Therapeutic hypothermia guidelines 2018 aha

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Whom to include criteria	Whom to exclude criteria
Initial rhythm of ventricular fibrillation or pulseless VT≤60 min from collapse to ROSC BP>90 mmHg (or MAP<60 mmHg) with no more than one vasopressor	Admission temperature <32°C (89.6°F) Evidence of neurological response to commands after resuscitation Cardiac arrest related to trauma Major head injury Recent major surgery (within 14 days)
Unconscious after successful ROSC with Glasgow Coma Scale≤8 < 6 h from ROSC	Systemic infection/sepsis Comatose state before cardiac arrest/coma from other causes Persistent hypotension (SBP≤90 mmHg, MAP<60 mmHg) despite one vasopressor for>30 min after ROSC Persistent hypoxemia (SaO_2<85%) after ROSC despite mechanical ventilation Pre-existing coagulopathy or bleeding "Do not resuscitate" or "do not intubate" code status or terminal illness prior to cardiac arrest

VT = ventricular tachycardia; SaO_2 = arterial oxygen saturation; SBP = systolic blood pressure; MAP = mean arterial pressure

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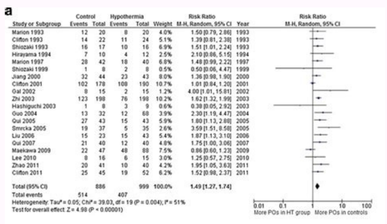

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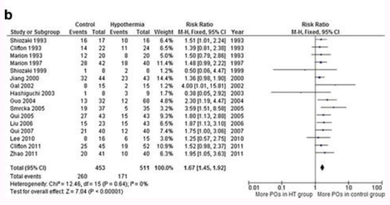
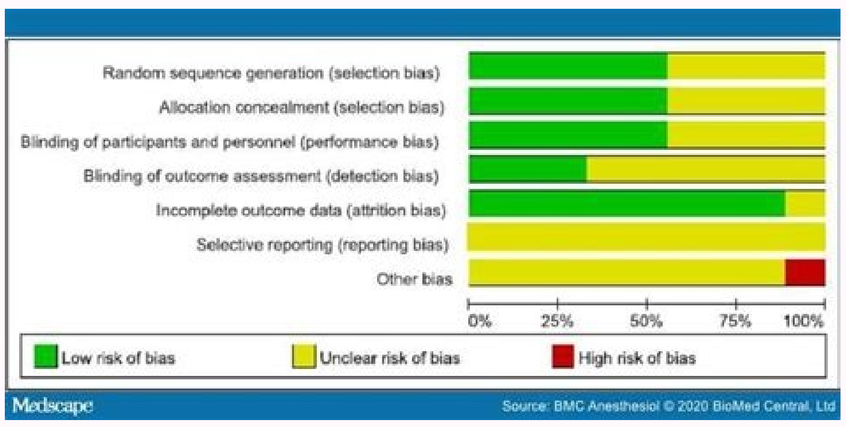


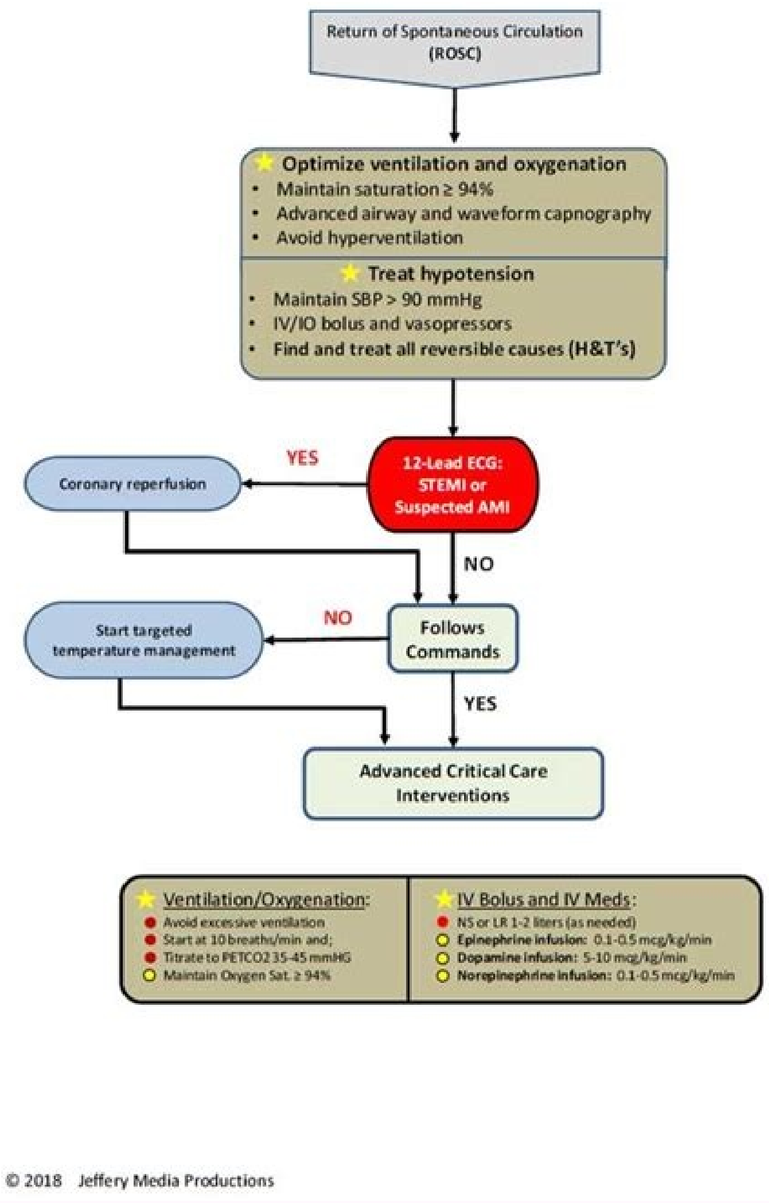
Table 1. Published Guidelines Specific To Therapeutic Hypothermia

Organization	Recommendations
Task Force on Scandinavian Therapeutic Hypothermia Guidelines, Clinical Practice Committee, Scandinavian Society of Anaesthesiology and Intensive Care Medicine[20] http://onlinelibrary.wiley.com/doi/10.1111/j.1399-6576.2008.01881.x/pdf	• Level I* evidence supports use of hypothermia after VF; therapy is also recommended for patients with ROSC after asystole and PEA • Protocol should be standardized and initiated as soon as possible • Evidence is insufficient to support recommendations on optimal target temperature, duration of cooling, and rewarming time.
Use of Hypothermia After Cardiac Arrest, Canadian Association of Emergency Physicians, Critical Care Committee[21] http://www.caep.ca/template.asp?id=37C951DE051A45979A9BDD0C5715C9FE	• Patients with nonperfusing VT or VF and ROSC who remain unresponsive should undergo therapeutic hypothermia (Grade A**) • Patients with asystole or PEA thought to be of cardiac origin and ROSC but who remain unconscious should be considered for therapeutic hypothermia (Grade D***) • Patients under 18 years of age and pregnant women may benefit from this therapy, but its role is unproven; consideration in these populations should be on a case-by-case basis (Grade D***)
Adult Advanced Life Support: Australian Resuscitation Council Guidelines 2006[22] http://onlinelibrary.wiley.com/doi/10.1111/j.1742-6723.2006.00890.x/abstract	• Unconscious adult patients with ROSC after out-of-hospital cardiac arrest, when the initial rhythm was VF, should be cooled to 32°C (90°F) to 34°C (93°) for 12 to 24 hours • Such cooling may also be beneficial in unconscious adult patients with ROSC after out-of-hospital cardiac arrest when the initial rhythm was not VF or after cardiac arrest in the hospital
2010 American Heart Association Guidelines for CPR and Emergency Cardiovascular Care Science[23] http://circ.ahajournals.org/content/vol122/18_suppl_3/	• Therapeutic hypothermia should be considered for any patient who is unable to follow verbal commands after ROSC

Abbreviations: PEA, pulseless electrical activity; RCT, randomized controlled trial; ROSC, return of spontaneous circulation; VF, ventricular fibrillation; VT, ventricular tachycardia.

*Level I evidence: Large, randomized trials with clear-cut results; low risk of false-positive error or false-negative error.
**Grade A: Consistent Level 1 evidence - systematic review [with homogeneity] of RCTs; individual RCT [with narrow confidence interval] studies.
***Grade D: Inconsistent or inconclusive studies of any level





Aha guidelines for hypothermia protocol. Aap guidelines for therapeutic hypothermia. Aha therapeutic hypothermia guidelines 2018.

Quick Takes Although, targeted temperature management is strongly recommended for neuroprotection in patients who remain comatose after resuscitation from a cardiac arrest, this recommendation is based on weak evidence of benefit, mostly from earlier trials that had many limitations. Recently, the Targeted Temperature Management-2 (TTM2) trial randomized 1,861 patients to targeted hypothermia (33°C) or targeted normothermia (37.8°C) and found no benefit of targeted hypothermia in improving survival at 6 months. There was also no difference in survival with severe neurological disability or quality of life, but a higher risk of arrhythmia in hypothermia treated patients. The TTM2 trial overcomes many of the limitations of earlier studies of hypothermia. Until future studies that compare other cooling strategies are completed, routine use of targeted hypothermia may no longer be necessary. Each year, more than 650,000 adult patients experience a cardiac arrest in the United States (US) alone.1 Although survival rates for both in-hospital (IHCA) and out-of-hospital cardiac arrest (OHCA) have improved in recent years, overall survival rates remain low.2,3 Among survivors, there is a substantial risk of neurological injury and disability which is due to a combination of whole body anoxia, ischemia/reperfusion injury, inflammation, and excitotoxicity.4 We provide a review of the key randomized controlled trials (RCT) of targeted temperature management (TTM) (Table 1). Table 1: Randomized Control Trials Evaluating Targeted Temperature Management for Cardiac Arrest Authors N Design Year Population Intervention vs. control Primary Outcome Major Findings The Hypothermia after Cardiac Arrest Study Group 275 RCT 2002 OHCA due to a shockable rhythm TTM 33°C vs. normothermia (37°C) Favorable neurologic outcome at 90 days Significantly higher survival and survival with favorable neurological outcome in hypothermia group Bernard et al. 77 RCT 2002 OHCA due to ventricular fibrillation TTM at 33°C vs. 37°C Survival to hospital discharge with sufficiently good neurologic function to be discharged to home or to a rehabilitation facility Significantly higher survival with favorable neurological outcome in hypothermia group Bernard et al. [RICH trial] 234 RCT 2010 OHCA due to ventricular fibrillation Cool IV fluids en-route to hospital vs. standard of care Survival to discharge No significant difference in survival to discharge Nielsen et al. [TTM trial] 939 RCT 2013 OHCA with a presumed cardiac cause TTM at 33°C vs. 36°C All-cause mortality through the end of the trial (mean period of 256 days) No significant differences between the groups Kim et al. 1359 RCT 2014 OHCA with either VF or non-shockable rhythms Pre-hospital cooling with 2 L of 4°C normal saline vs. standard care Survival to hospital discharge and neurological status at discharge No improvement in survival or neurological outcomes Lopez et al. [FROST-I trial] 150 RCT 2018 Witnessed OHCA with shockable rhythms TTM at 32°C, 33°C, and 34°C Favorable neurologic outcome at 90 days No significant difference in primary outcome between study groups Lascarrou et al. [HYPERION trial] 581 RCT 2019 OHCA and IHCA with non-shockable rhythms TTM at 33°C vs. normothermia 37.5°C Survival with a CPC of 1 or 2 at 90 days Significantly improved survival with a CPC of 1 or 2 in hypothermia group but no difference in overall mortality Dankiewicz et al. [TTM2 trial] 1861 RCT 2021 OHCA with a presumed cardiac cause TTM at 33°C vs. targeted normothermia 37.5°C Death from any cause at 6 months No significant differences between groups Abbreviations: CPC: Cerebral Performance Category; OHCA: Out-of-hospital cardiac arrest; TTM: Targeted Temperature Management In 2002, two landmark RCTs were published simultaneously that found therapeutic hypothermia (TH) to be effective in reducing the risk of neurological disability in patients with OHCA due to an initial shockable rhythm who were comatose post-arrest.5,6 These trials led to a rapid adoption of TH into clinical practice for prevention of neurological injury in post-arrest patients. TH also received a class I recommendation in resuscitation guidelines7 which has since expanded to include patients with non-shockable rhythms and patients with IHCA.8 However, there are key limitations of the earlier RCTs that merit discussion. First, both trials were small and included a total of 352 patients, raising the possibility of chance findings. Second, temperature was not actively managed in the control arm such that a substantial number of patients randomized to normothermia became febrile. Due to this, it is difficult to discern whether the positive findings were due to a true benefit of TH or due to the deleterious effects of fever on neurological recovery in the normothermia group. Importantly, treatment was not blinded and protocols for neuro-prognostication were not standardized between the treatment groups. Therefore, it is possible that worse survival in the normothermia group may have been driven, at least in part, by premature withdrawal of care. Finally, post-resuscitation care over the years has evolved with development of comprehensive treatment protocols across centers. Whether the large effect of TH seen in the earlier trials is consistent in contemporary practice remains unclear. Recent trials have attempted to address the above limitations. The Targeted Temperature Management (TTM) trial randomized 950 subjects with an OHCA to two different temperature targets: 33°C versus 36°C, with active temperature management in both groups.9 Unlike the earlier RCTs, no significant difference in mortality (50% vs. 48%; P = 0.51), or a composite of mortality and poor neurological outcome at 6 months (54% vs. 52%; P = 0.78) between the two treatment arms was observed. Other trials, although smaller than the TTM trial, corroborated the findings of the TTM trial.10 Collectively, these trials suggest that a strategy of intense cooling may not provide any additional benefit when compared to mild TH with avoidance of fever. However, neither of these studies included a normothermia group. Moreover, non-shockable rhythms were underrepresented in these trials; in the TTM trial non-shockable rhythms comprised only 20%. This is despite >75% of all cardiac arrests are due to asystole or pulseless electrical activity. The HYPERION trial studied the efficacy of TH (33°C) versus targeted normothermia (37°C) in 584 comatose patients admitted to an intensive care unit (ICU) after a cardiac arrest due to an initial non-shockable rhythm and included both OHCA and IHCA patients. The trial found a significant benefit in favor of TH for the primary end point of 90-day survival with a favorable neurological outcome (10.2% vs. 5.7%; 95% [CI], 0.1 to 8.9, P = 0.04), but no difference in overall mortality.11 While the trial demonstrated a benefit of TH compared to normothermia and is the only RCT to include IHCA patients, the effect estimate had a large confidence interval such that the occurrence of one additional primary endpoint in the normothermia group would have eliminated the statistical significance (i.e., a fragility index of the trial was 1).12 Accordingly, the recently published TTM2 trial is highly relevant as it compares TH with targeted normothermia in a large and diverse cohort of OHCA patients.13 The trial included 1,861 patients with OHCA at 61 sites across Australia, Europe and the US who were comatose post-arrest. Patients were randomized to TH of 33°C versus targeted normothermia (goal temperature: 90% of cardiac arrests were witnessed and approximately 80% received bystander cardiopulmonary resuscitation (CPR). Moreover, a high proportion of patients had an initial shockable rhythm, suggesting that the study findings may not be generalizable to all OHCA patients. Despite this, survival rates in this study were similar to survival reported in the earlier trials. Similarly, only OHCA patients were included and therefore findings may not apply to patients with IHCA. However, data supporting a benefit of TH in IHCA patients is limited given the limitations of the HYPERION trial noted above.14 Second, active cooling was used in 46% of patients in the normothermia group which highlights the high prevalence of fever and underscores the importance of active temperature management in the post-arrest setting. Therefore, the TTM2 trial should not be interpreted as no benefit of any temperature management. Third, although hypothermia was initiated quickly with a median time to achieve 34°C of 3 hours after randomization, it remains to be seen whether more rapid cooling would have demonstrated a benefit of TH. However, prior RCTs have not shown pre-hospital cooling to improve survival in OHCA.15,16 Finally, it should be noted that there were on average 136 minutes from patient contact until randomization, which increased the total time from patient contact to temperature goal to over 5 hours. This likely represents the real-world experience of cardiac arrest survivors, but future RCTs should test whether more rapid time-to-cooling will confer neuroprotection. In summary, based on the findings of TTM2 trial, TH is not superior to targeted normothermia for neuroprotection in OHCA patients. It is possible that the time window during which TH may provide patient benefit is narrow, and unrealistic to achieve using current cooling protocols. However, until future RCTs studies such as those evaluating intra-arrest cooling and selective cerebral hypothermia are completed, we believe that routine use of TH for neuroprotection may no longer be necessary. We recommend active temperature management to maintain normothermia in post-cardiac arrest patients. References Holmberg MJ, Ross CE, Fitzmaurice GM, et al. Annual incidence of adult and pediatric in-hospital cardiac arrest in the United States. Circ Cardiovasc Qual Outcomes 2019;12:e005580. Girotra S, Nallamothu BK, Spertus JA, et al. Trends in survival after in-hospital cardiac arrest. N Engl J Med 2012;367:1912-20. Chan PS, McNally B, Tang F, Kellermann A, Group CS. Recent trends in survival from out-of-hospital cardiac arrest in the United States. Circulation 2014;130:1876-82. 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