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ICM RAPID PRACTICE GUIDELINE

ERC-ESICM guidelines on temperature control after cardiac arrest in adults

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Abstract

The aim of these guidelines is to provide evidence-based guidance for temperature control in adults who are comatose after resuscitation from either in-hospital or out-of-hospital cardiac arrest, regardless of the underlying cardiac rhythm. These guidelines replace the recommendations on temperature management after cardiac arrest included in the 2021 post-resuscitation care guidelines co-issued by the European Resuscitation Council (ERC) and the European Society of Intensive Care Medicine (ESICM). The guideline panel included thirteen international clinical experts who authored the 2021 ERC-ESICM guidelines and two methodologists who participated in the evidence review completed on behalf of the International Liaison Committee on Resuscitation (ILCOR) of whom ERC is a member society. We followed the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to assess the certainty of evidence and grade recommendations. The panel provided suggestions on guideline implementation and identified priorities for future research. The certainty of evidence ranged from moderate to low. In patients who remain comatose after cardiac arrest, we recommend continuous monitoring of core temperature and actively preventing fever (defined as a temperature > 37.7 °C) for at least 72 h. There was insufficient evidence to recommend for or against temperature control at 32–36 °C or early cooling after cardiac arrest. We recommend not actively rewarming comatose patients with mild hypothermia after return of spontaneous circulation (ROSC) to achieve normothermia. We recommend not using prehospital cooling with rapid infusion of large volumes of cold intravenous fluids immediately after ROSC.

Keywords: Cardiac arrest, Coma, Prognosis, Hypothermia, Practice guidelines

Introduction

In comatose patients with presumed post-cardiac arrest brain injury [1] temperature control with a target of 32 to 36 °C body temperature was the only neuroprotective intervention to show a potential benefit and to enter international guidelines [2–4].

In recent years, the term targeted temperature management (TTM) has been used to describe temperature control after cardiac arrest. However, to avoid confusion with the names given specifically to the TTM and TTM-2 trials [5, 6], the Advanced Life Support (ALS) Task Force of the International Liaison Committee on Resuscitation (ILCOR) recently adopted the term 'temperature control' instead of TTM except when referring to the TTM trials.

The mission of ILCOR (www.ilcor.org) is to promote, disseminate and advocate for international implementation of evidence-informed resuscitation and first aid,

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using transparent evaluation and consensus summary of scientific data. The European Resuscitation Council (ERC) is one of the founding members of ILCOR and continues to work closely with ILCOR in pursuit of these goals. A key activity of ILCOR is the systematic assessment of evidence to produce international consensus on science with treatment recommendations (CoSTRs). CoSTRs were initially produced every 5 years. In 2017, ILCOR transitioned to a continuous evidence evaluation process. From 2017 the ERC has published annual updates linked to the publications of ILCOR CoSTRs. The ERC and the European Society of Intensive Care Medicine (ESICM) have collaborated to produce post resuscitation care guidelines resulting in the publication of the 2014 ERC-ESICM Advisory Statement on Prognostication in Comatose Survivors of Cardiac Arrest [7], and in the 2015 and 2021 Guidelines on Post-Resuscitation Care. The evidence informing both guidelines was based on ILCOR CoSTRs. In 2002, two randomised controlled trials (RCTs) showed that maintenance of core body temperature at 32–34 °C for 12–24 h in patients with post-cardiac arrest brain injury following resuscitation from out-of-hospital cardiac arrest (OHCA) due to witnessed shockable rhythm was associated with an improved survival to hospital discharge [8] and functional outcome at 6 months [9] when compared with standard care. Based on these studies, and supporting experimental data [10], the ILCOR ALS Task Force recommended in 2003 that comatose adult OHCA survivors should be cooled for 32–34 °C for 12–24 h when the initial rhythm was ventricular fibrillation [2]. Since then, several concerns have been raised about the high risk of bias in these studies [11]. In 2013, the TTM trial, including 939 comatose OHCA survivors, showed no difference in all-cause mortality or 6-month neurological function between patients who received temperature control to a target of 33 °C versus a target of 36 °C [6]. The findings of this trial led many clinicians to aim for a target temperature of 36 °C in post-cardiac arrest patients, while others continued to aim for 33 °C.

In 2019, the HYPERION trial documented an increase in 90-day favourable functional outcome with temperature control at 33 °C for 24 h compared with normothermia [12]. The study was conducted in 584 comatose survivors of cardiac arrest due to non-shockable rhythm (asystole or pulseless electrical activity); of those, 159 (27%) had in-hospital cardiac arrest (IHCA). Given the additional evidence provided by this trial, the 2020 ILCOR CoSTR recommended temperature control at 32–36 °C for at least 24 h for adults after either OHCA or IHCA who remain comatose after resuscitation from cardiac arrest, regardless of the initial rhythm [13]. The 2021 ERC-ESICM Guidelines for Post-resuscitation Care aligned with this recommendation [14, 15].

Two months after publication of these guidelines, the TTM-2 trial reported no difference in 6-month mortality or functional outcome among 1850 comatose OHCA survivors from any initial rhythm who were temperature controlled at 33 °C compared with only intervening when patients developed fever, defined as body temperature > 37.7 °C [5]. A recently published network meta-analysis of temperature control after OHCA showed no difference in 6-months mortality or functional outcome between hypothermia between 31 and 36 °C vs. normothermia (i.e., 37–37.8 °C) [16]. This meta-analysis also included the CAPITAL-CHILL trial, which compared target temperatures of 31 °C and 34 °C among comatose OHCA survivors [17] and reported similar survival rates between groups.

After the publication of these studies, the ILCOR ALS Task Force undertook a new evidence review aimed at providing updated guidelines for clinical practice. A systematic review and meta-analysis including evidence on both IHCA and OHCA from all rhythms was conducted [18] and resulted in the 2021 ILCOR CoSTR on temperature management in adult cardiac arrest, published online [19]. An ERC-ESICM panel was summoned to provide a rapid update based on this ILCOR report.

Scope and target audience

These guidelines apply to adults who are comatose after resuscitation from IHCA or OHCA, regardless of the underlying cardiac rhythm, cause, or severity of illness. The target users of these guidelines are intensive care units (ICU) and emergency medicine teams. The objective of this document is to update the recommendations on temperature management after cardiac arrest which were included in the 2021 ERC-ESICM post-resuscitation guidelines [14, 15]. As for the previous guidelines, the evidence informing this update is based on an ILCOR CoSTR[19].

Sponsoring organisation

The ERC and ESICM are the sponsoring organisations of these guidelines. Two authors (LWA, PTM, both members of the ILCOR ALS Task Force) were responsible for the methodological and statistical aspects.

Methods

The procedures to conduct the evidence review, reach consensus, and produce recommendations followed the ILCOR Evidence Evaluation Process and Management of Potential Conflicts of Interest [20].

The ILCOR systematic review and the subsequent COSTR were undertaken by members of the ILCOR ALS Task Force.

Table 1 The PICO (Population, Intervention, Comparator, Outcome) for the ILCOR systematic review

Population	Intervention	Comparator	Outcome
USE OF TARGETED TEMPERATURE CONTROL (TTM)			
Adults in any setting (in-hospital or out-of-hospital) with cardiac arrest	Temperature control targeting hypothermia at 32-34°C	Temperature control targeting normothermia or fever prevention	Any clinical outcome
DURATION			
Adults in any setting (in-hospital or out-of-hospital) with cardiac arrest	TTM for a specific duration (e.g.,48 hours)	TTM at a different specific duration (e.g.,24 hours)	Any clinical outcome
METHOD			
Adults in any setting (in-hospital or out-of-hospital) with cardiac arrest	TTM with a specific method (e.g., external)	TTM with a different specific method (e.g., internal)	Any clinical outcome
TEMPERATURE			
Adults in any setting (in-hospital or out-of-hospital) with cardiac arrest	TTM at a specific temperature (e.g.,33°C)	TTM at a different specific temperature (e.g.,36°C)	Any clinical outcome
TIMING			
Adults in any setting (in-hospital or out-of-hospital) with cardiac arrest	TTM induction before a specific time point (e.g., prehospital or intra-cardiac arrest, i.e., before return of spontaneous circulation (ROSC))	TTM induction after that specific time point	Any clinical outcome
REWARMING			
Adults in any setting (in-hospital or out-of-hospital) with cardiac arrest	TTM with a specific rewarming rate	TTM with a different specific rewarming rate or no specific rewarming rate	Any clinical outcome

Note: For all PICOs, clinical outcomes included, but were not necessarily limited to: ROSC, survival/survival with a favourable neurological outcome at hospital discharge/28/30 days, and survival/survival with a favourable neurological outcome after hospital discharge/28/30 days (e.g., 90 days, 180 days, 1 year). The final outcomes used depended on the available data. The ILCOR ALS Task Force ranked outcomes a priori with survival and longer-term neurological outcomes ranked as critical.

These members are selected with attention to diversity in international geographical representation, age, and gender. Before publication, the ILCOR draft COSTR was made available for public comment on the ILCOR website [19].

The present guideline panel included academic critical care clinicians, content experts, methodologists, and one allied healthcare professional (GL) who conducted primary research on the topic. A patient representative (JL) was also consulted and provided advice

during the formulation of the statements. Thirteen members of the panel were selected because they were authors of the 2021 ERC-ESICM guidelines on Post-Resuscitation Care. Six of them (BB, NN, JPN, CS, MS, and JS) were also members of the ILCOR ALS Task Force. The lead author of the ILCOR systematic review (LWA), who also served as a methodologist, and one methodologist from ILCOR (PTM) were also included in the group. Both of them were also content experts.

We followed a strict conflict of interest (COI) management process [20]. All panel members completed COI declarations, which were vetted by the ILCOR and/or ERC COI committees. All individual COIs were stated at the start of each panel discussion. It was agreed that none of the COIs warranted exclusion from discussions or voting; therefore, all panel members participated fully in discussions and voting. The PICO (Population, Intervention, Comparator, Outcome) used for the ILCOR systematic review included six points (Table 1).

The ILCOR ALS Task Force completed Evidence-to-Decision (EtD) tables [21] to address the balance and magnitude of benefits and harms, certainty of evidence, patients' values and preferences, cost and resources, feasibility, and acceptability. Multiple iterations of the EtD tables were drafted and amended over seven videoconference calls and three rounds of voting among the ALS Task Force Members from 17 June to 7 October 2021. The EtD tables are included in the ILCOR CoSTR [19]. A systematic review team, with input from the ILCOR ALS Task Force, carried out a systematic review and meta-analysis (PROSPERO CRD42020217954). The review identified a total of 32 trials. We report summary results of the meta-analysis below. Detailed results, along with the EtD tables, are included in the published paper [18]. The ILCOR ALS Task Force followed the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to assess the certainty of evidence [22]. This was categorised as very low, low, moderate, or high based on risk of bias, imprecision, indirectness, inconsistency, and publication bias [23]. In accordance with GRADE, good practice statements were made for issues that the panel considered important but not appropriate for a formal rating of the certainty of evidence [24]. These statements address issues for which there is little direct evidence, but which will help clinicians implement the guidelines.

Results of the systematic review and certainty of evidence

For temperature control with a target of 32–34 °C compared with normothermia/ fever prevention, six of the nine trials identified were included in meta-analyses. Temperature control with a target of 32–34 °C did not improve survival (risk ratio (RR) 1.08; 95% confidence interval 0.89–1.3) or favourable functional outcome (RR 1.21; 95% CI 0.91–1.61) at 90 to 180 days after the cardiac arrest (low certainty of evidence). There was substantial heterogeneity across the trials.

Ten trials compared prehospital cooling with no prehospital cooling and found no improvement in survival (RR 1.01, 95% CI 0.92–1.11) or favourable functional outcome (RR 1, 95% CI 0.9–1.11) at hospital discharge (moderate certainty of evidence).

Concerning specific temperature comparisons, one trial [6] compared controlled temperature targeted at 33 °C vs. 36 °C and found no difference in favourable neurological outcome at discharge (RR 0.96, 95% CI 0.83–1.11) and at 180 days (RR 0.98, 95% CI 0.86–1.13), and in survival at 180 days (RR 0.99, 95% CI 0.88–1.12) (low certainty of evidence).

Concerning methods for temperature control, three trials [25–27] compared endovascular cooling and surface cooling and found no difference in survival (RR 1.14, 95% CI 0.93–1.38) or neurological outcome (RR 1.22, 95% CI 0.95–1.56) to discharge/28 days (low certainty of evidence).

No trials on rewarming strategies were identified.

From evidence to recommendation

The process leading from evidence to decision is summarised here. The EtD tables are reported in detail on the ILCOR CoSTR on the ILCOR website [19]. They were used by the ERC-ESICM panel to inform discussion on recommendations, which was carried out over a series of videoconference calls. If consensus was not reached, the recommendations were approved using majority voting.

Although no PICO question addressed the use of continuous monitoring of core temperature, the panel added a recommendation in favour of continuous temperature monitoring after cardiac arrest, because it is a prerequisite for temperature control.

Neither the ILCOR systematic review [18] nor another recent systematic review and network meta-analysis limited to OHCA [16] found any difference in overall outcomes between temperature control with normothermia/ fever prevention and temperature control with hypothermia. However, despite the lack of evidence, there was consensus within the panel that fever prevention probably requires fewer resources and probably has fewer side effects compared with temperature control with hypothermia. The panel therefore favoured temperature control with normothermia/fever prevention vs. temperature control at a constant temperature within the range of 32–36 °C.

However, most (12/15) panel members were keen to leave open the option of targeting temperature control at a constant temperature within the range of 32–36 °C. The recommendation on this point was discussed over

multiple videoconference calls and amended over three rounds of anonymous voting among the panel from 26 November to 2 December 2021. Although our review found no evidence in favour of temperature control with a target of 32–36 °C in any patient subgroup, there remained a view from some panel members that some populations of cardiac arrest patients could potentially benefit from this treatment. Until such evidence is available, the majority (8/15) of the panel members agreed that targeting 32–36 °C according to local protocols may be considered in some patients.

Discussed points included:

- The HYPERION trial [12], conducted on patients resuscitated from non-shockable cardiac arrest, showed higher rates of 90-day survival with favourable functional outcome after temperature control with a target of 33 °C vs. 37 °C.
- The largest studies included in our review [5, 6, 28] included mainly cardiac arrests with a primary cardiac cause and their results may not be generalisable to all resuscitated cardiac arrest patients [29].
- Some panel members raised concerns that the temperatures did not differ between groups for many hours after resuscitation in the TTM trials and in the other interventional or observational studies in humans and that the duration of this period may exceed the therapeutic window. Experimental evidence suggests that faster cooling rates are associated with greater potential benefit after cardiac arrest [30]. The panel could not exclude the possibility that there may be a therapeutic window within which hypothermia is effective that has not been rigorously tested in randomized clinical trials. Intranasal cooling is feasible and enables a target temperature to be achieved more rapidly than most other methods [31, 32]. Extracorporeal cardiopulmonary resuscitation also enables rapid cooling but is not universally available and is used only in highly selected patients.

One study [33] showed that infusion of large amounts of cold IV fluids to reduce temperature immediately after ROSC from OHCA was potentially harmful, being associated with increased rates of pulmonary oedema and rearrest. Moreover, the ILCOR review [18] found no evidence that prehospital cooling improved outcomes. We therefore recommended against pre-hospital cooling using a rapid infusion of a large volume of cold IV fluid. This recommendation was unchanged from our 2015 guidelines [3, 4]. We did not make a specific recommendation about cooling during cardiac arrest for OHCA.

The ideal cooling technique would be easily implementable, would achieve target temperature rapidly and enable tight temperature control without complications. Results of our systematic review showed no difference in outcomes between surface and endovascular cooling. The panel agreed that either technique should be suggested when cooling is required.

There was consensus that the cooling device should include continuous temperature monitoring to enable active control and maintain a stable temperature. There is no evidence that a temperature control device that includes a feedback system based on continuous temperature monitoring improves outcomes, although this approach seems reasonable.

Our review included only one trial investigating duration of temperature control after cardiac arrest [28]. This trial showed no difference in outcomes between temperature control at 32–34 °C for 24 h vs. 48 h in adult patients resuscitated from OHCA. The panel was in favour of preventing fever for at least 72 h after ROSC, based on the TTM trials [5, 6] where body temperature was controlled for at least 72 h in patients who remained sedated or comatose and on observational data showing an association between post cardiac arrest hyperthermia and poor outcome [34, 35].

Despite the absence of direct evidence in our systematic review, the panel was in favour of avoiding active warming of patients who have passively become mildly hypothermic (e.g., 32–36 °C) immediately after ROSC because of concern that this may be a harmful intervention. The panel noted that in the TTM-2 trial [5], patients in the normothermia/fever prevention arm whose initial temperature was above 33 °C were not actively warmed. In the HYPERION trial[12], patients allocated to normothermia with an initial temperature below 36.5 °C were warmed at 0.25–0.5 °C h^{-1} and maintained at 36.5–37.5 °C.

Recommendations and suggestions

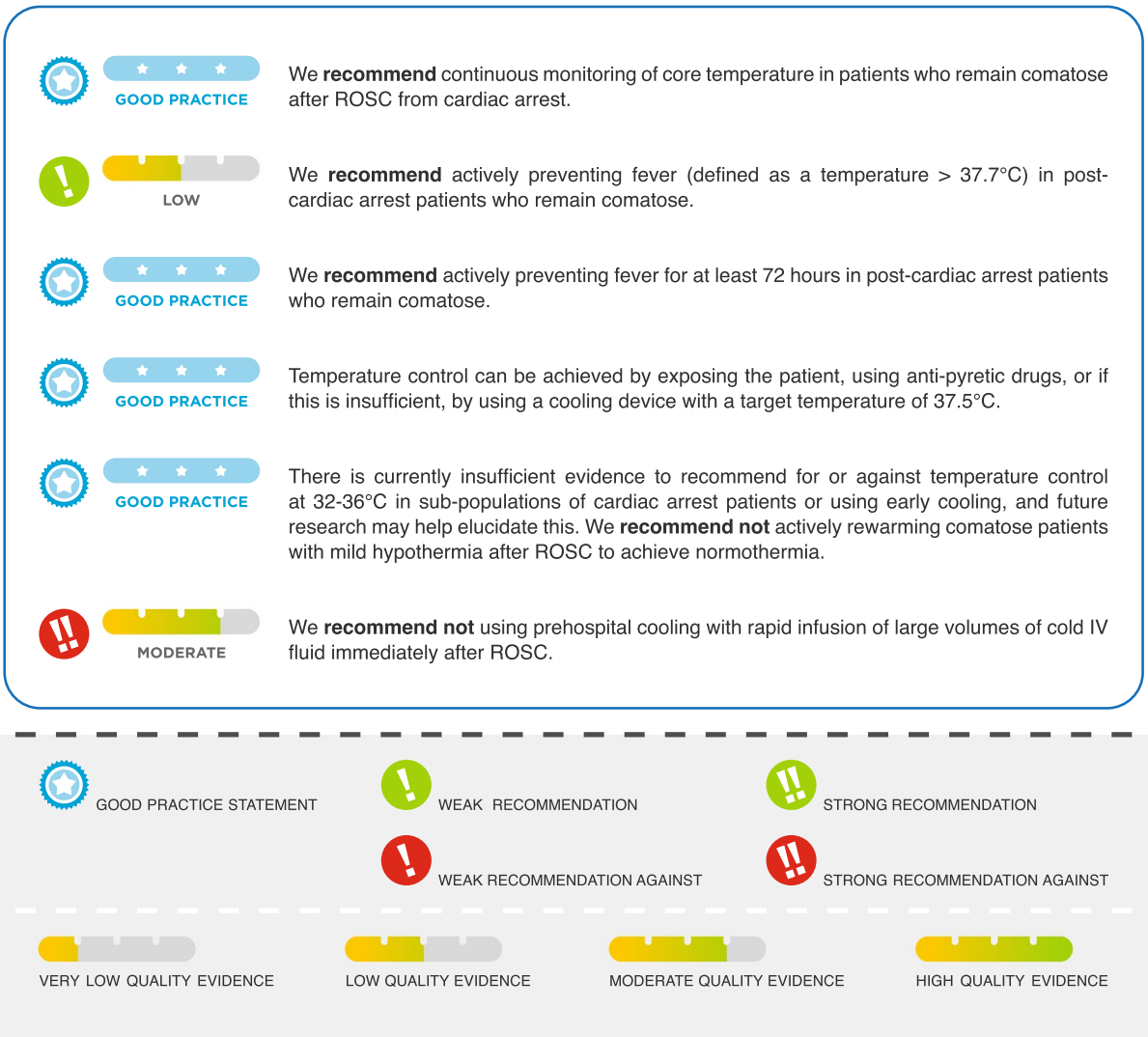
See Table 2.

Implementation of recommendations

There was discussion about the definitions of normothermia. In a cohort of 35,488 non-infectious outpatients (mean age 52.9 years, 64% women, 41% non-white race) in a large academic hospital in Northeast USA, the 95% range of body temperature was 35.7–37.3 °C, and the 99% range was 35.3–37.7 °C [36]. Whether these ranges can be generalised to the population of adult comatose post cardiac arrest patients remains uncertain.

There are concerns that poor implementation of temperature control may lead to patient harm. Observational

Table 2 ERC-ESICM Recommendations for temperature control after cardiac arrest in adults



evidence shows that after the publication of the TTM trial in 2013 the use of temperature control after cardiac arrest declined [37–39]. In one systematic review including nine of these observational studies (2014–2020) this was associated with worse neurological outcomes but no change in mortality [40]. Similarly, a recent analysis accounting for time trend and variation between 235 critical care units in United Kingdom found no significant change in crude mortality associated with the change in practice that followed the TTM publication [39]. All members of the Task Force agreed that we should continue to recommend active temperature control in post-cardiac arrest patients, although the evidence for this is limited.

The panel considered that post-resuscitation care is resource intensive, and that temperature control is feasible in most settings that provide this care. However, its implementation can be more challenging in low-resource settings. The panel noted that in the TTM-2 trial [5] pharmacological measures (e.g., paracetamol), uncovering the patient and lowering ambient temperature were used to maintain a temperature of $\leq$ 37.5 °C in the normothermia/fever prevention arm. If the temperature was more than 37.7 °C, a cooling device was used and set at a temperature of $\leq$ 37.5 °C. A cooling device was used in 46% of patients in the normothermia/fever prevention arm. Both intravascular cooling and external cooling with a feedback system are more expensive than simple surface cooling with wet towels and ice pack, and this should be considered in low-resource settings.

We made no recommendation regarding the rate of rewarming for temperature control after cardiac arrest. Our review did not identify any trial assessing the effects

Table 3 Conflicts of interest

Panel Member	Financial conflicts of interest	Intellectual conflicts of interest
Claudio Sandroni	None	Associate Editor, *Intensive Care Medicine;* Editorial Board member, *Resuscitation*
Jerry Nolan	Receives payment from Elsevier (Editor-in-Chief)	Editor-in-chief, *Resuscitation;* Board Member, European Resuscitation Council
Lars Andersen	None	None
Bernd Böttiger	Speaker fees: Forum für medizinische Fortbildung (FomF); Baxalta Deutschland GmbH; ZOLL Medical Deutschland GmbH; C.R. Bard GmbH; GS Elektromedizinische Geräte G; Stemple GmbH; Novartis Pharma GmbH; Philips GmbH Market DACH; Bioscience Valuation BSV GmbH	Board Member, European Resuscitation Council; Editorial Board member, *Resuscitation*
Alain Cariou	Speaker fees: Bard	Editorial Board member, *Resuscitation*
Tobias Cronberg	Receives funding for the TTM3 trial (co-applicant)	Steering Group member TTM, TTM2, and TTM3 trials; Editorial Board member, *Resuscitation*
Hans Friberg	Advisor TEQCool (Lund, Sweden)	Editorial Board member, *Resuscitation;* steering group member of TTM, TTM2, and TTM3 trials
Cornelia Genbrugge	None	None
Gisela Lilja	Receives funding for the TTM3 trial (co-applicant)	Steering group member of TTM2 and TTM3 trials
Peter Morley	ILCOR Chair of Scientific Advisory Committee (funded)	Editorial Board member, *Resuscitation*
Nikolaos Nikolaou	Research grants: SELECT EX9536-4388 NOVONORDISC, GALACTIC—HF AMGEN 20110203, LANDIUP AMOMED	Board Member, European Resuscitation Council
Theresa Olasveengen	None	Editorial Board member, *Resuscitation;* ILCOR BLS task Force Chair
Markus Skrifvars	Speaker's fee and travel reimbursement from BARD Medical (Ireland)	Editorial Board member, *Resuscitation*
Fabio Silvio Taccone	Speakers Fees: BD and Zoll	None
Jasmeet Soar	Receives payment from Elsevier (Editor)	Editor, *Resuscitation*; ILCOR ALS Task Force Chair

of rewarming rate in patients treated with temperature control. In two studies, the rewarming rate in the treatment arm targeting temperature control at 33 °C was 0.33 °C h^{-1} [5] or 0.25–0.5 °C h^{-1} [12].

We have made no comments on sedation use or its duration but noted that in the TTM2 trial [5] patients randomised to temperature control with normothermia/fever prevention were sedated for 40 h to ensure a similar duration of sedation to patients randomised to temperature control with hypothermia. We are uncertain of the optimal sedation strategy (drugs, dose, duration) after cardiac arrest but note that the use of short-acting sedatives may enable some post-cardiac arrest patients to awaken earlier [41].

Research priorities

Despite the publication of numerous trials on temperature control after cardiac arrest, several areas of uncertainty persist. Major knowledge gaps that remain to be addressed include:

- There are no trials comparing normothermia/fever prevention with no temperature control.
- There is limited evidence concerning the potential benefit of temperature control after IHCA. A multicentre RCT (NCT00457431) comparing temperature control with hypothermia and normothermia in patients resuscitated from IHCA has been completed, and its results are awaited.
- The therapeutic window within which temperature control with hypothermia may be effective in the clinical setting is unknown.
- The optimal duration of temperature control is unknown.
- It is unknown whether the clinical effectiveness of temperature control depends on providing the appropriate dose (target temperature and duration) based on the severity of brain injury.
- No specific subset of post-cardiac arrest patients who would benefit from temperature control with hypothermia has been identified.
- The optimal sedation strategy in post-cardiac arrest patients is unknown.

Conclusions

The panel made six recommendations on temperature control in adult patients who remain comatose after ROSC from cardiac arrest and are managed by ICU and emergency medicine teams. In patients who remain

comatose after cardiac arrest, we recommend continuous monitoring of core temperature and actively preventing fever (defined as a temperature > 37.7 °C) for at least 72 h. Fever prevention can be achieved by exposing the patient, using anti-pyretic drugs, or if this is insufficient, by using a cooling device with a target temperature of 37.5 °C. There is insufficient evidence to recommend for or against temperature control at 32–36 °C or early cooling after cardiac arrest. Actively rewarming comatose patients with mild hypothermia after ROSC to achieve normothermia is not recommended. Prehospital cooling with rapid infusion of large volumes of cold IV fluid immediately after ROSC is not recommended.

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Declarations

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See Table 3.

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