# History and current use of mild therapeutic hypothermia after cardiac arrest

Jiří Bonaventura, David Alan, Jiri Vejvoda, Jakub Honek, Josef Veselka

Department of Cardiology, 2nd Medical School, Charles University, University Hospital Motol, Prague, Czech Republic

**Submitted:** 16 March 2015
**Accepted:** 5 August 2015

Arch Med Sci 2016; 12, 5: 1135–1141
DOI: 10.5114/aoms.2016.61917


**Corresponding author:**
Jiri Bonaventura MD
Department of Cardiology
2nd Medical School
Charles University
University Hospital Motol
V Úvalu 84
150 00 Prague, Czech Republic
Phone: +420 224434900
E-mail: jiri.bonaventura@fnmotol.cz

## Abstract

In spite of many years of development and implementation of pre-hospital advanced life support programmes, the survival rate of out-of-hospital cardiac arrest (OHCA) used to be very poor. Neurologic injury from cerebral hypoxia is the most common cause of death in patients with OHCA. In the past two decades, post-resuscitation care has developed many new concepts aimed at improving the neurological outcome and survival rate of patients after cardiac arrest. Systematic post-cardiac arrest care after the return of spontaneous circulation, including induced mild therapeutic hypothermia (TH) in selected patients, is aimed at significantly improving rates of long-term neurologically intact survival. This review summarises the history and current knowledge in the field of mild TH after OHCA.

**Key words:** cardiopulmonary resuscitation, survival rate, post-resuscitation care, intravascular cooling.

## Introduction

Despite nearly 40 years of pre-hospital advanced life support, the survival rate of out-of-hospital cardiac arrest (OHCA) used to be very poor, but has been gradually improved over the past two decades [1, 2]. Of all patients in whom resuscitation is attempted, only 14–40% achieve return of spontaneous circulation (ROSC) and are admitted to a hospital [3]. Of those patients admitted to a hospital, only 7–30% are usually discharged from the hospital with a good neurological outcome [3]. The cardiac arrest incidence and outcome in the current literature vary greatly around the world [1, 4, 5], but these reported figures may be subject to publication bias and may not reflect reality. Leaving the possible regional variations aside, the average survival rate to hospital admission worldwide is now considered to be 24%, and survival to hospital discharge is only 8% [1]. Survival to hospital discharge is more likely when cardiac arrest is witnessed by a bystander and found in ventricular fibrillation (VF) or ventricular tachycardia [1]. However, the public awareness concerning the basic life support algorithms, including the use of an automatic external defibrillator, needs to be improved [6]. While the issue of OHCA is well described and the data are widely available, the incidence of in-hospital cardiac arrest (IHCA) is rarely reported in the literature. Values range between one and five events per 1,000 hospital admissions [7].

Neurologic injury is the most common cause of death in patients with OHCA and contributes to the mortality of inpatients with cardiac arrest [8]. Inducing mild therapeutic hypothermia (TH) in selected patients surviving OHCA could significantly improve rates of long-term neurologically intact survival and may prove to be one of the most important clinical advances in the science of resuscitation [9]. However, recent randomised trials have raised several important questions, and the field still remains intensively debated.

## Historical perspectives

Some early great physicians, including Hippocrates, recognised the utility of hypothermia in attenuating injury. For example, Hippocrates mentioned the use of snow and ice to reduce haemorrhage in patients [10]. The concept has experienced periodic re-emergence in the medical literature, and recent studies of the modality date back to the 1950s. The pathology underlying the clinical picture resulting from cerebral hypoxia and the rationale for utilising hypothermia in its treatment have been investigated by several authors [11–13]. The clinical use of hypothermia presupposed the generalised reduction of brain tissue metabolism with lower temperatures. This presumption was evidenced in 1954 by Rosomoff and Holaday [13], who found a linear fall in cerebral oxygen consumption in dogs as the temperature was lowered from 35°C to 26°C. A 3-fold reduction in oxygen consumption occurred at 26°C [13]. Two years later, animal models (including monkeys and dogs) showed evidence of reduced histopathology and favourable functional outcomes using hypothermia after total occlusion of the afferent circulation of the brain [14, 15]. These experiments approximated what occurs in cardiac arrest and predicted the clinical use of hypothermia in human medicine.

The first in-human study of hypothermia after cardiac arrest was performed in 1958 [16] and suggested decreased mortality. This exceptional study included 19 patients resuscitated after perioperative cardiac arrest. The chest of all patients was opened, and the heart was noted to be either in asystole or fibrillating. Those patients who were subjected to hypothermia were cooled using a blanket containing a circulating coolant. Body temperature was maintained at approximately 31–32°C. The duration of the cooling was based on clinical judgement. When improvement was noted, hypothermia was gradually stopped. Among the cooled survivors, the duration of hypothermia ranged from 34 to 84 h, while in the non-survivors it ranged from 3 h to 8 days. Seven patients did not receive hypothermia, and only one of them survived. Six out of 12 cooled patients survived, suggesting the improvement in survival rate from 14% to 50% [16]. However, additional studies with more patients were about to occur.

Until the year 2002, the evidence for mild TH lacked sufficient power and advisory panel support recommending its use in common practice. Two studies, European and Australian [9, 17], both published in 2002, demonstrated improved survival rates and neurological outcomes with the induction of mild TH for comatose survivors of OHCA due to VF. The Hypothermia after Cardiac Arrest Study Group (HACA), including nine centres in five European countries, showed that mild hypothermia (cooling to 32–34°C for 24 h) in 274 OHCA patients with ROSC provided significant improvement in functional recovery after hospital discharge (55% vs. 39%) [17]. It also led to a lower 6-month mortality rate when compared with patients who were not cooled (41% vs. 55%) [17]. Meanwhile, in Melbourne, Bernard *et al.* examined the endpoint of survival to hospital discharge in 77 patients and demonstrated a 49% survival rate in the hypothermia group (cooling to 33°C for 12 h) compared with 26% in the normothermic group [9].

Despite the rising evidence of efficacy [18–21] and published guidelines by the International Liaison Committee on Resuscitation (ILCOR) supporting the use of TH [22], the implementation of hypothermia treatment was slow, and the use among physicians in intensive care units (ICUs) greatly varied. The adoption of hypothermia guidelines in North America was lower than in Europe, while the highest proportion of patients after cardiac arrest was cooled in North European countries [23]. The identified barriers to implementation included insufficient knowledge of effective hypothermia techniques, lack of belief that TH would improve the outcome for individual patients, and controversies regarding the best method to reach the target temperatures – the hypothermia guidelines in 2005 did not contain a particular cooling protocol [22]. Five years later, new guidelines were published by ILCOR [24] and provided the material for regional resuscitation organisations, such as the American Heart Association (AHA) [25] or the European Resuscitation Council (ERC) [26], to write their resuscitation guidelines.

## Current recommendations

According to the latest guidelines written in 2010 [24, 25], there was sufficient evidence that TH improves the outcome after adult-witnessed OHCA caused by VF [9, 17]. The benefit of hypothermia after cardiac arrest due to other initial rhythms was not as clear in 2010 [24]. However, it was well established that hyperthermia must be avoided following cardiac arrest. Failure to control a patient's core temperature is associated with

the development of fever and worse neurologic outcomes [25]. Furthermore, active rewarming should be avoided in comatose patients who spontaneously develop a mild degree of hypothermia (above 32°C) during the first 48 h after ROSC [26].

Patients with ROSC after OHCA caused by VF should be cooled to 32–34°C for 12–24 h. Rapid infusion of ice-cold intravenous fluid and application of ice packs as a safe and simple method were recommended. These recommendations were adopted in the AHA and ERC guidelines [26, 27]. The animal data indicate that earlier cooling after ROSC produces better outcomes [28], and some clinical studies have shown that hypothermia can be initiated during advanced life support prior to arrival at the hospital [29]. Nevertheless, there were no human data in 2010 demonstrating that pre-hospital initiation of cooling was associated with improved post-discharge neurological outcomes [30]. A large Swedish registry-based study of 986 comatose post-cardiac arrest patients suggested that neither the time to initiate TH nor the time taken to reach the goal temperature had any significant association with improved neurological outcome after discharge [31]. In that study, published in 2009 [31], the median time from arrest to initiation of TH was 90 min, and the median time of achieving the target temperature (≤ 34°C) was 260 min [31], which shows cooling almost twice as fast as in the HACA study. In the HACA study, the median interval between the ROSC and the attainment of a temperature ≤ 34°C was 8 h, and 33°C was achieved after 12 h [17].

## New insights for TTM

Since 2010, many articles concerning TH have been written, and a major industry of cooling devices and accessories (e.g., cooling blankets, pads, heating exchangers) has been born. In 2013, the results of the TTM (Targeted Temperature Management 33°C versus 36°C after OHCA) trial were published in The *New England Journal of Medicine* [32]. The TTM trial was a large ($n$ = 939), randomised clinical trial recruiting patients in 36 ICUs in Europe and Australia, which compared a target body temperature of 33°C with one of 36°C in patients who had been resuscitated after OHCA due to a presumed cardiac cause. This superbly executed study was more than twice the size of the original trials combined, and the trial protocol and analysis plan were published in advance and attempted to address possible deficiencies in previous trials [33, 34]. The results of the TTM trial (which was designed as a superiority trial) showed that hypothermia at a targeted temperature of 33°C did not confer a benefit as compared with a targeted temperature of 36°C. No difference between the two groups in overall mortality at the end of the trial or in the composite endpoint of poor neurologic function or death at 180 days was found.

The overall conclusion of the TTM trial contradicted the previous trials by HACA and Bernard *et al.* from 2002. How could it be explained? i) The population in the TTM trial was less selected than in previous trials and included patients with shockable and non-shockable rhythms. ii) Many patients in the "normothermia" group of the HACA and Bernard trials in 2002 actually became hyperthermic [9, 17], which is known to be harmful now [26]. The exceptional rates of good outcomes in both the 33°C and 36°C groups in the TTM trial would then simply emphasize the importance of the active prevention of hyperthermia. iii) Within the past decade, there were improvements in overall patient intensive care that may have reduced the potential benefits of a single intervention like TH. iv) TH was already the standard of care in participating hospitals in the TTM study, and the default option for patients not enrolled in the trial was applying TH. Therefore, admitting physicians might have subconsciously selected patients with the potential to benefit from receiving regular TH rather than screening them for trial eligibility. v) Another important difference in the TTM trial was adoption of a protocol for withdrawal of life-sustaining treatment. Older studies of post-cardiac arrest care were biased by the fact that a very common cause of death was withdrawal of life support because of perceived poor neurologic prognosis, although there were no certain methods to establish long-term prognosis. The TTM trial authors clearly specified in advance in their study design [33] the criteria allowing the discontinuation of life support, in a total of 26% of patients. More patients in the 33°C group met the criteria for early withdrawal of care, suggesting greater severity of brain injury in the 33°C group. vi) There were also concerns about the rapid rate of active rewarming from 33°C to 36°C, which could negate the benefits of TH. The temperature graph in the TTM trial [32] showed wide error bars, potentially indicating large temperature swings that could be harmful. Nevertheless, the optimal rate of rewarming still remains unknown. In the TTM trial, it was undertaken at a maximum speed of 0.5°C per hour, according to the current guidelines [24, 26, 27]. The actual rewarming rate in the TTM trial was 0.36 ±0.13°C per hour [32]. vii) There was greater prevalence of spontaneous hypothermia in the 33°C group, potentially indicating greater severity of brain injury with a diminished shivering response [35].

In the TTM study, the authors reported that 33°C was achieved after 8 h, and the attainment

of a temperature ≤ 34°C was no longer than 3 h [32], which could be the fastest cooling so far. Nevertheless, an "inclusion window" (time from ROSC to randomization and intervention) of up to 4 h was allowed per study protocol [33], so the goal temperature of 33°C was not reached for some patients until 12 h after ROSC.

It raised an important question. Does faster cooling really means better outcome? The very recent large ($n$ = 1,359), randomised trial published by Kim *et al.* [36] found that pre-hospital, rapid infusion of up to 2 l of 4°C normal saline induced mild hypothermia faster than standard care, but did not improve survival or neurological status at discharge after resuscitation from pre-hospital shockable or non-shockable OHCA [36]. The patient who had a pre-hospital intervention reached the goal temperature about one hour sooner (4.2 vs. 5.5 h) than the control group, but the intervention was associated with a significantly increased incidence of re-arrest during transport, time spent in the pre-hospital setting and pulmonary oedema with early diuretic use. There were some limitations of the trial by Kim *et al.* [36]. i) Not all randomized patients were treated with TH. Only 74% with a shockable rhythm and 59% with non-shockable rhythm reached the target temperature. So the potential benefits of pre-hospital TH may have been spoiled because cooling did not continue after admission to hospital. ii) The temperature at the time of hospital admission was too similar between the intervention and the control group, with the difference less than 1°C. iii) The study used a goal threshold temperature of 34°C rather than 33°C. iv) Cardiac re-arrest possibly worsened brain ischemia, which did not affect early mortality but manifested as increased risk of death later during the hospitalization. v) Cold pre-hospital fluid administration was associated with significant reduction in first arterial blood gas pH and $PaO_2$ levels, which are both predictors of poor outcomes. vi) The trial measured end points only at the time of hospital discharge, despite the knowledge that functional status can improve for at least 6 months after resuscitation from cardiac arrest.

The time interval from collapse to ROSC has been reported to be a strong independent predictor of neurological outcome in comatose survivors of cardiac arrest [8, 26, 27]. The positive effect of mild TH seems to increase with cumulative time of complete circulatory standstill in patients with witnessed OHCA [37]. Treating patients with TH appears to be more beneficial than not treating them with TH if the time interval from collapse to ROSC is greater than 15 min [38]. From this point of view, the speed of cooling seems not to be the most important aspect of TH.

The TTM trial [32] and the trial by Kim *et al.* [36] have challenged the current practice in the treatment of patients with ROSC after OHCA and raised two important questions: i) Should the ice-cold intravenous fluid continue to be used for inducing hypothermia pre-hospital; and ii) should the target temperature be 32–34°C or 36°C for the management of comatose cardiac arrest survivors with ROSC? [37] ILCOR responded with a short statement in December 2013 [39] suggesting that clinicians should provide post-resuscitation care based on the current treatment recommendations published in 2010 [24, 26, 27] until a formal ILCOR consensus on optimal temperature management is made. The term "targeted temperature management" (TTM) became more used than TH and seemed to be more appropriate considering the fact that 36°C is "a little dose of hypothermia" but not physiological human temperature. ILCOR also accepted that clinicians could make a local decision to use a target temperature of 36°C before the formal evidence was reviewed to consider whether this new TTM regimen should be part of future treatment recommendations [39].

Even intra-arrest cooling performed in a recent smaller ($n$ = 245) randomised trial in France did not show more optimistic results [40]. Intra-arrest cooling with rapid infusions of up to 2 l of ice-cold fluids during OHCA decreased the core temperature by an average of 1.7°C prior to hospital admission, and shortened the time to reach 34°C by an average of 93 min compared to in-hospital TH alone. However, this was not associated with differences in markers of neurological injury or in neurological outcome [40]. The poor outcome could be influenced by a relatively low number of initial shockable rhythms in both groups (less than 30%) and the high frequency of initial asystole (65%), indicating that the included patients were too severely injured and not comparable to the patients in the HACA trial [17] or the TTM trial [32]. These results only contributed to the suspicion gained from the registry-based studies [41, 42] that TH is not associated with good outcomes in non-shockable patients.

There is little evidence regarding TH after IHCA, and our knowledge is based mostly on the result of one retrospective analysis [43] of 8,316 patients with IHCA. Only 214 (2.6%) patients received TH, and only 40% of these patients were documented to achieve a temperature between 32°C and 34°C. Induced TH was not associated with improved, worsened, or neurologically favourable survival [43]. Clearly, higher-quality controlled studies are required to better characterise the effect of induced hypothermia in this population.

## The future of hypothermia

In the year 2015, the new ILCOR guideline document, which is scheduled for online publication on the 15th of October [44], is highly anticipated. Meanwhile, the results of the recent studies have been intensively debated. The robust design of the TTM trial has been recognised by a number of commentators. The overall interpretation of the TTM results could be that they reinforce the importance of controlling temperature and the active prevention of hyperthermia. It seems plausible that we should not regress to a pre-2002 style of care that does not manage temperature at all. The concept of changing current guidelines and cooling to 36°C is supported by several authors, while the design of the pre-hospital cooling using the ice-cold intravenous fluid bolus is disapproved. Another approach of fast induction TH could be to use transnasal evaporative cooling, which allows TH to be initiated within minutes of the arrest without the increased risk of pulmonary oedema. The system has been tested in patients in a randomised field study, which showed promising results regarding feasibility and effectiveness [45]. A multicentre prospective study is currently recruiting to explore its ability to improve outcomes [46].

Perhaps the most important message to take from the mentioned trials is that modern post-resuscitation care, including targeted temperature management, is legitimate, making survival more likely than death when a patient is hospitalised after cardiopulmonary resuscitation (CPR). In contrast to a decade ago, one-half instead of one-third of patients with ROSC after OHCA can expect to survive to hospital discharge. The most important aspect of the TTM trial may be that it indicates knowledge gaps in post-cardiac arrest temperature management. The optimal temperature, method, onset, duration of temperature management, rewarming rate and therapeutic window remain to be supported by better evidence. The TH probably should not be started before hospital admission, at least not by using rapid infusion of a large amount of ice-cold fluids. Given the strong design and size of the TTM trial, there is little rationale for using 33°C, but no data suggest any harm in doing so. Whether certain subpopulations of cardiac arrest patients may benefit from lower (33°C) or higher (36°C) temperatures remains unknown, and further research may help to resolve this. A multicentre prospective study is currently recruiting participants to explore the outcome of OHCA patients with initial shockable rhythm for three different levels of hypothermia: 32°C, 33°C and 34°C [47]. Furthermore, a greatly expected multicentre prospective randomized trial, in which patients after successfully resuscitated nonshockable cardiac arrest are allocated to either TTM between 32.5°C and 33.5°C or TTM between 36.5°C and 37.5°C (therapeutic normothermia), is currently in progress and may provide an answer to this important issue [48]. Modern promising indicators of a poor prognosis after CPR, including plasma concentrations of the inflammatory markers [49] or neuron-specific enolase [50], might appear to be helpful in early selection of a suitable protocol. Further investigation is needed to determine the clear benefit of TH after OHCA from non-shockable initial rhythm and IHCA. From the unofficial data published by ILCOR on the websites so far weakly recommending cooling these patients [44], we will have to wait for the definitive answers for some time.

## Conflict of interest

The authors declare no conflict of interest.

## References


1. Sasson C, Rogers MA, Dahl J, Kellermann AL. Predictors of survival from out-of-hospital cardiac arrest: a systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes 2010; 3: 63-81.
2. Wissenberg M, Lippert FK, Folke F, et al. Association of national initiatives to improve cardiac arrest management with rates of bystander intervention and patient survival after out-of-hospital cardiac arrest. JAMA 2013; 310: 1377-84.
3. Arrich J, Holzer M, Herkner H, Müllner M. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. Cochrane Database Syst Rev 2009; 4: CD004128.
4. Atwood C, Eisenberg MS, Herlitz J, Rea TD. Incidence of EMS-treated out-of-hospital cardiac arrest in Europe. Resuscitation 2005; 67: 75-80.
5. Berdowski J, Berg RA, Tijssen JG, Koster RW. Global incidences of out-of-hospital cardiac arrest and survival rates: systematic review of 67 prospective studies. Resuscitation 2010; 81: 1479-87.
6. Kozłowski D, Kłosiewicz T, Kowalczyk A, Kowalczyk AK, Koźluk E, Dudziak M. The knowledge of public access to defibrillation in selected cities in Poland. Arch Med Sci 2013; 9: 27-33.
7. Sandroni C, Nolan J, Cavallaro F, Antonelli M. In-hospital cardiac arrest: incidence, prognosis and possible measures to improve survival. Intensive Care Med 2007; 33: 237-45.
8. Lemiale V, Dumas F, Mongardon N, et al. Intensive care unit mortality after cardiac arrest: the relative contribution of shock and brain injury in a large cohort. Intensive Care Med 2013; 39: 1972-80.
9. 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.
10. Hippocrates. De Vetere Medicina. Translation: Jones WHS, Withington ET. Loeb Classical Library, 460-375 BC.
11. Meyer JS, Hunter J. Effects of hypothermia on local blood flow and metabolism during cerebral ischemia and hypoxia. J Neurosurg 1957; 14: 210-27.

12. Marchand P, Allan JC. An experimental study of the effect of hypothermia on the heart and brain. S Afr J Med Sci 1956; 21: 127-41.
13. Rosomoff HL, Holaday DA. Cerebral blood flow and cerebral oxygen consumption during hypothermia. Am J Physiol 1954; 179: 85-8.
14. Marshall SB, Owens JC, Swan H. Temporary circulatory occlusion to the brain of the hypothermic dog. AMA Arch Surg 1956; 72: 98-106.
15. McMurrey JD, Bernhard WF, Taren JA, Bering EA. Studies on hypothermia in monkeys. I. The effect of hypothermia on the prolongation of permissible time of total occlusion of the afferent circulation of the brain. Surg Gynecol Obstet 1956; 102: 75-86.
16. Benson DW, Williams GR, Spencer FC. The use of hypothermia after cardiac arrest. Anesth Analg 1959; 38: 423-8.
17. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002; 346: 549-56.
18. Hachimi-Idrissi S, Corne L, Ebinger G, Michotte Y, Huyghens L. Mild hypothermia induced by a helmet device: a clinical feasibility study. Resuscitation 2001; 51: 275-81.
19. Laurent I, Adrie C, Vinsonneau C, et al. High-volume hemofiltration after out-of-hospital cardiac arrest: a randomized study. J Am Coll Cardiol 2005; 46: 432-7.
20. Mori K, Takeyama Y, Itoh Y, et al. A multivariate analysis of prognostic factors in survivors of out-of-hospital cardiac arrest with brain hypothermia therapy. Crit Care Med 2000; 28 (12 Suppl.): A168.
21. Arrich J, Holzer M, Havel C, Müllner M, Herkner H. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. Cochrane Database Syst Rev 2012; 9: CD004128.
22. International Liaison Committee on Resuscitation. 2005 International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Part 1: introduction. Resuscitation 2005; 67: 181-6.
23. Arrich J; European Resuscitation Council Hypothermia After Cardiac Arrest Registry Study Group. Clinical application of mild therapeutic hypothermia after cardiac arrest. Crit Care Med 2007; 35: 1041-7.
24. Morrison LJ, Deakin CD, Morley PT, et al. Part 8: advanced life support 2010 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Circulation 2010; 122 (16 Suppl): S345-421.
25. Zeiner A, Holzer M, Sterz F, et al. Hyperthermia after cardiac arrest is associated with an unfavorable neurologic outcome. Arch Intern Med 2001; 161: 2007-12.
26. Peberdy MA, Callaway CW, Neumar RW, et al. Part 9: post-cardiac arrest care 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010; 122 (3 Suppl.): S768-86.
27. Deakin CD, Nolan JP, Soar J, et al. European resuscitation council guidelines for resuscitation 2010 section 4. Adult advanced life support. Resuscitation 2010; 81: 1305-52.
28. Kuboyama K, Safar P, Radovsky A, Tisherman SA, Stezoski SW, Alexander H. Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: a prospective, randomized study. Crit Care Med 1993; 21: 1348-58.
29. Bruel C, Parienti JJ, Marie W, et al. Mild hypothermia during advanced life support: a preliminary study in out-of-hospital cardiac arrest. Crit Care 2008; 12: R31.
30. Bernard SA, Smith K, Cameron P, et al. Rapid Infusion of Cold Hartmanns [RICH] Investigators. Induction of therapeutic hypothermia by paramedics after resuscitation from out-of-hospital ventricular fibrillation cardiac arrest: a randomized controlled trial. Circulation 2010; 122: 737-42.
31. 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 2009; 53: 926-34.
32. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. N Engl J Med 2013; 369: 2197-206.
33. Nielsen N, Wetterslev J, al-Subaie N, et al. Target temperature management after out-of-hospital cardiac arrest – a randomized, parallel-group, assessor-blinded clinical trial – rationale and design. Am Heart J 2012; 163: 541-8.
34. Nielsen N, Winkel P, Cronberg T, et al. Detailed statistical analysis plan for the target temperature management after out-of-hospital cardiac arrest trial. Trials 2013; 14: 300.
35. Polderman KH. Mechanisms of action, physiological effects, and complications of hypothermia. Crit Care Med 2009; 37: S186-202.
36. 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 2014; 311: 45-52.
37. Testori C, Sterz F, Holzer M, et al. The beneficial effect of mild therapeutic hypothermia depends on the time of complete circulatory standstill in patients with cardiac arrest. Resuscitation 2012; 83: 596-601.
38. Kagawa E, Inoue I, Kawagoe T, et al. Who benefits most from mild therapeutic hypothermia in coronary intervention era? A retrospective and propensity-matched study. Crit Care 2010; 14: R155.
39. Jacobs I, Nadkarni V. Targeted temperature management following cardiac arrest: an update. ILCOR update 2013. http://www.ilcor.org/data/TTMILCOR-update-Dec-2013.pdf
40. Debaty G, Maignan M, Savary D, et al. Impact of intra-arrest therapeutic hypothermia in outcomes of prehospital cardiac arrest: a randomized controlled trial. Intensive Care Med 2014; 40: 1832-42.
41. Dumas F, Grimaldi D, Zuber B, et al. Is hypothermia after cardiac arrest effective in both shockable and nonshockable patients? Insights from a large registry. Circulation 2011; 123: 877-86.
42. Mader TJ, Nathanson BH, Soares WE, Coute RA, McNally BF. Comparative effectiveness of therapeutic hypothermia after out-of-hospital cardiac arrest: insight from a large data registry. Ther Hypothermia Temp Manag 2014; 4: 21-31.
43. Nichol G, Huszti E, Kim F, et al. Does induction of hypothermia improve outcomes after in-hospital cardiac arrest? Resuscitation 2013; 84: 620-5.
44. http://www.ilcor.org/home
45. Castrén M, Nordberg P, Svensson L, et al. Intra-arrest transnasal evaporative cooling a randomized, prehospital, multicenter study (PRINCE: Pre-ROSC IntraNasal Cooling Effectiveness). Circulation 2010; 122: 729-36.
46. Nordberg P, Taccone FS, Castren M, et al. Design of the PRINCESS trial: pre-hospital resuscitation intra-nasal

cooling effectiveness survival study (PRINCESS). BMC Emerg Med 2013; 13: 21.
47. https://clinicaltrials.gov/ct2/show/NCT02035839
48. Lascarrou JB, Meziani F, Le Gouge A, et al. Therapeutic hypothermia after nonshockable cardiac arrest: the HYPERION multicenter, randomized, controlled, assessor-blinded, superiority trial. Scand J Trauma Resusc Emerg Med 2015; 23: 26.
49. Samborska-Sablik A, Sablik Z, Gaszynski W. The role of the immuno-inflammatory response in patients after cardiac arrest. Arch Med Sci 2011; 7: 619-26.
50. Thömke F. Assessing prognosis following cardiopulmonary resuscitation and therapeutic hypothermia – a critical discussion of recent studies. Dtsch Arztebl Int 2013; 110: 137-43.