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Temperature Control in Hypoxic-Ischemic Brain Injury—a Focused Update

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Abstract

Purpose of Review Targeted temperature management (TTM) has been the mainstay of secondary brain injury prevention for unconscious cardiac arrest survivors. In this ever-changing landscape of post-cardiac arrest care, TTM practices are evolving with emergence of new evidence. We discuss the pre-clinical data paving the scientific premise for temperature control in hypoxic-ischemic brain injury and dissect through landmark TTM trials. We then describe how the practice of TTM has changed in response to the most pivotal trials and discuss exciting topics that are under investigation.

Recent Findings The advent of TTM2 has challenged the use of lower temperature targets in out-of-hospital cardiac arrest of presumed cardiac etiology by finding similar survival and neurological function at 6 months between cooling post-arrest patients to 33 °C for 24 h (followed by gradual rewarming and targeted normothermia) and actively preventing fever (< 37.8 °C) for 72 h.

Summary Temperature control remains the cornerstone in secondary brain injury prevention post-cardiac arrest, and practices surrounding temperature targets are evolving over time as new evidence emerges. Future studies on tailored temperature control to individualized factors, including depth and duration, as well as rate of rewarming will be crucial to address prevailing knowledge gaps.

Introduction

Cardiac arrest is a leading cause of morbidity and mortality worldwide. In the USA, the incidence of out-of-hospital cardiac arrest (OHCA) assisted by Emergency Medical Services (EMS) was estimated at 92.3 per 100,000 persons in 2021 [1, 2]. Survival to hospital discharge remains alarmingly low at 9.1% in OHCA [1]. This figure was even lower (7.2%) for adults surviving with a favorable neurological outcome (based on Cerebral Performance Category score of 1 or 2) [1]. Regardless of etiology, one of the primary roles of the neurologist is the recognition and prevention of secondary brain injury—one of the main determinants of outcome following hypoxic-ischemic brain injury. No other neuroprotective therapy has been as extensively studied and debated over than targeted temperature management (TTM). Promising preclinical data laid the groundwork for TTM nearly a century ago—and while initial landmark trials suggested a benefit in humans decades later—emerging conflicting evidence has since challenged the use of hypothermia in post-arrest care.

We will discuss the preclinical evidence that paved the way for the pivotal trials of TTM in humans, analyze the conflicting evidence that has challenged the scientific premise of its neuroprotective effects, and discuss the direction of future research by outlining prevailing knowledge gaps.

Why should we Care About Temperature?

Hypoxic-ischemic brain injury often leads to devastating neurological injury. Neurological damage inflicted by cardiac arrest is twofold, including both the initial ischemic event and the multifactorial process of secondary brain injury that occurs despite restoration of systemic circulation (ROSC). Primary injury is thought to be mediated by anoxic depolarizations—a massive influx of cations disrupting the transmembrane ionic gradient leading to spreading depolarization, cytotoxic edema, and release of glutamate [3]. Components of secondary brain injury include microcirculatory dysfunction, oxygen and nitrogen free radical production, loss of cerebral autoregulation, excitotoxicity, activation of protease cascades, and cerebral edema [4]. All of these processes may be exacerbated by further insults such as hypotension, hypoglycemia, and hyperthermia. Higher body temperatures lead to increased permeability of the blood–brain barrier, increased cerebral metabolism—in tissue that is already subjected to imbalances in bioenergetic supply and demand—and promotes release of inflammatory and pro-apoptotic cytokines [4]. The goal of TTM is to halt ongoing secondary injury pathways that are temperature sensitive.

Early case reports published in the 1950s document the first attempts of using temperature control following cardiac arrest in an array of etiologies [5].

All patients received hypothermia from 30 to 34 °C between 24 and 72 h and were found to have minimal to no neurological deficits days after rewarming [5]. There were no controls who did not receive temperature modulation, all cases were treated at a single center, and the study had a high risk of selection bias. A few years later, another case series documented the use of temperature control in 19 patients following cardiac arrest occurring either intraoperatively, during a procedure, or spontaneously in the "accident room" [6]. Neurological deficits were assessed at time of resuscitation and classified either as "none" (answering questions and moving all extremities), "moderate" (awake and responding "some" to verbal stimuli), or "severe" (comatose or convulsing). Only patients with moderate or severe neurological injury were included in the study. Goal temperatures ranged from 30 to 32 °C, achieved by use of blankets with circulating coolant, and meperidine or promethazine was used to treat shivering, if necessary. Similarly, various etiologies of arrest were included, and the duration of hypothermia ranged between 3 h and 8 days in the experimental group. Survival to hospital discharge was 14% in the control group (7 patients) and 50% in the group that received hypothermia (12 patients) [6].

Further evidence supporting neuroprotective effects of temperature control was demonstrated in animal models of hypoxic-ischemic brain injury. In a gerbil model of global ischemia, hypothermia to 32 °C for 12 or 24 h was associated with greater preservation of hippocampal CA1 neurons and improved memory function compared to controls [7]. A follow-up study found that this protective effect persisted at 6 months and was more pronounced when initiation of hypothermia was not delayed [8]. A canine model of ventricular fibrillation showed improved neurological function in dogs cooled to 30 °C and 34 °C for 1 h after induced cardiac arrest, compared to those cooled to 15 °C or maintained at 37.5 °C [9]. In addition to suggesting a potential benefit of hypothermia following cardiac arrest, this experiment demonstrated that a limit may exist at which lower temperatures become detrimental and lead to worse outcomes.

These early experiences with temperature modulation in humans and animal models paved the scientific premise for two pivotal, randomized controlled trials which led to a paradigm shift in temperature control following cardiac arrest in the early 2000s.

Landmark Clinical Trials

Several randomized clinical trials have studied temperature modulation in the post-cardiac arrest period for unconscious patients following ROSC with varying degrees of rigor. A comprehensive comparison of the details of eligibility criteria is summarized in Table 1.

The Hypothermia After Cardiac Arrest (HACA) trial enrolled patients across five European countries with out-of-hospital cardiac arrest (OHCA) and a shockable rhythm (i.e., ventricular fibrillation and/or pulseless ventricular tachycardia). A total of 138 subjects were randomized to receive no temperature intervention, and 137 had TTM at 32–34 °C for 24 h followed by 8 h of passive rewarming. Lower mortality (41% versus 55%) and higher proportion of favorable neurological outcome (i.e., Glasgow-Pittsburgh Cerebral

Table 1 Study design and eligibility criteria in landmark trials of temperature modulation for neuroprotection after cardiac arrest

Author and year	Study name	Study design and setting	Age and sex (years)	Arrest location and rhythm	Neurologic status	Arrest etiology and other exclusions	Downtime (no-flow + low-flow in min)	Hemodynamic instability exclusion	Standardized post-cardiac arrest care and physiologic targets	Neurologic outcome prediction
Bernard et al. 2002 [11]	Induced Hypothermia After Out-Of-Hospital Cardiac Arrest	Prospective Multicenter (4 centers), open label with blinded assessment, pseudorandomized* Superiority, powered (80%) for 14% vs 50% good outcome Melbourne, Australia Sep 1996-Jun 1999	♂ ≥18 ♀ ≥50	OHCA VF	Coma[a]	No pre-specified etiology, if potential confounders for source of coma were excluded (e.g., trauma, overdose, stroke)	NR	SBP < 90 mmHg despite EPI infusion	Midazolam (2–5 mg) + vecuronium (8–12 mg), once then prn lidocaine 1 mg/kg + 2 mg/min for 24 h ASA + thrombolytic or heparin infusion** PaO_2 100 mmHg $PaCO_2$ 40 mmHg MAP 90–100 mmHg*** K^+ 4 mmol/L Glucose 180 mg/dl	Life sustaining therapies withdrawn if deep coma[a] at 72 h from ROSC If prognosis uncertain, tracheostomy and discharge from ICU
HACA 2002 [10]	**HACA** Mild Therapeutic Hypothermia To Improve The Neurologic Outcome After Cardiac Arrest	Prospective, multicenter (9 centers), open label with blinded assessment, randomized (center stratum) Superiority, power NA. Enrollment stopped earlier due to slow enrollment Austria, Belgium, Finland, Germany, Italy Mar 1996-Jan 2001	18–75	OHCA VF or pVT	Lack of response to verbal commands after ROSC	Presumed cardiac etiology *Exclusions*: Unwitnessed arrest >15 min from collapse to EMS Marked spontaneous HT[b] Coma due to medication Pregnancy O_2 saturation < 85%[c] Terminal illness Recurrent cardiac arrest Coagulopathy Co-enrollment	<60 min	MAP < 60mmHg[c]	Sedation and NMB for 32 h: Midazolam (0.125 mg/kg/h) + fentanyl (2mcg/kg/h)[d] + pancuronium 0.1 mg/kg q2h	NA
Nielsen et al. 2013 [12]	**TTM 1** Targeted Temperature Management at 33 °C versus 36 °C after Cardiac Arrest	Prospective, multicenter (36 centers), open label with blinded assessment, randomized (center stratum) Superiority, powered (90%) for 20% relative risk reduction Australia, Czech Republic, Denmark, Italy, Luxembourg, The Netherlands, Norway, Sweden, Switzerland, UK Nov 2010-Jan 2013	≥18	OHCA VF, pVT, PEA, asystole ≥20 min ROSC	Lack of response to verbal commands (GCS < 8) after ROSC	Presumed cardiac etiology *Exclusions*: Unwitnessed arrests with asystole Marked spontaneous HT[b] Pregnancy Trauma Known bleeding diathesis Acute intracranial hemorrhage or stroke Known limitations in therapy and Do Not Resuscitate-order Known disease making 180 days survival unlikely Premorbid CPC 3 or 4 ROSC to screening > 240 min	NR	SBP < 80 mmHg despite fluid/vasopressor/inotropic medication/intra-aortic balloon pump	Sedation until normothermia[e]	Standardized after 72 h from randomization[f] by independent blinded physician Active treatment maintained for a minimum of 108 h from start of TTM Earlier WLST allowed if: myoclonic status within 24 h + absent N20 peaks on SSEP, suspected brain death

Table 1 (continued)

Author and year	Study name	Study design and setting	Age and sex (years)	Arrest location and rhythm	Neurologic status	Arrest etiology and other exclusions	Downtime (no-flow + low-flow in min)	Hemodynamic instability exclusion	Standardized post-cardiac arrest care and physiologic targets	Neurologic outcome prediction
Kirkegaard et al. 2017 [26]	**TH48** Targeted Temperature Management for 48 vs 24 Hours and Neurologic Outcome After Out-of-Hospital Cardiac Arrest	Prospective, multicenter (10), open label with blinded outcome assessment, randomized (center, <60 vs ≥ 60 years age, shockable vs nonshockable strata) Superiority, powered (80%) to detect 15% absolute difference Belgium Denmark Estonia Finland Germany Norway Feb 2013-Jun 2016	≥18 and < 80	OHCA VF, pVT, PEA, asystole ≥20 min ROSC	Lack of response to verbal commands (GCS < 8) after ROSC	Presumed cardiac etiology *Exclusions*: Unwitnessed arrest with asystole as initial rhythm Coagulopathy Terminal illness or Do Not Resuscitate-order Pregnancy Acute intracranial hemorrhage or stroke Premorbid CPC 3 or 4 Acute CABG Time from cardiac arrest to initiation of hypothermia > 240 min	< 60 min	SBP < 80 mmHg despite fluid/vasopressor/inotropic medication/intra-aortic balloon pump	Sedation for duration of cooling[g] $PaCO_2$ 4.5–5.5 kPa, pressure controlled ventilation, PEEP 5 cm H_2O, $SaO_2 \geq 95\%$ Cefuroxim prophylaxis 1.5 g × 3 MAP > 60 mmHg[h] Hematocrit ≥ 30% K^+ 3.5–4.54 mmol/L Glucose 6–8 mmol/L with intravenous insulin Positive balance on first 24 h and UOP > 1 cc/kg/h	Standardized ≥ 72 h after normothermia[i] Earlier WLST allowed if: suspected brain death, or refractory shock with multiple organ dysfunction
Lascarrou et al. 2019 [14]	**HYPERION** Targeted Temperature Management for Cardiac Arrest with Nonshockable Rhythm	Prospective, multicenter (25), open label with blinded outcome assessment, randomized (center and cardiac/noncardiac etiology strata) Superiority powered (80%) to detect 9% absolute difference France Jan 2014-Jan 2018	≥18	OHCA or IHCA Asystole, PEA	Coma (GCS score ≤ 8)	No pre-specified etiology *Exclusions*: Moribund condition Child–Pugh class C cirrhosis Pregnancy or breast-feeding Under guardianship (including inmate) Previous enrollment in trial for cardiac arrest with 90 day neurologic outcome assessment Lack of health insurance Time from cardiac arrest to screening > 300 min	No-flow time < 10 min Low-flow time < 60 min	EPI or Norepi infusion > 1 µg/kg/min	Sedation until 36 °C in HT and until 12 h from randomization in NT[j] Shivering protocol[k] MAP ≥ 65 mmHg, $ScvO_2 \geq 70\%$[l] $SpO_2 \geq 92\%$ $PaCO_2$ 35–40 mmHg Hemoglobin ≥ 7 g/dL or ≥ 10 g/dL if CAD Blood glucose 60–180 mg/dL[l]	Institution specific protocol[m]

Table 1 (continued)

Author and year	Study name	Study design and setting	Age and sex (years)	Arrest location and rhythm	Neurologic status	Arrest etiology and other exclusions	Downtime (no-flow + low-flow in min)	Hemodynamic instability exclusion	Standardized post-cardiac arrest care and physiologic targets	Neurologic outcome prediction
Dankiewicz et al. 2021 [16]	**TTM2** Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest	Prospective, multicenter (61), open label with blinded assessment, randomized (center stratum) Superiority, powered (90%) to detect 15% relative risk reduction of death Australia, Austria, Belgium, Czech Republic, Denmark, France, Germany, Italy, Norway, New Zealand, Sweden, Switzerland, UK, USA Nov 2017–Jan 2020	≥18	OHCA VF, pVT, PEA, asystole ≥20 min ROSC	Lack of response to verbal commands after ROSC (FOUR-score motor subscore < 4)	Presumed cardiac etiology or unknown *Exclusions*: Unwitnessed arrest with asystole as initial rhythm Marked spontaneous HT[b] Pregnancy Intracranial hemorrhage Severe COPD with long-term O_2 therapy ROSC to screening > 180 min Restrictions on level of ICU care	NR	ECMO prior to ROSC	Sedation for 40 h post-randomization[n] Shivering protocol[o] EEG 48–96 h post-randomization	Standardized after 96 h from randomization[p] by independent blinded physician Decision to withdraw made by treating physician + surrogate
Le May et al. 2021 [18]	**CAPITAL CHILL** Effect of Moderate vs Mild Therapeutic Hypothermia on Mortality and Neurologic Outcomes in Comatose Survivors of Out-of-Hospital Cardiac Arrest	Prospective, single center, partially blinded[q], randomized (shockable vs nonshockable stratum) Superiority, powered (80%) to detect 15% absolute risk reduction Canada Aug 2013-Mar 2020	≥18	OHCA VF, pVT, PEA, asystole	Coma (GCS score ≤ 8)	No pre-specified etiology *Exclusions*: Intracranial hemorrhage etiology for arrest Severe coagulopathy with evidence of major bleeding Coma not attributable to cardiac arrest Pregnancy Nursing home or assisted living facility resident Life expectancy < 1 year Known coagulation disorder[r] Endovascular device not available Previous enrollment in study with investigational drug or device < 4 weeks	NR	No formal criteria, but listed reason for exclusion refractory shock after randomization	Sedation[s] Shivering protocol with NMB[s]	Multimodal neuroprognostication[t] WLST decisions made by team including intensivist, neurologist, palliative care specialist and surrogate

In this table, decimals for numeric values were rounded to nearest round value

ASA aspirin, *BSAS* bedside shivering assessment score, *CABG* coronary artery bypass graft surgery, *COPD* chronic obstructive pulmonary disorder, *CT* computed tomography, *ECMO* extracorporeal membrane oxygenation, *EEG* electroencephalography, *EPI* epinephrine, *FOUR* full outline of unresponsiveness score, *GCS* Glasgow Coma Scale, *HT* hypothermia, *ICU* intensive care unit, *IHCA* inhospital cardiac arrest, *IV* intravenous, *MAP* mean arterial pressure, *MRI* magnetic resonance imaging, *NA* data not available/reported from original paper, *NMB* neuromuscular blockade, *NR* no requirements, *NT* normothermia, *OHCA* out-of-hospital cardiac arrest, *PEA* pulseless electrical activity, *pVT* pulseless ventricular tachycardia, *PR* per rectum, *RASS* Richmond Agitation-Sedation Scale, *ROSC* return of spontaneous circulation, *SBP* systolic blood pres-

Table 1 (continued)

sure, *SSEP* somatosentory evoked potentials, *$ScvO_2$* central venous oxygen saturation, *UK* United Kingdom, *UOP* urine output, *USA* United States of America, *VF* ventricular fibrillation, *WLST* withdrawal of life sustaining therapies

*Random assignment of subjects to hypothermia or normothermia according to the day of the month (odd-numbers = hypothermia); **Systemic thrombolytic if ECG suspicious for acute myocardium infarction, otherwise heparin infusion if coronary syndrome suspected; ***Standardized use of epinephrine or nitroglycerin to achieve MAP targets

[a]No definition provided for coma or deeply comatose

[b]Tympanic temperature < 30 °C on admission

[c]For > 30 min after ROSC and before randomization

[d]Initial infusion rates of sedatives, which were adjusted as needed

[e]Choices of sedatives, analgesics, and NMB agents were at the discretion of treatment team

[f]Performed in all subjects based on clinical neurologic examination (GCS, pupillary and corneal reflexes), SSEP and EEG. Biomarkers were not used for operational prognostication. WLST allowed if: brain death, severe myoclonus status (generalized convulsions in face and extremities for ≥ 30 min) in first 24 h after admission + bilateral absence of N20 on SSEP, coma with GCS motor score 1–2 + bilateral absence of N20 on SSEP, coma with GCS motor score 1–2 + refractory status epilepticus (> 50% of 30 min recording with repetitive epileptiform discharges ≥ 1 Hz and > 50 μV)

[g]Sedation with Propofol/Ultiva or Midazolam/Fentanyl depending on hemodynamic stability. Cisatracurium infusion until target of ≤ 34 °C achieved, then as needed for shivering

[h]Achieved with dopamine, dobutamine or norepinephrine first, if severe circulatory failure, individualized therapy with epinephrine, milrinone, levosimendan and intra-aortic balloon pump. If tachyarrhythmias, amiodarone supplemented with magnesium were first-line

[i]Performed in all subjects without regain of consciousness after rewarming based on the Danish Society of Intensive Care Medicine and the Danish Society of Anesthesiology and Intensive Care Medicine, which acknowledged importance of multimodal prognostication. EEG and SSEP performed at least 48–72 h post-rewarming. Combination of exam features (absence of brainstem reflexes, absence of motor response or extensor posture), status myoclonus (not defined), bilateral absence of N20 peaks on SSEP, non-reactive or other unfavorable EEG pattern (not defined), and CTH and MRI showing signs of hypoxic ischemic brain injury supported poor outcome. Other prognostic factors regarding circumstances of arrest (witnessed status, bystander CPR status, age, shockable, downtime) were encouraged to be factored in assessments

[j]All patients in HT received sedation with midazolam or propofol with fentanyl or sufentanyl targeting RASS-5 until 36 °C during rewarming. All patients in NT received sedation with midazolam or propofol with fentanyl or sufentanyl targeting RASS 0 for the first 12 h

[k]Standardized 3-step protocol adapted from (1); 85 targeting BSAS ≤ 1: step 1, bolus of hypnotic and opioid equal to the hourly infusion rate; step 2, bolus of nondepolarizing NMB agent; step 3, continuous infusion of nondepolarizing NMB agent

[l]Achieved with introduction of treatment at discretion of treatment team

[m]All institution-specific protocol for neuroprognostication and WLST must comply with the 2012 ethics committee of the French Intensive Care Society, which recommends multimodal prognostication. Combination of exam features (absence of pupillary or light reflexes on third day, absence of motor response on third day), persistent generalized myoclonus during first 24 h, SSEP with bilateral absence of N20 peaks after the third day upon complete rewarming, EEG (isoelectric line or burstOsuppression or anoxic-status epilepticus) during first week, and CTH and MRI showing signs of hypoxic ischemic brain injury supported poor outcome

[n]Sedation protocol not defined, short-acting medications or volatile anesthesia preferred targeting RASS-4

[o]Baseline: acetaminophen IV/PR unless liver contraindication for all; buspirone, magnesium, clonidine, meperidine and skin counterwarming if in local protocol. Step 1: ↑propofol (or midazolam if hemodynamically unstable)/dexmedetomidine and/or opioid. Step 2: NMB. Neuromuscular blockade was required in 66% of HT versus 45% of NT arms

[p]Performed in all subjects based on European Resuscitation Council & European Society for Intensive Care Medicine guidelines by blinded physician (neurologist, inten-

Table 1 (continued)

sivist, or other experienced specialist) to treatment allocation. Timing of final prognostic impressions may be delayed. Mandatory prognostic tools: motor response to pain, pupillary light reflex, corneal reflex, status myoclonus, EEG (48–96 h post-randomization or later). Optional prognostic tools: head CT, brain MRI (3–5 days), neuron specific enolase, SSEP (> 48 h post-randomization)

[q]Blinded: treating physician, committee of outcome assessor, follow up cardiologist, rehabilitation team, family members. Not blinded: treating nurse

[r]INR > 2, platelets < 100,000/mm^3

[s]Local cooling protocol (sufentanyl 0.1–0.3mcg/kg/h, propofol 10–20 mg bolus + 0–30 mcg/kg/min) dosing left at the discretion of treatment team. NMB for the duration of cooling targeting train-of-four 2:4 with cisatracurium bolus 0.1 mg/kg + 0.5–2mcg/kg/min infusion) and discontinued when temperature reached 36 °C and train-of-four 4:4

[t]No details reported on neuroprognostication process, other than it was multimodal including serial neurologic examination, EEG, CT, and MRI

Performance Categories Scale—CPC 1–2) (55% versus 39%) were found at 6 months in the TTM group compared to controls [10]. Also published in 2002, the Australian trial led by Bernard enrolled 77 adults with OHCA with ventricular fibrillation, who were allocated to either TTM to 33 °C for 12 h or standard care with no temperature control. Good neurological outcome (i.e., discharge to home or acute rehabilitation facility) was achieved in 49% of subjects in the TTM group versus 26% in the control group [11]. Notably, in both trials, normothermia was not actively maintained during the intervention period for the control groups, or after the intervention period for both groups.

These findings supported that adult patients who remained unable to follow verbal commands following OHCA should be cooled for 12 to 24 h to improve neurological outcomes, provided they had a shockable initial rhythm.

What is the Optimal Temperature?

Likely the subject of the most fervent debate regarding use of temperature control is the optimal temperature target during the post-arrest period. In the HACA trial, many patients in the control group had temperatures that were recorded ≥ 38 °C. The investigators of the TTM1 trial suspected that the benefit of temperature modulation could be accomplished with milder hypothermia. The TTM1 trial randomized 950 adult OHCA patients with any non-perfusing rhythm (except for asystole in unwitnessed arrests) to receive TTM to either 33 °C or 36 °C for 24 h, followed by slow rewarming and strict normothermia (37 °C) with active prevention of fever until 72 h post-arrest. There were no significant differences in all-cause mortality or poor neurological outcome (CPC 3 to 5 or modified Rankin scale [mRS] 4 to 6) between the two groups at 6 months. These findings suggested that following OHCA with a cardiac or presumed cardiac etiology, there was no strong indication for benefit of 33 °C over 36 °C, so long as a bundle of care with controlled slow rewarming, standardized post-cardiac arrest care and neuroprognostication was provided [12].

The findings of the TTM1 trial published in 2013 prompted a shift in target temperatures in many centers. The largest cohort documenting a single center experience transitioning TTM practices assessed survival and neurological outcomes of 453 unconscious OHCA patients from 2010 to 2017 [13]. In 2014, the standardized TTM target at this center was changed from 33 °C (258 patients) to 36 °C (195 patients). Patients in the 33 °C group were slightly older (mean 56.5 years versus 51.6 years; $p < 0.05$), more commonly had cardiac etiology of arrest (45.0% versus 35.4%; $p < 0.05$), and had faster time from 911 call to initiation of TTM (1.5 h versus 3.5 h; $p < 0.001$) compared to patients in the 36 °C group; otherwise, the groups were balanced. Forty percent of patients cooled to 33 °C had a favorable neurological outcome at discharge (CPC 1–2), compared to 30% of patients cooled to 36 °C ($p < 0.05$), but no significant difference between groups regarding survival to hospital discharge [13].

The first randomized clinical trial to include in-hospital cardiac arrest (IHCA), the HYPERION study, focused exclusively on non-shockable rhythms. In this study, 584 adults who remained unconscious following resuscitation were randomized to either 33 °C or 37 °C (+/− 0.5 °C) for 24 h, followed by controlled slow rewarming over 24 h and normothermia for additional 48 h. In the hypothermic arm, 10.2% of subjects achieved independence at 90 days versus 5.7% in the normothermia group ($p < 0.04$); however, both survival to hospital discharge and mortality at 90 days did not differ between groups. There was a high fragility index to this finding, indicating that the benefit only very narrowly achieved statistical significance [14•].

A prospective observational study assessed 270 patients with OHCA that were cooled to 33 °C for 24 h followed by gradual rewarming to 36.5 °C and no further use of temperature control other than antipyretics. Mortality and neurological deficit based on CPC was assessed at discharge and at 6-month follow-up, and patients were determined to have post-hypothermia fever if they had recorded temperature of 38.5 °C or higher. Compared with patients that had good neurological outcomes (CPC 1–2), patients with poor neurological outcomes (CPC 3–5) had higher maximum temperatures post-cooling (38.0–38.7 °C versus 38.1–39.2 °C, $p = 0.001$). Additionally, rebound hyperthermia was more prevalent (61% versus 45%, $p = 0.02$) and of longer duration (median 8 h versus 5 h, $p = 0.002$) in patients with poor versus good neurological outcomes, respectively [15].

To further test whether active prevention of fever was non-inferior to cooling to 33 °C following OHCA, the largest international multicenter trial in cardiac arrest, the TTM2 trial, randomized 1861 unconscious adult OHCA patients with any initial non-perfusing rhythm (except for unwitnessed arrests with asystole) and a presumed cardiac etiology to either 33 °C or early treatment of fever (i.e., ≥ 37.8 °C). This study was unprecedented in the field, both in number of subjects and in rigor of study design. Neuroprognostication was standardized and performed no earlier than 96 h after randomization by a physician blinded to treatment allocation. Patients in the 33 °C group were cooled for 28 h, followed by rewarming from 0.3 °C per hour, and controlled normothermia at 36.5 to 37.7 °C for 72 h. The normothermia group targeted < 37.8 °C, with active cooling via surface or endovascular cooling if conservative measures, such as antipyretics, were insufficient—these were required in 46% of patients to maintain target temperature. At 6 months, there were no significant differences in all-cause mortality or neurological outcome between groups. Patients in the 33 °C group experienced more clinically significant bradycardia (24% vs. 17%; $p < 0.001$), but no other differences in adverse events between the groups were found. As in the TTM1 study, over 70% of patients in both groups had a shockable rhythm [16••]. These data suggested that for patients with OHCA of presumed cardiac etiology, there is no additional neuroprotection benefit from lowering temperatures to 33 °C if a standardized bundle of care, including sedation, delayed neuroprognostication and active fever control is in place.

A meta-analysis published in 2021 assessed 10 randomized clinical trials studying the use of TTM after cardiac arrest of any initial rhythm or etiology [17]. Studies were included if subjects were randomized to TTM of at

least two different temperatures, one of which lower than 37 °C; temperature targets included 31–32 °C (6.5% of total subjects), 33–34 °C (49.5%), 35–36 °C (11.0%), and 37–37.8 °C (33%). The primary outcome was survival with good functional outcome at discharge (CPC 1–2, mRS 0–3, or blind clinical evaluation demonstrating mild, moderate or no disability) or latest time point recorded up to 6 months. There was no strong evidence of improvement with mild (35–36 °C; OR 1.44 [95% CI 0.74–2.80]), moderate (33–34 °C; OR 1.34 [95% CI 0.92–1.94]), or deep (31–32 °C; OR 1.30 [95% CI 0.73–2.30]) hypothermia on survival or good functional outcome at discharge compared with normothermia (37–37.8 °C) [17]. No additional benefit on survival or functional outcome between moderate and deep hypothermia was seen, though arrhythmias were significantly more common in subjects receiving deep hypothermia compared to those receiving moderate hypothermia (OR 2.47 [95% CI 1.25–4.88]). There were no significant differences in bleeding events or pneumonia between any groups. Subjects were not stratified by initial rhythm in this analysis and comprehensive details on presenting rhythm were not reported, therefore, the application of these findings to specific cardiac arrest subgroups is limited.

The Therapeutic Hypothermia Following Out-of-Hospital Cardiac Arrest (CAPITAL CHILL) trial randomized 367 adult unconscious OHCA patients of any non-perfusing rhythm to 31 °C or 34 °C for 24 h followed by gradual rewarming to 37 °C maintained for 48 h [18]. At 6 months, there were no significant differences in all-cause mortality or neurological function as determined by both mRS and Disability Rating Scale. There were also no significant differences in rate of pneumonia, seizures, or thrombosis in either group, though median length of ICU stay was significantly longer in the 31 °C group (10 versus 7 days in the 34 °C group; $p = 0.004$). Most patients in both groups had shockable initial rhythm (85.9% in the 31 °C and 86.3% in the 34 °C group), thus, the study likely was underpowered to assess the effect of 31 °C in the non-shockable subgroup [18].

A post hoc analysis of a prospective cohort assessed differences in neurological outcome at 33 °C vs. 36 °C based on the degree of encephalopathy determined by EEG in unconscious patients following OHCA or IHCA [19]. In this before (2010–2014, target 33 °C) and after (2014–2017, target 36 °C) study that captured a transition in temperature targets following TTM1 publication, patients were sub-divided into three groups—mild, moderate or severe encephalopathy—assessed at 12- and 24-h EEG post-arrest by blinded encephalographers. Following 24 h of TTM to either 33 °C or 36 °C and passive rewarming at 0.25–0.5 °C, temperature control targeting 36.5–37.5 °C was restarted for any unconscious patient who developed a temperature > 38 °C for 48 h. Patients were excluded if EEG data were missing at 12- or 24-h post-arrest, which was more common in the 36 °C group. Therefore, the severity of encephalopathy was only able to be determined in 48% of patients in the 36 °C group, compared with 67% in the 33 °C group. Ultimately, 479 patients were included in the analysis and neurological outcomes were similar between groups in the overall cohort, and among mild and severe encephalopathy subgroups. Nonetheless, in the subgroup with moderate encephalopathy, cooling to 33 °C was associated with increased

likelihood of achieving independence at 6 months compared with 36 °C group (66% versus 45%; OR 2.38 [95% CI = 1.32–4.30]; $p = 0.004$) [19]. One remarkable aspect of this study is the use of a tool that provides individualized information on the degree of hypoxic-ischemic injury by factoring in, albeit indirectly, the cerebral resilience of patients. The stratification of injury severity solely based on characteristics of the arrest misses this key component that is unique to each patient. The use of EEG in differentiating these populations to potentially guide treatment is an exciting prospect; however, follow-up randomized clinical trials are necessary to validate these findings.

How Early should we Start Temperature Control?

Preclinical data suggested that shorter time to target temperature improves neurological outcome [20].

In 2014, 1359 OHCA patients were randomized to receive either 2 l of normal saline at 4 °C as soon as possible after ROSC or initiation of cooling upon hospital arrival. The intervention arm also included neuromuscular blockade and 1–2 mg of diazepam. Both groups had a target temperature of 32–34 °C maintained for 24 h, which was achieved approximately 1 h faster in the prehospital cooling group. No significant differences were found in either mortality or neurological status by Glasgow Outcome Scale at discharge, or rates of hypotension requiring vasopressors; however, rearrest rates (26% versus 21%; $p = 0.008$) and early clinically significant pulmonary edema (41% versus 30%; $p < 0.001$) were more prevalent in the prehospital cooling group. While outcomes were assessed at discharge by evaluation of hospital charts, and long-term outcomes were not studied, these findings suggested that prehospital cooling with infusion of cold saline did not confer benefit to this population and may expose to unnecessary harm [21].

What if the goal temperature were achieved as close to the time of primary neurological injury as possible? The RINSE trial randomized 1198 subjects with OHCA to receive 30 cc/kg (maximum of 2 l) of normal saline at 3 °C *during* cardiac arrest or standard of care. After arrival at hospital, both groups received TTM to 33 °C for 24 h. Patients who received intra-arrest cooling had lower body temperatures at hospital arrival (34.7 °C versus 35.4 °C; $p < 0.001$); however, no difference in survival to hospital discharge between groups were found (10.2% intra-arrest cooling vs 11.4% control; $p = 0.71$). Compared to standard care, subjects with shockable initial rhythm who received intra-arrest cooling had decreased rates of ROSC (41.2% vs. 50.6%; $p = 0.03$) and a higher likelihood of death prior to hospital arrival (44.3% vs. 34.1%; $p = 0.01$). The intra-arrest group also had higher rates of acute pulmonary edema (10.0% vs. 4.5%; $p < 0.001$). Importantly, neurological function at discharge or long-term follow-up was not assessed [22]. These findings were confirmed by a meta-analysis comprising 10 randomized controlled trials which compared 4220 OHCA patients of any rhythm who received either prehospital cooling (either intra-arrest or after ROSC) or initiation of TTM upon hospital arrival. Of note, the assessment of neurological status

was not uniform across each study, and some utilized fairly crude measures of neurological function at discharge [23].

Could the adverse effect of the cooling method used in these trials—inherently associated with the risk of volume overload and pulmonary edema from infusion of chilled saline—have mitigated the potential benefit of ultra-early hypothermia? The PRINCESS trial randomized 671 patients with OHCA of cardiac etiology to receive either intra-arrest intranasal evaporative cooling or standard care alone, which included 24 h of TTM from 32 to 34 °C for 24 h followed by gradual rewarming and active fever prevention for 72 h. The primary outcome was survival with a good neurological outcome (CPC 1 or 2) at 30 days. Similar to the RINSE trial, patients who received intranasal cooling reached goal temperature faster (34.6 °C versus 35.8 °C on arrival; $p < 0.001$); however, there were no significant differences in survival or neurological outcome [24•].

Intriguingly, shorter duration between induction time to achieve 32–34 °C was associated with lower CPC score at discharge in a retrospective study of 321 subjects [25]. Patients in the poor neurological outcome group (CPC 3 to 5) also had significantly longer downtimes, were older and had lower rates of shockable rhythm than the group with CPC 1 to 2. The authors hypothesized that the relationship between poor neurological outcomes and shorter induction time to target temperature could be due to loss of thermoregulatory control in patients who suffered more severe neurological injury during their arrest.

How Long should Hypothermia be Maintained?

In the Bernard study, hypothermia was maintained for 12 h, and in HACA, patients were cooled for 24 h. The duration of 24 h for hypothermia phases was also used in TTM1, HYPERION, TTM2, and CAPITAL CHILL trials. In the TH48 trial, 355 unconscious patients following OHCA of any rhythm were randomized to receive either 24 or 48 h of temperature control at 33 °C followed by gradual rewarming [26]. No differences were found in CPC scores between groups at 6 months, though the 48-h group had premature rewarming in 6% of cases compared with 2% in the 24-h group; per study protocol, life-threatening arrhythmia or uncontrolled hemorrhage would trigger raising the TTM target to 36 °C. Patients in the 48-h group had significantly more hypotension (62% versus 49%; $p = 0.013$) and a higher number of adverse events (97% versus 91%; $p = 0.04$), though the 24-h group had more severe bleeding events (requiring more than 2 units of blood in 24 h, 4% versus 1%; $p = 0.013$) [26]. This trial provided evidence that 24 h of temperature control was non-inferior to 48 h and was associated with fewer adverse events. The ongoing ICECAP (Influence of Cooling Duration on Efficacy in Cardiac Arrest Patients) study is evaluating various durations of hypothermia on neurological outcomes following cardiac arrest, which will help broaden our understanding of this important variable in TTM [27].

How should we Control Temperature?

Most landmark trials have been agnostic to temperature control methods due to their pragmatic nature. A comparison of the various temperature control methods used in these trials is provided in Table 2.

A meta-analysis comprised of 22 studies including 8027 patients compared at least two temperature control methods for differences in either neurological outcome or mortality at any time point. Methods were classified either as "core" (e.g., cold intravenous saline infusion, extracorporeal membrane oxygenation, endovascular catheters, trans-nasal) or "surface" (e.g., ice packs, cooling blankets, adhesive cooling pads) and further subdivided into temperature feedback devices (TFD) and non-TFD. "Core cooling" devices and TFD were associated with a lower likelihood of unfavorable neurological outcome (CPC 3–5) than surface cooling (OR 0.85 [95% CI 0.75–0.96]; $p = 0.008$) or non-TFD (OR 0.64 [95% CI 0.56–0.74]; $p = 0.003$, respectively. There was no significant difference between core and surface cooling on survival. Importantly, statistical significance for these endpoints was obtained largely from prospective or retrospective cohorts, both of which are more susceptible to confounding effect. Time to goal temperature was significantly shorter with core and invasive methods in some studies, though invasive methods (such as endovascular cooling) were associated with less fluctuation in temperature during the cooling period and lower rates of unexpected rewarming [28]. Similar conclusions were reached in a separate meta-analysis, comprised of 12 studies and 5581 patients [29].

In the TTM2 trial, 46% of patients in the normothermia arm required active cooling with a device to maintain goal temperature. This rate is comparable to findings from a retrospective cohort study evaluating temperature trends in patients following cardiac arrest who received either no temperature intervention, antipyretics only, endovascular cooling only, or antipyretics plus endovascular cooling. The study was limited due to much lower number of patients receiving active cooling with a device and lack of standardization of antipyretic medications; however, normothermia (< 38 °C) over 48 h was achieved in only 57.7% of patients receiving antipyretics alone, compared with 82.1% in the endovascular cooling groups. This provides further evidence that cooling devices are often needed to maintain even physiologic temperatures following cardiac arrest [30].

The most recent ERC-ESICM guidelines do not make any recommendation regarding rate of rewarming following cardiac arrest due to lack of good evidence, as there have been no randomized trials comparing outcomes at various rewarming rates. In most trials discussed here, rewarming is accomplished by actively or passively increasing body temperature between 0.25 and 0.5 °C per hour.

Potential Complications

When caring for patients receiving TTM, it is important to be aware of the adverse effects that can be expected in this population; these are summarized in Fig. 1. Specific attention to electrolyte shifts, insulin requirements and

Table 2 Temperature modulation intervention methods in landmark trials of temperature modulation for neuroprotection after cardiac arrest

Author and year	Study name	Time to randomization (min)	Temperature targets and source	Cooling method	Time to cooling initiation and target	Cooling duration	Rewarming starting time (hours from cooling initiation) and method	Rewarming duration	Controlled normothermia method
Bernard et al. 2002 [11]	Induced Hypothermia After Out-Of-Hospital Cardiac Arrest	0* from cardiac arrest	33 °C vs 37 °C** Tympanic or bladder until PA catheter	Non-feedback loop***	NR[a]	12 h	18 h Active with heated-air blanket	6 h	NR
HACA 2002 [10]	**HACA** Mild Therapeutic Hypothermia To Improve The Neurologic Outcome After Cardiac Arrest		32–34 °C vs NT (target not specified) Tympanic then bladder	Non-feedback loop[b]	Goal reaching target within 4 h ROSC Median, IQR time (min) from ROSC to initiation 105, 61–192 Median, IQR time (hours) from ROSC to target 8, 4–16[C]	24 h (IQR 12–29)	24 h Passive target 36 °C	8 h (IQR 8–12)	NR
Nielsen et al. 2013 [12]	**TTM 1** Targeted Temperature Management at 33 °C versus 36 °C after Cardiac Arrest	<220 min from sustained ROSC	33 °C vs 36 °C Bladder, unless unable or oliguric, then esophageal or intravascular	Closed loop feedback device[d] Active warming to 33 °C if 30–33 °C (33 °C arm, no rate specified) Passive warming to 36 °C if 30–36 °C (36 °C arm, no rate specified)	Goal reaching target within 4 h ROSC	24 h Rewarmed to ≥36 °C before schedule 3% (arrhythmia, severe shock, bleeding, uncontrolled lactate rise, urgent CABG)	28 h from randomization Active rewarming with loop feedback at 0.5 °C/h to target 37 °C	8 h	36.5–37.5 °C for 36 h (until 72 h from randomization with any method)[e]
Kirkegaard et al. 2017 [26]	**TH48** Targeted Temperature Management for 48 vs 24 Hours and Neurologic Outcome After Out-of-Hospital Cardiac Arrest	<240 min from ROSC	33 °C±1 °C Bladder, nasopharynx	Surface and invasive cooling devices[f]	Goal of start cooling within 60 min ROSC Median, IQR time (min) from ROSC to initiation 102, 47–174 48H vs 112, 33–185 24H Median, IQR time (min) from ROSC to target 281, 217–360 48H vs 320, 241–410 24H	24 vs 48 h Rewarmed to ≥36 °C before schedule 6.3% 48H (arrhythmia, refractory arrest, shock, sedation needs, equipment malfunction) vs 1.7% 24H (brain death, unspecified)	24 or 48 h from target Active rewarming with loop feedback at 0.5 °C/h to target 37 °C Mean 0.3 °C/h in 48H 0.4 °C/h in 24H	Mean, SD (hours) 10,±4 in 48H vs 10,±3 24H	Fever control with paracetamol as needed

Table 2 (continued)

Author and year	Study name	Time to randomization (min)	Temperature targets and source	Cooling method	Time to cooling initiation and target	Cooling duration	Rewarming starting time (hours from cooling initiation) and method	Rewarming duration	Controlled normothermia method
Lascarrou et al. 2019 [14]	**HYPERION** Targeted Temperature Management for Cardiac Arrest with Nonshockable Rhythm	<300 min from cardiac arrest	33 °C vs 37 °C Bladder, esophageal, or intravascular	Surface and invasive cooling devices[g] Active warming to 37 °C if<37 °C (37 °C arm at 0.25–0.5 °C/h)	Goal of hypothermia within 180 min from randomization (420 min from ROSC) Median, IQR time from randomization to cooling initiation 16, 0–53 HT vs NT NR Median, IQR time from randomization to target 317, 214–477	24 h Rewarmed before schedule 13% (hemodynamic instability, arrhythmias, brain death, bleeding, other)	24 h from target Active rewarming with loop feedback at 0.25–0.5 °C/h to target 37 °C	NR	37 °C for 24 h (until 48 h from randomization) with nonpharmacologic method
Dankiewicz et al. 2021 [16]	**TTM2** Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest	180 min from ROSC	33 °C vs NT (37.5 °C)[h] Bladder, unless unable or oliguric, then esophageal or intravascular	Closed loop feedback device[e] Induction target 32 °C, then adjusted to 33 °C Active or passive warming to 33 °C if 30–33 °C (33 °C arm, no rate specified) Passive warming to in NT arm	Goal reaching target within 90 min	28 h from randomization Rewarmed before schedule 5.7% HT (hemodynamic compromise, arrhythmias, intracranial hemorrhage, bleeding, brain death, cardiac surgery, ECMO, skin complications, compartmental syndrome, unclear)	28 h from randomization HT—active with loop feedback device at 1/3 °C per hour to target 37 °C NT—maintenance of≤37.5 °C	12 h 1/3 °C per hour	36.5–37.7 °C for 32 h (until 72 h from randomization with any method)[i]
Le May et al. 2021 [18]	**CAPITAL CHILL** Effect of Moderate vs Mild Therapeutic Hypothermia on Mortality and Neurologic Outcomes in Comatose Survivors of Out-of-Hospital Cardiac Arrest	Median, IQR 228, 167–313 31 °C vs 204, 146–297 34 °C	31 °C vs 34 °C Endovascular correlated with nasopharyngeal and bladder probes	Endovascular closed loop feedback device[j] Active warming to 34 °C if<34 °C (34 °C arm; no specified rate of warming)	Goal NR Median, IQR from randomization to target 208, 163–282 31 °C vs 120, 80–174 34 °C	24 h Rewarmed (by 3 °C to either 34 °C or 37 °C—i.e., 31 °C group could undergo rewarming by 3 °C increment 2 × if clinical concern remained) before schedule for hemodynamic reasons in 17% 31 °C and 5.5% 34 °C	24 h from target Active rewarming with endovascular closed-loop device at 0.25 °C/h to target 37 °C	NR	48 h from start of rewarming

Table 2 (continued)

In this table, decimals for numeric values were rounded to nearest round value

CABG coronary artery bypass graft surgery, *ECMO* extracorporeal membrane oxygenation, *ICU* intensive care unit, *NR* no requirements, *PA* pulmonary artery, *ROSC* return of spontaneous circulation, *SD* standard deviation

*On odd-numbered days of the month, paramedics-initiated cooling of eligible subjects in the field; **Initially mildly hypothermic patients assigned to normothermia arm were passively rewarmed to target; ***Cold packs applied to head and torso in pre-hospital setting, followed by ice-packs in head, neck, torso, limbs until target; then ice-packs removed

[a]No specific cut-off time to achieve target; mean + SD temperatures were 33.3 ± 0.98 °C on ICU admission and 32.7 ± 1.19 °C at 6 h

[b]TheraKool® external cooling mattress with cover delivering cool air

[c]In 19 subjects (13.8%) target temperature could not be reached

[d]Any cooling method allowed if feedback controlled. During induction, neuromuscular blockade was encouraged, and intravenous 4 °C fluid allowed up to 30 cc/kg or 2 L

[e]As long as the patient remained in the ICU

[f]Surface or intravenous cooling, not specified if close loop feedback or not. Intravascular catheter was the most common method (62%). Adjuvant cooling in all subjects with intravenous 30 cc/kg 4 °C normal saline at 100 cc/min unless severe cardiogenic shock or renal replacement therapy

[g]Surface or intravenous cooling, not specified if close loop feedback or not. Adjuvant cooling with 4 °C normal saline (amount not specified) was recommended. Acetaminophen and aspirin use as pharmacologic agents in temperature management was discouraged. Dedicated close-loop used in 48% HT and 34% NT, basic external cooling in 37% HT vs 51% NT, intravascular cooling 15% HT and 15% NT

[h]Activation of device to a target of 37.5 °C only occurred if subject reaches 37.8 °C despite conservative and pharmacological measures. This occurred in 46% of this arm. Device could be applied upon randomization (prophylactically) or upon detection of a temperature rise

[i]Unless awake and extubated, thus controlled normothermia allowed to be aborted between hour 40–96 from randomization

[j]Thermogard XP ™ Temperature Management System (Zoll Medical Corporation) via femoral vein into inferior vena cava placed while in the catheterization lab or coronary care unit. Adjuvant cooling with ice packs to groin, neck and axillar in the pre-hospital setting encouraged

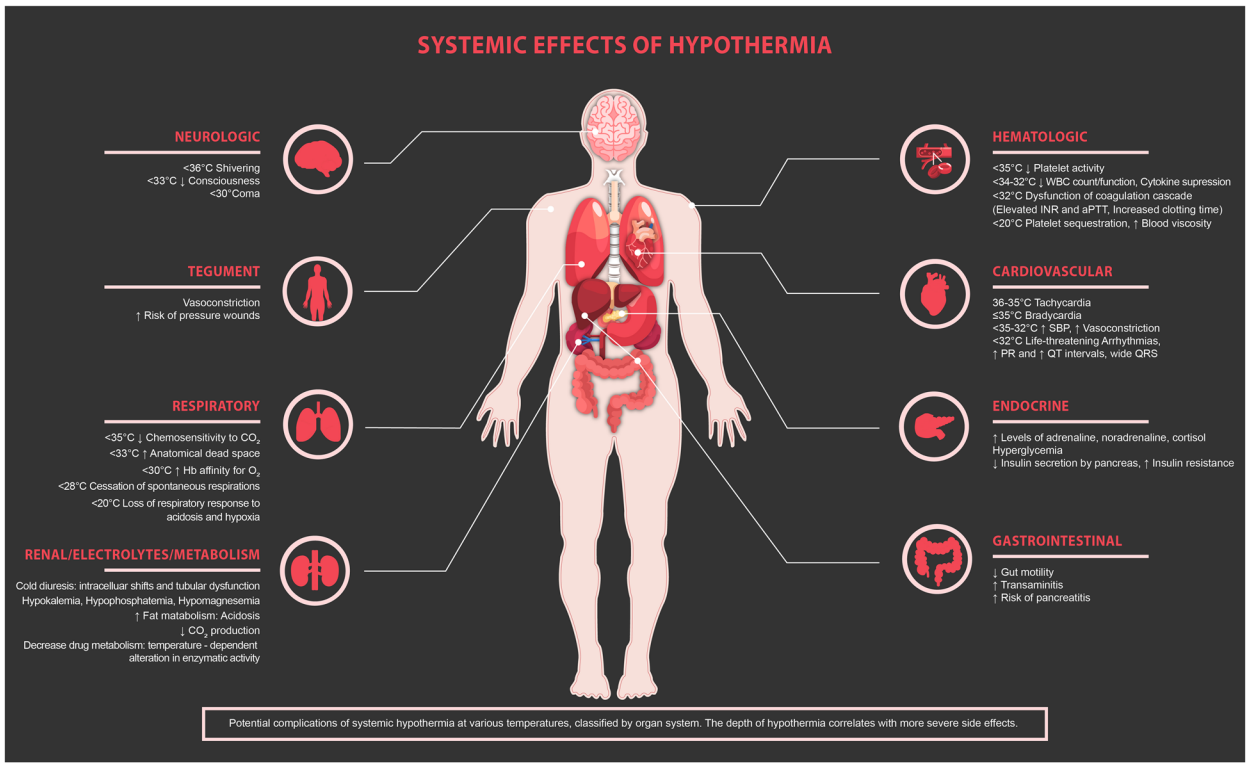

Fig. 1. Systemic effects of hypothermia.

metabolism of drugs is key when targeting lower temperatures, as the magnitude of the impact of TTM in each system hinges upon depth of hypothermia. Similarly, the effect of hypothermia on coagulation and the cardiovascular system is transient and temperature dependent. These complications have been covered in detail in other studies [31]. To maximize the potential benefit of TTM post-cardiac arrest, and minimize its deleterious effect, a standardized bundle of care focused on early achievement of target temperature during induction, stability of temperature during maintenance, aggressive shivering control across all phases, slow rewarming and controlled normothermia has been proposed [32].

Special Considerations in Pregnancy

Pregnancy has been among the most common exclusion criteria in trials on temperature control for cardiac arrest. Data supporting its use in this population is limited to case reports [33–35], which demonstrate feasibility of temperature control in pregnant patients, but do not provide sufficient evidence towards efficacy and safety in this population. The decision to initiate temperature control in pregnant patients should be made by transdisciplinary

consensus between maternal fetal medicine, obstetrics, and neurology on a case-by-case basis.

Summary and Current Recommendations

In January of 2022, the European Resuscitation Council released an updated set of guidelines regarding temperature control in patients who remain unconscious following cardiac arrest. These recommendations include continuous monitoring of core temperature and prevention of fever (defined as > 37.7 °C) for at least 72 h, with the use of antipyretic medications or a cooling device, if necessary [36••]. This recommendation is largely based on the TTM2 trial. The guidelines acknowledge the insufficient evidence to recommend for or against actively cooling patients to 32–36 °C (as in prior guidelines) or the use of early cooling post-arrest. Additionally, they recommended against the active rewarming of comatose patients following cardiac arrest who are hypothermic and recommended against using large volume infusions of cold fluid to cool patients immediately after achieving ROSC [36••]. A focused update from the American Heart Association on temperature control is in process and will consider new emerging evidence that has become available since its previous guidelines on this topic were published in 2020 [37].

Direction for Future Research

Most randomized controlled trials and meta-analyses utilize CPC or mRS scores to assess neurological status at discharge or long-term follow-up. These are relatively crude measures of neurological function and may miss important granular differences in outcome. This is important, as patients with a CPC of 1 or 2 may have new neurological deficits at one year follow-up, including mood disorders, emotional lability, or memory deficits, among others [38]—all of which could be missed by these outcome scales, especially if performed by someone who is not well trained in neurology or psychology as has often been the case in prior studies. Furthermore, many studies use even more rudimentary assessments of neurological status, such as hospital discharge disposition, and follow-up is often performed via telephone which significantly limits the accuracy of neurological assessments.

The ideal duration of hypothermia remains unclear, as only one trial has studied this variable [26]. The ICECAP study is currently enrolling patients and will assess the effect of different durations (from 6 to 72 h) of hypothermia targeting 33 °C in unconscious patients following OHCA using an adaptive design [27]. The PRECICECAP (Precision Care in Cardiac Arrest) is an ancillary study to ICECAP and represents the first rigorous initiative in precision care for TTM post-cardiac arrest aiming at identifying signatures based on individualized multimodal physiologic data to predict the optimal duration of cooling [39].

Unwitnessed arrest with asystole as the non-perfusing rhythm was excluded from both TTM1 and TTM2. These studies were likely underpowered to make a definitive recommendation on target temperature for non-shockable rhythms, and though the HYPERION study supported use of hypothermia at 33 °C, its low fragility index challenges this recommendation. The optimal temperature target for patients that were not heavily represented in robust trials of cardiac arrest, in particular IHCA and non-cardiac etiology, remains an important knowledge gap.

Conclusion

Despite ongoing controversies surrounding specific aspects of targeted temperature management, the use of a bundle of care including strict temperature control is associated with improved outcomes after cardiac arrest and should not be abandoned. It is crucial to recall that 46% of patients in the control arm of the TTM2 trial required active temperature control with a device to maintain strict normothermia. Temperature control is associated with improved outcomes following cardiac arrest and should remain an integral part of post-arrest care.

Compliance with Ethical Standards

Conflict of Interest
Nicholas Nelson declares that he has no conflict of interest. Briana Wasserstrom declares that she has no conflict of interest. Carolina Maciel declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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