROSC) [7–12]. Despite these laboratory findings, the vast majority of clinical studies have assessed the effect of delayed therapeutic hypothermia when cooling has been initiated after hospital arrival, often several hours after the cardiac arrest [13–15]. The delayed timing of hypothermia in recent clinical studies may not have adequately addressed the underlying pathophysiology of ischemia and reperfusion, and thus, there is a risk that the optimal time window for the greatest effectiveness of hypothermia will be missed [13].

To induce therapeutic hypothermia during CPR is challenging in real-world clinical practice. While rapid infusion with cold intravenous fluids is feasible for most emergency medical services (EMS), this approach has been associated with increased rate of hemodynamic adverse events [16–18], most likely due to the volume load to the heart and reduction in coronary perfusion pressure [19, 20]. In particular, these adverse events have been observed in patients with initial shockable rhythm (i.e., ventricular fibrillation or pulseless ventricular tachycardia [17].

In the recent PRINCESS trial, 677 bystander-witnessed out-of-hospital cardiac arrest (OHCA) patients were randomized to intra-arrest transnasal evaporative cooling or cooling started after hospital arrival. Transnasal evaporative cooling is a method to induce hypothermia without adding a volume load to the heart, primarily targeting rapid cooling of the brain [21–23]. In the study, time to reach target core body temperature of $<34^{\circ}\text{C}$ was significantly shortened in the intra-arrest cooling group. The difference in survival with favorable neurologic outcome, Cerebral Performance Category (CPC) 1–2, was 16.6% vs 13.5% ($p=0.25$) in favor of the intra-arrest cooling group. In patients with shockable rhythms, CPC 1–2 survival was 34.8% in the intra-arrest cooling group vs 25.9% in controls ($p=0.11$). [24].

Although early intra-arrest therapeutic hypothermia was targeted in the PRINCESS trial, the median time from collapse to start of intra-arrest cooling was 19 min which may have been too long for optimal neurologic outcome. Thus, the fact that about 50% of the patients

Take-home message

Intra-arrest cooling initiated by the emergency medical services within 20 min from cardiac arrest was associated with improved favorable neurologic outcome and complete recovery in patients with initial shockable rhythms. These results entirely match the concept of intra-arrest cooling seen in experimental trials, and to our knowledge, this is the first time that this association has been shown in a clinical trial. No outcome differences were seen in patients with initial non-shockable rhythms.

in the intervention group had intra-arrest cooling initiated later than 20 min from the collapse may have influenced the overall results. The main hypothesis of this study was that the earlier intra-arrest therapeutic hypothermia could be initiated, the better effect on mitigating ischemia and reperfusion injuries and thereby improving neurologic outcome among survivors.

The aim of this secondary analysis of the PRINCESS trial data was to investigate the association between the group of OHCA patients who received earlier initiation (i.e., <20 min from collapse) of intra-arrest therapeutic hypothermia and survival with favorable neurologic outcome.

Methods

Study design

A prespecified sub-analysis of data from the PRINCESS trial [22], a European multicenter randomized clinical trial comparing the effects of transnasal evaporative intra-arrest cooling when compared to standard advanced life support (ALS) and subsequent cooling after hospital arrival in bystander-witnessed OHCA (Trial registration: NCT01400373). Randomization in the PRINCESS trial was generated in blocks of 4 without stratification on subgroups. Primary outcome was survival with favorable neurologic outcome, defined as CPC 1–2, at 90 days [24].

A secondary analysis with regard to time to cooling was prespecified in the study protocol [22]. Initially, a cut of time of 15 min to initiate cooling from the collapse was considered feasible and within the time period where many of the key mechanisms for primary brain injury are induced [6, 9, 22, 24]. However, this time point was changed post hoc from 15 min to <20 min (i.e., median time to initiate cooling in the PRINCESS trial) as too few patients actually received intra-arrest cooling within 15 min from collapse to perform a statistically appropriate analysis. Thus, in this secondary analysis, hypothermia initiated within the median time to start cooling in the PRINCESS trial was used to define early cooling (i.e. <20 min from cardiac arrest). Ethics and institutional committees in each

participating country approved the study protocol as previously described. Written informed consent was obtained from the closest relative or a legal representative after hospital admission and from each patient who regained mental capacity.

Patients

We included bystander-witnessed OHCA patients randomized in the PRINCESS trial. Exclusion criteria were age ≥ 80 years of age; known terminal disease; an existing do-not-resuscitate order; severe bleeding; EMS response time (collapse to EMS arrival) > 15 min; ROSC prior to randomization; pregnancy; hypothermia at time of evaluation; or an anatomical barrier to place the intra-nasal catheters. In this sub-analysis assessing early cooling, we excluded patients in the intervention group where cooling had been started after ≥ 20 min from the cardiac arrest (i.e., after the median time to start cooling in the PRINCESS trial), and patients randomized to the intervention group, but did not receive intra-arrest cooling.

Treatment protocol and outcome assessment

After airway management (i.e., endotracheal intubation or laryngeal mask), patients were screened for eligibility and randomized by EMS to intra-arrest cooling during ALS, or standard ALS. In most of the study sites, the cooling device was in the second tier. Transnasal evaporative cooling is a noninvasive method where intranasal catheters are used to deliver a chemically inert cooling liquid perfluorohexane mixed with oxygen or air. The method was developed to primarily cool the brain [21–23]. Admitted patients were treated with hypothermia to 32–34°C for 24 h, regardless of randomization assignment.

Prehospital data were collected by the ALS team according to the Utstein template [25]. Neurologic outcome assessment at 90 days was performed by a structured telephone interview or person-to-person using the CPC scale [26], where CPC 1 represents good recovery (alert with normal cerebral function), CPC 2, moderate disability (alert with 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 CPC 5, dead. EMS or hospital personnel were not blinded to treatment due to nature of the intervention. Nurses/physicians performing neurological assessment at 90 days as well as data managers and researchers were blinded to the patients' group assignment.

Outcomes

Primary outcome was survival with favorable neurologic outcome (CPC 1–2) at 90 days. Secondary outcomes were overall survival at 90 days and survival with complete neurologic recovery (CPC 1) at 90 days. The outcome of CPC 1 at 90 days was added post hoc in the main study [24]. Additional post hoc end points were CPC 1–2 in different time intervals (i.e., 0–9, 10–19, 20–29, ≥ 30 min).

Statistical analysis

Continuous variables not normally distributed are reported as medians and interquartile ranges. Categorical variables are reported as counts and percentages. In the primary analysis, patients with time to start of intra-arrest cooling < 20 min were analyzed, i.e., within the median time to start cooling in the PRINCESS trial. Propensity score matching (1:1) using nearest neighbor with a caliper width of 0.2 was used to find corresponding patients in the control group and to balance covariates between these groups. Variables included in the propensity score calculations were 'time to randomization', age, gender, bystander CPR, initial rhythm, study site, etiology and patient weight. Time to randomization was used as the matching time stamp. 'Time to randomization' had the highest correlation with 'time to cooling' (0.93). Balance between covariates before and after matching was compared using standardized mean difference (SMD). Conditional logistic regression was used for the main outcome analyses. Multiple imputations were not performed because there were no missing values for the primary, secondary or post hoc outcomes. Patients included in the primary analysis had complete data in variables used for propensity score matching.

Furthermore, a crude comparison between groups was made based on the time from cardiac arrest to randomization where patients were divided into different time intervals (i.e., 0–9, 10–19, 20–29, ≥ 30 min). Patients with initial shockable and non-shockable rhythms were predefined subgroups. Thus, the data sets are presented in the following groups: all patients; patients with initial shockable rhythm; and patients with initial non-shockable rhythm. All probability values were two-sided, with values less than 0.05 regarded as statistically significant. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary and post hoc end points should be interpreted as exploratory. Statistical analyses were performed with the method R software (version 3.6.0). For matching, the MatchIt package was used and confidence intervals are calculated with PropCIs package.

Results

Among the 343 patients randomized to intra-arrest cooling in the PRINCESS trial, 156 patients with complete study variables had cooling initiated <20 min from the arrest. Out of these, propensity score matching (1:1) could be performed in 150 patients with corresponding patients in the control group, and thus, 300 patients were included in the primary analysis (see Fig. 1). Baseline characteristics before and after propensity score matching in patients (all patients and patients with initial shockable and non-shockable rhythm) are presented in Table 1. The time to target temperature (<34 °C) was significantly shorter in patients receiving intra-arrest cooling (Table 1). The rate of ROSC was similar between groups (STable 1). Additional patient characteristics are presented in STable 1.

Primary outcome

After propensity score matching, the proportion of patients with favorable neurological outcome, CPC 1–2, at 90 days were 23.3% in the intervention group vs 16% in the control group, conditional odds ratio (OR) 1.92, 95% CI 0.95–3.85, $p=0.068$ for all patients (Table 2 and Fig. 2). In the subgroup of patients with initial shockable rhythm, the proportions of patients with CPC 1–2 were 50.9% in the intervention group versus 29.8% in the control group, conditional OR 3.25, 95% CI 1.06–9.97, $p=0.039$ (Fig. 2). In the subgroup of patients with initial non-shockable rhythm, the proportions with CPC

1–2 were 6.5% in the intervention group versus 7.5% in the control group, conditional OR 1.33, 95% CI 0.3–5.96, $p=0.71$ (Fig. 2). Kaplan Meier curves on the probability of survival with CPC 1–2 at 90 days are presented in Supplement (SFigure 1 and 2).

Secondary outcomes

The proportions of patients with complete neurological outcome (CPC 1) at 90 days were 20.7% in the intervention group vs 11.3% in the control group, conditional odds ratio (OR) 2.27, 95% CI 1.12–4.62, $p=0.023$ for all patients (Fig. 2). In the subgroup of patients with initial shockable rhythm, the proportions with CPC 1 were 47.4% in the intervention group versus 21.1% in the control group, conditional OR 5.33, 95% CI 1.55–18.3, $p=0.008$ (Fig. 2). In the subgroup of patients with initial non-shockable rhythm, the proportions with CPC 1 were 4.3% in the intervention group versus 5.4% in the control group, conditional OR 0.67, 95% CI 0.11–3.99, $p=0.66$ (Fig. 2).

The proportions of patients alive at 90 days were 24.7% in the intervention group vs 19.3% in the control group, conditional odds ratio (OR) 1.57, 95% CI 0.80–3.07, $p=0.19$ for all patients (Fig. 2). In the subgroup of patients with initial shockable rhythm, the proportions alive at 90 days were 52.6% in the intervention group versus 38.6% in the control group, conditional OR 1.92, 95% CI 0.68–4.96, $p=0.23$ (Fig. 2). In the subgroup of patients with initial non-shockable rhythm, the proportions alive

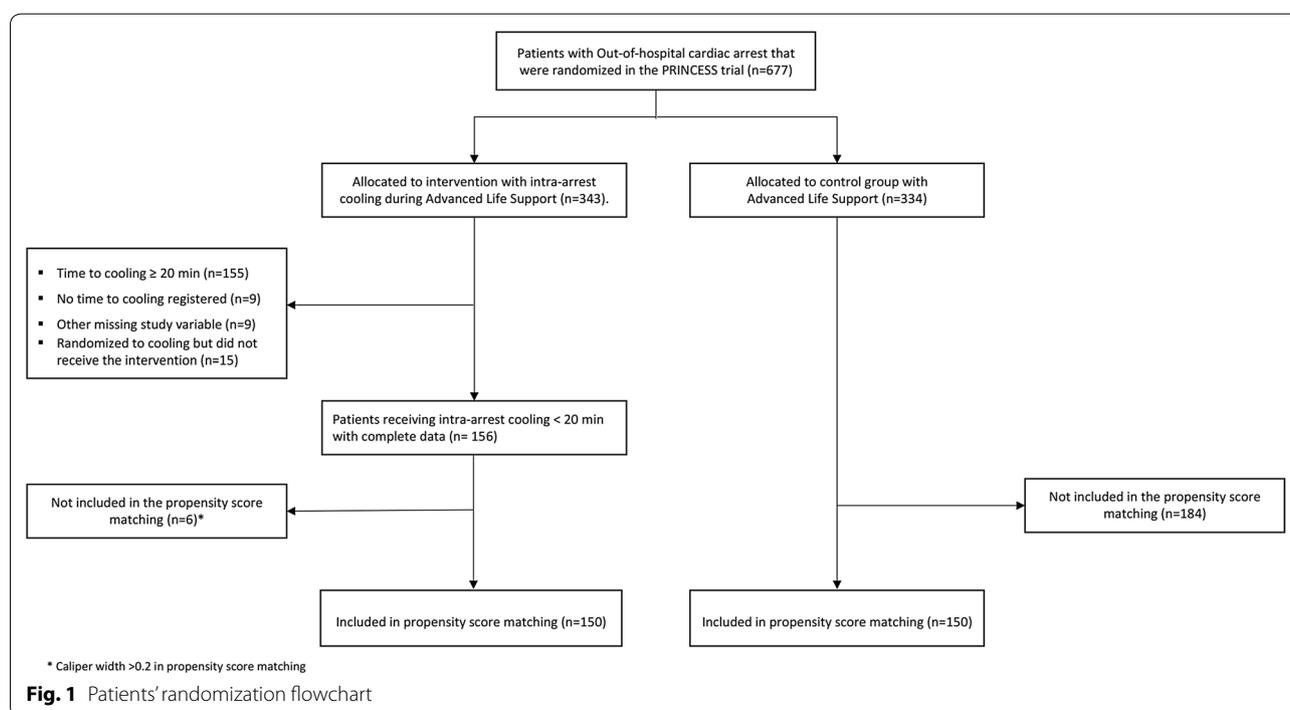


Table 1 Baseline characteristics prior to randomization and times to target temperature before and after propensity score matching

	Before matching			After matching		
	Control	Intervention	SMD*	Control	Intervention	SMD
All patients						
<i>n</i>	334	165		150	150	
Age, median [IQR**]	66 [56, 72]	63 [55, 72]	0.108	66 [58, 72]	63 [55, 71]	0.156
Sex, women <i>n</i> (%)	81 (24.3)	39 (23.6)	0.016	36 (24)	36 (24)	<0.001
Height (mean (SD))	175 (8)	175 (10)	0.030	175.22 (8.38)	175.31 (8.28)	0.010
Weight (mean (SD))	85 (17)	82 (15)	0.187	85.99 (17.54)	82.01 (15.05)	0.243
Location, at home, <i>n</i> (%)	198 (64.7)	82 (53.9)	0.220	81 (60.4)	75 (54.3)	0.124
Bystander CPR, <i>n</i> (%)	194 (59.7)	97 (59.9)	0.004	85 (56.7)	89 (59.3)	0.054
Shockable rhythms (%)	135 (40.4)	64 (38.8)	0.033	57 (38)	57 (38)	<0.001
Time to EMS*** CPR, min (median [IQR])	9 (6, 12)	7 (6, 9)	0.504	7 (6, 10)	7 (6, 9)	0.098
Time to ALS, (median [IQR])	13 (9, 17)	10 (8, 12)	0.689	10 (8, 13)	10 (8, 12)	0.091
Time to airway, min (median [IQR])	14 (11, 17)	11 (9, 14)	0.602	12 (10, 14)	12 (10, 14)	0.008
Time to randomization, min (median [IQR])	15 [12, 20]	13 [11, 15]	0.780	13 [11, 15]	13 [11, 15]	0.025
Time to tympanic temperature < 34°C, min, median [IQR]	149 (110, 215)	82 (64, 101)	<i>p</i> <0.001	157 (112, 198)	84 (65, 102)	<i>p</i> <0.001
Time to core body temperature < 34°C, min, median [IQR]	182 (132, 312)	94 (75, 111)	<i>p</i> <0.001	157 (136, 250)	95 (78, 111)	<i>p</i> <0.001
Patients with shockable rhythms						
<i>n</i>	135	64		57	57	
Age, median [IQR]	64 [57, 70]	61 [54, 68]	0.161	63 [58, 69]	60 [53, 68]	0.224
Sex, women <i>n</i> (%)	19 (14.2)	8 (12.5)	0.049	7 (12.3)	8 (14)	0.052
Height (mean (SD))	177 (7)	178 (7)	0.208	178 (7)	178 (7)	0.034
Weight (mean (SD))	85 (18)	85 (12)	0.008	87 (21)	85 (13)	0.130
Location, at home, <i>n</i> (%)	68 (56.2)	23 (38.3)	0.364	25 (51)	21 (39.6)	0.230
Bystander CPR, <i>n</i> (%)	99 (76.2)	44 (71)	0.118	46 (80.7)	41 (71.9)	0.207
Time to EMS CPR, min (median [IQR])	9 (7, 13)	7 (5, 9)	0.678	8 (6, 11)	7 (6, 9)	0.242
Time to ALS, (median [IQR])	13 (9, 18)	9 (7, 12)	0.824	10 (7, 14)	9 (7, 12)	0.309
Time to airway, min (median [IQR])	14 (10, 17)	11 (8, 14)	0.594	11 (8, 14)	12 (9, 14)	0.041
Time to randomization, min (median [IQR])	16 [12, 21]	13 [11, 15]	0.861	13 [10, 15]	13 [11, 15]	0.062
Time to tympanic temperature < 34°C, min, median [IQR]	144 (108, 264)	82 (65, 102)	<i>p</i> <0.001	136 (106, 254)	82 (65, 104)	<i>p</i> <0.001
Time to core body temperature < 34°C, min, median [IQR]	236 (158, 415)	96 (77, 110)	<i>p</i> <0.001	182 (140, 266)	96 (78, 139)	<i>p</i> <0.001
Patients with non-shockable rhythms						
<i>n</i>	199	101		93	93	
Age, median [IQR]	66 [56, 73]	64 [56, 73]	0.082	67 [58, 74]	64 [56, 74]	0.121
Sex, women <i>n</i> (%)	62 (31.2)	31 (30.7)	0.010	29 (31.2)	28 (30.1)	0.023
Height (mean (SD))	174 (9)	173 (11)	0.140	173.79 (8.8)	173.7 (8.68)	0.011
Weight (mean (SD))	86 (17)	81 (16)	0.303	85.43 (15.18)	80.36 (16.15)	0.324
Location, at home, <i>n</i> (%)	130 (70.3)	59 (64.1)	0.131	56 (65.9)	54 (63.5)	0.049
Bystander CPR, <i>n</i> (%)	95 (48.7)	53 (53)	0.086	39 (41.9)	48 (51.6)	0.195
Time to EMS CPR, min (median [IQR])	8 (6, 12)	7 (6, 9)	0.418	7 (6, 9)	7 (6, 9)	0.009
Time to ALS, (median [IQR])	12 (9, 17)	10 (8, 12)	0.595	10 (8, 13)	10 (8, 13)	0.081
Time to airway, min (median [IQR])	13 (11, 17)	11 (10, 14)	0.608	12 (10, 14)	12 (10, 14)	0.033
Time to randomization, min (median [IQR])	15 [12, 20]	13 [11, 14]	0.723	13 [11, 15]	14 [11, 15]	<0.001
Time to tympanic temperature < 34°C, min, median [IQR]	157 (121, 202)	84 (62, 100)	<i>p</i> <0.001	164 (130, 196)	85 (66, 99)	<i>p</i> <0.001
Time to core body temperature < 34°C, min, median [IQR]	152 (125, 202)	93 (69, 114)	<i>p</i> <0.001	156 (134, 196)	93 (78, 104)	<i>p</i> <0.001

The patient populations are all patients and the subgroup of patients with initial shockable (i.e., ventricular fibrillation and ventricular tachycardia) and non-shockable (asystole and pulseless electric activity) rhythms

*Standard mean deviation; **interquartile range; ***emergency medicine service

Table 2 Outcomes before and after propensity score matching

	Before matching			After matching		
	Control	Intervention	P chi ^a	Control	Intervention	P chi ^a , P clog ^b
All patients						
<i>n</i>	334	165		150	150	
CPC 1–2 at 90 days, <i>n</i> (%)	45 (13.5)	38 (23)	0.007	24 (16)	35 (23.3)	0.110, 0.068
CPC 1 at 90 days, <i>n</i> (%)	35 (10.5)	34 (20.6)	0.002	17 (11.3)	31 (20.7)	0.041, 0.023
Survival at 90 days, <i>n</i> (%)	53 (15.9)	40 (24.2)	0.024	29 (19.3)	37 (24.7)	0.264, 0.186
Patients with shockable rhythms						
<i>n</i>	135	64		57	57	
CPC 1–2 at 90 days, <i>n</i> (%)	35 (25.9)	32 (50)	<0.001	17 (29.8)	29 (50.9)	0.020, 0.039
CPC 1 at 90 days, <i>n</i> (%)	27 (20)	30 (46.9)	<0.0001	12 (21.1)	27 (47.4)	0.003, 0.008
Survival at 90 days, <i>n</i> (%)	42 (31.1)	33 (51.6)	0.005	22 (38.6)	30 (52.6)	0.132, 0.232
Patients with non-shockable rhythms						
<i>n</i>	199	101		93	93	
CPC 1–2 at 90 days, <i>n</i> (%)	10 (5)	6 (5.9)	0.738	7 (7.5)	6 (6.5)	1.000*, 0.706
CPC 1 at 90 days, <i>n</i> (%)	8 (4)	4 (4)	1.000*	5 (5.4)	4 (4.3)	1.000*, 0.657
Survival at 90 days, <i>n</i> (%)	11 (5.5)	7 (6.9)	0.628	7 (7.5)	7 (7.5)	1.000, 0.706

The patient populations are all patients and the subgroup of patients with initial shockable (i.e., ventricular fibrillation and ventricular tachycardia) and non-shockable (asystole and pulseless electric activity) rhythms

*Fisher's exact test

^a *p* value after chi² test, ^b *p* value in the conditional logistic regression

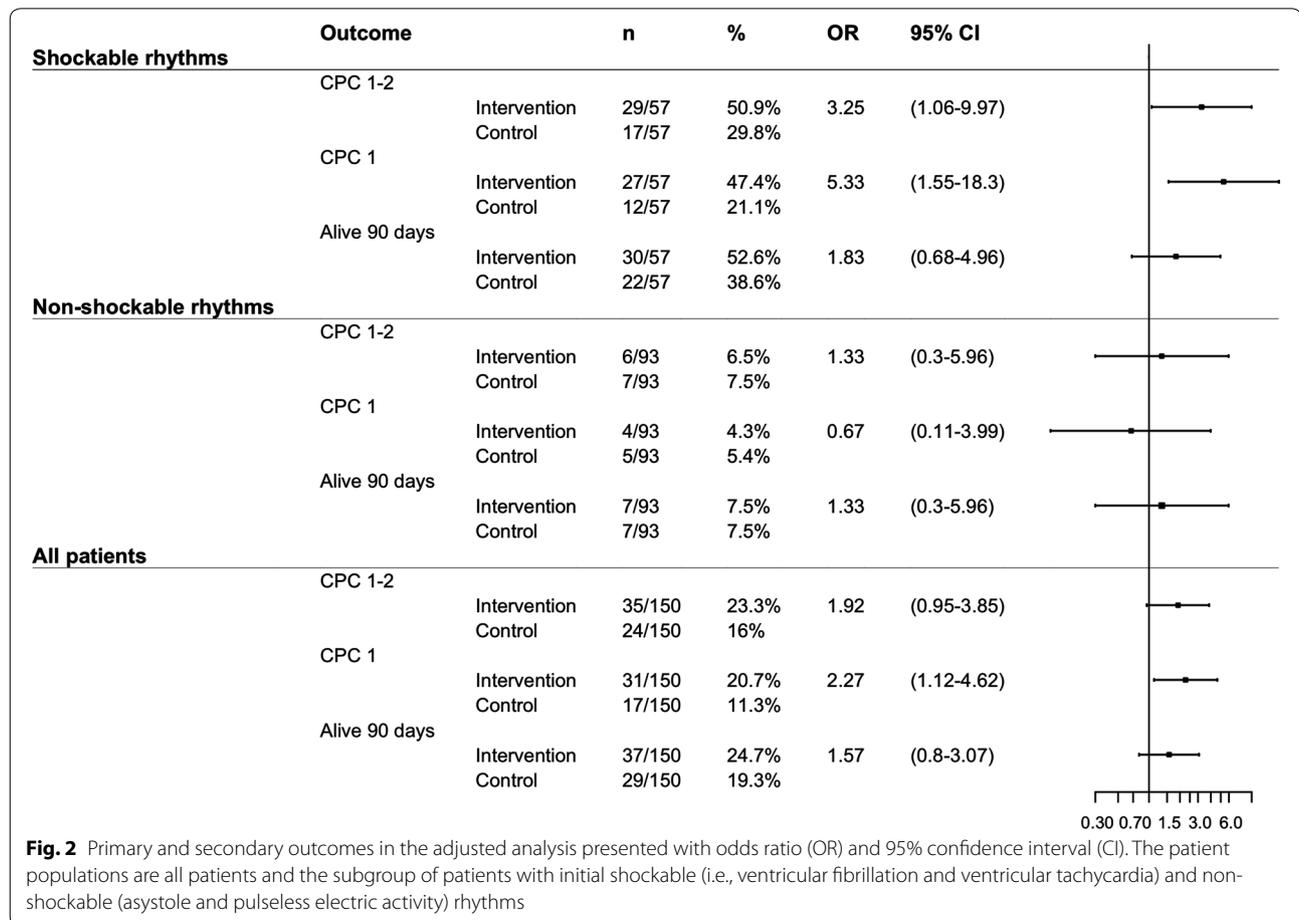
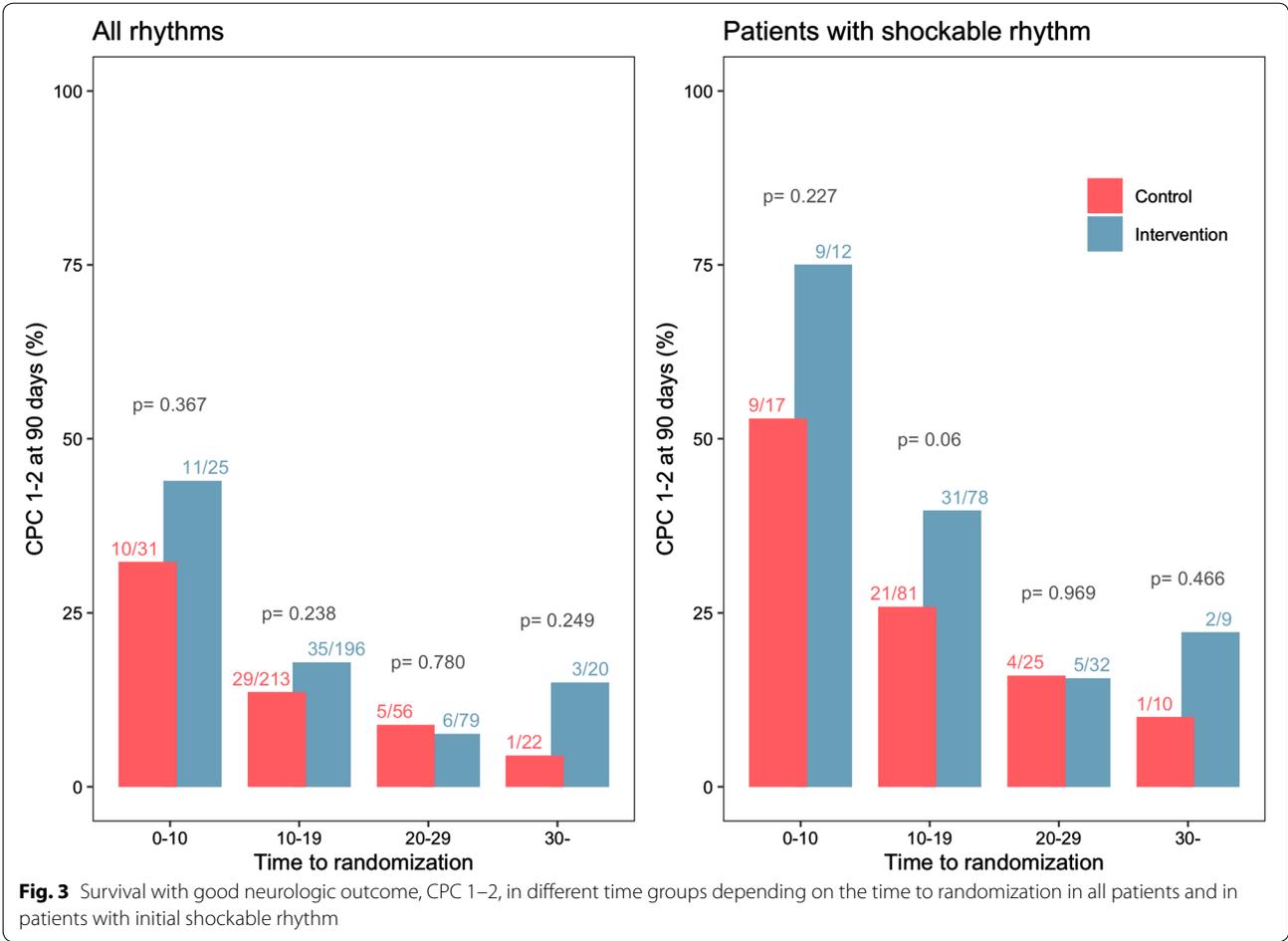


Fig. 2 Primary and secondary outcomes in the adjusted analysis presented with odds ratio (OR) and 95% confidence interval (CI). The patient populations are all patients and the subgroup of patients with initial shockable (i.e., ventricular fibrillation and ventricular tachycardia) and non-shockable (asystole and pulseless electric activity) rhythms



at 90 days were 7.5% in the intervention group versus 7.5% in the control group, conditional OR 1.33, 95% CI 0.3–5.96, $p=0.71$ (Fig. 2).

In Fig. 3, crude outcome data (i.e., survival with CPC 1–2 and CPC 1) are presented in different patient groups depending on the time to randomization. Predicted probability of CPC score and corresponding interaction p value between time to randomization are presented in Supplement (SFigure 3).

Discussion

In this secondary analysis of the PRINCESS trial where patients were randomized at the scene of the arrest to intra-arrest cooling versus standard ALS and subsequent initiation of systemic cooling at hospital, we assessed a potential association between time to initiate intra-arrest cooling before 20 min from the collapse and survival with favorable neurologic outcome (CPC1-2) at 90 days. There are several potentially important findings of the study. First, the difference observed in favorable neurologic outcome at 90 days was not statistically significant

in the whole patient cohort. Second, in the subgroup of patients with initial shockable rhythms, early intra-arrest cooling is associated with improved favorable neurologic outcome, whereas no difference is seen in patients with non-shockable rhythms. Third, there are significant differences in complete neurologic outcome in the whole patient cohort, but with the most apparent differences in patients with initial shockable rhythm. Fourth, intra-arrest transnasal evaporative cooling was not associated with decreased rate of ROSC which has been the case of earlier intra-arrest studies when cooling has been performed with cold fluids. Thus, early, intra-arrest cooling per se does not seem convey hemodynamic side effects if you use a method that does not add volume load to the heart.

Crucial knowledge gaps remain regarding how to attenuate reperfusion brain injury after cardiac arrests. The pathophysiologic mechanisms following ROSC are triggered promptly; in clinical practice, this means prior to hospital arrival. The immediate injuries caused by ischemia will deplete intracellular ATP within minutes

inducing several pathophysiologic pathways [6]. Within 15 min of reperfusion, formation of free oxygen radicals and dysfunctional calcium regulation promote subsequent damage to cellular membranes and alterations in cerebral blood flow [6]. Thus, therapeutic strategies to mitigate brain injury in this population may be more effective if established during resuscitation itself or immediately following ROSC.

A key question for clinicians is whether there is a time window for best effectiveness of therapeutic hypothermia in cardiac arrest as suggested in prior experimental studies [8–10, 12]. The approach to assess the effect of therapeutic hypothermia was different in PRINCESS compared to most previous studies. In the pragmatic TTM trial, there was a four-hour window allowed from ROSC (not collapse) to randomization (not initiation of treatment) [13]. This could be an important methodological issue when trying to reduce the highly time-sensitive ischemic and reperfusion brain injury after cardiac arrest. In this earlier cooling subgroup analysis with bystander-witnessed OHCA, we observed a signal toward a higher rate of favorable neurologic outcome and complete recovery in patients where intra-arrest cooling had been initiated <20 min from collapse compared to standard care where cooling was initiated after hospital arrival. Although 20 min must be seen as an explorative time stamp, the results suggest that an earlier initiation of intra-arrest cooling in refractory cardiac arrest may improve the chance to influence neurologic outcome compared to cooling started after hospital arrival. The time to initiate cooling is different than the time required to reach the target temperature. In this population, the initiation of intra-arrest cooling reduced the time to reach target temperature significantly. We believe that this strategy of fast cooling is important even if the time interval to reach target temperature may vary for several reasons and could be confounded by the severity of the brain injury. Thus, patients with more extensive brain injuries may be easier to cool rapidly because they no longer have the compensatory physiology to defend core body temperature [27, 28].

Consistent with prior cardiac arrest trials, the vast majority of survivors in the current investigation were within the patient subgroup with initial shockable rhythms. It is also in this subgroup that a potential benefit in neurologic outcomes with an earlier cooling initiation was observed. In a recent study [29] of OHCA and in-hospital cardiac arrest patients with non-shockable rhythms, a benefit of therapeutic hypothermia initiated during intensive care was seen also in these patients compared to normothermia. We did not see any signal toward improved outcome in these patients. However, this population with non-shockable rhythms in the

PRINCESS trial was randomized prior to ROSC which make direct comparisons difficult. When patients with non-shockable rhythms, especially asystole, are included in randomized cardiac arrest trials, the potential benefit of a specific intervention may be masked due to the extreme poor chances of survival in that specific group [30]. Based on our data, further studies of intra-arrest cooling should focus primarily on the patients with initial shockable rhythms.

While many prior studies have grouped CPC 1 and 2 outcomes, more granular analysis suggests potential differences in outcome in the current cohort. When evaluating CPC scores in the PRINCESS trial itself, there was a post hoc finding with a higher proportion of patients with CPC 1 in the intra-arrest cooling group among patients with initial shockable rhythms. The current sub-analysis suggests that this potential benefit is more pronounced in the patients that receive start of intra-arrest cooling within 20 min from collapse. Future studies should preferably include more subtle neurological and cognitive end points such as the modified Rankin Scale and Glasgow Coma Outcome Scale extended [31].

Limitations

This secondary analysis has several limitations. Firstly, we included patients from a randomized clinical trial where allocation of early versus late randomization per se was not randomized. Secondly, although the groups have similar baseline characteristics and propensity score matching was performed, the risk of residual confounding needs to be acknowledged. Thirdly, although patients with shockable rhythms are a well-recognized subgroup in cardiac arrest studies, a subgroup analysis always introduces a risk of selection bias and may alter the generalizability of the results. Fourth, we have limited data on whether it was a presumed cardiac cause of the arrest or not. Finally, although the outcome assessors were blinded to the treatment allocation, the EMS and hospital personnel were not which may have influenced their management.

Conclusion

In the whole study population, intra-arrest cooling initiated <20 min from collapse compared to cooling initiated at hospital was not associated with improved favorable neurologic outcome. In the subgroup with shockable rhythms, early cooling was associated with improved favorable outcome and complete recovery. No outcome differences were seen in patients with initial non-shockable rhythms. The findings should be seen as hypothesis generating and warranting future intra-arrest cooling studies.

Electronic supplementary material

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Authors contributions

AA, PN, MJ and LS prepared this paper; all authors collaborated in the design of the study; PAA, PN, MJ and LS prepared this paper; all authors collaborated in the design of the study; PN and LS were responsible for study governance and roll out of the main trial. PN was responsible for logistical support of the study. All authors contributed substantially to analyzing and interpretation of data. AA and PN drafted the manuscript which then was critically revised by all the authors. All authors have read and approved the final manuscript. N and LS were responsible for study governance and roll out of the main trial. PN was responsible for logistical support of the study. All authors contributed substantially to analyzing and interpretation of data. AA and PN drafted the manuscript which then was critically revised by all the authors. All authors have read and approved the final manuscript.

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Compliance with ethical standards**Conflicts of interest**

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