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Critical Care Neurology (K Sheth, Section Editor)

Normothermia and Stroke

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Opinion statement

In the past two decades, there has been much focus on the adverse effect of fever on neurologic outcome, the benefits of hypothermia on functional outcomes, and the interplay of associated complications. Despite decades of experience regarding randomized, safety and feasibility, case-controlled, retrospective studies, there has yet to be a large, randomized, multicenter, clinical trial with the appropriate power to address the potential benefits of targeted temperature modulation compared to hypothermia alone. What remains unanswered is the appropriate timing of initiation, duration, rewarming speed, and depth of targeted temperature management. We learn from the cardiac arrest literature that there is a neuroprotective value to hypothermia and, most recently, near normothermia (36 °C) as well. We have also established that increased depths of cooling are associated with increases in shivering, which warrant more aggressive pharmacologic management. Normothermia also has the advantage of allowing for more rapid clearance of sedating medications and less confounding of neuroprognostication. More difficult to quantify is the increased nursing and patient care complexity associated with moderate hypothermia compared to normothermia. It remains crucial, for those patients who are being considered for hypothermia/normothermia, to be cared for in an experienced ICU, driven under protocol, with aggressive shivering management and an expectation and acceptance of the complications associated with targeted temperature management. If targeted temperature management is not of consideration, then aggressive fever control should be undertaken pharmacologically and non-invasively, as they have been shown to be safe.

Introduction

Recent attention has shifted toward the impact of normothermia in stroke, with a transition away from hypothermia given its riskier safety profile. Despite the flux in the depth of temperatures studied, the deleterious effects of fever are well established. In 2008, Greer and colleagues [1], in a pooled analysis of 14,431 patients with stroke and other brain injuries, established that fever is associated with worse outcomes across multiple measures. Worse outcomes with their respective relative risks included modified Rankin scale (mRS) 2.2, Canadian stroke scale 1.4, intensive care length of stay 2.8, and hospital stay 3.2. These numbers may be an underestimate of the worse outcomes in the examined stroke population as compared to all brain-injured patients. In their analysis, they noticed differences in the timing of temperature measurement with 67% in the intracerebral hemorrhage (ICH) studies evaluated temperature results within the first 24 h, 40% in the ischemic stroke (AIS) studies, and only 20% in the traumatic brain injury (TBI) studies. The heterogeneity of populations and variability in the timing of temperature evaluation makes the application to clinical practice less feasible, compelling investigators to study select patient groups with a narrower window of temperature management strategies.

Another area of study has been the depth of hypothermia as related to neurologic protection and overall safety. This was brought to attention in the recent TTM trial [2••], an international trial examining 950 cardiac arrest patients randomized to targeted temperature management at either 33 or 36 °C. They concluded that targeted temperature of 33 °C did not confer a benefit compared with a targeted temperature of 36 °C, with a similar adverse effect profile. In the antecedent therapeutic hypothermia in cardiac arrest trials [3, 4], Bernard and the HACA group conferred improved functional outcomes and survival with hypothermia (32–34 °C) after cardiac arrest. What the studies failed to elaborate upon is that the control (or "normothermia") group was relatively hyperthermic on average. This leaves it unclear as to whether there was benefit from hypothermia or potential worsening from hyperthermia. These data dictate further exploration of fever prevention, some of which are underway and to be discussed, rather than hypothermia and its associated adversities, to prevent secondary brain injury and to improve outcomes.

Current guidelines

The American Heart Association (AHA)/American Stroke Association (ASA) guidelines for early management in patients with AIS [5] acknowledge that hyperthermia is associated with poor neurological outcome. The guidelines further quote several trials looking at pharmacologic management of fevers with NSAIDS and/or acetaminophen as not having a significant effect on patients with higher temperatures (>38 °C) [6], on the difference in mean temperatures after 24 h [7], or convincing data for a robust clinical impact [8]. They further refer to the PAIS trial, a large, randomized, double-blinded study of a proposed 2500 patients comparing early acetaminophen to control in improving functional outcome by reducing body temperature. There was no significant difference in the primary or secondary measures of improved neurologic outcomes in this early terminated study (1400 patients enrolled). Although, post hoc analyses were promising, suggesting a beneficial effect of paracetamol on both improved neurologic outcomes as well as larger temperature reductions (0.3 °C) in patients with higher baseline temperatures 37 to 39 °C [9]. The class I guideline recommendation remained that hyperthermia (>38 °C) should be treated with medication, without recommendation of more aggressive temperature management measures.

With respect to hypothermia, the AIS guidelines refer to the mixed results of two

small studies [10, 11] and a systematic review by Den Hertog et al. [12]. None of these studies suggested compelling evidence to suggest the use of therapeutic hypothermia (Class IIb), especially in the setting of known complications with lower temperatures including hypotension, cardiac arrhythmias, pneumonia, and thrombocytopenia. Ongoing clinical feasibility and clinical trials were recommended. There is no data referred in the guidelines that address targeting of normothermia, temperatures ranging 35 to 38 °C.

The 2015 AHA/ASA Guidelines for the Management of Spontaneous ICH [13] are even less robust when recommending fever control or therapeutic hypothermia management. They maintain that the data provide "rationale" that treatment of fever may be reasonable (Class IIb). They further hold that mild hypothermia should be considered investigational.

The most full-bodied recommendations to treat fevers are in the aneurysmal subarachnoid guidelines. The AHA/ASA Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage (SAH) [14] suggest Class IIa/Level B evidence in favor of aggressive control of fever to normothermia by standard means. The counterpart to these guidelines is the Recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference [15]. They strongly recommend (high quality evidence) that fever control is desirable especially during the delayed cerebral ischemia risk period, with the intensity of control reflecting the patients relative risk for ischemia. They quote several trials which deem acetaminophen, ibuprofen, fanning, evaporating cooling, ice packs and cooling blankets as ineffective. They also give a strong recommendation for surface and intravascular cooling devices, in appropriate patients, when antipyretics fail. There is also mention of shivering and the importance of its control/prevention. However, the recommendations contained in these SAH guidelines were not based on any known randomized controlled clinical trials.

Deleterious effects of fever

The healthy brain is about 0.5 to 1 °C warmer than the body and injured areas can be even up to 2 °C higher due to transient hyperactivity [16]. It is this hyperactivity that can lead to neuronal injury, necessitating immediate attention. Every year, close to 800,000 people suffer from a stroke in the USA [17]. Stroke is also a leading cause of serious long-term disability in the USA [18]. Fever contributes to disability, through a range of pathophysiologic mechanisms in the various stroke subtypes. The literature has been conclusive on the deleterious effects of fever, despite different etiologies, timing of fever, and treatments studied.

In order to determine predictors of early neurologic deterioration, Leira et al., in a multicenter prospective study, looked at 236 patients with spontaneous supratentorial ICH admitted within 12 h of stroke. They illustrated that fever, elevated neutrophil count and elevated plasma fibrinogen, were independently associated with early neurologic deterioration in close to 23% of the cases, as well as an eightfold increase in poor outcome [19]. Neurologic deterioration from fevers can worsen beyond the initial admission period. In a retrospective study of 251 consecutive patients with ICH admitted within 24 h of onset, Schwartz et al. found that increased body temperatures on admission were associated with the presence of

intraventricular blood. Furthermore, 91% of the patients had a temperature 37.5 °C or more at least once during the 72-h observation period, with the duration of fever 24 to 48 h in 36%, and more than 48 h in 21%. They concluded that the incidence of fever in ICH is high, and in survivors of the 72 h observation period, a longer duration of fever is independently associated with poor outcome [20]. More recently, Rincon et al. extracted data from the Virtual International Stroke Trials Archive and illustrated a temporal association between fever and hematoma growth, as well as poor functional outcome at 90 days. Similar to Schwarz et al., they observed more fevers after the initial 24 h after admission. They suggested an inflammatory process causing hematoma growth, with an independent association of both hematoma volume and growth to temperature elevation, after adjustment for additional predictors of temperature elevation (white blood cell count, infection, phenytoin exposure, hematoma volume, and IVH) [21].

In 1996, Reith et al. showed that there was an association between temperature, initial stroke severity, infarct size, mortality, and outcome. Causality was not determined [22]. In 2002, the Copenhagen Stroke Study went further to illustrate that admission body temperature was a major determinant for long-term mortality after stroke, with lower body temperatures predicting better outcomes. Further, they showed a 1 °C increase in admission body temperature corresponded to a 30% difference in the relative risk of long term mortality [23]. The causality between acute ischemic stroke, fever, and mortality was further clarified in the Prasad meta-analysis. They showed that early fever was increased in AIS and almost doubled the risk of short term mortality, independent of age and stroke severity [24]. In a more recent and novel clinical and imaging study of 40 patients, Karaszewski et al. attempted to clarify the association between body and brain temperature and their relation to outcome. By comparing the ischemic to the contralateral/unaffected hemispheric temperatures, they were able to differentiate that elevated ischemic brain temperature reflects a local tissue response, whereas temperatures in the unaffected brain reflects a systemic response to stroke which occur later, with the latter being associated with poor 3 month functional outcomes [25]. An interesting contrary report was presented in the same year by de Ridder et al. (PAIS investigators), suggesting that patients receiving IV tPA and a high body temperature (≥37.0 °C) may benefit more compared to lower body temperature [26]. Although the PAIS trial was not designed to assess this effect, it brought attention to the relationship of tPA metabolism and body temperature.

When addressing SAH, of importance is the interplay between intraventricular hemorrhage (IVH), delayed cerebral ischemia (DCI), vasospasm, and fever. Oliveria-Filho et al. found that patients with symptomatic vasospasm were at an increased risk of developing fever (OR = 5), suggesting a possible common pathogenesis. Poor outcome were also independently associated with fevers [27]. Fernandez et al. then demonstrate that poor-grade SAH and IVH are predictors of refractory fevers, which translate to increased mortality, more disability, and cognitive impairment [28]. Larger infarcts and worse outcomes were seen with higher temperatures in experimental models [15]. Similar to ICH and AIS, the

SAH literature has established the ill effects of fever on outcome and functional recovery. In 2008, Naidech et al. prospectively studied 94 patients with SAH and found that the good grade patients with higher fevers had worse mRS scores at 14 days and incomplete recovery. Poor grade patients with fevers were shown to have a delayed recovery, further underpinning the importance of treating fevers, as prognostication was more difficult in a febrile population [29].

Lack of effectiveness of therapeutic hypothermia

Temperature modulation has long been of interest in stroke treatment. The majority of research in this field has focused on the delirious effects of hyperthermia, but there have not been large enough trials illustrating convincing evidence for benefits of therapeutic hypothermia (TH). Knowing the ill effects of hyperthermia, the study of targeted temperature management was a natural gravitation after the promising therapeutic hypothermia in cardiac arrest trails in the early 2000s. The most studied is AIS with TH, with or without modifiers such as tPA and caffeinol. The studies with TH in SAH have focused more on intraoperative hypothermia, and the data in ICH is sparse.

Hypothermia and AIS has been studied most of all the stroke subtypes; but even here, the data is not robust. There are no large multicenter clinical trials assessing benefit of outcomes and mortality. Most of the studies were to assess feasibility and safety or were quasi-experimental. In an open pilot feasibility safety study, Schwab et al. planned to assess the safety of moderate (33 °C) hypothermia and intracranial pressure (ICP) changes in malignant MCA infarction. In short, they found that moderate hypothermia can help to control critically elevated ICP, but after rewarming there was a rebound in ICP, and in some cases, exaggerated initial ICP levels, leading to herniation and death [30]. This brought to light the importance of the rewarming phase. Several years later Schwab et al. again assessed the effects of moderate hypothermia and ICP, and this time were able to cool the patients faster but again found that rewarming, when the metabolic demand of the brain increased, constantly led to a secondary rise in ICP. And again, they held that an excessive ICP rise leading to the deaths was associated with the rewarming period [31]. The COOLAID trials were open pilot studies assessing feasibility of moderate (32–33 °C) hypothermia in AIS, using either surface or endovascular cooling methods. Neither trial showed significant differences in mRS or mortality between the hypothermic and control groups, although the studies were not powered for this effect [32, 33]. The ICTuS trial was also an efficacy trial of hypothermia (33 °C) in the awake patient at 2 durations (12 or 24 h of cooling), with no outcomes reported [34]. The follow-up trial was the ICTuS-L, combining 24 h of endovascular cooling (33 °C) after IV tPA, showing feasibility and safety of the combination, but no significant difference in the 3-month mRS or mortality between control and treatment groups [35]. The ReCCLAIM phase I trial was novel in that they assessed the safety/efficacy of hypothermia (33 °C) after intra-arterial recanalization. They had promising results since they showed safety/efficacy, and

possibly even better outcomes, but the trial was not control matched [36]. The ReCCLAIM phase II trial was stopped as it was not able to be funded. Most recently, Su and colleagues piloted a randomized control trial of hypothermia (33–34 °C) compared to normothermia in massive AIS and enrolled a total of 35 patients. They found no statistically significant difference in mortality or neurologic outcome after 6 months, but the trend was toward improved outcomes in the hypothermia group [37]. These studies all bring to light the necessity for larger studies powered to address the effects of hypothermia on mortality and neurologic outcome.

Three contemporary meta-analyses evaluating hypothermia and AIS, aim at creating more power to determine effects of hypothermia on outcome. In 2012 Lakhan et al. concluded that hypothermia does not significantly improve stroke severity [38]. The Mendez et al. analysis concluded that not only is there no significant difference in neurologic outcomes, but a tendency towards higher mortality in the patients undergoing hypothermia [39]. Wan et al. reinforced this stance with their meta-analysis also suggesting no difference in neurologic outcomes [40].

The initial studies in SAH focused on intraoperative hypothermia. In a Cochrane review of 3 randomized clinical trials (Hindman 1999, Chouhan 2006, IHAST 2005), including 1158 patients undergoing intraoperative hypothermia for neuroprotection, Li et at concluded that that even though animal models have shown hypothermia (32–35 °C) to be neuroprotective, there was no statistical significance in preventing death or improving neurologic outcomes in good-grade SAH human SAH patients. The effect was unclear in poor-grade SAH [41]. In 2009, Seule et al. evaluated a total of 441 consecutive patients for the feasibility and safety of hypothermia (33–34 °C) in aneurysmal SAH for refractory elevated ICP and/or cerebral vasospasm. The majority of these patients were poor-grade, and 100 underwent TH or a combination of TH and barbiturate coma. They concluded that prolonged systemic hypothermia could be considered as a last resort in a very select population, and that the severe complications they encountered required the expertise of intensive care unit staff familiar with hypothermia treatment [42]. In 2012, Seule et al. published a review for the Innsbruck Hypothermia Symposium, in which he evaluated hypothermia in patients with poor grade SAH. There were 4, small retrospective studies of hypothermia (32–34 °C) started within 24 h of aneurysm rupture. He notes that overall "outcomes were unsatisfactory with a mortality rate of 47.4% and favorable outcome in less than one-quarter of cases [43]." Seule and colleagues evaluated 20 patients with SAH in vasospasm treated with hypothermia. They concluded that mean flow velocity, as measured by transcranial Doppler, was decreased in the middle cerebral artery (MCA), but could not contribute this decrease to hypothermia or resolving vasospasm [44]. Thus far, the SAH literature has not shown any conclusive benefit for hypothermia in the perioperative or postoperative periods or for refractory ICP/vasospasm. The studies have been mostly inadequately powered and non-randomized, and mostly single center.

There is even less robust literature for hypothermia and ICH. There are no clinical or preclinical trials that evaluate outcomes of hypothermia in ICH. Worth mentioning is the multicenter, randomized, control Eurotherm trial, which was meant to examine hypothermia (32–35 °C) used to treat elevated

ICP in TBI. the trial was stopped early, in 2014, due to patient safety concerns. Even though hypothermia helped reduce elevated ICP, the hypothermia group had worse 6 month functional outcomes compared to the control group [45]. There are trials underway investigating hypothermia and ICH, which will be discussed in a later section.

Safety concerns and complications associated with hypothermia

There is an increased layer of complexity added to the management of an acute stroke patient when therapeutic hypothermia is introduced. Safety and feasibility trials have shown hypothermia to be a safe entity to investigate, yet it may be hard to justify subjecting patients to complications if the benefit is in question. Protocolizing the management of the hypothermic patient has helped mitigate some adverse effects, but has not eliminated them. In the TTM trial of cardiac arrest, serious complications (defined as seizures, bleeding, infection, arrhythmia, metabolic disorders and necessity of renal replacement therapy) occurred in at least 90% of either 33 or 36 °C group [2••]. Sedatives and paralytics used in hypothermia protocols can further confound the neurologic examination. Shivering is a common complication of TH, and may not only create discomfort but can worsen outcomes if not treated appropriately. Drug metabolism is also altered due to hypothermia, and this can not only delay, but result in inappropriate timing or inaccurate prognostication.

Infection is cited as a common occurrence in many of the therapeutic hypothermia trials. Den Hertog et al. found, in their review of the Cochrane Stroke Group trials register, that more infections were reported in the temperature reduction arms of trials examined, but the pooled analysis showed no significant difference in infections between the treatment and control groups [12]. They also noted that cardiac arrhythmias, hypotension, and deep venous thromboses were all more common in the intervention groups.

There are also specific complications associated with common cooling devices. Wu and Grotta listed these concisely in a review of Hypothermia in Acute Ischemic Stroke in the Lancet in 2013 [46]. Ice cold saline infusions runs the risk of fluid overload and can be imperfect; endovascular cooling increases the risk of bleeding, infections, and venous thrombosis; and cooling helmets and nasal cooling devices are slow to cool and are only used locally. Surface cooling devices have the less common risks of skin necrosis and breakdown, but most notably induce shivering.

Shivering has been an area of interest, not only because of the unappealing appearance and source of patient discomfort but because of its metabolic consequences. The attention it has drawn led Badjatia et al. to create the bedside shivering assessment scale as a tool for evaluating the metabolic stress of shivering [47]. They measured shivering in 64% of their patients with a strong association with increases in systemic metabolism. They also found higher doses of sedatives used with more severe shivering, the use of which was associated with higher energy expenditure. They elaborate that the neuroprotective benefit obtained by reducing the cerebral metabolic rate (15% for every 1 °C reduction) can be offset by uncontrolled shivering. Oddo et al. measured the effects of shivering in induced normothermia patients using brain tissue oxygenation. They also found a correlation between cooler circulating system water temperatures

and the magnitude of shivering, which were also associated with a decrease in brain tissue oxygenation [48]. This thought is particularly concerning for therapeutic hypothermia protocols that call for cooler target temperatures. Efforts should be taken to minimize shivering and sedation by adding guidance to institutional hypothermia protocols. Our institution employs a combination of acetaminophen, surface counter warming measures (Bair Hugger), buspirone, meperidine, fentanyl, dexmedetomidine, propofol, and even paralysis. Please see Fig. 1 for an adaptation of the Columbia Anti-Shivering Protocol [49], similar to the one we use at our institution.

The neuroprotective benefits of hypothermia can only be realized if patients survive, and often the data is skewed by the self-fulfilling prophecy of early withdrawal of life-sustaining therapy. Neuroprognostication has been confounded in the era of therapeutic hypothermia. In a review of neuroprognostication of hypoxic-ischemic coma in therapeutic hypothermia, Greer et al. described that therapeutic hypothermia impairs drug metabolism, impairs hepatic and renal clearance, increases sedative concentrations, and alters ancillary prognostication tests such as EEG and SSEP. They emphasized that caution be used in the interpretation of the clinical exam and ancillary tests in the setting of hypothermia, advocating for a multimodal approach to prognostication.

Benefits of mild hypothermia and normothermia

The topic of this review pertains to normothermia and stroke, so a distinction has been made in this review between those studies who used moderate hypothermia (<35 °C) and those who used mild hypothermia and normothermia (≥35 °C) as the targeted temperature. The clinical importance of this distinction has yet to be proven, as studies have been underpowered to comment on differential effects. What has been made clear is the association of complications related to hypothermia.

In 2009, Broessner et al. designed a prospective, randomized, controlled trial to compare prophylactic, catheter-based normothermia (36.5 °C) to

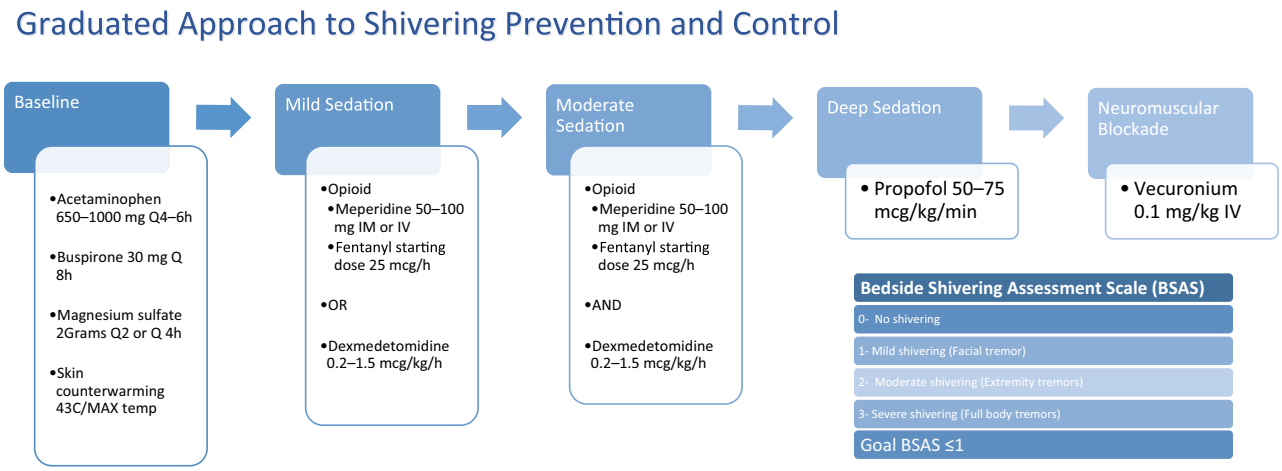

Fig. 1. Graduated medical approach to shiver prevention and control with escalation of therapy with a goal BSAS ≤1 [47, 49].

conventional fever management in all strokes subtypes. Results of 102 patients indicated that prophylactic normothermia did not lead to more adverse events, effectively reduced overall fever burden, but showed no significant difference for mortality or neurologic outcome [50]. In a follow-up study in 2015, Fischer, Broesssner, and colleagues, retrospectively analyzed the cool bath temperature data of almost all of the patients that had been randomized to the prophylactic normothermia group. They concluded that patients with higher cooling activity during the 168-h cooling period had more favorable neurologic outcomes at 180 days when compared to patients with lower cooling activity [51••].

We previously discussed the pre-clinical trials of hypothermia in AIS, but some employed normothermia as a target as well. In 2000, The Copenhagen Stroke Study Group established the safety and feasibility of induction of normothermia (35 to 37 °C) with "forced air" in AIS [52]. They found that outcomes were no worse in the normothermia group. The follow-up study showed the deleterious effects of hyperthermia in the same stroke population [23]. In 2006, Els and colleagues studied the safety and outcomes of hemicraniectomy combined with mild hypothermia (35 °C) compared with hemicraniectomy alone in patients with malignant ischemic strokes [53]. In this prospective study, they randomized 25 patients and found that hypothermia plus hemicraniectomy is not associated with increased adverse effects and had a trend toward improved functional outcome. They postulated that the absence of any severe side effects may have been due to mild hypothermia at 35 °C and not the lower 33 °C which their contemporaries were using. In 2014, Piironen and colleagues published on the safety and feasibility of mild hypothermia (35 °C) post tPA compared to standard care, in a prospective, randomized trial of 36 patients. They found that their rate of adverse events were lower compared with previous hypothermia studies using cooler target temperatures, with a mortality of 0%, also lower than other contemporary trials (COOLAID I/II ICTuS-L), albeit there were differences in stroke severity. They also found no differences in neurologic outcome at 3 months between the two groups [54].

Kollmar and colleagues have been involved in three studies investigating mild hypothermia and ICH. First in 2010, they published results of reducing perihematomal edema after ICH [55]. They enrolled 12 patients with large supratentorial ICH, matched to controls from their database of 312 patients, who underwent hypothermia (35 °C) for a total of 10 days, and measured edema using head CT. They established that hypothermia prevented the increase in perihematomal edema, without rebound edema during rewarming. A year later, in a post hoc analysis, their results showed not only favorable short-term, but also long-term outcomes and mortality rates compared to matched data, and this survival may have allowed for the increase in functional recovery seen (ability to talk) from the 3- to 12-month timeframe [56]. After these results, they established an institutional protocol to regularly use hypothermia (35 °C) and enrolled another 20 patients, compared to a historical control group of 25 patients. They found that hypothermia led to no ICP crises (compared to 11 in the control group), prevention of perihematomal edema, acceptable long-term outcomes compared to their historical control, and importantly, no rebound edema. They attributed these promising results to the absence of edema, which can cause secondary brain injury as well as herniation which can lead to death [57••]. More recently, Lord and colleagues performed a case-controlled study of a total of 80 patients with ICH from a prospective database [58]. Patients enrolled in the

treatment arm were those who had a temperature targeted to 37 °C, compared to the historical Columbia ICH database. Overall, their results were not promising, in that, amongst the therapeutic normothermia group, there was an increased duration of sedation, mechanical ventilation and ICU stay, but no difference in *discharge* outcomes, albeit the study power was too low to assess for this effect. They appropriately brought into question the potential net benefit of normothermia with known "measureable" associated risks.

Interestingly, the Columbia group, again evaluated results from 40 consecutive febrile patients from the University SAH outcomes database who underwent therapeutic normothermia (37 °C), matched to 80 historical controls, but held different opinions on benefit of normothermia [59]. In the normothermia group, they found higher, but not statistically significant, rates of pneumonias, arrhythmias (which may have been transiently associated with shivering), tracheostomies, and longer duration of sedation. They further detail that the prolonged mechanical ventilation may have led to worse outcomes at the 14-day and 3-month intervals, but normothermia was a significant predictor of a good 12-month outcome, as compared to matched patients, yet again not adequately powered.

Future trials

As demonstrated in this review, there is a paucity of clinical trial data investigating hypothermia and even normothermia in the setting of stroke. Neuroprotection has been seen in animal models, but the neuroprotective benefit on outcomes has yet to be established. Unfortunately, hypothermia comes with its associated complications and these need to be balanced against the benefits. There are a number of notable clinical trials which are evaluating the benefits of hypothermia or normothermia in the stroke population. Table 1 summarizes notable and ongoing trials.

AIS has the most active trials. ICTuS 2/3 is a randomized, safety/efficacy trial to determine whether the combination of IV tPA and hypothermia (33 °C) is superior to tPA alone. They considered comparing 33 °C against 35 °C, as well as various cooling periods, but decided on the cooler temperature [60]. An interesting ancillary study to the ICTuS 2/3 trial is the HASTIER study, assessing perfusion imaging changes in the treatment and control patients of the ICTuS group. Another follow-up study is the PAIS 2 trial (paracetamol in stroke) trial, which is a multicenter, randomized, double-blinded, controlled clinical trial aimed at enrolling 1500 patients (AIS of ICH) to be treated with high dose paracetamol or placebo to assess the effect on clinical outcome [61]. COAST II (cooling in acute stroke) is another trial aimed at assessing the safety/efficacy of hypothermia with IV tPA versus tPA alone. In this trial, they will cool to 35 °C for 24 h. The EuroHYP-1 trial is a multicenter, randomized, safety/efficacy, phase III clinical trial comparing hypothermia with best medical management, compared to best medical management alone [62]. They are using target temperatures of 34–35 °C for 24 h, with functional outcome assessment at 3 months as the primary outcome. The HAIS-SE prospective trial is comparing surface versus endovascular cooling in awake stroke patients, with the primary endpoint being time to reach 34 °C.

There are several studies that aim to investigate hypothermia in ICH. CINCH will be a prospective, multicenter, randomized, phase II trial, with plans to enroll

Table 1. Notable future trials assessing targeted temperature management and stroke

	Trial design stroke type (*n* patients)	Enrollment timeframe	Intervention (device)	Depth of cooling	Intervention duration (rewarming time → target temp)	1° Outcome (2° outcome)	Other
ICTuS 2/3	Multicenter, RCT AIS (400)	Within 6 h from IV tPA	Hypothermia + thrombolysis (endovascular cooling)	33 °C	24 h (12 h → 36.5 °C)	Target temperature within 6 h, no increased PNA, no fluid overload with bolus (functional outcomes, 36 h edema on CT)	If phase 2, milestones met will transition to ICTuS phase 3 (*n* = 1200)
COAST II	Monocenter, S/E, RCT AIS (50)	Within 3 h of stroke onset	Hypothermia + IV tPA (endovascular cooling)	35 °C	24 h	Safety and feasibility, (functional outcomes, incidence, and volume of hemorrhage on MRI)	
EuroHYP-1	Multicenter, RCT AIS (1500)	Within 6 h of stroke onset	Hypothermia + medical management (surface or endovascular)	34–35 °C	24 h (0.2 °C/h → 36 °C)	Functional outcomes	Phase 3, surface or endovascular cooling at discretion of local provider
HAIS-SE	Monocenter, RCT, S/E AIS (60)	Unknown	Endovascular vs surface	34 °C	48 h	Core temp (S/E)	
CINCH	Multicenter, RCT ICH (50)	6 to 18 h of stroke onset	Hypothermia (endovascular)	35 °C	192 h (~40 h → ? temp)	Hemorrhage + edema volume on CT on day 8 and 11, 30-day mortality (other mortality,	

Table 1. (Continued)

	Trial design stroke type (*n* patients)	Enrollment timeframe	Intervention (device)	Depth of cooling	Intervention duration (rewarming time → target temp)	1° Outcome (2° outcome)	Other
						functional outcomes)	
TTM-ICH	Monocenter, RCT ICH (50)	Within 18 h of stroke onset	Hypothermia vs normothermia (endovascular)	32–34 or 36–37 °C	72 h (0.05–0.1 °C/h → 36–37 °C)	Serious adverse events (in hospital neuro deterioration, mortality, functional outcomes, hematoma, and edema volume)	Phase 2, kept at normo-thermia for 168 h
PAIS 2	Multicenter, RCT AIS and ICH (1500)	Within 12 h of stroke onset	Paracetamol 6gm/day (if temp ≥36.5 °C)	N/A	72 h or until discharge	Functional outcomes (body temp, markers of inflammation)	
INTREPID	Multicenter, RCT AIS, ICH, and SAH (1176)	Varies depending on stroke type	Fever prevention (surface)	37 °C	Up to 14 days or discharge from stroke	Daily fever burden (functional outcome, mortality, ICU, and hospital length of stay)	

Legend: *PNA* pneumonia, *RCT* randomized controlled trial, *S/E* safety/efficacy

50 patients. The patients in the hypothermia arm will be cooled to 35 °C for 8 days with controlled rewarming, with the primary endpoints being mortality at 30 days and development of total lesion (hemorrhage plus perihemorrhage edema) volume [63]. The TTM-ICH will be a prospective, single-center, randomized, two-arm phase II trial that plans to enroll 50 patients into either a 32–34 °C group or a 36–37 °C group, with functional outcomes as a secondary endpoint [64]. Another registered study is the SNICH trial (active but not recruiting) which is meant to measure perihematomal edema based on MRI in the standard care group versus normothermia (36.5 °C), with functional outcomes as a secondary measure.

Lastly, INTREPID will be a multicenter, randomized, clinical trial aimed to assess surface cooling to prevent fever in brain-injured patients and the impact on fever burden, functional outcomes, mortality and length of ICU and hospital stay. They aim to enroll over 1176 patients of all stroke subtypes, with a target temperature of 37 °C. The rationale is that prevention rather than reaction to fever may be most neuroprotective.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflicts 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.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

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