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| Question |
| **Temperature control in adult cardiac arrest** |
| **Population:** | **Adults in any setting (in-hospital or out-of-hospital) with cardiac arrest** |
| **Intervention 1:** | **Temperature control [Temperature control studies targeting hypothermia at 32-34 C included in the systematic review]** |
| **Comparison 1:** | **No Temperature control [Temperature control studies targeting normothermia or fever prevention included in the systematic review]** |
| **Intervention 2:** | **Temperature control induction before a specific time point (e.g. prehospital or intra-cardiac arrest, i.e. before return of spontaneous circulation (ROSC))** |
| **Comparison 2:** | **Temperature control induction after that specific time point** |
| **Intervention 3:** | **Temperature control at a specific temperature (e.g. 33°C)** |
| **Comparison 3:** | **Temperature control at a different specific temperature (e.g. 36°C)** |
| **Intervention 4:** | **Temperature control for a specific duration (e.g. 48 hours)**  |
| **Comparison 4:** | **Temperature control at a different specific duration (e.g. 24 hours)** |
| **Intervention 5:** | **Temperature control with a specific method (e.g. external)** |
| **Comparison 5:** | **Temperature control with a different specific method (e.g. internal)** |
| **Intervention 6:** | **Temperature control with a specific rewarming rate** |
| **Comparison 6:** | **Temperature control with a different specific rewarming rate or no specific rewarming rate** |
| **Main outcomes:** | **Any clinical outcome, including Survival to hospital discharge ; Favourable neurological outcome at hospital discharge or 30 days; Survival to 90 or 180 days; Favourable neurological outcome at 90 or 180 days** |
| **Setting:** | Any setting |
| **Perspective:** |  |
| **Background:** |  |
| **Conflict of interests:** | Soar J, Nolan JP, Andersen LW, Granfeldt A Holmberg MJ. None of the SR authors have any financial conflicts of interests and none of the authors have academic conflicts related to ongoing or planned trials Soar J, Nolan JP Andersen LW, Böttiger BW, Couper K, Deakin CD, Drennan I, Hirsch KG, Hsu CH, Nicholson TC, O’Neil BJ, Paiva EF, Parr MJ, Reynolds JC, Sandroni C, Wang TL, Callaway CW, Donnino MW, Granfeldt A, Holmberg MJ, Lavonas EJ, Morrison LJ, Nation K, Neumar RW, Nikolaou, Skrifvars MB, Welsford M, Morley PT, Berg KMCHH, JCR, KGH, RWN declared intellectual conflicts on going trials. BWB, MBS and BO'N declared speaker fees.  |

# Assessment

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| ProblemIs the problem a priority? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no○ Probably yes● Yes○ Varies○ Don't know | Cardiac arrest mortality remains very high. Neurologic injury is the leading cause of death in those who obtain return of spontaneous circulation but do not survive to hospital discharge. Among those who do survive, neurologic injury is also common. Post-arrest temperature control has long been thought to be one of the only interventions that improves neurologic outcome, but recent trials have not replicated the benefits seen in earlier studies, making this an important question to address. This topic includes consideration of whether or not to control temperature, whether to start temperature control intra-arrest or before hospital arrival, whether there is an optimal temperature to use, how long to control temperature, what method to use for controlling temperature, and how to approach rewarming. | In 2022 ILCOR moved away from the term targeted temperature management and adopted terminology that includes hypothermic temperature control, normothermic temperature control, fever prevention temperature control, and no temperature control. .  |
| Desirable EffectsHow substantial are the desirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial● Small○ Moderate○ Large○ Varies○ Don't know | While the earliest trials suggested a benefit from temperature control with hypothermia, this has not been replicated in more recent and larger trials. Although the exact intervention and comparison groups differ somewhat across trials and the certainty of evidence is low for most aspects of the temperature control topic (moderate certainty for avoiding pre-hospital cooling with cold IV fluids), it appears clear that if there are any desirable effects they are small, and have not been detectable in recent trials. | The TF discussed the fact that trials have largely not been able to get patients to the target hypothermic temperature faster than 4-8 hours after ROSC. Whether faster cooling after arrest would be beneficial is unknown.  |
| Undesirable EffectsHow substantial are the undesirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Large**● Moderate● Small○** Trivial○ Varies○ Don't know | Range of TF opinion small to moderate Task force members differed in their opinions on the TTM2 trial and whether the level of harm caused by 33 C v normothermia/fever prevention is significant or trivial given no difference in overall outcomes. Adverse events that were more common in the 33 C group included arrhythmia resulting in haemodynamic compromise, 24% v 16%. No difference in other complications - pneumonia, sepsis, bleeding, skin problemsFor pre-hospital cooling, more rearrest was noted with the used of cold IV fluids in the pre-hospital setting, with no counterbalancing benefit seen.  |  |
| Certainty of evidenceWhat is the overall certainty of the evidence of effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Very low● Low●Moderate○ High○ No included studies | Certainty of evidence was low for most treatment recommendations, and moderate for pre-hospital cooling with intravenous fluids. Some statements were created as good practice statements since the task force thought there was not enough evidence available to provide a degree of certainty. Although there are many clinical trials of temperature management, the specific areas of duration of temperature control, rewarming rate and whether temperature control devices should include feedback systems based on continuous temperature monitoring do not have sufficient trial data to support a treatment recommendation with certainty of evidence.  |  |
| ValuesIs there important uncertainty about or variability in how much people value the main outcomes? |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability○ Possibly important uncertainty or variability○ Probably no important uncertainty or variability● No important uncertainty or variability | Survival and survival with favorable neurologic outcome are generally accepted as critical.  |   |
| Balance of effectsDoes the balance between desirable and undesirable effects favor the intervention or the comparison? |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison○ Probably favors the comparison○ Does not favor either the intervention or the comparison○ Probably favors the intervention○ Favors the intervention● Varies○ Don't know | The task force generally supported fever prevention, given the lack of evidence for using more hypothermic temperatures in the available trials. The task force agreed that whether certain subpopulations of cardiac arrest patients (such as those with a non-cardiac cause of cardiac arrest or in-hospital cardiac arrest) may benefit from targeting hypothermia at 32-34 C, a more rapid induction of hypothermia, or a longer duration of temperature prevention and sedation remains unknown.This EtD includes several aspects of temperature control, and the balance of effects varies across these PICOS. The balance favors fever prevention (comparison) over hypothermic temperature control, and favors not using cold IV fluids for pre-hospital cooling. The balance of effects is unclear in other comparisons, which is why in some cases the task force generated good practice statements in place of treatment recommendations.  | In 2015 we wrote an additional statement:Whether certain subpopulations of cardiac arrest patients may benefit from lower (32 C–34 C) or higher (36 C) temperatures remains unknown, and further research may help elucidate this. |
| Resources requiredHow large are the resource requirements (costs)? |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs○ Moderate costs○ Negligible costs and savings○ Moderate savings○ Large savings● Varies○ Don't know | In settings where temperature control with a device is already used, these recommendations will not require additional resources. Some settings likely do not have resources to use temperature control devices. The evolution of temperature control recommendations over the past several years is likely leading to a slight decrease in resources required overall, as not all patients will need a device for fever prevention, although 46% in the normothermia group in TTM2 did require a device.  |  |
| Certainty of evidence of required resourcesWhat is the certainty of the evidence of resource requirements (costs)? |
| Judgement | Research evidence | Additional considerations |
| ○ Very low○ Low○ Moderate○ High● No included studies | We have not identified recent studies on this issue | Post resuscitation care and temperature control at any temperature target does require significant critical care resources to optimise outcome and costs will vary across settings. Fewer patients require active cooling when normothermia or fever control targeted.  |
| Cost effectivenessDoes the cost-effectiveness of the intervention favor the intervention or the comparison? |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison○ Probably favors the comparison○ Does not favor either the intervention or the comparison○ Probably favors the intervention○ Favors the intervention○ Varies● No included studies | We did not do a specific cost effectiveness analysis. We identified one modelling study in the review conducted for 2022 (of which this review is an update). Merchant RM, Becker LB, Abella BS, Asch DA, Groeneveld PW. Cost-effectiveness of therapeutic hypothermia after cardiac arrest. Circ Cardiovasc Qual Outcomes. 2009;2(5):421-428. | No current cost effectiveness data.  |
| EquityWhat would be the impact on health equity? |
| Judgement | Research evidence | Additional considerations |
| ○ Reduced○ Probably reduced○ Probably no impact○ Probably increased○ Increased● Varies○ Don't know | No studies identified - probably varies | Post resuscitation care and TTM at any temperature target does require significant resources to optimise outcome  |
| AcceptabilityIs the intervention acceptable to key stakeholders? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no○ Probably yes○ Yes● Varies○ Don't know | No formal studies identified that looked at acceptability of hypothermia but both fever prevention and hypothermic temperature control are used widely already.  | The points below were noted when this review was updated for 2022, and remain true. Within ALS TF and different settings/regions there is considerable variation as to the acceptance of either intervention at 32-34 v normothermia Animal data of early/immediate post ROSC cooling show a consistent and strong protective effect across animal species and models.Reasons have been put forward as to why the largest and most recent RCTs have not managed to replicate animal data - cooling too late, too slow, wrong dose duration, wrong patient population.Some observational evidence or concerns that using 'normothermia' targets or switch from 32-34 to 36 C has been associated with worse outcomes. Most recent large observational study from UK does not suggest this and raises the issue that ICU risk models and risk adjustment cannot differentiate between therapeutic and pathological temperature changes when looking at observational data. Nolan JP, et al. Changes in temperature management and outcome after out-of-hospital cardiac arrest in United Kingdom intensive care units following publication of the targeted temperature management trial. Resuscitation. 2021 May;162:304-311.  |
| FeasibilityIs the intervention feasible to implement? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no● Probably yes○ Yes○ Varies○ Don't know | Both intervention (hypothermia) and normothermia/fever prevention are feasible in most settings that care for post cardiac arrest patients and already use TTM. | TF considered that post resuscitation care is resource intensive, and temperature control is feasible in most settings that provide this care. Yes - in high resource settings.Hypothermia more challenging in low resource settings  |

# Summary of judgements

|  | **Judgement** |
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| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | Trivial | **Small** | Moderate | Large |  | Varies | Don't know |
| **Undesirable Effects** | Large | **Moderate** | **Small** | Trivial |  | Varies | Don't know |
| **Certainty of evidence** | Very low | **Low** | **Moderate** | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | Probably no important uncertainty or variability | **No important uncertainty or variability** |  |  |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | **Varies** | Don't know |
| **Resources required** | Large costs | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | **Varies** | Don't know |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | Probably reduced | Probably no impact | Probably increased | Increased | **Varies** | Don't know |
| **Acceptability** | No | Probably no | Probably yes | Yes |  | **Varies** | Don't know |
| **Feasibility** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |

# Type of recommendation

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| Strong recommendation against the intervention | **Conditional recommendation against the intervention** | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention |
| ○  | **●**  | ○  | ○  | ○  |

\*\*Strength of recommendation varies for each of the

# Conclusions

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| Recommendation |
| **We suggest actively preventing fever by targeting a temperature** $\leq $**37.5°C for those patients who remain comatose after ROSC from cardiac arrest (weak recommendation, low certainty evidence).****Whether subpopulations of cardiac arrest patients may benefit from targeting hypothermia at 32-34oC remains uncertain.** **Comatose patients with mild hypothermia after ROSC should not be actively warmed to achieve normothermia (good practice statement).****We recommend against the routine use of prehospital cooling with rapid infusion of large volumes of cold IV fluid immediately after ROSC (strong recommendation, moderate certainty evidence).****We suggest surface or endovascular temperature control techniques when temperature control is used in comatose patients after ROSC (weak recommendation, low certainty of evidence).****When a cooling device is used, we suggest using a temperature control device that includes a feedback system based on continuous temperature monitoring to maintain the target temperature (good practice statement).****We suggest active prevention of fever for 36–72 hours in post-cardiac arrest patients who remain comatose (good practice statement).** |
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| Justification |

* This topic was prioritized by the ALS Task Force due to the emergence of additional trial data since the prior review in 2022.

Defining Post-Cardiac Arrest Temperature Management Strategies

* The term TTM on its own is not helpful and it is preferable to use the terms active temperature control, hypothermia, normothermia, or fever prevention. To provide additional clarity for interpreting future clinical trials, systematic reviews and CoSTRs we propose the following terms are used:
	+ Hypothermic TTM (H-TTM) = active temperature control with the target temperature below the normal range.
	+ Normothermic TTM = active temperature control with the target temperature in the normal range.
	+ Fever prevention TTM (FP-TTM) = monitoring temperature and actively preventing and treating temperature above the normal range
	+ No TTM = no protocolised active temperature control strategy.

Hypothermia v normothermia or prevention of fever

* The majority of the Task Force favored fever prevention for comatose patients following ROSC as opposed to hypothermia, based on the systematic review and because this intervention requires fewer resources and had fewer side effects than hypothermia treatment.
* The Task Force noted that in the TTM2 trial (Dankiewicz 2021 2283), pharmacological measures (acetaminophen), uncovering the patient, and lowering ambient temperature were used to maintain a temperature of $\leq $ 37.5 C (99.5 F) in the normothermia/fever prevention group. If the temperature was > 37.7 C (99.9 F) a cooling device was used and set at a target temperature of $\leq $ 37.5 C (99.5 F). 95% of patients in the hypothermia group and 46% in the fever prevention group received temperature control with a device.
* We chose prevention of fever as opposed to normothermia in the treatment recommendation.
* The Task Force acknowledged that the systematic review found no difference in overall outcomes between patients treated with hypothermia and normothermia or fever prevention.
* Several members of the Task Force were keen to leave open the option to use hypothermia (33oC). The discussions included:
	+ No trials have shown that normothermia is better than hypothermia.
	+ Among non-shockable cardiac arrest patients, the Hyperion trial (Lascarrou 2019 2327) showed better survival with favorable functional outcome in the hypothermia group (although 90-day survival was not significantly different and the Fragility Index was only 1).
	+ Although our systematic review did not find evidence favoring TTM with hypothermia in multiple subgroups, there remained a view that some populations of cardiac arrest patient could potentially benefit from hypothermia treatment at 32-34 C. Specifically, the largest TTM studies (TTM1 and TTM2) have mainly included cardiac arrests with a primary cardiac cause and this may not reflect the total population of post cardiac arrest patients treated (Chen 2018 33).
	+ There was a suggestion that we should only advocate fever prevention for those with a primary cardiac arrest in the main treatment recommendation – our systematic review did not find any evidence supporting targeting hypothermia in patients with a cardiac arrest due to other causes.
	+ Concerns were raised that the TTM2 trial cooling rates were too slow and that the time to target temperature was outside the therapeutic window. In animal studies rapid induction of hypothermia after ROSC is required for a beneficial effect (Arrich 2021 47). The time to target temperature in TTM-2 is consistent with virtually all other human observational studies and RCTs including those where there was no delay caused by the need for consent/randomization (see ETD). Of the RCTs included, only the Bernard study (Bernard 2002 557) had a rapid time (2 hours after ROSC) to achieve target temperature (33.5 C). It remains possible that there is a therapeutic window within which hypothermia is effective that has not been rigorously tested in randomized clinical trials.
	+ There was a unanimous desire to leave open the opportunity for further research on post-cardiac arrest hypothermia, not least because animal models have shown consistent and convincing evidence of benefit.
	+ Finally, there are concerns that poor implementation of temperature control may lead to patient harm - for example the publication of the TTM trial in 2013 (Nielsen 2013 2197) may have led to some clinicians abandoning temperature control after cardiac arrest which in turn was associated with worse outcomes (Bray 2017 39, Salter 2018 1722, Nolan 2021 304). Whether this was caused by abandoning the use of temperature control is uncertain.
* In our meta-analysis we decided to use a random effects model a priori (as opposed to fixed effects). The point estimates of the random-effects meta-analysis favors hypothermia. However, the random effects model assigns a relatively higher weight to smaller studies; thus, the smaller and older less methodologically robust studies published in 2002 (Bernard 2002 557, HACA 2002 549) had a greater influence on the point estimate than would be expected based on the trial sizes.
* We chose the term 'comatose' instead of 'unresponsive' to define the population of patients who do not wake up after ROSC. Another option considered was 'unconscious' – in the TTM2 trial this was defined as not being able to obey verbal commands and no verbal response to pain after sustained ROSC. The Task Force acknowledges that patients are unconscious and sedated after ROSC for a number of reasons in addition to a hypoxic ischemic brain injury including the need for airway protection with a tracheal tube, lung injury, and to facilitate interventions.
* We have made no comments on sedation use or its duration but noted that in the TTM2 trial, patients in the normothermia/fever prevention arm were sedated for 40 hours to ensure a similar duration of sedation to the hypothermia arm.
* Although there was no direct evidence in our systematic review, the Task Force made a good practice statement supporting the avoidance of active warming of patients who have passively become mildly hypothermia (e.g. 32-36 ) immediately after ROSC there was concern that this may be a harmful intervention. The Task Force noted that in the TTM2 trial, patients in the normothermia/fever prevention arm with an initial temperature above 33 C were not actively warmed. The Task Force noted that in the Hyperion trial (Lascarrou 2019 2327), patients allocated to normothermia whose temperature was below 36.5 C at randomization were warmed at 0.25 - 0.5 C/hour and then maintained at 36.5 - 37.5 C.
* There was discussion about the definitions of normothermia and fever. Among a diverse cohort of 35,488 hospital patients the 99% range for normal temperature was 35.3-37.7°C, and 95% range was 35.7 to 37.3 C (Obermeyer 2017 j5468). Whether these ranges can be generalized to the adult post cardiac arrest patient population is uncertain.

Alternate temperature comparisons

* In addition, in our systematic review and meta-analysis we looked at comparisons between 33 v 36 C (Nielsen 2013 2197), 32 v 34 C (Lopez-de-Sa 2018 1807, Lopez-de-Sa 2012 2826), 33 v 34 C (Lopez-de-Sa 2018 1807) and 33 v 32 C (Lopez-de-Sa 2018 1807). There was no difference between control and intervention groups for all these comparisons and the certainty of evidence was low for all comparisons.
* The comparison between 33 v 36 C (Nielsen 2013 2197) was included in a sensitivity analysis of 33 C v normothermia/fever prevention, as 36 C falls within the normothermia temperature range – this did not change the point estimates in favor of either group.

Prehospital cooling (Unchanged)

* Our TR for prehospital cooling stays unchanged from our 2015 recommendation.
* We found no evidence that any method of prehospital cooling improved outcomes.
* The rapid infusion of large amounts of cold fluid immediately after achieving ROSC and in the prehospital setting could theoretically be harmful, as indicated by increased rates of rearrest and pulmonary edema in the largest of the included studies (Kim 2014 45). Any potential harm from this therapy may relate specifically to the prehospital setting, where there may be less control over the environment, fewer personnel, and reduced monitoring capabilities.
* We have not made a treatment recommendation about intra-arrest cooling for OHCA.

Cooling devices (Unchanged)

* Task Force members agreed that based on our systematic review either surface or endovascular cooling should be suggested when cooling is required.
* There was no consensus on whether a feedback surface cooling device should be routinely used so this was added as a good practice statement as there is no evidence that this approach improves outcomes. There was consensus that temperature should be continually monitored by the cooling device in order to maintain a stable temperature.
* There was a comment that endovascular cooling may be superior for temperature control – there are two recent systematic reviews with conflicting conclusions: Bartlett ES (Bartlett 2020 82) ­ showed intravascular cooling is associated with improved neurological outcome, but Kim JG (Kim 2020 14) found no association with survival or neurological outcomes.

Duration of temperature control

* Our previous TR was a good practice statement based on trials controlling temperature for at least 72 h in those patients who remained sedated or comatose.
* One trial showed no difference between 24 and 48 hours of hypothermia (Kirkegaard 2017 3410) and one trial showed no difference between 12-24 and 36 hours of hypothermia (Tahara 2021 368).
* One trial comparing temperature control for a total duration of 36 hours vs. 72 hours showed no difference in outcomes (Hassager 2023 888). The trial included temperature control targeting 36°C for 24 hours followed by active fever prevention for 12 hours (total duration of 36 hours) or 48 hours (total duration of 72 hours)
* The same trial included temperature control with a surface cooling device at one site and an intravenous cooling device at the other site. Whether results are applicable to temperature control without a device or different cooling devices is unknown.
* Non–device-based treatment of fever was allowed in both groups
* The task force was not able to reach consensus on a treatment recommendation on duration of temperature control or fever prevention. After discussion about the lack of consistency in the interventions and comparators across the available studies, the task force agreed that there was not enough trial evidence to support a recommendation specifically on how long to prevent fever. All task force members agreed on the good practice statement, which allows for a range of duration that is supported by the limited data and by expert opinion.

Rewarming

* We identified one study comparing rewarming at 0.25C°/h vs 0.50C°/h with no difference between groups (Lascarrou 2021 434). The task force discussed that although there is no evidence that active rewarming is harmful, expert opinion is that it is generally unwarranted and can be avoided.

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| Research priorities |

* There are no RCTs of no TTM versus fever prevention TTM.
* There are few RCTs of TTM after eCPR.
* There are no large RCTs of TTM after in-hospital cardiac arrest.

Is there a therapeutic window within which hypothermic TTM (H-TTM) is effective in the clinical setting?If a therapeutic window exists, are there clinically feasible cooling strategies that can rapidly achieve therapeutic target temperatures within the therapeutic window?Is the clinical effectiveness of hypothermia dependent on providing the appropriate dose (target temperature and duration) based on the severity of brain injury?Are there unidentified subsets of post-cardiac arrest patient who would benefit from H-TTM as currently practiced?* Is TTM using a cooling device with feedback more effective than TTM without a feedback controlled cooling device?
 |