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Review

Targeted Temperature Management after Resuscitation of Cardiac Arrest: A Review

Jianan Su[1], Xiaoxu Ren[1], Xiaofeng Yang[2,*]

[1]Departments of Physical Medicine and Rehabilitation, The First Affiliated Hospital, Zhejiang University School of Medicine, 310003 Hangzhou, Zhejiang, China
[2]Emergency and Trauma Center, The First Affiliated Hospital, Zhejiang University School of Medicine, 310003 Hangzhou, Zhejiang, China
*Correspondence: zjcswk@zju.edu.cn (Xiaofeng Yang)

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Abstract

Cardiac arrest (CA) is a leading cause of mortality worldwide, with cerebral injury resulting from hypoxia being its most significant complication. This condition is associated with low survival rates and unfavorable neurological prognosis. Cerebral injury following CA is a major contributor to both mortality and long-term disability. Recently, Targeted Temperature Management (TTM) has garnered considerable attention as a non-pharmacological treatment modality for brain protection, aiming to reduce hypoxia-induced damage and improve neurological outcomes following CA. This work aims to provide a comprehensive review of TTM following CA, focusing on its current status, underlying mechanisms, research advancements, and future prospects for clinical application.

Keywords: cardiac arrest; targeted temperature management; mild hypothermia therapy; brain injury

1. Introduction

Cardiac arrest (CA) is a major public health concern, with approximately 290,000 adults experiencing in-hospital CA (IHCA) [1] annually and an estimated 347,000 adults suffering out-of-hospital CA (OHCA) each year in the United States [2]. The overall survival rates following CA are poor, ranging from 7% to 10% [3]. Even when spontaneous circulation is restored through cardiopulmonary resuscitation (CPR), the brain remains highly vulnerable to the effects of ischemia and hypoxia [4], often resulting in neurologic dysfunction [5]. Ischemia-reperfusion injury can further aggravate brain damage, influencing patient prognosis. Consequently, reducing neurological injury after CA and improving survival rates and quality of life have become critical objectives in clinical research.

In 1958, researchers from the Johns Hopkins University School of Medicine published four case reports demonstrating that induced hypothermia treatment (30–34 °C) could significantly improve the neurological functions in patients who remained in a coma after IHCA resuscitation [6]. Subsequent data analysis revealed that the survival rate among patients with CA in the hypothermia treatment group was significantly higher compared to those in the non-hypothermia treatment group (50% versus 14%). This study marked the beginning of clinical research on the effectiveness and safety of temperature management in brain resuscitation after CA.

Recently, controlling body temperature has garnered growing recognition as a therapeutic strategy. In 2011, five international professional associations recommended replacing terms like "therapeutic hypothermia" and "mild hypothermia" with "Targeted Temperature Management (TTM)" [7] to reflect the breadth and significance of precise temperature control, encompassing both hypothermia and normothermia targets. TTM refers to the planned intervention to achieve and maintain a specific core body temperature range in patients, often following events like CA, to mitigate secondary injury, particularly to the brain. Mild Hypothermia Therapy (MHT), historically referring to cooling between 32–34 °C, is now often considered a component within the broader TTM strategy. 2023 American Heart Association guidelines suggest TTM can involve target temperatures ranging from 32 °C to 37.5 °C [8]. TTM is increasingly adopted worldwide and has essentially encompassed previous practices.

2. Pathophysiology

The brain employs complex mechanisms to monitor blood volume, assess oxygen content, and regulate blood demand. Through cerebral blood flow autoregulation, it can adjust the flow by modifying the supplying blood vessels [9]. However, during CA, these self-regulating systems fail to cope with sudden blood flow cessation [10]. While high-quality CPR can partially restore cerebral circulation, it is less effective than normal heart function. Inadequate perfusion initiates destructive processes leading to hypoxic-ischemic brain injury and neuronal damage.

Patients typically lose consciousness within seconds as oxygen reserves are depleted [11]. After about 4 minutes of sustained hypoxia, irreversible cell damage begins. Cellular energy stores in the form of adenosine triphosphate (ATP) deplete quickly, halting energy-dependent pumps in

the membrane. This loss of membrane integrity releases inflammatory chemicals called cytokines that trigger further inflammation. Concurrently, calcium influx disrupts metabolic functions [12]. Additionally, neurotransmitter release causes excitotoxicity due to excessive electrical activity, resulting in chemical and water influx into cells—leading to swelling and eventual cell death.

Secondary injuries significantly contribute to neuronal death; reperfusion injury is a key mechanism where restored blood flow paradoxically induces cell death [13]. Following hypoperfusion during CA, a transient hyperperfusion phase occurs once circulation is restored. During this time, the cerebral vascular system and blood-brain barrier (BBB) integrity are compromised, hindering their ability to isolate harmful metabolites. Tissue edema may arise due to water diffusion through the fragile intima [14]. Additionally, thrombus formation can occur in blood vessels due to decreased production of endogenous anticoagulants. Cells with weakened defense mechanisms from shock suffer further damage from pro-inflammatory compounds and reactive oxygen species (ROS) that extract electrons from cellular structures, potentially harming cellular contents and DNA/RNA frameworks [15]. Unfortunately, damage continues beyond this stage; delayed brain injury can affect the site for several days. Understanding these complex pathophysiological processes is crucial for developing neuroprotective strategies like TTM.

3. Potential Mechanisms of Action of TTM

Important Note: While TTM shows significant neuroprotective potential, much of the foundational research investigating the specific mechanisms described below, particularly at the cellular level, comes from animal studies or smaller clinical trials. Extrapolating these findings directly to large, diverse human populations requires caution, and efficacy in large-scale human trials needs continued validation.

TTM, particularly when employing hypothermic targets (often referred to as MHT), may protect brain tissue after hypoxia-ischemia through several mechanisms.

3.1 Reduction in Cerebral Metabolic Rate

One of the main proposed mechanisms of therapeutic hypothermia is its ability to lower the brain's metabolic rate, reducing cellular energy and oxygen demands, thus potentially mitigating neuronal damage. After an ischemic event, the brain faces increased oxygen and glucose needs, leading to rapid metabolic impairment in hypoxia. During cooling, a 1 °C decrease in body temperature can reduce brain metabolism by about 6% to 10% [16]. This decline lowers oxygen demand while potentially preventing lactic acid and free radical accumulation. Such early intervention might effectively reduce secondary damage and create conditions conducive to cellular repair.

3.2 Inhibition of Excitatory Amino Acid Release

The release of excitatory amino acids, particularly glutamate, significantly contributes to neuronal damage in the early stages after brain injury [17]. Following cerebral ischemia, excessive glutamate leads to calcium influx via over-activation of N-methyl-D-aspartate (NMDA) receptors. This initiates harmful intracellular processes such as ROS production, mitochondrial dysfunction, and protein denaturation. Hypothermia may reduce neuronal damage by inhibiting glutamate release and NMDA receptor overactivation. Studies suggest hypothermia can lower excitatory amino acid levels in the brain, potentially protecting neurons from ischemic injury [18].

3.3 Reduction in the Generation of Reactive Oxygen Species (ROS)

Reperfusion following cerebral ischemia produces large quantities of ROS, including free radicals, which significantly contribute to cellular damage. These free radicals primarily target lipids, proteins, and nucleic acids in cell membranes, leading to lipid peroxidation, protein denaturation, and DNA damage that trigger apoptosis and necrosis. Hypothermia may reduce free radical production by lowering metabolic rates and inhibiting lipid peroxidation. Additionally, hypothermia might enhance the activity of antioxidant enzymes like superoxide dismutase and glutathione peroxidase, which neutralize free radicals and further reduce oxidative stress-induced damage to nerve cells [19].

3.4 Regulating the Inflammatory Response

The inflammatory response after brain injury significantly contributes to secondary damage [20], primarily through neuroglial cell activation and the release of inflammatory factors like TNF-α, IL-1β, and IL-6. Hypothermia has been shown in some studies to reduce nerve damage linked to this inflammatory response by inhibiting the expression and release of these mediators [21]. Furthermore, hypothermia might prevent leukocyte migration and adhesion at the injury site, reduce BBB disruption, and lower the incidence of brain edema [22]. Studies indicate that hypothermia may not only alleviate acute inflammation but also potentially mitigate the long-term effects of chronic inflammation on brain tissue.

3.5 Inhibition of Apoptotic Pathways

Apoptosis, or programmed cell death, is a key pathway in neuronal loss following brain injury. In ischemic and reperfusion injuries after CA, the apoptotic pathway is heavily activated, leading to significant neuronal damage. Hypothermia may inhibit apoptosis through several mechanisms: potentially upregulating the anti-apoptotic protein B-cell lymphoma 2 (Bcl-2), suppressing pro-apoptotic protein Bax expression, and reducing Caspase-3 activity [23]. Additionally, hypothermia might help maintain mitochondrial function and prevent loss of mitochondrial membrane

potential, thereby hindering apoptosis initiation. These coordinated mechanisms could effectively protect neurons and reduce nerve damage.

3.6 Facilitating the Stabilization of the Blood-brain Barrier (BBB)

The BBB is essential for maintaining brain tissue homeostasis. Brain injuries, especially ischemic ones, often disrupt the BBB, allowing harmful substances to enter and worsen the injury [24]. Hypothermia may help preserve BBB integrity and reduce permeability by counteracting factors that impair its function, such as matrix metalloproteinases [25]. This protective effect could be crucial in the acute phase, potentially reducing brain edema and preventing further damage to brain tissue.

3.7 Preservation of Mitochondrial Function

Mitochondria are central to intracellular energy metabolism and play a crucial role in regulating apoptosis. After cerebral ischemia, mitochondrial dysfunction is a major contributor to cell death [26]. Hypothermia therapy may preserve mitochondrial function by reducing calcium overload, suppressing ROS generation, and stabilizing the mitochondrial membrane potential. This maintenance of mitochondrial integrity could support ATP synthesis and reduce cell death linked to impaired energy metabolism. Additionally, hypothermia might offer neuroprotective benefits by inhibiting the mitochondria-dependent apoptotic pathway [27].

Although these mechanisms suggest significant neuroprotective potential, confirming the effectiveness and safety of TTM, particularly specific temperature targets, through large multicenter randomized controlled trials (RCTs) remains crucial, especially in CA, stroke, and brain trauma. The results from ongoing and future large-scale trials will provide a stronger scientific foundation for the wider application of TTM and aid in developing more standardized and potentially individualized treatment guidelines.

4. The Targeted Temperature Management (TTM) Procedure

Implementing TTM involves several distinct phases: initiation and cooling, maintenance at the target temperature, and controlled rewarming. Precise management throughout these stages is critical for maximizing potential benefits and minimizing complications.

4.1 Initiation Timing

In 2023, the American Heart Association (AHA) released guidelines for CPR and cardiovascular emergency care, recommending that for adult patients with CA who regain spontaneous circulation but remain in a coma, TTM treatment should be administered [8]. Prompt initiation is generally advocated. One study demonstrated that controlling the time from hospital arrival to TTM initiation within 122 min significantly improved survival rates of patients with CA presenting with shockable rhythms [28]. Studies have suggested that promptly initiating TTM following CPR can help reduce reperfusion injury. Delaying the initiation of TTM by even 1 hour has been associated with an approximately 20% increase in the patient's risk of mortality in some observational data [29].

However, the benefit of pre-hospital cooling remains controversial. Although early cooling strategies offer theoretical benefits, some RCTs have found that rapid induction of hypothermia using large volumes of ice-cold saline either pre-hospital or during CPR did not improve patient outcomes and might even increase the risk of re-arrest or pulmonary edema [30,31]. Additionally, although nasal cooling devices can significantly shorten the time required to achieve the target temperature, they have not been demonstrated to significantly improve the patient's neurological outcomes or survival rates [32]. Considering the heterogeneity of patients with CA and the need for bundled post-resuscitation care, demonstrating the isolated benefit of very early pre-hospital TTM initiation remains challenging. Current recommendations focus on initiating TTM promptly upon hospital arrival for eligible patients.

4.2 Target Temperature Selection

The 2023 AHA guidelines recommend that patients receiving TTM maintain a core temperature between 32 °C and 37.5 °C. There is ongoing debate about the most effective target temperature within this range [33], fueled by results from major clinical trials (discussed in Section 6). CA is a heterogeneous condition characterized by varying types of injury and degrees of hypoxic ischemic brain damage, making a uniform target temperature for all CA patients potentially inappropriate. Some research suggests patient severity might influence optimal temperature targets. A clinical study involving 6925 CA patients used a modified version of the Cardiac Arrest Hospital (mCAHP) score to classify severity, they found that those with mild and severe CA appeared to benefit more from TTM at 32–36 °C, while moderate CA patients did not show similar benefits [34]. Another study with 1319 CA patients indicated that those with mild to moderate cases might benefit from a TTM target of 36 °C, whereas severe cases showed potentially greater benefit at a target temperature of 33 °C [35].

Regardless of the target temperature set, precise control is essential during TTM [36]. Accurate core temperature monitoring is crucial. In emergencies, measuring central circulation or brain tissue temperature can be challenging, so alternative sites like the bladder, rectum, or esophagus are often used [37–39]. Esophageal and bladder temperatures are considered reliable surrogates for core temperature. Current guidelines do not mandate a specific measurement site. If using methods without integrated feedback (like basic surface cooling), measuring core body tempera-

ture at two different sites is advised [40]. Monitoring temperature simultaneously in the esophagus and in the urinary bladder is an accessible and reliable combination, although esophageal measurements seem to better reflect the dynamics of temperature changes, thus it seems to be more appropriate for MHT control [41].

An effective approach involves grading the severity of the patient's condition, which can be achieved by assessing physiological parameters and biomarkers. In addition, multimodal brain assessments, including electroencephalography (EEG), magnetic resonance imaging (MRI), and cerebral blood flow monitoring, can provide more detailed insights into brain function and injury severity. Based on this comprehensive information, a tailored target temperature might be determined as part of an individualized treatment strategy. This approach aims to optimize treatment outcomes and ultimately improve patient survival and neurological recovery.

4.3 Cooling Phase

During the cooling phase of TTM, early initiation post-resuscitation of cardiac arrest (ROCA) is generally advised, but research on the impact of the rate of cooling on patient prognosis is inconsistent. A study suggests that rapidly lowering core body temperature to a target level may enhance survival and neurological outcomes [42]. However, in patients with severe neurological injury, damage to the thermoregulatory center can lead to an excessive drop in body temperature below the target range (overshooting), which is often associated with poorer prognosis [43]. Therefore, precise control and maintenance of core body temperature at a stable target level are essential. Automated temperature control devices (both surface and endovascular) with feedback mechanisms can help achieve target temperatures more predictably, reduce temperature fluctuations, and potentially improve neurological function outcomes [44].

Cooling methods primarily include surface cooling and intravascular (endovascular) cooling.

4.3.1 Surface Cooling

Traditional techniques like ice packs, cooling blankets, and cold water sponging are simple and non-invasive. However, basic methods often lack precision in achieving and maintaining target temperatures. Modern surface cooling systems utilize adhesive pads with circulating cold water and incorporate temperature feedback mechanisms for better control. Rapid infusion of large volumes (e.g., 2000 mL) of ice-cold saline can lower core body temperature but has not been shown to improve survival or neurological outcomes and may increase risks like pulmonary edema [30].

4.3.2 Intravascular Cooling

These devices cool blood directly using catheters inserted into large central veins (e.g., femoral, subclavian). Temperature-controlled fluid circulates within the catheter. Some studies suggested intravascular cooling might lead to better neurological outcomes, but comparator groups often used less precise surface cooling methods without feedback systems [45]. Currently, there is a lack of high-quality RCTs directly comparing modern surface cooling with feedback systems to intravascular cooling regarding patient neurological outcomes and mortality. Intravascular cooling carries potential risks associated with central venous catheterization, such as infection, bleeding at catheter sites, and deep vein thrombosis [46,47].

The choice of cooling method often depends on institutional resources, expertise, and patient factors. The priority is achieving and maintaining the target temperature accurately and safely.

4.4 Hypothermia Maintenance Stage

The 2023 AHA guidelines recommend maintaining temperature control for at least 24 hours after reaching the target temperature [8]. There is ongoing debate about whether extending TTM duration beyond 24 hours provides additional benefits. One RCT showed a non-significant trend towards improved neurological outcomes with 48 hours of TTM compared to 24 hours [48]. A large RCT (NCT04217551) [49] is currently assessing the effects of prolonged hypothermia. It may be reasonable to tailor TTM duration based on the extent of brain function impairment in CA patients. A multicenter study found that the ratio of TTM duration to ischemic time positively correlated with functional prognosis, though this relationship might partly reflect the duration of resuscitation efforts (ROSC time) [50].

The potential neuroprotective effects of TTM during the maintenance phase include reducing brain edema, improving cerebral tissue oxygenation, potentially improving EEG activity, lowering brain injury markers, and possibly restoring cerebral autoregulation. However, extended hypothermia treatment carries risks such as infection and bleeding (discussed in Section 5). Therefore, continuous assessment of neurological recovery and patient tolerance to TTM is crucial. The timing for initiating rewarming should be determined based on these evaluations. Advancements in multimodal brain monitoring techniques—such as continuous EEG, cerebral oxygenation measurement, and injury marker analysis—may help guide decisions about TTM duration in the future.

4.5 Rewarming Phase

Controlled rewarming is a critical phase of TTM. Rapid rewarming can be detrimental. A multicenter study suggested that a slow rewarming strategy (e.g., 0.25 °C per hour, equivalent to roughly 1 °C/4 h) might be associated with improved neurological outcomes compared to faster rates [50]. Clinical practice generally aims for a controlled rewarming rate, often around 0.25–0.5 °C per hour.

During rewarming, a "rebound" hyperthermia phenomenon may occur, causing body temperature to spike above desired levels (e.g., >38.5 °C), which can worsen neurological injury [51]. This necessitates the use of TTM devices with temperature feedback systems for precise control over the rewarming process and prevention of overshooting.

Furthermore, fever following the completion of TTM can also worsen neurological damage. Actively preventing fever (maintaining normothermia, typically ≤37.7 °C) for an extended period (e.g., up to 72 hours) after rewarming is crucial. A 2021 RCT published in The New England Journal of Medicine (TTM2 trial) actively managed temperature between 36.5–37.7 °C for at least 72 hours in both study arms after the initial intervention period [52].

While many studies have focused on the rewarming phase, research on using multimodal brain monitoring to *guide* this process remains limited. During rewarming, patients are at risk for complications like increased cerebral oxygen consumption and aggravated cerebral edema. Therefore, the medical team should closely monitor neurological status and physiological parameters, adjusting the rewarming rate or even considering resuming cooling if necessary. Greater application of quantitative brain function assessments may enhance personalized management during this phase.

5. Common Complications and Side Effects of TTM

5.1 Chills and Shivering

Actively controlling chills and shivering during TTM is essential, as they significantly increase metabolic rate and oxygen consumption, counteracting the intended therapeutic effects and potentially worsening outcomes. A standardized assessment tool like the Bedside Shivering Assessment Scale is recommended for evaluation and management [53]. Initial management should focus on non-pharmacological interventions, such as surface counter-warming (e.g., forced air warming blankets applied to non-cooled areas, gloves, socks) [54]. If these methods are insufficient, pharmacological interventions are necessary. This typically involves adequate sedation and analgesia. Short-acting agents are preferred to minimize drug accumulation and avoid delays in neurological assessment upon rewarming. Common strategies include combinations of sedatives (e.g., propofol, dexmedetomidine), opioids (e.g., fentanyl, remifentanil), and sometimes adjunctive medications like magnesium, buspirone, or paracetamol. In refractory cases, neuromuscular blocking agents (paralytics) may be required, but their use necessitates deep sedation and mechanical ventilation [55]. Management strategies should be adjusted based on the cooling method (surface vs. endovascular) and patient response.

5.2 Infection Risk

Hypothermia can potentially impair immune function, possibly increasing the risk of infections like pneumonia and sepsis [56]. This may be related to effects such as inhibiting white blood cell migration and phagocytosis [57]. Additionally, sedative and analgesic drugs used for shivering control can impair cough reflexes and increase the risk of aspiration and lung infections. While prophylactic antibiotics are not routinely recommended solely due to TTM, strict aseptic techniques for all procedures are crucial. Regular monitoring of indicators of infection, such as blood counts, C-reactive protein, and procalcitonin levels, is essential for early detection and timely treatment of infections [58].

5.3 Bleeding Risk

Hypothermia can impair coagulation by inhibiting platelet function and slowing the activity of coagulation factors, potentially prolonging clotting times and increasing bleeding risk [59]. This risk is particularly relevant in patients who have undergone surgery, experienced trauma, or require anticoagulation/antiplatelet therapy [60]. Monitoring coagulation parameters (e.g., prothrombin time, activated partial thromboplastin time, platelet count, fibrinogen) is important during TTM [61]. For patients at high bleeding risk, the decision to use TTM, the target temperature, and duration should be carefully considered [62]. In cases of significant bleeding, TTM might need to be interrupted or discontinued, and appropriate measures like transfusion or coagulation factor replacement may be necessary.

5.4 Arrhythmias

Lower temperatures can alter cardiac electrophysiology, increasing the risk of arrhythmias. Bradycardia is common and often well-tolerated; treatment is usually unnecessary unless it causes hemodynamic instability [63, 64]. Atropine may be ineffective for hypothermia-induced bradycardia [65]. Other arrhythmias like atrial fibrillation or ventricular ectopy can occur. While hypothermia itself has a relatively minor direct impact on myocardial contractility, the associated bradycardia can reduce cardiac output [66]. Gradual cooling may help minimize arrhythmias. Close electrocardiogram monitoring is essential, especially in patients with pre-existing heart disease or electrolyte imbalances. Adjustments to the cooling protocol or antiarrhythmic drugs may be needed if significant arrhythmias occur.

5.5 Digestive System Disorders

Hypothermia can potentially reduce gastrointestinal motility and impair gastric emptying, possibly leading to ileus or gastric retention. This may be due to direct effects on smooth muscle and blood flow, as well as the inhibitory effects of sedative and analgesic medications. Close monitoring of gastrointestinal function (e.g., bowel sounds, ab-

dominal distension, feeding tolerance) is necessary. Enteral nutrition should be initiated when feasible, potentially using post-pyloric feeding tubes to reduce the risk of aspiration if gastric retention is a concern [67].

5.6 Electrolyte Imbalances

TTM can disrupt fluid and electrolyte balance. Hypothermia can induce a "cold diuresis" initially. Electrolyte shifts are common; hypokalemia, hypomagnesemia, hypophosphatemia, and hypocalcemia can occur during cooling as ions shift intracellularly. Conversely, during rewarming, these ions may shift back into the extracellular space, potentially causing hyperkalemia and other imbalances. These disturbances can affect cardiac and neurological function. Therefore, regular monitoring of electrolytes (especially potassium, magnesium, phosphate, calcium) and appropriate supplementation or management during both cooling and rewarming phases are essential [68].

5.7 Metabolic Disorders (Glucose)

Hypothermia can affect glucose metabolism. It may decrease insulin secretion and increase insulin resistance, potentially leading to hyperglycemia, which itself can be detrimental to the injured brain [69]. Conversely, during rewarming, insulin sensitivity may increase, and metabolic rate rises, potentially increasing the risk of hypoglycemia if insulin infusions are not adjusted accordingly [70,71]. Careful blood glucose monitoring and management, often targeting a moderate range (e.g., 144–180 mg/dL or 8–10 mmol/L, though institutional protocols vary), are crucial to avoid both hyperglycemia and hypoglycemia.

5.8 Neurological Complications

While TTM aims to be neuroprotective, potential neurological complications exist. Seizures can occur in post-CA patients, and hypothermia might mask clinical signs while potentially altering seizure threshold or EEG patterns [72]. Continuous EEG monitoring is strongly recommended during TTM and after rewarming in comatose post-CA survivors to detect seizures, including non-convulsive seizures [73]. If seizures occur, prompt treatment is necessary. Prolonged sedation required for TTM can also complicate neurological assessments.

With advancements in neurocritical care, improved TTM methods, and enhanced multimodal monitoring, the overall systemic adverse effects have become more manageable. However, implementing TTM remains a complex process requiring a skilled multidisciplinary team and clear protocols to minimize adverse reactions while optimizing efficacy.

6. Clinical Evidence and Progress of TTM After Resuscitation of CA

The use of TTM after CA gained significant traction following landmark trials published in 2002 (Fig. 1 summarizes key trial developments). Two major clinical trials, the Bernard Trial [74] and the Hypothermia After Cardiac Arrest (HACA) trial [75], provided initial strong evidence supporting TTM. These studies indicated that inducing and maintaining hypothermia at 32–34 °C for 12–24 hours in comatose survivors of OHCA (primarily with initial shockable rhythms like ventricular fibrillation) led to significantly better neurological outcomes and improved survival rates at six months compared to standard care (normothermia at the time). This established TTM (specifically MHT at 32–34 °C) as a standard of care.

Subsequent research aimed to refine TTM protocols, leading to significant debate.

TTM1 Trial (2013): The Targeted Temperature Management trial (TTM1) [31] compared two hypothermic targets, 33 °C versus 36 °C, in nearly 1000 unconscious survivors of OHCA (regardless of initial rhythm). It found no significant difference in mortality or neurological outcome between the two groups, suggesting that targeting 36 °C might be as effective as 33 °C. This led many centers to adopt 36 °C as their target.

HYPERION Trial (2019): This trial [32] focused specifically on 584 comatose CA survivors with initial non-shockable rhythms (like asystole or pulseless electrical activity), a group often excluded or underrepresented in earlier trials. It compared moderate hypothermia (33 °C for 24 h) versus targeted normothermia (37 °C). The intervention group (33 °C) had a significantly higher rate of favorable neurological outcome at 90 days compared to the normothermia group. Mortality rates were similar between groups. This provided evidence supporting hypothermia (33 °C) specifically for patients with non-shockable rhythms.

TTM2 Trial (2021): The Targeted Hypothermia versus Targeted Normothermia after Out-of-Hospital Cardiac Arrest (TTM2) trial [52] was a large trial involving over 1800 OHCA patients (all rhythms). It compared targeted hypothermia (33 °C) versus targeted normothermia (actively preventing fever, keeping temperature $\leq$37.8 °C, with a target of 37.5 °C if fever occurred). The results showed no significant difference in six-month mortality (50% vs. 48%) or poor functional outcome (55% vs. 55%) between the hypothermia and normothermia groups. This trial raised significant questions about the benefit of targeted hypothermia (33 °C) compared to simply actively preventing fever in the broader OHCA population.

Following TTM2, debate continues regarding whether temperature control beyond strict fever prevention (i.e., targeting $\leq$37.7 °C) offers additional benefit for neurological recovery after CA.

However, registry data often show associations between hypothermia use and better outcomes, although these are subject to selection bias. For example, an analysis of over 33,000 patients from the German Resuscitation Registry (GRR) [36], including both OHCA and IHCA, found that patients who received MHT (target temperatures

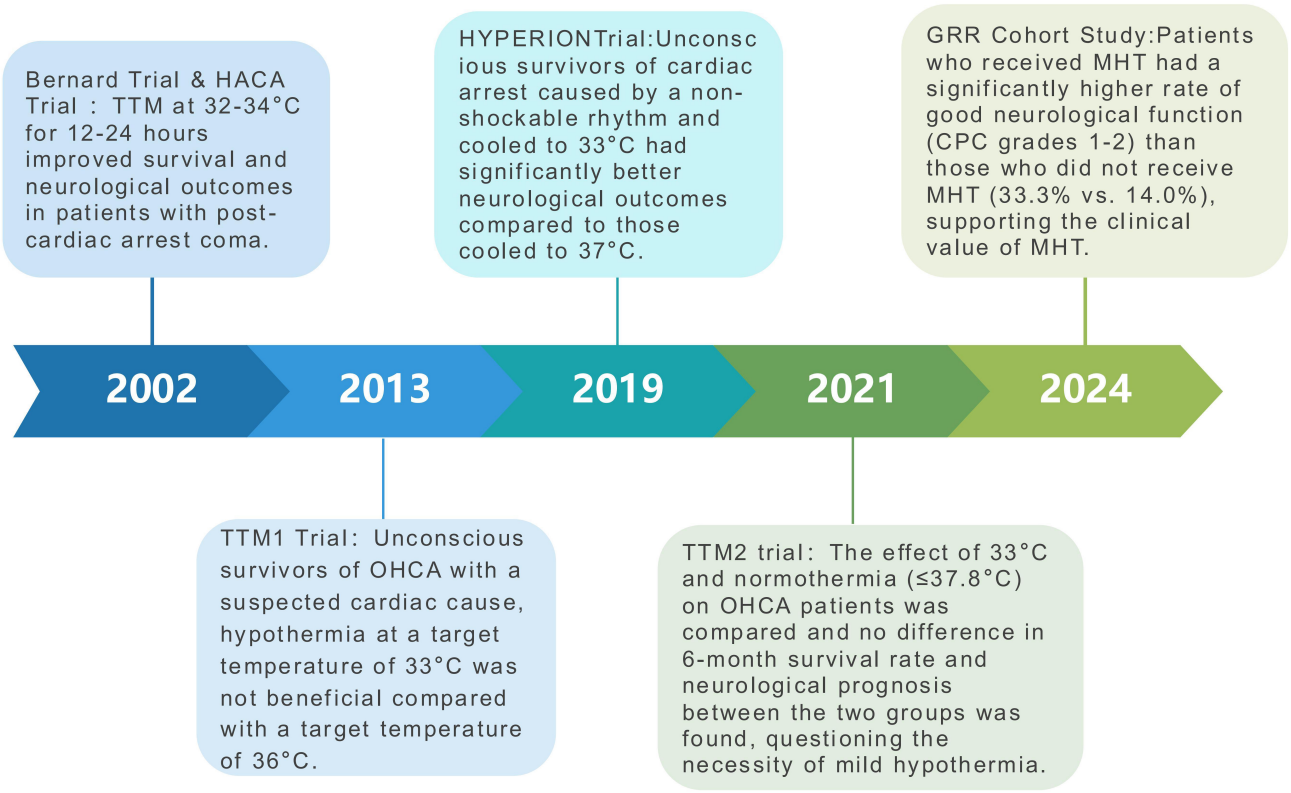

Fig. 1. Evolution of targeted temperature management trials for cardiac arrest. HACA, Hypothermia After Cardiac Arrest; TTM, Targeted Temperature Management; OHCA, out-of-hospital cardiac arrest; GRR, German Resuscitation Registry; CPC, Cerebral Performance Category; MHT, Mild Hypothermia Therapy.

likely varied but were generally hypothermic) had a significantly higher rate of favorable neurological outcomes (Cerebral Performance Category [CPC] grade 1/2) at discharge (33.3%) compared to those who did not receive MHT (14.0%, $p < 0.001$). Thirty-day survival was also higher in the MHT group (42.3% vs. 17.3%, $p < 0.001$). While significant differences in baseline prognostic factors existed between the groups, these registry findings are often cited to support the continued clinical value of TTM, particularly hypothermia, in practice.

The conflicting results between RCTs (especially TTM1 and TTM2) and registry data, along with subgroup findings (HYPERION), highlight the complexity and the likely need for more individualized approaches to TTM after CA. Current guidelines (e.g., AHA 2023) continue to recommend TTM, allowing a target range of 32–37.5 °C, while emphasizing the critical importance of actively preventing fever in all post-CA comatose patients [8].

7. Future Research Directions

Despite progress, several areas require further investigation to optimize TTM after CA.

7.1 Individualized Treatment Protocols

Tailoring TTM strategies will be a key focus of future research. This includes determining optimal target temperatures for specific patient subgroups (e.g., based on initial rhythm, severity of injury, cause of arrest), establishing ideal timing and duration for TTM, and refining rewarming protocols. Significant variability exists in baseline conditions and causes of CA among patients, which likely affects their response to TTM. Personalized approaches based on patient characteristics and potentially guided by real-time monitoring may improve outcomes.

7.2 Enhancement of Neurological Function Assessment and Prognostication

Current primary indices for evaluating TTM efficacy include survival rates and neurological function recovery scales (like CPC or modified Rankin Scale), which can be relatively rudimentary, especially for early prognostication. Biomarkers are being investigated. Studies have suggested that blood levels of brain-derived neurotrophic factor (BDNF), neuron-specific enolase (NSE), S-100B protein, tau protein, neurofilament light chain (NFL), glial fibrillary acidic protein (GFAP), and ubiquitin C-terminal hydrolase-L1 (UCH-L1) might serve as markers for neurological prognosis after TTM [72,73]. However, their sensitivity, speci-

ficity, and optimal timing require further validation. Continuous EEG and other multimodal monitoring techniques also play a role. Seeking better early predictive tools remains crucial to provide accurate information to families and potentially guide decisions about ongoing care.

7.3 Exploration of Combined Therapeutic Strategies

As understanding of post-CA pathophysiology deepens, researchers are increasingly exploring the concurrent use of TTM with alternative therapeutic approaches. Examples include combining TTM with specific pharmacological interventions, such as antioxidants, anti-inflammatory agents, or other neuroprotective drugs [74]. Additionally, emerging modalities like novel neurostimulation techniques or stem cell therapy are gaining attention and might potentially be integrated with TTM in the future to further augment neuroprotective efficacy [75,76].

8. Conclusions

TTM is a critical component of post-cardiac arrest care aimed at improving neurological outcomes. While early trials strongly supported MHT (32–34 °C), more recent large RCTs (TTM1, TTM2) have shown similar outcomes between 33 °C and 36 °C, and between 33 °C and controlled normothermia (actively preventing fever $\leq$37.7 °C), leading to 2023 American Heart Association guidelines recommending a broader target range (32–37.5 °C) while emphasizing universal fever prevention [8]. TTM likely exerts its potential benefits through multiple mechanisms including reduced metabolic rate, inflammation, and excitotoxicity. However, it also carries risks like shivering, infection, bleeding, and electrolyte disturbances that require careful management.

More comprehensive research is needed to determine optimal TTM regimens, potentially through individualized strategies based on patient characteristics and injury severity, guided by advanced monitoring. Investigating combined treatment strategies also holds promise. With ongoing advancements in basic research and clinical trials, TTM is anticipated to remain a cornerstone of post-CA care, with efforts focused on refining its application to provide the most effective neuroprotective solution for patients recovering from CA.

Author Contributions

JS, XR and XY designed the research study, collected, analyzed literatures and contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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Conflict of Interest

The authors declare no conflict of interest.

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