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REVIEW ARTICLE

Temperature management in acute brain injury: A narrative review

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Abstract Temperature management has been used in patients with acute brain injury resulting from different conditions, such as post-cardiac arrest hypoxic-ischaemic insult, acute ischaemic stroke, and severe traumatic brain injury. However, current evidence offers inconsistent and often contradictory results regarding the clinical benefit of this therapeutic strategy on mortality and functional outcomes. Current guidelines have focused mainly on active prevention and treatment of fever, while therapeutic hypothermia (TH) has fallen into disuse, although doubts persist as to its effectiveness according to the method of application and appropriate patient selection. This narrative review presents the most relevant clinical evidence on the effects of TH in patients with acute neurological damage, and the pathophysiological concepts supporting its use.

PALABRAS CLAVE
Control selectivo de la temperatura;
Hipotermia inducida;
Hipotermia terapéutica;

Control térmico en el daño cerebral agudo: revisión narrativa

Resumen El control de la temperatura corporal se ha utilizado en pacientes con daño cerebral agudo ocasionado por distintas patologías como daño hipóxico-isquémico post-parada cardíaca, accidente cerebro vascular isquémico agudo y traumatismo craneoencefálico grave. Sin embargo, la evidencia actual ofrece resultados poco consistentes y a menudo

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contradictorios en cuanto al beneficio clínico de esta estrategia terapéutica sobre la mortalidad y los resultados funcionales. Las guías actuales han centrado su atención fundamentalmente en la prevención activa y el tratamiento de la fiebre, mientras que la hipotermia terapéutica (HT) ha caído en desuso, aún cuando persisten dudas sobre su efectividad de acuerdo con el modo de aplicación y la adecuada selección de pacientes. En esta revisión narrativa se presenta la evidencia clínica más relevante sobre los efectos de la HT en pacientes con daño neurológico agudo, así como de los conceptos fisiopatológicos en los que se fundamenta su uso.

Introduction

Temperature changes in neurocritical patients are frequent and have deleterious effects on brain metabolism, causing or exacerbating neuronal damage.[1–3] Central body temperature control at a specific level can be used to induce hypothermia or prevent fever and has been used in the management of various situations such as post-cardiac arrest hypoxic-ischemic damage, acute ischemic stroke (AIS), and severe traumatic brain injury (TBI) to reduce neurological damage and improve functional outcomes. However, evidence is scarce and difficult to interpret due to the variety of cooling methods used, different target temperatures, and heterogeneity of patient groups.

The present narrative review details the pathophysiological concepts underlying the use of therapeutic hypothermia (TH) and summarizes the most relevant evidence regarding the clinical impact of temperature control in patients with acute brain injury.

Mechanisms of neurological damage

A cascade of temperature-dependent events and destructive processes, exacerbated by fever (>37.5 °C) and mitigated by mild-to-moderate hypothermia (31–35 °C), starts at cellular level minutes to hours after an initial injury, which may be ischemic or traumatic. Ischemia may be induced by cessation of cerebral blood flow after a cardiac arrest or following the obstruction of a blood vessel by pressure/edema, or other mechanisms involved.[4]

Primary neurological injury

At cellular level, decreased cerebral oxygen supply manifests as reduced neuronal aerobic metabolism, leading to decreased cellular production of the high-energy substrate adenosine triphosphate (ATP). ATP depletion results in the dysfunction of the ATP-dependent Na+/K+ ion exchange pump, leading to massive entry of sodium and water into the cell, and intracellular cytotoxic edema. Potassium efflux and membrane depolarization lead to opening of voltage-gated Ca++ channels and intracellular calcium influx. Additionally, endothelial dysfunction occurs in the microvasculature, this leading to increased blood-brain barrier permeability, vasogenic cerebral edema formation, the formation of microthrombi, and limited cerebral blood flow exacerbating cellular ischemia.[5,6]

Secondary neurological injury

Reperfusion of the ischemic cerebrovascular bed triggers a series of mechanisms leading to secondary brain injury. Increased intracellular Ca++ caused by the primary injury leads to the release of glutamate, an excitatory neurotransmitter that binds to cell membrane receptors causing further intracellular Ca++ influx. The accumulation of intracellular Ca++ activates lytic enzymes such as caspase, proteases, and phospholipases, and causes mitochondrial dysfunction, and the release of pro-apoptotic proteins and reactive oxygen species. This results in additional neuronal damage and energy failure, leading to apoptosis and cell death.

Another consequence of reperfusion injury is activation of the innate immune system, leading to an inflammatory response. Resident macrophages, called microglia, and circulating monocytes adhere to cerebral microvasculature endothelial cells and infiltrate neuronal tissue, secreting proinflammatory cytokines. Complement cascade activation also occurs, further propagating inflammatory injury.

Role of hypothermia on the mechanisms of neurological damage

The protective effects of hypothermia are primarily based on its ability to reduce cerebral oxygen and glucose metabolic consumption. Cerebral metabolism decreases by 6%–10% for every 1 °C drop in body temperature. However, metabolic rate reduction is only one of the many neuroprotective mechanisms of hypothermia. Hypothermia attenuates cellular damage via apoptosis through caspase enzyme inhibition, mitochondrial dysfunction prevention, decreased excitatory neurotransmitter overload, and intracellular ion concentration changes. Additionally, hypothermia decreases neuroinflammatory response by reducing the release of proinflammatory mediators, complement activation, and the production of free radicals and nitric oxide. This stabilizes the changes described in the blood-brain barrier and cell membranes and reduces vascular permeability (increased by endothelial damage mediated by nitric oxide), thus decreasing the formation of cerebral edema and intracranial hypertension. Finally, hypothermia also decreases the local release of vasoconstrictor agents (endothelin and thromboxane A2) and the activation of the coagulation cascade, which may generate hypoperfusion and the formation of microthrombi in injured cerebral areas.[4–6]

Application of therapeutic hypothermia

Induced hypothermia can be divided into 3 different phases: induction, maintenance, and rewarming. In the induction phase, the goal is to rapidly reduce temperature to the target level. In the maintenance phase, central temperature should be strictly controlled, with minimal or no fluctuations at all (maximum of 0.2 °C up to 0.5 °C). In the rewarming phase, slow and controlled heating should be achieved at a rate of 0.2 °C to 0.5 °C per hour for patients in cardiac arrest, and 0.1 °C up to 0.2 °C per hour for those with neurological injuries from different causes. After rewarming, strict normothermia should be maintained, as fever is associated with unfavorable outcomes in all types of neurological injuries[7–9] (supplementary data).

In recent decades, various cooling systems have been developed to achieve faster induction and more reliable maintenance of temperature. The ideal device should rapidly reach the desired temperature, allow for precise maintenance, slow and controlled rewarming, and prevent post-cooling fever.

There are different methods for inducing hypothermia. Traditional systems, such as skin exposure, the IV administration of cold fluids, fans, or air circulation blankets, though easy to use and inexpensive, are not very effective as they only allow for low induction speeds with unpredictable variations in body temperature, so their use is ill-advised during the maintenance and rewarming phases.[10] Modern cooling systems, such as intravascular devices (catheters with cold saline-filled balloons or refrigerated metal components) and advanced surface devices (with cold water circulation blankets or hydrogel), achieve high cooling speeds, allowing for faster attainment of the target temperature and maintaining the temperature within the desired range for longer periods of time (i.e., they cause less overcooling and rebound hyperthermia), through the use of a feedback system for precise temperature control. Intravascular devices carry the risks usually associated with the insertion and maintenance of intravascular catheters, such as catheter-associated bacteremia and catheter-related deep venous thrombosis.

The clinical trials[11–15] that compared endovascular cooling with surface cooling showed no differences in survival or neurological outcomes at hospital discharge, although endovascular cooling devices were more accurate and effective in inducing and maintaining hypothermia.

Other alternative cooling systems aim to avoid the risks of intravascular access and the difficulties of transferring heat through the skin, such as esophageal devices and selective brain cooling, which may prevent systemic complications associated with whole-body cooling[16,17] (supplementary data: Tables 1e, 2e, and 3e).

Clinical trials on the effects of using therapeutic hypothermia

The literature search methodology for this section is included in the supplementary data.

Post-cardiac arrest hypoxic-ischemic damage

In 2002, 2 randomized clinical trials (RCTs)[18,19] were published, showing improved survival with favorable neurological outcomes after having induced TH between 32 °C and 34 °C for 12–24 h in patients with witnessed out-of-hospital cardiac arrest (OHCA) and initial shockable rhythm. However, these promising results have not been confirmed in subsequent studies. In 2013, the first large-sample RCT—the TTM1 (20)—was published, including 950 unconscious patients after OHCA with shockable and non-shockable initial rhythms, without noticeable differences in mortality or functional outcomes with the application of TH. Unlike the studies from 2002,[18,19] the researchers of the TTM1 used a protocolized approach to establish neurological prognosis, and temperature in both arms was actively controlled. However, the main limitations of the TTM1 study were the time to reach the target temperature (approximately 9 h on average to reach 33 °C) and the high rate of withdrawal of life-sustaining therapy based on neurological prognosis.

Then, in 2019, the HYPERION trial[21] included 584 comatose patients after in- and out-of-hospital cardiac arrest with non-shockable rhythm and compared TH (33 °C) with thermal control (37 °C) for 24 h. No mortality differences were reported (81.3% and 83.2%, respectively), but in survivors, the rate of patients with favorable neurological outcomes was higher in the hypothermia group (10.2% vs 5.7%, $P = .04$). We should mention that the HYPERION trial had a fragility index of 1, suggesting that if only 1 patient had a different outcome (changing from a good neurological outcome to a bad one), the findings would not have reached statistical significance.

The most rigorous and largest-sample RCT (TTM2) was published 2 years later.[22] In this study, 1850 adults in a coma after out-of-hospital cardiac arrest of presumed cardiac cause or unknown cause were randomized to receive TH (33 °C for 28 h) or normothermia. No differences in mortality rates (50% vs 48%, $P = .37$) or functional outcomes were reported. No differences were reported wither in clinical outcomes based on time to return of spontaneous circulation (ROSC) (> or <25 min) and the initial rhythm. Among the main limitations of the TTM2 study, we should mention that although the protocol required reaching the target temperature in 90 min or less, half of the study population needed 7 h from ROSC to TH, perhaps due to the low intravascular cooling rate used in the trial (29%). Additionally, nearly 50% of the patients from both groups showed inadequate fever control after 72 h, and, once again, a high rate of withdrawal of life-sustaining therapy based on neurological prognosis established according to the trial protocol was reported. Another argument used to justify the lack of clinical benefit of hypothermia in the TTM2 trial is the high percentage of patients sedated with propofol, a potentially neurotoxic drug associated with mitochondrial dysfunction, one of the causes of hypoxic-ischemic brain injury.[23]

More recently, the CAPITAL CHILL trial[24] addressed the question of whether an even lower temperature would be more beneficial for neurological recovery. The RCT included 367 comatose patients after out-of-hospital cardiac arrest regardless of rhythm and compared moderate (31 °C) to mild

hypothermia (34 °C) for 24 h. No differences were reported in the composite outcome of death or unfavorable functional outcomes at 180 days. We should mention that this was a single-center study and probably did not have enough statistical power for the detection of any clinically significant differences. Moreover, this study[24] compared 2 hypothermia strategies (moderate and mild) and did not include a group not subjected to hypothermia, which means that no conclusions can be drawn from the study on the efficacy of hypothermia therapy (vs normothermia).

Most patients included in studies conducted so far, except for the HYPERION study,[21] had experienced out-of-hospital cardiac arrest with an initial shockable heart rhythm and a known or presumed primary cardiac cause,[20,22,25] which suggests that in other categories of patients, temperature control with hypothermia might be more effective. TTM researchers conducted a meta-analysis of individual patient data from the TTM-1 and TTM-2 studies to assess whether the effects of hypothermia differ depending on the circumstances of the cardiac arrest or the characteristics of the patients.[26] Patients from the 36 °C group in TTM-1 were combined with those from the normothermia group in TTM-2 and compared to patients from the 33 °C groups in both TTM studies. The primary endpoint, 6-month all-cause mortality rate (47.9% vs 49.4%, $P = .41$), and results in predefined subgroups including age, sex, initial heart rhythm (shockable or non-shockable), time to ROSC, and circulatory shock at admission showed no significant differences between the 2 groups. On the other hand, a recent study[27] conducted among 249 resuscitated patients after in-hospital cardiac arrest in Germany, confirmed that inducing hypothermia (32–34 °C) produced no benefits on mortality. However, other observational studies have identified a benefit in neurological recovery associated with 33 °C TH vs 36 °C in patients with greater severity of post-arrest neurological injury.[28–30]

In 2021, a systematic review and meta-analysis[31] analyzed the safety and efficacy profile of maintaining different temperature targets after out-of-hospital cardiac arrest. A total of 10 RCTs with 4218 patients were included, and their results confirmed that TH at 31—32 °C, 33—34 °C, and 35—36 °C did not improve survival with good functional outcomes vs normothermia at 37–37.8 °C, while a higher incidence of arrhythmias was observed among patients treated with hypothermia at 31—32 °C and 33—34 °C. That same year, another meta-analysis conducted by the International Liaison Committee on Resuscitation (ILCOR)[32] identified 9 RCTs, 6 of which were included in the meta-analysis, and concluded that treatment aimed at achieving a target temperature of 32°–34 °C did not improve survival or produced favorable neurological outcomes (low level of evidence). Three trials evaluated different hypothermic temperature targets and found no differences in outcomes between 33 °C and 36 °C or between 32 °C, 33 °C, and 34 °C (low level of evidence). Based on these results, the ILCOR ALS Task Force published its recommendations,[33] summarized in Table 1, suggesting actively preventing fever (defined as a temperature > 37.7 °C) by targeting temperatures ≤ 37.5 °C (weak recommendation, low level of evidence), rather than recommending hypothermia to treat patients remaining comatose after post-cardiac arrest ROSC.

In 2022, the European Resuscitation Council (ERC) and the European Society of Intensive Care Medicine (ESICM),[34,35] in line with the ILCOR consensus document, recommended continuous monitoring of core temperature and actively preventing fever (>37.7 °C) for, at least, 72 h in patients remaining comatose after cardiac arrest (Table 1). One possible reason for the lack of clinical benefit of hypothermia after cardiac arrest is that in the studies conducted so far, the target temperature was reached several hours after ROSC and potentially outside the therapeutic window. In a RCT,[36] the pre-hospital infusion of up to 2 l of physiological saline at 4 °C after ROSC reduced the time needed to reach a temperature of 34 °C by more than an hour. However, this strategy did not improve survival or neurological status in patients resuscitated after pre-hospital ventricular fibrillation, or in patients without ventricular fibrillation, and was associated with significantly higher rates of recurrent arrest and pulmonary edema on the first thoracic x-ray.

The optimal duration of TH remains a topic of discussion. The only trial included in the ILCOR review that addressed the issue of temperature control duration did not show any differences in outcomes between temperature control at 32°–34 °C for 24 h vs 48 h after cardiac arrest.[25] The duration of active fever prevention does not seem to have an impact on the clinical outcomes either. In a much more recent trial[37] with 789 patients in a coma after out-of-hospital cardiac arrest presumably of cardiac causes, temperature control was compared with a target of 36 °C for 24 h, followed by control at 37 °C for an additional 12 h or 48 h, or until the patient regained consciousness. The occurrence of death or severe brain disability or coma within 90 days did not significantly differ after 36 h or 72 h of active fever prevention.

Finally, the most recent Cochrane review of 12 studies with 3956 patients, concludes that TH with a target temperature of 32–34 °C may improve neurological outcomes after cardiac arrest, although with a low level of evidence.[38]

Currently, the ICECAP trial (NCT04217551) is in the recruitment phase.[39] This is a multicenter, randomized, adaptively allocated clinical trial to determine whether increasing the duration of TH is associated with a higher rate of good neurological outcomes in survivors in a coma after cardiac arrest.

Should therapeutic hypothermia be used to treat patients who remain in a coma after post-cardiac arrest ROSC?

Taking everything into account, the current evidence (Table 2) leaves unanswered the question of what the optimal temperature management is for patients in cardiac arrest with initial non-shockable rhythms, for patients in whom cardiac arrest is due to non-cardiac causes, and for those with more severe neurological injuries. This raises the hypothesis that the clinical benefit of TH after cardiac arrest may depend on factors that we still do not fully understand.

The authors of this review propose prioritizing active fever prevention (≤37.5 °C), optimization of hemodynamics, oxygenation, ventilation, and, perhaps most importantly, avoiding early prognostic assessment and premature withdrawal of life-sustaining therapy, general measures that

Table 1 Summary of recommendations from major clinical practice guidelines on thermal control.

Hypoxic-ischemic brain injury post-cardiac arrest:

The ILCOR Guidelines (2021)[22]:

- Active prevention of fever is suggested by targeting temperatures ≤ 37.5 °C for patients who remain comatose after ROSC post-cardiac arrest (weak recommendation, low level of evidence).
- It is unclear if subpopulations of cardiac arrest patients may benefit from hypothermia at 32—34 °C.
- Comatose patients with mild hypothermia following ROSC should not be actively warmed to achieve normothermia (statement of good practice).
- Routine pre-hospital cooling with rapid infusion of large volumes of cold IV fluids immediately after ROSC is ill-advised (strong recommendation, moderate level of evidence).
- The use of surface or endovascular temperature control techniques is advised when using temperature control in comatose patients following ROSC (weak recommendation, low level of evidence).
- When using a cooling device, it is advised to use a temperature control device that should include a feedback system based on continuous temperature monitoring to maintain the target temperature (statement of good practice).
- Active prevention of fever for, at least, 72 h is advised in comatose patients in cardiac arrest (statement of good practice).

The ERC and ESICM Guidelines (2022)[23,24]:

- Continuous monitoring of core temperature and active prevention of fever (>37.7 °C) for, at least, 72 h are advised in patients who remain comatose after cardiac arrest.

Acute ischemic stroke:

ESO Guidelines (2015)[39]:

- In patients with acute ischemic stroke and hyperthermia, no recommendation can be made to treat hyperthermia as a way to improve functional outcomes and/or survival (weak recommendation, low level of evidence).
- In patients with acute ischemic stroke and normothermia, systematic prevention of hyperthermia with antipyretics is ill-advosed as a way to improve functional outcomes, and/or survival (weak recommendation, moderate level of evidence).
- Induction of hypothermia is ill-advised as a way to improve functional outcomes, and/or survival in patients with acute ischemic stroke (weak recommendation, very low level of evidence).

AHA/American Stroke Association Guidelines (2019)[40]:

- The benefit of induced hypothermia in patients with acute ischemic stroke is uncertain (moderate recommendation, moderate level of evidence).

Traumatic brain injury:

BTF Guidelines 4th Edition (2016)[48]:

- Early (within 2.5 h) and short-term (48 h post-injury) prophylactic hypothermia is ill-advised to improve outcomes in patients with diffuse injuries (II B level of evidence).

SIBICC Consensus Conference (2019)[49,50]:

- Mild therapeutic hypothermia (35—36 °C) is advised as a level 3 intervention to reduce intracranial pressure in patients with ongoing intracranial hypertension once other level 1 and 2 interventions have been exhausted (IV level of evidence. Expert opinion).

AHA, American Heart Association; BTF, Brain Trauma Foundation; ERC, European Resuscitation Council; ESICM: European Society of Intensive Care Medicine; ESO, European Stroke Organisation; ROSC, return of spontaneous circulation; SIBICC, Seattle International Severe Traumatic Brain Injury Consensus Conference.

have consistently been associated with better clinical outcomes.[40–42]

Acute ischemic stroke (AIS)

In 2009, a Cochrane review[43] including 5 RCTs found no statistically significant effects of pharmacological or physical temperature reduction therapy on reducing the risk of death or dependence. Both interventions were associated with a non-significant increase in infection rates.

Another subsequent meta-analysis,[44] which included 3 studies in 131 patients with large hemispheric infarctions, suggested that TH was not associated with a decrease in mortality; however, it was associated with improved neurological outcomes in survivors, albeit with a higher risk of adverse events during treatment.

A recent meta-analysis evaluated current literature on the efficacy of TH to treat AIS.[45] Twelve studies with a total of 778 patients were included. Functional independence did not differ between groups, although 5 studies showed a trend towards better functional outcomes with hypothermia (OR, 1.57, 95%CI, 1.01—2.44; $P = .05$). General complications were higher with hypothermia (RR, 1.18, 95%CI, 1.06—1.32; $P < .01$).

The European Stroke Organization (ESO) guidelines[46] do not recommend induction of hypothermia as a way improve functional outcome and/or survival in patients with acute ischemic stroke, with a weak grade of recommendation and a very low level of evidence. Similarly, the American Heart Association/American Stroke Association guidelines[47] state that, in patients with acute ischemic stroke, the benefit of TH is still under discussion, with a moderate grade of

Table 2 Summary of the evidence on the thermal control in patients with post-cardiac arrest hypoxic-ischemic injury.

Author	Patients	Temperature	Study type	Cooling device	Clinical outcomes (TH vs normothermia)
Holtzer et al. 2002 [18]	275 Out-of-hospital CA and initial shockable rhythm	32–34 °C, 24 h vs normothermia	RCT	Surface: mattress with a cover distributing cold air throughout the body (TheraKool, Kinetic Concepts, Wareham, United Kingdom)	Favorable neurological outcomes (CPC 1–2) at 6 months: 55% vs 39% (RR, 1.4; 95%CI, 1.08—1.81). Lower mortality at 6 months: 41% vs 55%, (RR, 0.74; 95%CI, 0.58–0.95). No differences reported regarding adverse events.
Bernard et al. 2002 [19]	77 Out-of-hospital CA and initial shockable rhythm	33 °C, 24 h vs normothermia	RCT	Surface: ice bags around the head, neck, torso, and limbs	Favorable neurological outcomes (home discharge or to a rehabilitation center): 49% vs 26% (OR, 5.25; 95%CI, 1.47–18.76). No differences reported regarding adverse events. Still, TH was associated with a lower cardiac index, a higher systemic vascular resistance, and hyperglycemia.
Nielsen et al. TTM1 2013 [20]	950 Out-of-hospital CA and shockable and non-shockable rhythms	33 °C vs 36 °C, 36 h + Active fever prevention, 72 h	RCT	Iced fluids, ice bags, and intravascular or surface temperature control devices as per center discretion	Favorable functional outcomes (CPC 1–2 or mRS 0–3) at 6 months: no differences (RR, 1.02; 95%CI, 0.88—1.16). 6-month mortality: no differences reported (HR, 1.06; 95%CI, 0.89–1.23). No differences reported regarding adverse events, except for hypokalemia (19% vs 13%; $P = .02$).
Lascarrou et al. HYPERION 2019 [21]	584 Out-of-hospital CA and non-shockable rhythm	33 °C vs 37 °C, 24 h	RCT	Active internal cooling with a specific device, active external cooling with a specific device, or active external cooling without a specific device	Favorable functional outcomes (CPC 1–2) at 90 days: 10.2% vs 5.7%, 4.5 percentage point difference; 95%CI, 0.1–8.9; $P = .04$); 90-day mortality: no differences (81.3% vs 83.2%, −1.9 percentage point difference; 95%CI, −8.0 to −4.3). No differences reported regarding adverse events.
Dankiewicz et al. TTM2 2021 [22]	1850 Out-of-hospital CA of presumed cardiac cause or unknown causes	33 °C, 28 h vs ≤ 37.5 °C, 72 h + Early fever treatment (≥37.8 °C)	RCT	Surface or intravascular	Unfavorable functional outcomes (mRS ≥ 4) at 6 months: no differences (55% vs 55%; RR, 1.00; 95%CI, 0.92–1.09); 6-month mortality: no differences (50% vs 48%; RR, 1.04; 95%CI, 0.94–1.14; $P = .37$). Adverse events: arrhythmias with hemodynamic compromise (24% vs 17%; $P < .001$).

Table 2 (*Continued*)

Author	Patients	Temperature	Study type	Cooling device	Clinical outcomes (TH vs normothermia)
Le May et al. CAPITAL CHILL 2021 [24]	367 Out-of-hospital CA and shockable and non-shockable rhythms	31 °C, 24 h vs 34 °C, 24 h + ≤ 37 °C, 48 h	RCT	Endovascular device (Zoll Quattro), inserted via femoral vein into the inferior vena cava and connected to a temperature management system (Thermogard XP Temperature Management System, Zoll Medical Corporation)	Composite endpoint of death or severe functional outcomes (DRS > 5) at 180 days: no differences (48.4% vs 45.4%; *P* = .56; RR, 1.07; 95%CI, 0.86–1.33). Adverse events: deep vein thrombosis in 11.4% vs 10.9%, 31 °C vs 34 °C.
Hassager et al. BOX 2023 [37]	789 Out-of-hospital CA of presumed cardiac cause	36 °C, 24 h + 37 °C, 12 h vs 37 °C, 48 h	RCT	Group 37 °C, 12 h (n = 286): surface cooling, CritiCool and Allon, Belmont Medical Technologies. Group 37 °C, 48 h (n = 503): IV cooling, Thermogard XP and Cool Line Catheter, Zoll	Composite endpoint of death or severe brain disability at 90 days: no differencess (32.3%, Group 37 °C, 12 h vs 33.6%, Group 37 °C, 48 h; HR, 0.99; 95%CI, 0.77–1.26; *P* = .70). No differences reported regarding adverse events.
Fernando et al. 2021 [31]	10 studies n = 4218	31—32 °C, 33—34 °C, and 35—36 °C vs normothermia (37–37.8 °C)	Meta-analysis		TH did not improve survival with good functional outcomes: (OR, 1.30; 95%CI, 0.73–2.30; OR, 1.34; 95%CI, 0.92—1.94; and OR, 1.44; 95%CI, 0.74—2.80, respectively).
Granfeldt et al. 2021 [32]	32 studies	32–34 °C vs normothermia	Meta-analysis		TH did not result in improved survival (RR, 1.08; 95%CI, 0.89–1.30) or favorable neurological outcomes (RR, 1.21; 95%CI, 0.91–1.61) between 90 and 180 days.
ILCOR 2021 [33]	6 studies n = 2867	32 °C – 34 °C vs normothermia (36.5–38 °C)	Meta-analysis		TH did not improve survival (RR, 1.08; 95%CI, 0.89–1.30) or functional outcomes at 90 and 180 days (RR, 1.21; 95%CI, 0.91–1.61).
Arrich J et al. 2023 [39]	12 studies n = 3956	32–34 °C vs standard care (11 studies, n = 3914) 32–34 °C vs fever prevention (8 studies, n = 2870) 32–34 °C vs thermal control (36 °C) (3 studies, n = 1044)			TH increased the likelihood of achieving a favorable neurological outcome in all 3 comparisons: (RR, 1.41; 95%CI, 1.12–1.76 RR, 1.60; 95%CI, 1.15–2.23 RR, 1.78; 95%CI, 0.70–4.53, respectively)

CA, cardiac arrest; CI, confidence interval; CPC, cerebral-performance category; DRS, Disability Rating Scale; h, hours; vs, versus; HR, hazard ratio; mRS, modified Rankin scale; OR, odds ratio; RCA, randomized clinical trial; RR, relative risk; TH, therapeutic hypothermia.

Table 3 Summary of evidence on thermal control in patients with acute ischemic stroke (AIS).

Author	Patients	Temperature	Study type	Cooling device	Clinical outcomes (TH vs normothermia)
De Georgia et al. COOL-AID 2004 [48]	40	AIS anterior circulation, < 12 h symptom onset	RCT	Intravascular: Reprieve Endovascular Temperature Management System (Radiant Medical, Redwood City, CA, United States)	No significant differences reported in clinical outcomes. Infarct volume growth was lower in the TH group, but not significant.
Hertog den et al. 2009 [43]	423	–	Meta-analysis	5 trials: pharmacological reduction of temperature 3 trials: physical cooling	No significant effects of pharmacological or physical temperature reduction therapy on decreasing risk of dependence (OR, 0.9; 95%CI, 0.6–1.4) or death (OR, 0.9; 95%CI 0.5–1.5). Adverse events: nonsignificant increase in infections in both interventions.
Hemmen et al. ICTuS-L 2010 [49]	59 AIS with IV fibrinolysis in < 6 h	AIS with IV fibrinolysis <6 h	RCT	Intravascular: Celsius Control system, (Innercool, San Diego, CA, United States)	Favorable functional outcomes at 3 months (mRS 0–2): no differences (18% vs 24%; $P < .77$). Mortality: no difference (21% vs 17%, NS). Adverse events: pneumonia in 14 patients from the TH group vs 3 from the normothermia group ($P = .001$).
Lyden et al. ICTuS2 2016 [50]	120 AIS with IV fibrinolysis in < 3 h	33 °C, 24 h vs normothermia	RCT	Cold saline infusions at 4 °C + intravascular device (Celsius Catheter, Innercool, Carlsbad)	Favorable functional outcomes (mRS 0–1) at 90 days: no differences (33% vs 38%; OR, 0.81; 95%CI, 0.36—1.85. Mortality: 15.9% vs 8.8%; OR, 1.95; 95%CI, 0.56—7.79. Adverse events: pneumonia 19% vs 10.5%; OR, 1.99; 95%CI, 0.63—6.98.
Neugebauer et al. 2019 [51]	50	33 °C ± 1 °C, 72 g (<12 h after surgery) vs standard care	RCT	Cold saline + intravascular or surface cooling	Functional outcomes at 12 months: no differences.

Table 3 (*Continued*)

Author	Patients	Temperature	Study type	Cooling device	Clinical outcomes (TH vs normothermia)
	Malignant cerebral infarction + early decompressive surgery				14-day mortality: no differences (19% vs 13%; OR, 1.65; 95%CI, 0.28—12.01; $P = .70$) Severe adverse events: 80% vs 43% (HR, 2.54; 95%CI, 1.29—5.00).
Li et al. 2020 [44]	131 3 RCTs	< 36 °C	Meta-analysis	Endovascular, surface, or pharmacological cooling	Favorable functional outcomes (mRS 0–3) associated with TH (RR, 2.09; 95%CI, 1.14–3.82). Mortality not associated with TH (RR, 1.12; 95%CI, 0.76–1.65). Adverse events associated with TH: GI bleeding, gastric retention, electrolyte imbalance, and shivering.
Kuczynski et al. 2020 [45]	778 12 studies (4 RCTs 8 prospective observational)		Meta-analysis		Functional outcomes: no differences (RR, 1.17; 95%CI, 0.93—1.46; $P = .2$). Favorable functional outcomes (mRS ≤ 2) associated with TH in 5 studies (OR, 1.57; 95%CI, 1.01—2.44; $P = .05$). Adverse events: associated with TH (RR, 1.18, 95%CI, 1.06—1.32; $P < .01$).

AIS, acute ischemic stroke; CI, confidence interval; h, hours; vs, versus; mRS, modified Rankin Scale; NS, not significant; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk; TH, therapeutic hypothermia.

Table 4 Summary of evidence on thermal control in patients with severe traumatic brain injury (TBI).

Author	Patients	Temperature	Study type	Cooling device	Clinical outcomes (TH vs normothermia)
Clifton et al. 2001 [58]	392	33 °C, 48 h vs normothermia	RCT	Ice packs, gastric lavage with cold fluids, ambient air in ventilator circuit	Unfavorable functional outcomes at 6 months (severe disability, vegetative state, or death): no differences (57% in both groups). 6-month mortality: no difference (28% vs 27%; $P = .79$). Longer length of stay and more adverse events, but lower TH related ICP elevation
Sydenham et al. 2009 [59]	1614 23 RCT Prophylactic TH or to treat refractory TH	$\leq$ 35 °C, $\geq$12 h vs normothermia	Meta-analysis	Surface: liquid-filled cooling blanket, air cooling device, or cold water lavage	TH was associated with a non-significant drop in mortality (OR, 0.96; 95%CI, 0.68–1.35) and unfavorable outcomes (OR, 0.79; 95%CI, 0.57–1.08). TH was associated with a non-significant increase in pneumonia risk (OR, 1.06; 95%CI, 0.38–2.97).
Clifton et al. NABISH II 2011 [60]	97 < 2.5 h after TBI	33 °C, 48 h vs normothermia	RCT	IV instillation of up to 2 l of cold crystalloid and application of wet sheets or gel packs	Unfavorable functional outcomes (severe disability, vegetative state, or death) at 6 months: no differences (60% vs 56%; RR, 1.08; 95%CI, 0.76–1.53; $P = .67$). Mortality: no differences reported (23% vs 18%; RR, 1.30; 95%CI, 0.58–2.52; $P = .52$). TH was associated with more episodes of increased ICP ($P = .003$).
Andrews et al. Eurotherm 3235 Trial 2015 [52]	387	32–35 °C, $\geq$ 48 h vs standard care	RCT	IV administered chilled 0.9% sodium chloride solution (20 ml–30 ml per kg of body weight) + standard cooling technique used at each site	TH was associated with more unfavorable functional outcomes (GOS-E 1–4) at 6 months (OR, 1.53; 95%CI, 1.02–2.30; $P = .04$) and a higher mortality rate (31% vs 22%; HR 1.45; 95%CI, 1.01–2.10, $P = .047$).

Table 4 (*Continued*)

Author	Patients	Temperature	Study type	Cooling device	Clinical outcomes (TH vs normothermia)
	TH to treat refractory ICH				
Cooper et al. POLAR 2018 [54]	511	33–35 °C, ≥72 h–7 days vs 37 °C, 7 days	RCT	Bolus of up to 2000 ml of IV 0.9% saline solution chilled (4 °C) + surface cooling	Favorable functional outcomes (GOS-E 5–8) at 6 months: no differences (48.8% vs 49.1%; risk difference, 0.4%; 95%CI, −9.4%–8.7%; RR, 0.99; 95%CI, 0.82−1.19; *P* = .94). Adverse events: no differences in the rates of pneumonia (55% vs 51.3%) or intracranial hemorrhage (18.1% vs 15.4%)
	Early prophylactic TH (out-of-hospital or emergency TH)				
Hui et al. LTH-1 2021[53]	302	34–35 °C, 5 days vs normothermia (37 °C)	RCT	Cooling blankets (MTRE Advanced Technologies Ltd, Israel)	Favorable functional outcomes (GOS 4–5) at 6 months: no differences (OR, 1.55; 95%CI, 0.91–2.64; *P* = .105). Subgroup with initial ICP ≥ 30 mm Hg: TH significantly increased favorable outcomes (60.82% vs 42.71%; OR, 1.861, 95%CI, 1.031−3.361; *P* = .039); 6-month mortality: no differences reported (*P* = .111). Adverse events (pneumonia, hypokalemia, GI bleeding): no differences reported.
	Severe TBI (GCS 4–8) + initial ICH (ICP ≥ 25 mmHg)				
Hergen-roeder et al HOPES 2022[61]	32	33 °C, 48 h vs normothermia (37 °C)	RCT	Intravascular catheter (Thermogard XP System with Quattro catheter; ZOLL Circulation Inc, San Jose, CA, United States)	Favorable functional outcomes (GOS-E 5–8) at 6 months: no differences (38% vs 25%; OR, 1.8; 95%CI, 0.39–∞, *P* = .35). Adverse events: no differences reported.
	Traumatic SDH (GCS, motor ≤ 5) + Surgical evacuation < 6 h				

CI, confidence interval; GCS, Glasgow Coma Scale; GOS-E, extended Glasgow Outcome Scale; GOS, Glasgow Outcome Scale; h: hours; HR, hazard ratio; ICH, intracranial hypertension; ICP, intracranial pressure; OR, odds ratio; RCT, randomized clinical trial; RR, relative risk; SDH, subdural hematoma; TBI, traumatic brain injury; TH, therapeutic hypothermia; vs, versus.

recommendation and a moderate level of evidence. These guidelines recommend identifying the causes of hyperthermia (temperature > 38 °C) and administering antipyretics to lower the temperature in AIS patients, with a strong grade of recommendation and a low level of evidence (Table 1).

The evidence on temperature control in AIS patients is summarized in Table 3.[43–45,48–51]

Should hypothermia be applied to treat AIS patients?

Although some studies have shown a trend towards better functional outcomes in AIS patients treated with TH, no overall beneficial effect has been observed, and its use is associated with more complications. Therefore, based on the analysis of the evidence presented here, the application TH in this clinical context is ill-advised, and once again we believe that the priority should be the prevention and active treatment of fever.

Severe traumatic brain injury (TBI)

Clinical trials on TH in the management of TBI have yielded disparate results, and meta-analyses have drawn contradictory conclusions. Inconsistent results may be due to differences in the study design. RCTs of TH in the management of severe TBI can be categorized into those where TH was used to treat elevated intracranial pressure (ICP) and those where TH was used as neuroprotection to halt the biochemical cascade following injury.

In 2015, the Eurotherm3235 trial[52] evaluated 387 patients with severe TBI and intracranial hypertension (ICH) with failed first-line ICP control measures and compared TH (32–35 °C for $\geq$48 h) to standard care. Increased mortality (31% vs 22%; HR, 1.45, 95%CI 1.01–2.10, P = .047) and more unfavorable functional outcomes 6 months after the TBI (OR, 1.53; 95%CI, 1.02–2.30; P = .04) were observed in the TH group. Another more recent study[53] compared prolonged mild TH (34–35 °C for 5 days) to normothermia in 302 patients with severe TBI (Glasgow Coma Scale 4–8) and initial ICH (ICP $\geq$ 25 mmHg). No inter-group differences were detected in neurological outcomes or mortality. In patients with initial ICP $\geq$ 30 mm Hg, TH significantly increased favorable outcomes (60.8% vs 42.7%; OR, 1.86; 95%CI, 1.03–3.36; P = .039).

The largest RCT on TH in TBI patients to date, the POLAR trial,[54] found no neurological benefit with the application of prophylactic TH (33–35 °C) for 72 h in 511 patients with Glasgow Coma Scale score < 9. This study was included in a systematic review[1] along with 6 other RCTs with a total of 1843 TBI patients addressing the relationship between TH (33–35 °C) and functional outcomes and mortality, with again discordant results.

The most recent Brain Trauma Foundation guidelines on the management of severe TBI do not recommend early (within 2.5 h) or short-term (48 h post-TBI) prophylactic TH to improve the outcomes of patients with diffuse injuries, with a II B level of evidence.[55]

On the other hand, the International Consensus Conference on Brain Injury in Seattle (SIBICC) recommends mild TH (35—36 °C) as a level 3 intervention to reduce ICP in patients with ongoing ICH, once other level 1 and 2 interventions have been exhausted, with a IV level evidence (expert opinion)[56,57] (Table 1).

The evidence available on temperature control in TBI patients is summarized in Table 4.[52–54,58–61]

Should hypothermia be applied to treat patients with severe TBI?

TH in patients with severe TBI, used as neuroprotection or for ICP treatment, does not improve functional outcomes or mortality, and may even be harmful. Therefore its use is ill-advised.

Conclusions

Although TH was presumed to be a promising strategy for improving neurological outcomes in various neurological conditions, available evidence has not demonstrated its clinical benefit, and its application is associated with adverse events. Current guidelines generally recommend active prevention and treatment of fever largely based on the observed association between fever and worse clinical outcomes. However, fundamental questions remain unanswered on the most appropriate cooling method, target temperature, optimal duration of temperature control, and which patients should be selected. The results of ongoing clinical trials and future studies on temperature control may provide new evidence on the effects of hypothermia and help define therapeutic approaches that allow for individualized care of critically ill neurological patients.

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Conflicts of interest

None declared.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.medine.2024.03.001.

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