Cold fluids for induction of targeted temperature management

A sub-study of the TTH48 trial

Holm, Aki; Kirkegaard, Hans; Taccone, Fabio; Søreide, Eldar; Grejs, Anders; Duez, Christophe; Jeppesen, Anni; Toome, Valdo; Hassager C, Christian; Rasmussen, Bodil S; Laitio, Timo; Storm, Christian; Hästbacka, Johanna; Skrifvars, Markus B

Published in:
Resuscitation

DOI (link to publication from Publisher):
10.1016/j.resuscitation.2019.11.031

Publication date:
2020

Document Version
Accepted author manuscript, peer reviewed version

Cold fluids for induction of targeted temperature management: A sub-study of the TTH48 trial

Aki Holm[1], Hans Kirkegaard[2], Fabio Taccone [3], Eldar Soreide[4, 5], Anders Grejs[6], Christophe Duez[7], Anni Jeppesen[8], Valdo Toome[9], Christian Hassager C[10], Bodil S Rasmussen[11], Timo Laitio[12], Christian Storm[13], Johanna Hästbacka[14], Markus B Skrifvars[14, 15]

1. Faculty of Medicine, University of Helsinki, Helsinki, Finland
2. Research Center for Emergency Medicine, Department of Emergency Medicine and Department of Clinical Medicine, Aarhus University Hospital and Aarhus University, Aarhus, Denmark
3. Department of Intensive Care, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium
4. Critical Care and Anaesthesiology Research Group, Stavanger University Hospital, Stavanger, Norway
5. Department Clinical Medicine, University of Bergen, Bergen, Norway
6. Department of Intensive Care Medicine, Aarhus University Hospital, Aarhus, Denmark
7. Research Center for Emergency Medicine, Department of Emergency Medicine and Department of Clinical Medicine, Aarhus University Hospital and Aarhus University, Aarhus, Denmark
8. Department of Anaesthesiology, Aarhus University Hospital, Aarhus, Denmark
9. Department of Intensive Cardiac Care, North Estonia Medical Centre, Tallinn, Estonia
10. Department of Cardiology, Rigshospitalet and Dept of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
11. Department of Anesthesiology and Intensive Care Medicine, Aalborg University Hospital, and Clinical Institute, Aalborg University, Aalborg, Denmark
12. Division of Perioperative Services, Intensive Care Medicine and Pain Management, Turku University Hospital and University of Turku, Finland
13. Department of Internal Medicine, Nephrology and Intensive Care, Charité-Universitätsmedizin Berlin, Berlin, Germany
14. Department of Anesthesiology, Intensive Care and Paine Medicine, University of Helsinki and Helsinki University Hospital
15. Department of Emergency Care and Services, University of Helsinki and Helsinki University Hospital

For the TTH48 investigators.

Corresponding author:

MD, PhD, EDIC, FCICM, professor Markus B Skrifvars

Department of Emergency Care and Services, University of Helsinki and Helsinki University Hospital, Finland

markus.skrifvars@hus.fi +358504272424

Funding:

Funding/Support: The study was funded by independent research grants from The Danish Heart Foundation, The Laerdal Foundation, The Scandinavian Society of Anaesthesiology and Intensive Care Medicine, The Danish Society of

Anaesthesiology and Intensive Care Medicine and The Augustinus Foundation and, Finska Lakaresallskapet, Medicinska Understodsforeningen Liv och Halsa and Stiftelsen Dorothea Olivia, Karl Walter och Jarl Walter Perklens minne.

Conflicts of interest:

Markus Skrifvars reports having received a research grant from GE Healthcare, travel reimbursements and lecture fees from BARD Medical. CS reports having received travel reimbursements and speaker fees from BD BARD and Zoll GmbH, as well as honorarium for consultancy from BD BARD, Benechill and Sedana Medical. Anders Grejs and Anni Jeppesen reports having received lecture fees from Novartis. All other authors report that they have no conflicts of interest.

Abstract

Background

Pre-intensive care unit (ICU) induction of targeted temperature management (TTM) with cold intravenous (i.v.) fluids does not appear to improve outcomes after in out-of-hospital cardiac arrest (OHCA). We hypothesized that this may be due to ineffective cooling and side effects.

Methods

A post hoc analysis of a sub-group of patients (n=352) in the TTH48 trial (NCT01689077) who received or did not receive pre-ICU cooling using cold i.v. fluids. Data collection included patient characteristics, cardiac arrest factors, cooling methods, side effects and continuous core temperature measurements. The primary endpoint was the time to target temperature (TTT, < 34°C), and the secondary endpoints included the incidence of circulatory side effects, abnormal electrolyte levels and hypoxia within the first 24 h of ICU care. A difference of 1 h in the TTT was determined as clinically significant a priori.

Results

Of 352 patients included in the present analysis, 110 received pre-ICU cold fluids. The **median** time to the return of spontaneous circulation (ROSC) and TTT in the pre-ICU cold fluids group was longer than that of the group that did not receive pre-ICU cold fluids (**318 vs. 281 min, p < 0.01**). In a linear regression model including the treatment centre, body mass index (BMI), chronic heart failure, diabetes mellitus and time to ROSC, the use of pre-ICU cold i.v. fluids was not associated with a shorter time to the target temperature (standardized beta coefficient: 0.06, 95% CI for B -49 and 16, p = 0.32). According to the receipt or not of pre-ICU cold i.v. fluids, there was no difference in the proportion of patients with hypoxia on ICU admission (1.8% vs. 3.3%, p = 0.43) or the proportion of patients with electrolyte abnormalities (hyponatremia: 1.8% vs. 2.9% p = 0.54; hypokalaemia: 1.8% vs. 4.5%, p = 0.20). Furthermore, there was no difference in hospital mortality between the groups.

Conclusions

The initiation of TTM with cold i.v. fluids before ICU arrival did not decrease the TTT. We detected no significant between-group difference in mortality or the incidence of side effects according to the administration or not of pre-ICU cold i.v fluids.

Keywords: Targeted temperature management; Pre-ICU cooling, Time to target temperature, Intravenous cooling

Introduction

Targeted temperature management (TTM) is commonly utilised in the treatment of out-of- hospital cardiac arrest (OHCA) patients.[1,2] The optimal mode and timing of induction are unclear.[3] Although several cooling methods are used in the intensive care unit (ICU), pre-ICU cooling is generally performed using cold intravenous (i.v.) fluids, given the simplicity of the method. According to some small studies, potential benefits associated with this pre-ICU cold i.v. fluids included a shorter time to the target temperature (TTT).[4-6] However, a previous study reported that the administration of cold i.v. fluids prior to the time to return of spontaneous circulation (ROSC) led to increased side effects.[7] Some recent resuscitation guidelines have advised against the use of pre-ICU cold i.v. fluids.[8] In a large randomised controlled trial (RCT) on the use of pre-hospital cold fluids for TTM (*N* = 1,000), Kim et al. found no clear survival benefit and an elevated risk of pulmonary oedema.[4] Intuitively, rapid cooling after cardiac arrest should improve outcomes. However, it is not clear how possible benefits and disadvantages of rapid cooling interact, resulting in mixed evidence on the value of pre-ICU cold i.v. fluids.[3,4,9-16] We hypothesized that the lack of a clear benefit may be due to ineffective cooling or side effects of the cold pre-ICU i.v. fluids. If these side effects were better understood, it might be possible to tailor treatments and ultimately use cold i.v. fluids as a cheap, simple and applicable method to induce hypothermia before ICU admission.

In the present study, we aimed to determine the effects of pre-ICU cooling using cold i.v. fluids on the TTT and incidence of side effects in a sub-group of patients treated with either standard or prolonged TTM at 33°C included in the TTH48 trial.[17]

Methods

Study population and setting

We performed a post hoc analysis of a sub-group of patients in the TTH48 trial (NCT01689077) who received or did not receive pre-ICU cooling using cold i.v. fluids. The original study compared TTM

at 33°C for 48 h versus 24 h in the ICU after OHCA. The protocol and statistical analysis of the TTH48 trial have been published previously.[17,18] The original study included 355 unconscious OHCA patients in 10 European ICUs who were randomized to TTM at 33°C for either 48 or 24 h. The inclusion criteria were a Glasgow Coma Scale score of less than 8, aged between 18 and 80 y and ROSC sustainment for more than 20 min prior to randomization. The exclusion criteria included terminal disease or a do-not-resuscitate order, systolic blood pressure less than 80 mmHg, non-cardiac cause of cardiac arrest, time to ROSC longer than 60 min, in-hospital cardiac arrest, severe coagulopathy, initial rhythm asystole in an unwitnessed OHCA, time from cardiac arrest to initiation of cooling of > 240 min, neurological disease with cognitive impairment, persistent cardiogenic shock, an acute stroke or intracerebral bleeding and acute coronary bypass surgery.

On the first hospital day, the patients were screened in the ICU and could be included until 23 h from reaching the target temperature. In some patients, TTM was initiated before ICU arrival using cold fluids, and the amount and type of fluid were recorded in the case report form (CRF). There was no protocol for pre-ICU cold i.v. fluids administration (i.e. fluids were given as deemed appropriate by the treating clinician). Core bladder, rectum or oesophagus temperatures were measured using intravascular probes. Target temperature was maintained using either invasive or surface cooling devices. After TTM was maintained at 33°C for the duration mandated by randomization, rewarming was started at a rate of 0.5°C/h until a temperature of 37°C was reached. In cases of severe adverse events, such as a recurring cardiac arrest, the treating clinician could select to rewarm patients early at a rate of 0.5°C/h to 36°C.

Endpoints

The primary endpoint was the time from ROSC to reaching a target temperature of < 34°C. A reduction of at least 1 h in the TTT was considered clinically significant. We created composite endpoints to compare successful cooling and the global efficacy of cooling. Successful cooling was

defined as the time from ROSC to reaching the target temperature of less than 294 min (median). Globally effective cooling was defined as successful cooling without any of following: severe arrhythmia, considered pulseless ventricular tachycardia/ventricular fibrillation or unstable haemodynamics, despite treatment; a severe circulatory adverse event, defined as MAP of < 60 mmHg, despite comprehensive treatment; or hypoxia, defined as paO2 of < 8 kPa. Other outcome endpoints included any occurrence of abnormal electrolyte levels or hypoxia during the first 24 h of ICU care, adverse events during the ICU stay and survival and neurological outcomes 6mo after hospital discharge. Survival status after 24, 48 and 72 h was recorded, in addition to seizures, circulatory hypotension, arrhythmias, gastrointestinal adverse events, renal replacement, pneumonia, infections, sepsis, bleeding and transfusions. We used the same definitions for adverse effects and a favourable neurological outcome (CPC1 or 2) as those applied in the original TTH48 study.[17] In terms of electrolyte abnormalities, hypernatremia hyponatremia, hypokalaemia and hypochloraemia were classified as $Na^+ > 145$ mmol/L, $Na^+ < 130$ mmol/L, $K^+ < 3.0$ mmol/L and $Cl^- > 109$ mmol/L, respectively. Any respiratory adverse event was considered hypoxia.

Statistical methods

The study population was divided into two groups according to whether pre-ICU cold i.v. fluids were administered. Categorical data are presented as **numbers of patients and percentages.** Continuous parameters were assessed for normality and presented either as means (standard deviation [SD]) or medians (interquartile range [IQR]). Categorical parameters were compared using a chi-square test. Continuous variables were compared using the Student's *T*-test or Mann–Whitney *U* test.

We performed a multivariate linear regression to determine the effects of pre-ICU cold i.v. fluid cooling on the time from ROSC to reaching the target temperature. We analysed baseline factors associated with successful cooling and performed univariate linear regression analysis on ROSC to target temperature time for baseline factors associated with successful cooling with $p < 0.20$. In the

multivariate linear regression analysis, factors with a *p* value of < 0.05 in the univariate analysis were included. Factors included in the multivariate linear regression model were the use of pre-ICU cold i.v. fluids, ROSC delay, treatment centre, previous heart failure, diabetes mellitus and body mass index (BMI). Weight was excluded to avoid collinearity with BMI. The mean (SD) hourly temperatures of each patient were calculated during the first 24 h and compared using a mixed linear model with compound symmetry that included the interaction between cold fluid use with time. In cases where data on mean hourly temperatures of a patient were missing, the patient was excluded from the mean hour temperature analysis. All other patient-related measurements were included in the model. Mortality and time to death were visualized using Kaplan–Meier curves, and the mortality between groups was compared using a log rank test. A *p* value of < 0.05 was considered significant. All analyses were conducted using IBM SPSS Statistics for Windows, Version 25.0. (IBM Corporation, Armonk, NY, USA) and Microsoft Excel 2016 (Microsoft Corporation, Redmond, Washington, USA)

Results

Included patients

Of the 355 patients included in the original trial, 352 were included in the present analysis, of which 110 received pre-ICU cold i.v. fluids. Exact cooling times were available for 345 patients, and these data were included in the TTT analysis. The pre-ICU cold fluids administered included 500–3,000 ml **(median 1000ml IQR 1000-2000 ml)** of 4°C saline, Ringer's solution or another crystalloid solution, such as salt solutions (e.g. saline) with small molecules.

Baseline characteristics

The baseline and resuscitation characteristics of the patients who received cold fluids and those who did not were compared (Table 1). There were more patients with chronic heart failure (NYHA class 4) in the group given pre-ICU cold fluids (11.8% vs. 2.1%, *p* < 0.001), as shown in Table 1. There

were no other significant between-group differences in the baseline characteristics of the patients, including cardiac arrest- or resuscitation-related factors (Table 1).

TTM-related factors

Table 2 provides information on factors relating to the induction and maintenance of TTM. **The mean (347 min vs. 268 min, p = 0.01) and median (318 min vs. 281 min, p < 0.01) times from ROSC to reaching the target temperature increased significantly in the group given pre-ICU cold i.v. fluids.** The most common cooling method in the ICU was invasive cooling using an intravascular catheter (*n* = 218, 62%), with no significant between-group difference in the type of device used. All the patients were cooled in the ICU using an intravascular catheter or some other device.

In the group given pre-ICU cold i.v. fluids, a higher number of patients received surface cooling as compared with that in the group that did not receive this treatment (50% vs. 42%, p = 0.02).

Correlation of pre-ICU fluid cooling and TTT

Several factors were associated with more rapid cooling in the univariate analysis (Supplementary online Table 1). Accordingly, several factors were related to the TTT in the linear regression analysis (Table 3). In the univariate analysis, the use of pre-ICU cold i.v. fluids (standardized beta coefficient: 0.14, 95% CI for B 11 and 76, *p* = 0.01) was associated with a longer TTT. However, in a multiple linear regression model that included significant factors (e.g. ROSC delay, treatment centre, heart failure, diabetes mellitus, and BMI) associated with the TTT, the use of pre-ICU cold i.v. fluids was not associated with any change in the TTT (standardized beta coefficient: 0.06, 95% CI for B -49 and 16, *p* = 0.32). In contrast, BMI (standardized beta coefficient: 0.29, 95% CI for B 6 and 12, *p* < 0.01) and previous heart failure (standardized beta coefficient: 0.13, 95% CI for B 22 and 156, *p* = 0.01) were associated with prolonged time from ROSC to target temperature. The linear regression model results are presented in Table 3.

Patients' temperatures in the ICU

238 The mean patient temperatures for the first 24 h from ICU admission are shown in Figure 1. In a
239 mixed linear model, the use of pre-ICU cold fluids was associated with higher mean temperatures
240 for the first 24 h from ICU admission (p = 0.003), without any clear interaction with time. There was
241 no difference in the proportion of patients successfully cooled or the global effectiveness of cooling
242 between groups (Table 2).

243 **Adverse events and outcomes**

244 The occurrence of adverse events was not different in patients who did or did not receive pre-ICU
245 fluids (Table 4). There were no significant differences in mortality after 24, 48 or 72 h (Table 4). In
246 addition, there was no difference in the time to mortality or 180-d mortality (p = 0.8), as shown in
247 Figure 2. Furthermore, there was no significant between-group differences in favourable
248 neurological outcomes (CPC1 or 2) at discharge (3.9% absolute difference, p = 0.46) or 6 mo post-
249 discharge (0.6% absolute difference, p = 0.78).

250 **Discussion**

251 **Main findings**

252 We studied the effects of TTM induction using pre-ICU cold i.v. fluids on the TTT and side effects of
253 cold fluids in patients included in the randomized TTH48 trial, comparing 24 and 48 h of TTM at
254 33°C. Patients who received pre-ICU cold fluids did not have a shorter TTT than those who did not.
255 In addition, the body temperatures of the patients in the group that received cold fluids were higher
256 than those of the patients who did not, despite TTM induction during the first 24 h of admission.
257 We detected no between-group difference in side effects, such as electrolyte abnormalities or
258 hypoxia. In accordance with the findings of previous research,[19] a high BMI was associated with a
259 prolonged TTT in the present study. The study design precludes conclusions about causality.
260 However, taken together, the findings do not the support benefits of routine clinical use of cold
261 fluids in TTM in the pre-ICU setting. It may well be that early TTM may be achieved using more novel

methods, such as trans-nasal-evaporative cooling, which was recently shown to be feasible in the pre-hospital setting.[20]

Previous animal studies on TTM induction showed that faster induction of the target temperature was beneficial.[21,22] In patients, the evidence is mixed and furthermore, the efficacy of rapid cooling is difficult to ascertain in patients with severe neurological injuries given the apparent ease of cooling.[3,4,12,14,23] Due to its simplicity, the use of cold fluids is appealing. However, Scales et al. reported that pre-hospital cooling initiated 5 min after ROSC did not increase the likelihood of achieving a target temperature of 32–34°C within 6 h of hospital arrival.[23] On the other hand, a slightly older study by Larsson et al. pointed to the efficacy of TTM induction and maintenance with cold and ice packs in the ICU.[24] In one of only a few large RCTs on TTM induction with cold fluids, the authors showed that although the use of cold fluids in the ambulance initially decreased each patient's temperature by almost 1°C, the effect had almost disappeared 1 h later.[6,25] Our study not only supports these findings but points to problems with temperature management during the following 24 h in the ICU. The results of the present study may be due to the mode of cooling, with cold fluids administered as part of a treatment protocol that favours non-invasive methods, which have been shown to be less efficient than intra-vascular cooling.[26] However, as our adjusted model included the TTM treatment, the aforementioned factor cannot completely account for the lack of efficacy of pre-ICU cold i.v. fluids. Less aggressive initiation of ICU TTM by the treating team due to a false sense of security may be an alternative explanation for the TTT not decreasing in the group that received pre-ICU cold i.v. fluids. The infusion of cold fluid may also have resulted in some form of rebound hyperthermia or shivering, which would require deeper sedation. We found no difference in the initial use of sedation between the two groups. In some centres, the patients were transferred directly to the cardiac angiography suite, which may have delayed ICU admission and ICU cooling. In such cases, TTM may have been induced and maintained by the cold i.v. fluids. This

286 may have introduced bias, including the finding of a longer time to effective cooling in the group
287 given pre-ICU cold i.v. fluids. However, despite a numerically longer time from ROSC to ICU
288 admission in this group, this between-group difference in ROSC to ICU admission time was not
289 statistically significant.
290 We found no difference in outcomes, depending on whether the patients received or did not receive
291 cold fluids. Nie et al. analysed five RCTs and concluded that pre-hospital TTM induced by i.v. infusion
292 of ice-cold fluids did not improve survival to hospital discharge or neurological outcomes.[14] The
293 results of the present study are in line with those in the field. In a large RCT conducted by Kim et al.,
294 the use of pre-hospital cold fluids also failed to improve outcomes. However, the study by Kim et al.
295 was criticized, as not all the included patients received TTM in an ICU, and the cold fluids were
296 administered for only a few minutes using a pressure bag.[27] In contrast, in the present study, all the
297 patients were admitted to an ICU for either 24 or 48 h of TTM.
298 Potential side effects of cold fluids may also explain the lack of benefit of cold fluids in terms of
299 survival. However, in the present study, there were no increases in severe electrolyte disturbances,
300 adverse haemodynamics or hypoxia. Hypoxia may develop due to fluid overload, , especially when
301 large volumes of cold fluids are administered. Jacobshagen et al. reported that pulmonary function
302 worsened when inducing TTM with cold fluid.[28]
303 **Acknowledgements**
304 The current study has several strengths. The patients were from a large multicentre RCT, with
305 variables collected in a prospective manner, which increases the generalizability of our results. In
306 addition, the temperature data at ICU was extensive, and side effects were documented for at least
307 96 hours after ICU admission.
308 We acknowledge some limitations. The use of cold fluids overall and the volume and infusion rates
309 used, were as per the treating clinicians. Therefore our study precludes conclusion on causality. In

addition, we did not have exact data on the surface-cooling pad size or incidence of shivering and our patient quantity was limited. Furthermore, we did not have a mandatory sedation or shivering protocol. Finally, the post hoc setting limits the generalization of the results.

Conclusions

In the current study, the initiation of TTM before ICU arrival using cold i.v. fluids was not associated with a decrease in the time required to reach a target temperature of < 34℃. Furthermore, patients who received cold fluids had slightly higher temperatures during the first 24 h as compared with those who did not receive cold fluids. We did not find any association between cold fluid use and electrolyte abnormalities, circulatory adverse effects, or outcomes.

References

1. Bernard SA, Gray TW, Buist MD et al. Treatment of Comatose Survivors of Out-of-Hospital Cardiac Arrest with Induced Hypothermia. N Engl J Med. 2002; 346:557-63.
2. M. Holzer, E. Cerchiari, P.Martens et. al. Hypothermia after CASG. Mild Therapeutic Hypothermia to Improve the Neurologic Outcome after Cardiac Arrest. N Engl J Med [Internet]. 2002 Feb 21346(8):549–56 (Accessed 23 Mar 2019 at http://www.ncbi.nlm.nih.gov/pubmed/11856793)
3. Schenfeld EM, Studnek J, Heffner AC, Nussbaum M, Kraft K, Pearson DA. Effect of prehospital initiation of therapeutic hypothermia in adults with cardiac arrest on time-to-target temperature. CJEM [Internet]. 2015 May 2;17(3):240–7. (Accessed 6 May 2019 at

http://www.ncbi.nlm.nih.gov/pubmed/26034909)

4. Kim F, Nichol G, Maynard C, et al. Effect of prehospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest a randomized clinical trial. JAMA - J Am Med Assoc. 2014; 311(1):45–52

5. Huang F-Y, Huang B-T, Wang P-J, et al. The efficacy and safety of prehospital therapeutic hypothermia in patients with out-of-hospital cardiac arrest: A systematic review and meta-analysis. Resuscitation [Internet] 2015 Nov;96:170–9 (Accessed 13 May 2019 at https://linkinghub.elsevier.com/retrieve/pii/S0300957215003767)

6. Bernard SA, Smith K, Cameron P, et al. Induction of Therapeutic Hypothermia by Paramedics After Resuscitation From Out-of-Hospital Ventricular Fibrillation Cardiac Arrest. Circulation [Internet]. 2010 Aug 17;122(7):737–42. (Accessed 31 May 2019 at http://www.ncbi.nlm.nih.gov/pubmed/20679551)

7. Bernard SA, Smith K, Finn J, et al. Induction of Therapeutic Hypothermia during Out-of-Hospital Cardiac Arrest Using a Rapid Infusion of Cold Saline: The RINSE Trial (Rapid Infusion of Cold Normal Saline). Circulation. 2016; Sep 13;134(11):797-805

8. Donnino MW, Andersen LW, Berg KM, Reynolds JC, Nolan JP, Morley PT, et al. Temperature Management After Cardiac Arrest. Circulation [Internet]. 2015 Dec ;132(25):2448–56 (Accessed 14 Jun 2019 at https://www.ahajournals.org/doi/10.1161/CIR.0000000000000313)

9. Lee BK, Jeung KW, Jung YH, et al. Relationship between timing of cooling and outcomes in adult comatose cardiac arrest patients treated with targeted temperature management. Resuscitation. 2017; Apr;113:135-141

10. Schock RB, Janata A, Peacock WF, Deal NS, Kalra S, Sterz F. Time to Cooling Is Associated with Resuscitation Outcomes. Ther Hypothermia Temp Manag [Internet]. 2016 Dec ;6(4):208–17 (Accessed 2 Jan 2019 at http://www.ncbi.nlm.nih.gov/pubmed/27906641)

11. Moler FW, Silverstein FS, Nadkarni VM, et al. Pediatric out-of-hospital cardiac arrest: Time to goal target temperature and outcomes. Resuscitation [Internet]. 2018 Dec 17 135:88-97 (Accessed Jan 2 2019 at http://www.ncbi.nlm.nih.gov/pubmed/30572071)

12. Nielsen N, Friberg H. Temperature management after cardiac arrest. Curr Opin Crit Care [Internet]. 2015 Jun;21(3):202–8. (Accessed 3 Jan 2019 at http://www.ncbi.nlm.nih.gov/pubmed/25922893)

13. Perman SM, Ellenberg JH, Grossestreuer A V, et al. Shorter time to target temperature is associated with poor neurologic outcome in post-arrest patients treated with targeted temperature management. Resuscitation [Internet]. 2015 Mar; 88:114–9. (Accessed 2 Jan 2019 at http://www.ncbi.nlm.nih.gov/pubmed/25447429)

14. Nie C, Dong J, Zhang P, Liu X, Han F. Prehospital therapeutic hypothermia after out-of-hospital cardiac arrest: a systematic review and meta-analysis. American Journal of Emergency Medicine. 2016 Nov;34(11):2209-2216.

15. Italian Cooling Experience (ICE) Study Group. Early- versus late-initiation of therapeutic hypothermia after cardiac arrest: Preliminary observations from the experience of 17 Italian intensive care units. Resuscitation [Internet]. 2012 Jul 1;83(7):823–8. (Accessed 6 May 2019

https://linkinghub.elsevier.com/retrieve/pii/S0300957211006885)

16. Nielsen N, Hovdenes J, Nilsson F, et al. Outcome, timing and adverse events in therapeutic hypothermia after out-of-hospital cardiac arrest. Acta Anaesthesiol Scand [Internet]. 2009 Aug 1; 53(7):926–34. (Accessed 6 May 2019 at http://doi.wiley.com/10.1111/j.1399-6576.2009.02021.x)

17. Kirkegaard H, Rasmussen BS, de Haas I, et al. Time-differentiated target temperature management after out-of-hospital cardiac arrest: a multicentre, randomised, parallel-group, assessor-blinded clinical trial (the TTH48 trial): study protocol for a randomised controlled trial. Trials [Internet]. 2016 Dec 4;17(1):228. (Accessed 9 May 2019 at http://www.ncbi.nlm.nih.gov/pubmed/27142588)

18. Kirkegaard H, Pedersen AR, Pettilä V, et al. A statistical analysis protocol for the time-differentiated target temperature management after out-of-hospital cardiac arrest (TTH48) clinical trial. Scand J Trauma Resusc Emerg Med [Internet]. 2016 Dec 28;24(1):138. (Accessed 28 May 2019 at http://www.ncbi.nlm.nih.gov/pubmed/27894327)

19. Leary M, Cinousis MJ, Mikkelsen ME, The association of body mass index with time to target temperature and outcomes following post-arrest targeted temperature management. Resuscitation [Internet]. 2014 Feb;85(2):244–7. (Accessed 3 Jul 2019 at http://www.ncbi.nlm.nih.gov/pubmed/24231571)

20. Nordberg P, Taccone FS, Truhlar A, et al. Effect of Trans-Nasal Evaporative Intra-arrest Cooling on Functional Neurologic Outcome in Out-of-Hospital Cardiac Arrest. JAMA [Internet]. 2019 May 7;321(17):1677. (Accessed 9 May 2019 at http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2019.4149)

21. Abella BS, Zhao D, Alvarado J, Hamann K, Vanden Hoek TL, Becker LB. Intra-Arrest Cooling Improves Outcomes in a Murine Cardiac Arrest Model. Circulation [Internet]. 2004 Jun 8;109(22):2786–91. (Accessed 13 May 2019 at http://www.ncbi.nlm.nih.gov/pubmed/15159295)

22. Che D, Li L, Kopil CM, Liu Z, Guo W, Neumar RW. Impact of therapeutic hypothermia onset and duration on survival, neurologic function, and neurodegeneration after cardiac arrest. Crit Care Med [Internet]. 2011 Jun;39(6):1423–30. (Accessed 13 May 2019 at http://www.ncbi.nlm.nih.gov/pubmed/21610611)

23. Scales DC, Cheskes S, Verbeek PR, et al. Prehospital cooling to improve successful targeted temperature management after cardiac arrest: A randomized controlled trial. Resuscitation [Internet]. 2017 Dec ;121:187–94. (Accessed 2 Jan 2019 at http://www.ncbi.nlm.nih.gov/pubmed/28988962)

24. Larsson I-M, Wallin E, Rubertsson S. Cold saline infusion and ice packs alone are effective in inducing and maintaining therapeutic hypothermia after cardiac arrest. Resuscitation [Internet]. 2010 Jan 1;81(1):15–9. (Accessed 15 Jul 2019 at https://linkinghub.elsevier.com/retrieve/pii/S0300957209004882)

25. Arulkumaran N, Suleman R, Ball J. Use of ice-cold crystalloid for inducing mild therapeutic hypothermia following out-of-hospital cardiac arrest. Resuscitation 2012 Feb;83(2):151-8

26. Deye N, Cariou A, Girardie P, et al. Endovascular Versus External Targeted Temperature

Management for Patients With Out-of-Hospital Cardiac Arrest. Circulation [Internet]. 2015 Jul 21;132(3):182–93. (Accessed 3 Jan 2019 at http://www.ncbi.nlm.nih.gov/pubmed/26092673)

27. Dell'Anna AM, Taccone FS. Prehospital Therapeutic Hypothermia in Patients With Out-Of-Hospital Cardiac Arrest. JAMA. 2014;311(21):2233.

28. Jacobshagen C, Pax A, Unsöld BW, et al. Effects of large volume, ice-cold intravenous fluid infusion on respiratory function in cardiac arrest survivors. Resuscitation. 2009 Nov;80(11):1223-8

Table 1. Demographic characteristics and type of resuscitation.

Variable	**Pre-ICU cold i.v. fluids given** ***n* = 110**	**Pre-ICU cold i.v. fluids not given** ***n* = 242**	***P* value**
Age (y), median (IQR)	62 (54 to 69)	62 (53 to 69)	0.97
Male sex, No. of patients (%)	86 (78)	207 (86)	0.09
Weight (kg), median (IQR)[a]	87 (76 to 97)	83 (75 to 92)	0.11
Neurological function pre-arrest, No. of patients (%)			
Normal (CPC 1)	108 (98)	234 (97)	0.44
Some disability (CPC 2)	2 (2)	8 (3)	
Medical history, No. of patients (%)			
Previous myocardial infarction	18 (16)	36 (15)	0.75
Previous PCI or CABG	15 (14)	40 (17)	0.48
Previous cardiac arrest	1 (1)	2 (1)	0.94
Chronic heart failure (NYHA IV)	13 (12)	5 (2)	<0.01
Chronic obstructive pulmonary disease	7 (6)	17 (7)	0.82
Liver cirrhosis	0 (0)	3 (1)	0.25
Chronic renal failure with dialysis	1 (0.9)	1 (0.4)	0.57
Diabetes mellitus	17 (16)	46 (19)	0.44
Immunosuppression	1 (1)	2 (1)	0.94

Cardiac arrest location, No. of patients (%)			
Home	62 (56)	130 (54)	0.37
Public place	38 (35)	98 (41)	
Other out-of-hospital	10 (9)	14 (6)	
Arrest witnessed, No. of patients (%)			
Bystander	95 (86)	206 (85)	0.29
Emergency medical services	9 (8)	5 (13)	
Unwitnessed	6 (6)	23 (10)	
Type of resuscitation, No. of patients (%)			
Bystander-initiated CPR	86 (78)	207 (86)	0.09
Shockable rhythm	94 (86)	218 (90)	0.20
Defibrillation with AED	19 (17)	61 (25)	0.05
Mechanical chest compression	23 (21)	67 (28)	0.16
Intubation	109 (99)	228 (95)	0.05
Prehospital treatment			
Epinephrine (yes), No. of patients (%)	66 (60)	155 (64)	0.47
Amiodarone (yes), No. of patients (%)	40 (36)	105 (43)	0.21
Time to ROSC (min), mean (SD)[b]	21 (11.5)	25 (20.1)	0.06

[a]Data missing for one patient. In some cases, the patient's weight was estimated and not measured. [b]Data missing for three patients.

Acronym key: IQR= interquartile range, SD= standard deviation, CPC= cerebral performance category, PCI= percutaneous coronary intervention, CABG= coronary artery bypass graft, NYHA=New York Heart Association classification, CPR= cardiopulmonary resuscitation, AED= automated external defibrillator, ROSC= return of spontaneous circulation

444

445

446

447

448

449

450

451

452

453 **Table 2.** Cooling-related factors.

Variable	**Pre-ICU cold i.v. fluids given** ***n*** **=110**	**Pre-ICU cold i.v. fluids not given** ***n*** **= 242**	***P*** **value**
Time from ROSC to ICU admission (min) Median (IQR)[a]	135 (86 to 191)	125 (76 to 170)	0.11
Time from ROSC to TT (min) Median (IQR)[b]	318 (245 to 418)	281 (214 to 367)	<0.01
Amount of cold pre-ICU fluids given No. of patients (%)[c]			
500ml	3(4)		
1000ml	37(49)		
1500ml	8(11)		
2000ml	21(28)		
2500ml	3(4)		
3000ml	3(4)		
Successful cooling[d] No. of patients (%)	47 (43)	125 (52)	0.14
Globally effective cooling, No. of patients (%)	36 (33)	97 (40)	0.20

Pre-ICU and pre-hospital cooling, No. of patients (%)			
Pre-hospital	43 (39)	21 (9)	<0.001
In hospital (pre-ICU)	59 (54)	12 (5)	
Both	8 (7)	4 (2)	
Cooling methods in the ICU, No. of patients (%)			
Surface cooling	60 (50)	97 (42)	0.02
Invasive cooling	67 (61)	151 (62)	0.79
Diuresis until TT, median (IQR)	368 (180 to 593)	330 (176 to 581)	0.20
Sedation administered[f]	109 (99)	235 (97)	0.34
Opioids administered[g]	86 (78)	167 (69)	0.08
Core temperature Measurement location,[h] No. of patients (%)			
Bladder	74 (90)	103 (81)	0.06
Nasopharynx	8 (10)	25 (20)	
Temperature 72 h after time 0, mean (SD)	37.4 (0.59)	37.3 (0.85)	0.12

[a]Data missing for 7 patients, [b]data missing for 12 patients, [c]data missing for 35 patients, [d]data missing for 7 patients, [e]data missing for 8 patients, [f]propofol or midazolam, [g]fentanyl or remifentanil, and [h]data missing for 142 patients.

Acronym key: IQR= interquartile range, SD= standard deviation, ICU= intensive care unit, ROSC= return of spontaneous circulation TT= target temperature

458

459 **Table 3.** Multiple linear regression of factors associated with the TTT.

Independent variable	**Standardized beta coefficients in univariate analysis (95% CIs for B)**	***P* value**	**Standardized beta coefficients in multivariate analysis (95% CIs for B)**	***P* value**
Weight	0.32 (2.0 and 3.8)	<0.01		
BMI	0.32 (6.9 and 13)	<0.01	0.29 (6 and 12)	<0.01
Previous AMI	-0.08 (-72 and 11)	0.15		
Chronic obstructive pulmonary disease	0.06 (-27 and 95)	0.27		
Liver cirrhosis	0.06 (-70 and 260)	0.26		
Previous heart failure NYHA classification 4	0.18 (43 and 180)	<0.01	0.13 (22 and 156)	0.01
Diabetes mellitus	-0.12 (-83 and -3.7)	0.03	-0.09 (-71 and 7.5)	0.11
ROSC delay (min)	-0.12 (-1.8 and -0.13)	0.02	-0.07 (-2.0 and 0.42)	0.20
Pre-ICU cold i.v. fluid treatment	0.14 (11 and 76)	0.01	0.06 (-49 and 16)	0.32
Cardiac arrest to ICU admission time (min)	0.06 (-0.001 and 0.004)	0.24		
Hospital/site	-0.11 (-1.1 and -0.02)	0.04	-0.07 (-0.94 and 0.15)	0.16

460

461 Acronym key: BMI= body mass index, AMI= acute myocardial ICU= intensive care unit, ROSC= return of spontaneous

462 circulation, TTT= time to target temperature

463

464

465

466

467

468

469 **Table 4.** Adverse events and patient outcomes.

Variable	**Pre-ICU cold i.v. fluids given** ***n*** **= 110**	**Pre-ICU cold i.v. fluids not given** ***n*** **= 242**	***P*** **value**
Seizure, No. of patients (%)			
Local	13 (12)	32 (13)	0.74
Global	16 (15)	48 (20)	0.23
Circulation, No. of patients (%)			
Mild	46 (42)	67 (28)	0.08
Moderate	14 (13)	39 (16)	
Severe	6 (6)	9 (4)	
Circulatory failure	4 (4)	9 (4)	
Mild arrhythmia	25 (22)	45 (19)	0.26
Moderate arrhythmia	16 (15)	29 (12)	
Severe arrhythmia	13 (12)	27 (11)	
Pacing	7 (6)	12 (5)	0.59
Pulmonary, No. of patients (%)			
Hypoxia (paO2 < 8 kPa)	2 (2)	8 (3)	0.43
Pneumonia	48 (44)	114 (47)	0.54
Gastrointestinal, No. of patients (%)			
Mild	7 (6)	14 (6)	0.37
Moderate	6 (6)	5 (2)	
Severe	3 (3)	9 (4)	
Renal, No. of patients (%)			
Renal replacement therapy	8 (7)	19 (8)	0.85
Infection, No. of patients (%)	40 (36)	89 (37)	0.92
Patient outcomes			
Died, No. of patients (%)			

Within 24 h	1 (0.9)	1(0.4)	0.57
Within 48 h	2 (2)	4 (2)	0.91
Within 72 h	3 (3)	9 (4)	0.63
In hospital	26 (24)	58 (24)	0.94
CPC1 or 2 at ICU discharge, No. of patients (%)	62 (56)	127 (53)	0.46
GCS score at ICU discharge,[a] No. of patients (%)			
3–8	8 (7)	15 (6)	0.58
9–12	2 (2)	7 (3)	
Died within 6 mo, No. of patients (%)	34 (31)	74 (31)	0.95
CPC1 or 2 at 6 mo, No. of patients (%)	72 (66)	160 (66)	0.78
Length of hospital stay (d), median (IQR)	12 (7 to 20)	11 (6 to 19)	0.31
Survivors	14(11)	13 (11)	0.93
Non-survivors	5(7)	5(5)	0.22

[a]Data missing for two patients.

Acronym key: IQR= interquartile range, SD= standard deviation, ICU= intensive care unit, ROSC= return of spontaneous circulation, CPC= cerebral performance category, GCS= Glasgow coma scale,

Supplementary online Table 1. Factors associated with successful cooling.

Variable	**Successful cooling (ROSC to TT< 294 min)** ***n* = 173**	**Unsuccessful cooling (ROSC to TT> 294 min)** ***n* = 172**	***P* value**
Age (y), median (IQR)	61,5 (53 to 69)	62 (54 to 69)	0.89
Male sex, No. of patients (%)	145 (83)	142 (83)	0.76
Weight[a] (kg), median (IQR)	80 (75 to 90)	90 (80 to 100)	<0.01
BMI, median (IQR)	25.3 (23.8 to 27.8)	27.7 (24.8 to 30.8)	<0.01
Neurological function pre-arrest, No. of patients (%)			0.20
Normal (CPC1)	170 (98)	165 (96)	
Some disability (CPC2)	3 (2)	7 (4)	
Medical history, No. of patients (%)			

Previous myocardial infarction	26 (15)	28 (16)	0.70
Previous PCI or CABG	25 (14)	30 (17)	0.43
Previous cardiac arrest	0 (0)	3 (2)	0.08
Chronic heart failure (NYHA IV)	4 (2)	14 (8)	0.02
Chronic obstructive pulmonary disease	15 (9)	8 (5)	0.14
Liver cirrhosis	3 (2)	0 (0)	0.08
Chronic renal failure with dialysis	1 (1)	1 (1)	0.99
Diabetes mellitus	26 (15)	37 (22)	0.11
Immunosuppression	1 (1)	2 (1)	0.56
Cardiac arrest location, No. of patients (%)			
Home	93 (54)	94 (55)	0.88
Public place	69 (40)	65 (38)	
Other out-of-hospital	11 (6)	10 (6)	
Arrest witnessed, No. of patients (%)			
Bystander	148 (86)	147 (85)	0.52
Emergency medical services	13 (8)	9 (5)	
Unwitnessed	12 (7)	16 (9)	
Type of resuscitation, No. of patients (%)			
Bystander-initiated CPR	144 (83)	144 (84)	0.90
Shockable rhythm	153 (88)	154 (88)	0.98
Defibrillation with AED	33 (19)	46 (27)	0.49
Mechanical chest compression used	48 (28)	41 (24)	0.48
Intubation	167 (97)	164 (95)	0.58
Pre-hospital treatment, No. of patients (%)			
Pre-ICU cold i.v. fluid bolus	48 (28)	59 (34)	0.19
Pre-ICU cold i.v. fluid amount (ml) median (IQR)	1500 (1000 to 2000)	1000 (1000 to 2000)	0.56
Epinephrine	110 (64)	109 (63)	0.97
Amiodarone	73 (42)	70 (40)	0.78

[a]Data missing for one patient. In some cases, the patient's weight was estimated and not measured.

Acronym key: IQR= interquartile range, SD= standard deviation, CPC= cerebral performance category, PCI= percutaneous coronary intervention, CABG= coronary artery bypass graft, NYHA=New York Heart Association

478 classification, CPR= cardiopulmonary resuscitation, AED= automated external defibrillator, ROSC= return of

479 spontaneous circulation, TT= target temperature

480

481 **Supplementary online Table 2.** ICU admission outcomes.

Variable	**Pre-ICU cold i.v. fluids given** ***n* = 110**	**Pre-ICU cold i.v. fluids not given** ***n* = 242**	***P* value**
FiO_2[a], median (IQR)	60 (50 to 60)	51 (41 to 60)	0.44
PaO_2 [b], median (IQR)	15 (11 to 22)	16 (12 to 23)	0.79
Saturation[c], median (IQR)	97 (92 to 99)	98 (91 to 99)	0.23
Hyponatremia,[d] No. of patients (%)	2 (2)	7 (3)	0.54
Hypernatremia,[g] No. of patients (%)	0 (0)	4 (2)	0.17
Na, median (IQR)	139 (136 to 140)	138 (136 to 140)	0.32
Hypokalaemia,[e] No. of patients (%)	2 (2)	11 (5)	0.20
K, median (IQR)	4 (3 to 4)	4 (4 to 5)	0.11
Hypochloraemia,[f] No. of patients (%)	25 (23)	59 (24)	0.80
Cl, Median (IQR)	107 (104 to 110)	107 (104 to 110)	0.90
Na, K or Cl abnormality[h] No. of patients (%)	28 (25)	79 (33)	0.21

482 [a]Data missing for 8 patients, [b]data missing for 2 patients, [c]data missing for 36 patients, [d]data missing for 7 patients,
483 [e]data missing for 6 patients, [f]data missing for 57 patients, [g]data missing for 7 patients, and [h]data missing for 52
484 patients.

485 Acronym key: IQR= interquartile range, FiO_2= Fraction of inspired oxygen, PaO_2= partial pressure of oxygen

486