Targeted Temperature Management in Postresuscitation Care After Incorporating Results of the TTM2 Trial

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Cardiac arrest still accounts for a substantial proportion of cardiovascular related deaths and is associated with a tremendous risk of neurological injury and, among the few survivors, poor quality of life. Critical determinants of survival and long-term functional status after cardiac arrest are timely initiation of cardiopulmonary resuscitation and use of an external defibrillator for patients with a shockable rhythm. Outcomes are still far from satisfactory, despite ongoing efforts to improve cardiac arrest response systems, as well as elaborate postresuscitation algorithms. Targeted temperature management at the wide range between 32 °C and 36 °C has been one of the main therapeutic strategies to improve neurological outcome in postresuscitation care. This recommendation has been mainly based on 2 small randomized trials that were published 20 years ago. Most recent data derived from the TTM2 (Targeted Hypothermia Versus Targeted Normothermia After Out-of-Hospital Cardiac Arrest) trial, which included 1861 patients, challenge this strategy. It showed no benefit of targeted hypothermia at 33 °C over normothermia at 36 °C to 37.5 °C with fever prevention. Because temperature management at lower temperatures also correlated with an increased risk of side effects without any benefit in the TTM2 trial, a modification of the guidelines with harmonizing temperature management to normothermia might be necessary.

Key Words: cardiac arrest ■ postresuscitation care ■ targeted-temperature management ■ therapeutic hypothermia ■ TTM2 trial

Cardiac arrest (CA) still accounts for a substantial proportion of cardiovascular-related deaths and is associated with a tremendous risk of neurological injury and, among the few survivors, poor quality of life.1–3 Comprehensive registries, including the EuReCa TWO (European Registry of Cardiac Arrest–Study TWO), and the GWTG-R (Get With The Guidelines-Resuscitation Registry), originating from the American Heart Association’s National Registry of Cardiopulmonary Resuscitation, have found similar annual incidences of out-of-hospital cardiac arrest (OHCA) in Europe and the United States (Europe: ~89 events/100,000 inhabitants, United States: ~100 events/100,000 inhabitants).4,5 On the contrary, valid data on in-hospital cardiac arrest (IHCA) are limited, restricting an assessment of the public health burden. Registries from Denmark and the United Kingdom state 1.5 to 2.8 events per 1000 hospital admissions, whereas, in the United States, an IHCA rate of 6 to 7 per 1000 admitted patients has been reported.5–9 CA commonly results from ischemic heart disease, end-stage valvular heart disease, heart failure, pulmonary (vascular) disease, and intoxication. However, overall prognosis in these patients largely depends on the level of initial neurological damage.10 Critical determinants of...
survival and the long-term functional status after CA are timely initiation of cardiopulmonary resuscitation (CPR) and the use of an external defibrillator for patients with a shockable rhythm.\textsuperscript{11} International networks, including the European Union–funded ESCAPE-NET (European Sudden Cardiac Arrest Network: Towards Prevention, Education, and New Effective Treatments Project), further investigated the risk factors and underlying pathologies with the aim of improving survival rates and neurologic outcomes.\textsuperscript{12} Outcomes are still far from satisfactory despite ongoing efforts to improve CA response systems as well as elaborated postresuscitation algorithms.\textsuperscript{13}

After return of spontaneous circulation, postresuscitation care for patients in a coma comprises recognition and treatment of reversible causes of CA, respiratory support, sedation management, stabilization of cerebral and coronary perfusion, as well as using effective neuroprotection.\textsuperscript{10,14–16}

The control of core body temperature by targeted temperature management (TTM) has been an important neuroprotective strategy in postresuscitation care. Options in temperature management comprise targeted hypothermia, usually defined as lowering core body temperature to 32 °C to 36 °C, and targeted normothermia, which aims for a core body temperature of <37.7 °C, with fever prevention in the further course of treatment. Temperature management remains controversial, and against the background of the most recently published TTM2 trial, a new debate about its effectiveness has arisen. This review aims to provide a comprehensive and structured synopsis on TTM. It discusses, in detail, the evidence from randomized controlled trials (RCTs) on outcome categories and complication rates related to different treatment regimens. Moreover, it provides a guide of how results from the TTM2 trial could change the standardized operational procedures for temperature management in our daily clinical practice.

TARGETED TEMPERATURE MANAGEMENT IN PATIENTS AFTER CA: PATHOPHYSIOLOGICAL RATIONALE FOR TARGETED TEMPERATURE MANAGEMENT

Neuronal cell death results from hypoperfusion/ischemia during CA, but also from a variety of complex biochemical and circulatory reactions during the first days following ROSC.\textsuperscript{17} The latter includes successive stages of vasoparalysis and relative hyperemia, disturbed vasoconstriction and dilation, and eventual restoration of regular cerebral blood flow.\textsuperscript{18} Preclinical studies have shown that although targeted hypothermia does not modulate cerebral circulation, it has beneficial effects on many of the pathophysiologic characteristics of reperfusion injury to the central nervous system. Hypothermia-induced decrease in cerebral metabolism and lactate production limits excitotoxicity by preventing the detrimental effects of catecholamine release and calcium-triggered tissue degeneration, the aftermath of halted brain perfusion and anaerobic metabolism. It also improves the oxygen supply–demand imbalance.\textsuperscript{19} Additionally, preclinical studies have shown a decrease in reactive oxygen species production, mitochondrial membrane permeability, immune cell infiltration, production of inflammatory cytokines, and preservation of the blood–brain barrier. Intracranial pressure is reduced with a low target temperature by reducing vasogenic edema.\textsuperscript{19–22}

Considering that fever is not uncommon following CA and compromises recovery, targeted normothermia in theory offers management potential by reducing negative hyperthermia-induced side effects.\textsuperscript{13,23,24} This knowledge has culminated in a series of RCTs conducted since the late 1990s to investigate outcomes after CA with different temperature management strategies.

COOLING TECHNIQUES FOR TARGETED TEMPERATURE MANAGEMENT

Ice packs applied to the torso, neck, and proximal limbs (Figure 1A), as well as intravenous infusion of cold saline (Figure 1B) have been the first techniques implemented in temperature management in clinical practice. Although precise, controlled, cooling, temperature maintenance and rewarming is not possible, the above-mentioned techniques are still being used because of their ease of application and their cost-effectiveness.

More elaborate surface-based cooling systems use circulating water/air or gel pads in conjunction with computerized temperature control units (Figure 1C).

Nonstandard Abbreviations and Acronyms

| CA       | cardiac arrest                        |
| CPC      | Cerebral Performance Category         |
| ECLS     | extracorporeal life support           |
| IHCA     | in-hospital cardiac arrest            |
| mRS      | modified Rankin Scale                 |
| OHCA     | out-of-hospital cardiac arrest        |
| RCT      | randomized controlled trial           |
| ROSC     | return of spontaneous circulation     |
| TTM      | targeted temperature management       |
Figure 1. Cooling techniques for targeted temperature management.
A. Ice packs applied to the torso, neck, and proximal limbs. B. Infusion of cold saline via central access. C. Surface-based cooling system using circulating water/air or gel pads in conjunction with computerized temperature control unit. D. Cooling catheter inserted into the femoral vein with closed-loop intravascular circulation of cooling fluids. E. Intranasal cooling system featuring evaporated liquid coolant mixed with air and delivered through bilateral nasal cannulae for induction of brain hypothermia. F. Heat exchanger module directly incorporated in an extracorporeal life support circuit.
Cooling catheters can be inserted into the subclavian, jugular, or femoral vein with closed-loop intravascular circulation of cooling fluids (Figure 1D). Novel intranasal cooling devices featuring evaporated liquid coolant mixed with air and delivered through bilateral nasal cannulas, have been developed specifically for hypothermia induction in a prehospital setting (Figure 1E). Finally, heat exchanger modules directly incorporated in an extracorporeal life support circuit, can be used for temperature management (Figure 1F).

CONTRAINDICATIONS FOR TARGETED TEMPERATURE MANAGEMENT

Few contraindications limit the use of therapeutic hypothermia in patients who are critically ill, and it mainly stems from the exclusion criteria of the previous RCTs on temperature management. In general, the induction of mild hypothermia should not be used for responsive patients (Glasgow Coma Scale >8) as well as patients with active bleeding, especially intracranial hemorrhage, which may worsen with decreasing core temperature.10,14 Severe clinical scenarios (ie, CA attributable to trauma, sepsis, or hemorrhagic shock) are also considered contraindications. Concurrent anticoagulation therapy during hypothermia is particularly challenging.25 Hence, known coagulopathy can be regarded as a relative contraindication. Furthermore, hypothermia may aggravate hypotension, and patients who are hemodynamically unstable may not tolerate temperature management. It is unclear if cardiogenic shock patients in the most severe stage E (Society for Cardiovascular Angiography and Interventions) undergoing temporary circulatory support, such as extracorporeal life support treatment, can profit from temperature management. These patients are prone to suffer from severe bleeds (eg, access site bleeding) because of a severe consumptive coagulopathy and thrombocytopenia.

PRIMARY OUTCOMES IN THE LANDMARK TRIALS

The 2 pioneer RCTs on TTM published in 2002 by Bernard et al and the Hypothermia After Cardiac Arrest Study Group, both compared functional outcomes in mild hypothermia after OHCA (33 °C for 12 hours and 32 °C–34 °C for 24 hours, respectively) with targeted normothermia (Table 1 and Figure 2).26,27,41,44,45 Bernard et al defined favorable outcome as discharged to home or into a rehabilitation facility, whereas death or discharge to a long-term nursing home was considered a poor outcome. With induced hypothermia, the rate of good outcome was 49% compared with 26% in the targeted normothermia group (P=0.046; adjusted odds ratio [age and time from collapse to ROSC] 5.25 [95% CI, 1.47–18.76], P=0.011).45 Participants of the HACA (Hypothermia After Cardiac Arrest) trial showed a similar trend toward improved functional outcomes with targeted hypothermia. Fifty-five percent of subjects in this group had a Cerebral Performance Category (CPC) score of 1 to 2, as opposed to 39% in the control group (P=0.009).44

In the HACA trial, which included 275 patients, mortality after 6 months was significantly lower in patients treated with targeted hypothermia (n=137) compared with the control group (n=138) (41% versus 55%, P=0.02).44 Although overall survival after CA according to the EuReCa TWO registry is as low as 28%,46,47 the better survival in the HACA trial may be explained by its restrictive inclusion criteria (ie, initial shockable rhythm, witnessed CA, estimated interval of 5 to 15 minutes from CA to first resuscitation attempt, and a maximum timespan of 60 minutes from CA to ROSC). For the final enrollment of 275 patients into this trial, 3551 patients were initially screened, and of these, 3246 patients did not meet the inclusion criteria. Furthermore, the trial protocol did not specify a target temperature for the normothermic control group resulting in a median core temperature in this study arm of >37 °C, over the 24-hour intervention period. Bernard et al included adults suffering OHCA only if the initial rhythm was ventricular fibrillation (VF). The authors detected no difference in mortality at hospital discharge between the hypothermia and normothermia group (51% versus 66%, P=0.145).46 However, mortality was a prespecified secondary outcome in both trials.

Both trials suffered from major limitations such as small sample sizes, unblinded treating physicians, and insufficiently standardized protocols, and particularly a lack of standardized neuro-prognostication and withdrawal of care. These factors were implemented in the TTM2 trial. Moreover, randomization was performed by closed envelopes because digital central randomization was not available yet. There was inadequate temperature control in the normothermia group in both trials, with average temperatures being >37 °C. The latter may have aggravated neurological injury because of fever in the control groups considering the association between post-CA fever and poor neurological outcomes. Nonetheless, the promising findings of both trials led to an incorporation of temperature management as a basic element of post-CA care for patients with a shockable rhythm.

The TTM1 (Target Temperature Management 33 °C Versus 36 °C After Out-of-Hospital Cardiac Arrest) trial by Nielsen et al, with close to 1000 participants, was powered for mortality outcome analysis and compared hypothermia at 33 °C with a target temperature management of 36 °C. Unlike in the previously discussed
| Author          | Year published | Type of study | Enrollment period | Research question | Inclusion criteria                                                                 | Exclusion criteria | Total no. of patients | Group I | Group II | Cause of CA | Follow-up time | Primary outcome | Additional major outcomes                                                                 | Complications/Adverse events |
|-----------------|----------------|---------------|-------------------|-------------------|-------------------------------------------------------------------------------------|-------------------|-----------------------|---------|----------|-------------|----------------|----------------|--------------------------------------------------------------------------------------------|------------------------------|
| Dankiewicz et al<sup>26</sup> | 2021 | RCT (TTM2) | 2017–2020 | Benefits and adverse effects of hypothermia as compared with normothermia and early treatment of fever in patients after cardiac arrest | Age >18y, OHCA or unknown cause irrespective of initial rhythm, unconsciousness without response to verbal commands or pain, >30 min of spontaneous circulation after resuscitation | Interval of >180 min from ROSC to screening, unwitnessed cardiac arrest, asystole as initial rhythm, limitations in care, spontaneous hypothermia <30 °C; ICMO initiation before ROSC, pregnancy, intracranial hemorrhage, severe COPD | n=981 | n=930 (mean age: 64 y; 60% men, VF: 62%, pulseless VT: 3%, PEA: 13%, asystole 13%); induced hypothermia using surface (70%) or intracranial (30%) temperature management device, TT 33 °C for 28 h, rewarming rate 0.33 °C per h | n=931 (mean age: 63 y; 79% men, VF: 63%, pulseless VT: 3%, PEA: 12%, asystole 11%); induced normothermia for 72 h; rewarming from 31 °C to 37.5 °C | N/A | 0 mo | 6 mo mortality rate: 52% (hypothermia), 48% (normothermia) (P=0.37) | 46% of patients in the normothermia group received cooling with a device for (sub)febrile temperature >37.8 °C; mRS score of 4–6 after 6 mo: 55% (hypothermia), 55% (normothermia); mean EQ-5D-5L score: 74 (hypothermia), 75 (normothermia) | Atrial fibrillation resulting in hemodynamic compromise: 24% (hypothermia), 17% (normothermia) (P=0.001); bleeding: 9% (hypothermia), 5% (normothermia) (P=0.8); skin complication: 1% (hypothermia), 1% (normothermia) (P=0.21); pneumonia: 36% (hypothermia), 35% (normothermia) (P=0.7); sepsis: 11% (hypothermia), 9% (normothermia) (P=0.22) |
| Lascarrou et al<sup>27</sup> | 2019 | RCT (HYPERION) | 2014–2018 | Neurologic outcomes in patients with successful resuscitation after CA with nonshockable rhythm with targeted temperature at 33 °C compared with normothermia | Age >18y, OHCA or in-hospital CA with nonshockable initial rhythm (asystole or pulseless electrical activity), GCS ≤8 | Interval >10 min from collapse to CPR initiation, internal >60 min from CPR to ROSC, hemodynamic instability, interval of >300 min from CA to screening, terminal illness, severe hepatic dysfunction, pregnancy/breastfeeding, lack of insurance | n=581 | n=284 (median age: 67 y; 65% men, PEA: 12%, asystole: 78%, unknown 11%); induced hypothermia using intracranial (15.1%) or external cooling devices, TT 33 °C for 24 h, rewarming rate 0.25–0.5 °C per h | n=297 (median age: 67 y; 63% men, PEA: 12%, asystole: 81%, unknown 7%); induced normothermia using intracranial (14.8%) or external cooling devices, TT 33 °C for 48 h | Asphyxia: 59%, cardiac cause: 27%, anaphylaxis: 15%, neurologic cause: 2.3%, pulmonary embolism: 3.8%, other medical cause: 7.2%, trauma: 0.6%, drug poisoning: 1.4%, drowning 1.1% | 90 d | Favorable neurologic outcome (CPC 1–2) at 90 d: 10.2% (hypothermia), 0.7% (normothermia) (P=0.04) | 90-d mortality rate: 83.3% (hypothermia), 83.2% (normothermia) (n=17) | Severe cardiac arrhythmia between 0 and 7 d: 12.3% (hypothermia), 10.4% (normothermia) (P=0.48); sepsis between 0 and 7 d: 23.6% (hypothermia), 24.2% (normothermia) (P=0.73); acute pulmonary edema: 6.7% (hypothermia), 8.7% (normothermia) (P=0.33) | (Continued) |
### Table 1. (Continued)

| Author         | Year published | Type of study | Enrolment period | Research question | Inclusion criteria | Exclusion criteria | Total no. of patients | Group I | Group II | Cause of CA | Follow-up time | Primary outcome | Additional major outcomes | Complications/Adverse events |
|----------------|----------------|---------------|------------------|-------------------|--------------------|-------------------|---------------------|---------|----------|-------------|----------------|----------------|--------------------------|-----------------------------|
| Nordberg et al | 2019           | RCT (PRINCESS) | 2010–2018        | Survival and neurologic outcome with intra-aneurysm transnasal evaporative cooling additional to hypothermia after hospital admission compared with standard prehospital care and hypothermia after admission | Age 18–60 y, witnessed CA irrespective of initial rhythm | Trauma, severe bleeding, drug overdose, cerebrovascular accident, drowning, smoke inhalation, electrocution, hanging, spontaneous hypothermia, anatomial contraindications for nasal catheter, DNR order, terminal illness, pregnancy, known coagulopathy, ROSC before randomization, interval >15 min from collapse to EMS arrival, need for supplemental oxygen | n=677 | n=337 (median age: 64 y, 75% men, shockable rhythm: 41%), intra-arrest induced hypothermia using transnasal evaporative cooling, TT 32–34 °C for 90 d | Presumed cardiac cause: 85% | 90 d | 90-d survival with good neurologic outcome (CPC 1–2): 16.6% (transnasal cooling), 13.3% (control) (P=0.25); 90-d survival with good neurologic outcome (CPC 1–2) in patients with initial shockable rhythm: 34.8% (transnasal cooling), 25.9% (control) (P=0.1); overall 90-d survival rate: 17.8% (transnasal cooling), 15.6% (control) (P=0.44) | Mediantympanic temperature at ROSC: 35.7 °C (transnasal cooling), 36.0 °C (control) (P=0.02); median temperature at hospital admission: 34.6 °C (transnasal cooling), 35.8 °C (control) (P=0.001); Severe cooling-related norepinephrine bleeding in 4 patients, pneumocephalus in 1 patient (resolved, patient survived with good neurologic outcome), adverse event rate within 7 d after randomization: 50.4% (transnasal cooling), 48.8% (control) |
| Lopez-de-Sa et al | 2018          | RCT (FROST-I)  | 2014–2016        | Neurological outcomes with different hypothermia levels (32 °C, 33 °C, 34 °C) | Age 18–80 y, witnessed OHCA of presumed cardiac cause, shockable initial rhythm, interval >20 min from collapse to CPR initiation, interval >60 min from collapse to ROSC | Trauma, toxicological cause, pregnancy, DNR order, interval >240 min from ROSC to randomization, spontaneous hypothermia <34 °C, intracranial bleeding, stroke, neurological disability before event, terminal illness | n=150 | n=49 (mean age: 57 y, 75% men); induced hypothermia using an intravascular temperature management device (Zoll Medical, San Jose, CA), TT 32 °C for 24 h, rewarming rate 0.1–0.2 °C per h | N/A | 90 d | Favorable neurologic outcome (mRS 0–3) at 90 d: 63.3% (32 °C), 68.2% (33 °C), 65.1% (34 °C) (ns) | 90-d mortality rate: 30.6% (32 °C), 26.5% (33 °C), 29.3% (34 °C) (ns) | Number of patients with 1 or more complications: 84.6% (32 °C), 79.6% (33 °C), 87.8% (34 °C) (ns); respiratory tract infections: 21.2% (32 °C), 49.0% (33 °C), 36.7% (34 °C) (P=0.012) |

(Continued)
## Table 1. (Continued)

| Author          | Year published | Type of study | Enrollment period | Research question                                                                 | Inclusion criteria                                                                 | Exclusion criteria | Total no. of patients | Group I | Group II | Cause of CA | Follow-up time | Primary outcome                                                                 | Additional major outcomes                                                                 | Complications/Adverse events |
|-----------------|----------------|---------------|------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------|-----------------------|---------|----------|-------------|----------------|--------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|-----------------------------|
| Kirkegaard et al 30 | 2017            | RCT           | 2013–2016        | Outcomes with therapeutic hypothermia at 33 °C for 24 h compared with 48 h           | Age 17–80 y, OHCA of presumed cardiac cause irrespective of initial rhythm, sustained ROSC for >20 min, GCS <8 | Unwitnessed CA, asystole as Initial rhythm | n=355    |          |             | NA             | 6 mo | Favorable neurologic outcome (CPC 1–2 at 6 mo): 69% (48 h), 64% (24 h) (P=0.33) | 6- mo mortality rate: 27% (48 h), 34% (24 h) (P=0.19); ICU length of stay: 10 h (48 h), 11 h (24 h) (P=0.01); | Number of patients with 1 or more complications: 97% (48 h), 91% (24 h) (P=0.03); Hypotension: 60% (48 h), 40% (24 h) (P=0.01); Pneumonia: 49% (48 h), 43% (24 h) (P=0.24); Severe bleeding: 4% (48 h), 1% (24 h) (P=0.02) |
| Look et al 31   | 2017            | RCT           | 2008–2014        | Survival to discharge and neurological outcomes of patients with CA with internal vs external cooling | Age 18–80 y, OHCA or in-hospital CA irrespective of initial rhythm, ROSC for >30 min, unresponsiveness after ROSC | Trauma, intracerebral hemorrhage, women <50y, pregnancy, terminal illness, hemodynamic instability | n=45     |          |             | NA             | 6 mo | Hospitalization survival to discharge: OR, 3.36 (1.13–10.41) (internal cooling vs control); OR, 1.96 (0.59–6.66) (internal vs external); OR, 2.44 (0.95–6.30) (intervention vs control) | Favorable neurologic outcome (CPC 1–2): OR, 1.49 (0.39–5.06) (internal cooling vs control); OR, 1.55 (0.56–4.26) (intervention vs control) | Any cardiac arrhythmias: OR, 0.18 (0.04–0.63) (internal cooling vs control); OR, 0.26 (0.10–0.70) (intervention vs control) |

(Continued)
| Author          | Year published | Type of study | Enrollment period | Research question | Inclusion criteria                                                                 | Exclusion criteria                                                                 | Total n. of patients | Follow-up time | Hospitalization | Primary outcome | Additional major outcomes | Complications/ Adverse events |
|-----------------|----------------|---------------|-------------------|-------------------|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|----------------------|----------------|----------------|----------------|--------------------------|-------------------------------|
| Scales et al 32 | 2017           | RCT           | 2012–2016         | Rates of successful targeted hypothermia within 6h by prehospital cooling compared with standard care | Age > 18y, OHCA, with sustained ROSC > 5 min, unresponsive to verbal stimuli or requiring intubation | Trauma, burn, spontaneous hypothermia, severe bleeding, severe sepsis, known coagulopathy, DNR order, pregnancy, prisoner status | n=585               |                |                |                |                        |                               |
|                  |                |               |                   |                    |                                                                                   |                                                                                      |                      |                |                |                |                        |                               |
| Bernard et al 33 | 2016           | RCT (RINSE)   | 2010–2014         | Outcomes with induction of therapeutic hypothermia during CPR compared with standard care | Age > 18y, OHCA, established IV access, CA sustained after initial resuscitation treatment | Trauma, suspected intracranial bleeding, pregnancy, spontaneous hypothermia < 34.5°C, DNR order | n=1198              |                |                |                |                        |                               |
| Pang et al 34    | 2016           | RCT           | 2013–2015         | Survival and neurologic outcome with induced hypothermia in patients requiring ECLS for severe cardiogenic shock compared with normothermia | Age > 21y, CA irrespective of initial rhythm, interval < 60 min from onset of CA to ACLS initiation, comatose state, and unresponsiveness after ROSC, intubated with mechanical ventilation, total ACLS time < 60 min | CPR duration > 45 min, severe coagulopathy, drug overdose, head trauma, stroke, pregnancy, terminal illness, spontaneous hypothermia < 30°C | n=21                | 6 mo           |                |                |                        |                               |
Table 1. (Continued)

| Author         | Year published | Type of study | Enrolment period | Research question | Inclusion criteria | Exclusion criteria | Tota/Total no. of patients | Group I | Group II | Cause of CA | Follow-up time | Primary outcome | Additional major outcomes | Complications/Adverse events |
|---------------|----------------|--------------|------------------|------------------|-------------------|-------------------|-------------------------|---------|----------|--------------|----------------|----------------|----------------------------|-----------------------------|
| Cronberg et al35 | 2015            | TTM trial   | 2010–2013        | Effects of targeted temperature management on long-term cognitive function and quality of life after cardiac arrest | Age >18y, OHCA of presumed cardiac cause irrespective of initial rhythm, >20min of spontaneous circulation after resuscitation | >240min from ROSC to screening, unwitnessed CA with asystole as initial rhythm, intracranial hemorrhage or stroke, spontaneous hypothermia <30°C | n=473 (mean age: 61y, 86% men, VF: pulseless VT: 93%, PEA: 4%, asystole: 3%); induced hypothermia with intravascular (24%) or surface temperature management (76%) devices; TT 33°C for 28h, rewarming rate 0.5°C per h | n=466 (mean age: 59y, 80% men, VF: pulseless VT: 94%, PEA: 1%, asystole: 4%); induced normothermia with intravascular (24%) or surface temperature management (76%) devices; TT 36°C for 28h, rewarming rate 0.5°C per h | N/A | 96d | Median Mini-Mental State Examination score for all patients including nonsurvivors: 14 (33°C), 17 (36°C) (P=0.077); median IQCODE score for all patients including nonsurvivors: 115 (33°C), 115 (36°C) (P=0.077) | Increased need for help in daily life: 18.8% (3°C), 17.5% (6°C) (P=0.71); subjective assessment of complete mental recovery: 66.9% (33°C), 61.8% (36°C) (P=0.32); mean mental component summary score: 49.1 (33°C), 49.0 (36°C) (P=0.77) |
| Deye et al36 | 2015            | RCT (ICEREA) | 2006–2009        | Outcome, precision, and complications of endovascular cooling compared with basic conventional external cooling | Age 18–79y, OHCA of presumed cardiac cause, estimated interval of ≤50min from collapse to ROSC, <4h from ROSC to cooling initiation, unconscious patient, availability of endovascular cooling device | Terminal disease, DNR order, pregnancy, uncontrolled bleeding, known coagulopathy, spontaneous hypothermia <30°C, OHCA of extracardiac cause, in-hospital cardiac arrest, contraindication to endovascular device, immediate need for ECLS or renal replacement therapy | n=400 | n=203 (mean age: 60y, 76% men, VF: 31%; pulseless VT: 4%; PEA: 4%, asystole: 38%); induced hypothermia with endovascular cooling device (icy catheter with Coolgard [256]); TT 33°C for 24h, active rewarming rate ≤0.5°C per h | n=197 (mean age: 61y, 85% men, VF: 29%; pulseless VT: 8%; PEA: 7%, asystole: 34%); induced hypothermia using external cooling methods (fans, homemade tent, ice packs placed on vascular accesses, head, and torso); TT 36°C for 24h, passive rewarming rate ≤0.5°C per h | Arhythmia: 64%, ACS: 47%, acute pulmonary edema: 7%, other causes: 11% | 90d | Survival without major neurological damage (GCS 1–2 at day 28: 36.0% (endovascular), 28.4% (external) (P=0.017)) | 90-d survival rate: 41.9% (endovascular), 38.1% (external) (P=0.44); delay to reach target temperature was shorter and stability of temperature values was better in endovascular group; time dedicated to specific TTM-related nurses’ interventions: 10.0min (endovascular), 38.0min (external) (P=0.0001); overall nursing workload: 429.5min (endovascular), 530.0min (external) (P=0.03) | Increased bleeding, hematoma, aneurysm, arteriovenous fistula: 43.9% (endovascular), 28.4% (external); microbiological colonization of central venous catheters: 38.5% (endovascular), 26.4% (external); patients experiencing at least 1 cooling-related side effect: 24.6% (endovascular), 14.2% (external) (P=0.003); 3 patients experienced deep accidental hypothermia (all in external group) |
| Author            | Year published | Type of study | Enrollment period | Research question | Inclusion criteria | Exclusion criteria | Total no. of patients | Group I | Group II | Cause of CA | Follow-up time | Primary outcome | Additional major outcomes | Complications/Adverse events |
|-------------------|----------------|---------------|-------------------|-------------------|-------------------|-------------------|---------------------|---------|----------|-------------|----------------|----------------|--------------------------|-----------------------------|
| Maynard et al27   | 2015           | Kim et al 2014
substudy     | 2007–2012      | Long-term neurological outcome and survival with prehospital cooling after resuscitation from CA compared with standard prehospital care | Age ≥18 y, ROSC after OHCA irrespective of initial rhythm, endotracheal intubation, established IV access, successful placement of esophageal temperature probe, unconsciousness | Trauma, spontaneous hypothermia <34 °C | n=373               | n=195 (mean age: 61 y, 71% men, VF 71%); prehospital induced hypothermia using up to 2 L of ice-cold saline, TT <34 °C for 24 h | N/A         | 1 y      | No difference between CPC or mRS scores 3 mo after randomization (P=0.70 and P=0.49, respectively) | 1-y survival rate: 87% (prehospital hypothermia), 84% (control) (P=0.42); 1-y survival rate: 82% (CPC 1 at discharge), 40% (CPC 4 at discharge) | N/A |
| Debaty et al38    | 2014           | RCT           | 2009–2012        | Impact of intra-arrest therapeutic hypothermia on neurological outcome and inflammation following OHCA | Age ≥18 y, patients with OHCA eligible for advanced life support irrespective of initial rhythm | Trauma, hemorrhage, asphyxia, spontaneous hypothermia <34 °C, ROSC before randomization, DNR order, pregnancy | n=245               | n=123 (median age: 66 y, 72% men, VF/pulseless VT 29%, PEA 7%, asystole 64%; intra-arrest induced hypothermia, infusion of up to 2000 mL ice-cold 0.9% saline solution at 100 mL/min, surface cooling using gel pads [Colpac, Chattanooga Medical Supply], TT 32–34 °C for 24 h, controlled rewarming rate 0.3–0.5 °C per h) | n=122 (median age: 69 y, 71% men, VF/pulseless VT 26%, PEA 7%, asystole 66%; induced hypothermia initiated at hospital using cold saline infusion, cooling mattress, cold air circulation or ECLS temperature control, TT 32–34 °C for 24 h, controlled rewarming rate 0.2–0.5 °C per h) | Cardiac cause: 80% | 1 y | No differences in concentration of IL6 (P=0.74), IL8 (P=0.59), IL10 (P=0.97) between intra-arrest and hospital hypothermia group; survival-to-discharge rate: 5.7% (intra-arrest), 4.1% (hospital) (P=0.73); 1-y survival rate: 5.7% (intra-arrest), 4.1% (hospital) (P=0.73); 1-y survival rate: 4.1% (intra-arrest), 4.1% (hospital) (P=0.99) | Pulmonary edema: n=7 (intra-arrest), n=8 (hospital) (P=0.59); pneumonia: n=7 (intra-arrest), n=3 (hospital) (P=0.24); hyperthermia: n=9 (intra-arrest), n=5 (hospital) (P=0.36); bacteremia: n=1 (intra-arrest), n=0 (hospital) (P=1); hemorrhage: n=3 (intra-arrest), n=3 (hospital) (P=0.98); arrhythmia: n=5 (intra-arrest), n=7 (hospital) (P=0.39); convulsion: n=8 (intra-arrest), n=2 (hospital) (P=0.00) |
Table 1. (Continued)

| Author | Year published | Type of study | Enrollment period | Research question | Inclusion criteria | Exclusion criteria | Total no. of patients | Group I | Group II | Cause of CA | Follow-up time | Primary outcome | Additional major outcomes | Complications/Adverse events |
|--------|----------------|--------------|-------------------|-------------------|-------------------|-------------------|---------------------|--------|--------|------------|----------------|----------------|-----------------------------|-----------------------------|
| Kim et al | 2014 | RCT | 2007–2012 | Outcomes with prehospital cooling after resuscitation from CA compared with standard prehospital care | Age >18 y, ROSC after OHCA irrespective of initial rhythm, endotracheal intubation, established IV access, successful placement of esophageal temperature probe, unconsciousness | Trauma, spontaneous hypothermia <34 °C | n=690 (median age: 62/69 y, 76/55% men); prehospital induced hypothermia using up to 2L of ice-cold saline, TT <34 °C for 24 h | n=369 | n=321 | Standard prehospital care (nearly all patients in intervention and control group received induced hypothermia after hospital admission) | N/A | Hospitalization | Survival to hospital discharge: 62.7% (prehospital hypothermia), 64.3% (control) (P=0.69) (VF); 19.2% (prehospital hypothermia), 16.3% (control) (P=0.30) (non-VF); full recovery or mild neurological impairment at discharge: 87.5% (prehospital hypothermia), 81.9% (control) (P=0.69) (VF); 14.4% (prehospital hypothermia), 13.4% (control) (P=0.30) (non-VF) | Decrease in mean core temperature by 1.2 °C (VF) and by 1.3 °C (non-VF) |
| Lilja et al | 2014 | TTM trial substudy | 2010–2013 | Cognitive outcomes in patients treated with 33 °C compared with 36 °C after CA, and both groups compared with control group with STEMI but without CA | Age >18 y, OHCA of presumed cardiac cause irrespective of initial rhythm, >20 min of spontaneous circulation after resuscitation | >240 min from ROSC to screening, unwitnessed CA with asystole as initial rhythm, intracranial hemorrhage or stroke, spontaneous hypothermia <30 °C | n=652 (median age: 65 y, 83% men, shockable rhythm: 82%); induced hypothermia with intravascular (24%) or surface temperature management (76%) devices, TT 33 °C for 28 h, rewarming rate 0.5 °C per h | n=328 (median age: 65 y, 80% men, shockable rhythm: 81%); normothermia with intravascular (24%) or surface temperature management (76%) devices, TT 36 °C for 28 h, rewarming rate 0.5 °C per h | N/A | 180 d | Cognitive function assessed by memory, executive function, and attention/mental speed test did not differ between 33 °C and 36 °C group; attention/mental speed was more affected in all patients with CA compared with STEMI controls | Return to previous employment: 46% (OHCA group), 72% (STEMI control group) (P=0.008) | N/A | (Continued)
| Author          | Year published | Type of study | Enrollment period | Research question | Inclusion criteria                                                                 | Exclusion criteria                                                                 | Total no. of patients | Group I | Group II | Cause of CA | Follow-up time | Primary outcome                                                                 | Additional major outcomes | Complications/Adverse events |
|-----------------|-----------------|---------------|-------------------|-------------------|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-----------------------|----------|----------|-------------|----------------|-----------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|-----------------------------|
| Nielsen et al 41 | 2013            | RCT (TTM)     | 2010–2013         | Benefits and adverse effects of 2 targeted temperature regimens (33 °C vs 36 °C) in patients with CA | Age >18 y, OHCA of presumed cardiac cause irrespective of initial rhythm, ≥20 min of spontaneous circulation after resuscitation | n=939                                                                                   | n=476 (mean age: 64 y, 83% men, VF: 76%, pulseless VT: 3%, PEA: 8%, asystole: 12%); induced hypothermia with intravascular (24%) or surface temperature management (76%) devices, TT 33 °C for 28 h, rewarming rate 0.5 °C per h | n=476 (mean age: 64 y, 79% men, VF: 77%, pulseless VT: 3%, PEA: 6%, asystole: 12%); induced normothermia with intravascular (24%) or surface temperature management (76%) devices, TT 36 °C for 28 h, rewarming rate 0.5 °C per h | N/A                  | 25.6 d   | All-cause mortality: 50% (33 °C), 48% (36 °C) (\(P=0.51\))                                                                 |
| Bernard et al 42 | 2010            | RCT           | 2005–2007         | Outcomes with cooling initiated by paramedics after resuscitation compared with cooling initiated after hospital arrival | Age >15 y, OHCA with initial cardiac rhythm of VF, ROSC, systolic blood pressure <90 mm Hg, cardiac arrest time >10 min, established IV access | n=234                                                                                   | n=118 (mean age: 63 y, 83% men); induced hypothermia initiated by paramedics using 2000 mL of ice-cold lactated Ringer's solution at 100 mL/min during transport to hospital, TT 33 °C for 24 h, rewarming rate 0.25 °C per h | n=118 (mean age: 63 y, 88% men); induced hypothermia initiated at hospital, TT 33 °C for 24 h, rewarming rate 0.25 °C per h | N/A                  | Hospitalization                                                                        | Rate of favorable outcome (discharge home or to rehabilitation facility): 47.5% (early hypothermia), 52.6% (hospital hypothermia) (\(P=0.43\)) | Number of patients with 1 or more complications: 90% (33 °C), 90% (36 °C) (\(P=0.00\)); hypokalemia: 19% (33 °C), 13% (36 °C) (\(P=0.02\)) |
### Table 1. (Continued)

| Author, Year Published | Type of Study | Enroll. Period | Research Question | Inclusion Criteria | Exclusion Criteria | Total No. of Patients | Group 1 | Group 2 | Cause of CA | Follow-up Time | Primary Outcome | Additional Major Outcomes | Complications/Adverse Events |
|------------------------|---------------|----------------|------------------|-------------------|-------------------|----------------------|---------|---------|-------------|---------------|----------------|--------------------------|----------------------------|
| Castrén et al43 2010   | RCT           | 2008–2009      | Safety, feasibility, and cooling efficacy of prehospital transnasal cooling and its effects on neurologically intact survival to hospital discharge | Age >18y, OHCA irrespective of initial rhythm, witnessed CA, CPR initiated within 20 min of collapse | Trauma, drug overdose, cerebrovascular accident, known coagulopathy, asphyxia or known requirement for supplemental oxygen, electrocution, spontaneous hypothermia, ROSC before randomization, DNR order, transnasal obstruction | n=200                | n=104 (mean age: 66 y, 72% men, VF: 29%, PEA: 20%, asystole: 51%) | n=104 (mean age: 64 y, 78% men, VF: 32%, PEA: 23%, asystole: 46%) | Cardiac cause: 87% | Hospitalization | Median interval from collapse to transnasal cooling: 26 min; median interval from collapse to systemic cooling: 113 min; median time to target core temperature (34 °C): 115 min (transnasal cooling), 284 min (control); mean core temperature on hospital arrival: 35.1 °C (transnasal cooling), 35.8 °C (control) (P=0.01) | ROSC achieved: 37.0% (transnasal cooling), 42.6% (control) (P=0.48); survival to hospital discharge: 43.8% (transnasal cooling), 31.0% (control) (P=0.26); survival to hospital discharge with good neurological function (CPC 1–2): 21.4% (transnasal cooling), 34.4% (control) (P=0.2) |
| Hypothermia After Cardiac Arrest Study Group44 2002 | RCT (HACA) | 1996–2001 | Neurologic outcome with induced hypothermia in patients with CA because of ventricular fibrillation/ non-fibrillating ventricular tachycardia | Age 18–75y, witnessed cardiac arrest with shockable initial rhythm (VT, VF), CA of presumed cardiac cause, estimated interval of 0–15 min from collapse to first resuscitation attempt, <60 min from collapse to ROSC | Spontaneous hypothermia <30 °C, pregnancy, known coagulopathy, terminal disease, comatose state before CA, response to verbal commands after ROSC, hypothermia <30 °C after ROSC, hypoxemia for >30 min after ROSC | n=275                | n=137 (median age: 59y, 76% men, shockable rhythm: 97%) | n=138 (median age: 59y, 77% men, shockable rhythm: 98%) | Presumed cardiac cause: 99% | 6 mo | Favorable neurologic outcome (CPC 1–2) at 6 mo: 55% (hypothermia), 39% (normothermia) (P=0.009) | 6 mo mortality rate: 41% (hypothermia), 55% (normothermia) (P=0.02) | Nasal whitening: 14% (resolved in all survivors); epistaxis: 3.2% (serious bleeding in 1 patient with underlying coagulopathy); periorbital emphysema: 1% (resolved within 24 h); total serious adverse events: n=7 (transnasal cooling), n=14 (control) (P=0.23) |

(Continued)
| Author | Year published | Type of study | Enrollment period | Research question | Inclusion criteria | Exclusion criteria | Total no. of patients | Group I | Group II | Cause of CA | Follow-up time | Primary outcome | Additional major outcomes | Complications/Adverse events |
|--------|----------------|---------------|-------------------|-------------------|--------------------|--------------------|---------------------|---------|---------|-------------|----------------|----------------|-------------------------|-----------------------------|
| Bernard et al. | 2002 | RCT | 1996–1999 | Effects of normothermia and moderate hypothermia in patients who remain unconscious after resuscitation from OHCA | Age >18y (≥60 y for women), OHCA with initial cardiac rhythm of VF, persistent coma after ROSC | Cardiogenic shock, drug overdose, trauma, cerebrovascular accident, pregnancy | n=77 | n=43 (median age: 67 y, 58% men); induced hypothermia using ice packs placed on head, neck, torso and limbs, TT 33°C for 12h, rewarming within 6h | n=34 (median age: 65 y, 79% men); induced normothermia, TT 37°C for 24h | N/A | Hospitalization | Discharge with good neurologic outcome: 49% (hypothermia), 26% (normothermia) (P=0.046); for each 2-year increase in age, 9% decrease in likelihood of good outcome (OR, 0.91; P=0.014); for each 1.5 min in time from collapse to ROSC, 14% decrease in likelihood of good outcome (OR, 0.86; P=0.001); multivariate logistic regression analysis for good outcome: OR, 5.25 in hypothermia group (P=0.011) | Overall mortality: 51% (hypothermia), 68% (normothermia) (P=0.145) | No clinically significant arrhythmias in the hypothermia group, no statistically significant differences in platelet and white cell count |

ACLS indicates advanced cardiac life support; ACS, acute coronary syndrome; CA, cardiac arrest; COPD, chronic obstructive pulmonary disease; CPC, Cerebral Performance Category; CPR, cardiopulmonary resuscitation; DNR, do not resuscitate; ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; EMS, emergency medical services; FROST-I, Finding the Optimal Cooling Temperature After Out-of-Hospital Cardiac Arrest; GCS, Glasgow Coma Scale; HACA, Hypothermia After Cardiac Arrest; ICU, intensive care unit; IL, interleukin; HYPERION, Therapeutic Hypothermia after Cardiac Arrest in Nonshockable Rhythm; ICEREA, Clinical and Economical Interest of Endovascular Cooling in the Management of Cardiac Arrest; IQCODE, Informant Questionnaire of Cognitive Decline for the Elderly; mRS, modified Rankin Scale; N/A, not available; ns, not significant; NSE, neuron-specific enolase; OHCA, out-of-hospital cardiac arrest; OR, odds ratio; PaO2, partial pressure of oxygen; PEA, pulseless electric activity; PRINCESS, Prehospital Resuscitation Intra Nasal Cooling Effectiveness Survival Study; RCT, randomized controlled trial; RINSE, Rapid Infusion of Cold Normal Saline; ROSC, return of spontaneous circulation; STEMI, ST-segment–elevation myocardial infarction; TT, target temperature; TTM, targeted temperature management; TTM2, Targeted Hypothermia Versus Targeted Normothermia After Out-of-Hospital Cardiac Arrest; VF, ventricular fibrillation; and VT, ventricular tachycardia.
studies, patients with an initial nonshockable rhythm were included, except for asystole in an unwitnessed CA. Neuroprognostication was standardized across both study arms with blinded neurological prognosticators instead of reliance on unblinded clinical teams. All-cause mortality, after a mean follow-up period of 256 days, for all patients was 50% in the 33 °C group (n=473) compared with 48% in the 36 °C group (n=466) (P=0.51). This suggests that a wider target temperature range or even normothermia may be acceptable for neuroprotection. The groups did not differ significantly with respect to the composite outcome of death or poor neurologic function at 180 days, with the use of either the CPC scale (risk ratio for a CPC score of 3–5 in the 33 °C group, 1.02 [95% CI, 0.88–1.16]; P=0.78) or the modified Rankin Scale (mRS) score (risk ratio for a mRS score of 4–6 in the 33 °C group, 1.01 [95% CI, 0.89–1.14]; P=0.87). However, to adequately interpret these results, it is essential to consider that in the TTM1 trial, in contrast to the previous studies, tight temperature control was maintained in the 36 °C group.

A more detailed assessment of the functional outcome in the TTM1 trial was presented in the 2 substudies by Lilja et al and Cronberg et al. In the first follow-up study, survivors underwent the Rivermead Behavioral Memory Test, Frontal Assessment Battery, Symbol Digit Modalities Test, and the Hospital Anxiety and Depression Rating for more precise cognitive and psychological outcome analysis. The test results showed no difference between the 2 trial groups. In the substudy by Cronberg et al, cognitive performance, additionally assessed by Mini-Mental State Examination scores and Informant Questionnaire of Cognitive Decline for the Elderly, was also similar in both the 33 °C and 36 °C groups. Overall, around 82% of survivors did not require help in everyday activities (81.2% versus 82.9%, P=0.71), and within this cohort, 66.5% in the 33 °C group and 61.8% in the 36 °C group felt they have recovered fully in terms of their mental abilities (P=0.32). The employment rate at 6 months after arrest was 30.1% and 33.2% (not significant), respectively.

According to the International Liaison Committee on Resuscitation’s worldwide collection of regional and national data, 62.2% to 93.5% of patients suffering OHCA present with an initial nonshockable rhythm. To date, the HYPERION (Hypothermia After Cardiac Arrest With Nonshockable Rhythm) trial published by Lascarrou et al in 2019, is the only RCT explicitly dedicated to this patient population. The main cause of CA was asphyxia (55%) followed by primary cardiac causes (27%). Patients initially presenting with pulseless electrical activity or asystole received targeted hypothermia of 33 °C for 24 hours or targeted normothermia of 36.5 °C to 37.5 °C for 48 hours. Given that an initial nonshockable rhythm is one of the most severe risk factors for a dismal prognosis, the 90-day overall mortality rate was, as expected, extremely high.
at 82.3%. Survival to intensive care unit (ICU) discharge was not significantly different between groups (hazard ratio, 1.07), and mortality after 90 days was 81.3% in the hypothermia group (n=284) and 83.2% in the control group (n=297). The primary end point of the study, defined as survival with a favorable neurologic outcome (CPC 1–2), was found in 10.2% of those managed at 33 °C and 5.7% of those in the targeted normothermia group, respectively (P=0.04).27 The trial suffered from several major limitations: (1) Many patients in the normothermia group had fever, which could have biased the results in favor of the hypothermia arm. (2) There was no differentiation between patients with OHCA and IHCA. (3) Primary outcome was assessed during a phone interview rather than a face-to-face encounter. (4) Temperature management was used for a longer period (56 to 64 hours) in the hypothermia than in the normothermia group (48 hours). (5) The study’s fragility index value was 1; thus, a single patient could have changed significance of the primary outcome causing a marginality of the benefit’s significance seen in the hypothermia group.

The recently published TTM2 was the first adequately powered randomized controlled trial to answer the question of whether targeted hypothermia provides a survival benefit compared with normothermia. With 1861 patients included, the study population was much larger compared with its predecessors. Approximately two-thirds of both the intervention (n=930) and control group (n=931) had an initial shockable rhythm. This is considerably higher than the general rate of shockable rhythms in US cohorts, thus limiting generalizability.46 The authors found no significant difference in the 6-month mortality between the hypothermia group (33 °C for 28 hours) and the targeted normothermia group (<37.8 °C) (60% versus 48%, P=0.37). Notably, mortality was also similar in a subgroup analysis of patients with initial nonshockable and shockable rhythms (relative risk [RR], 1.04; RR, 1.00, respectively). Furthermore, the TTM2 trial did not confirm the neurologic outcomes found in the HYPERION trial. In the corresponding subgroup (initial nonshockable rhythm), poor functional outcome, defined as a mRS score of 4 to 6, was similar in both the hypothermia and normothermia group (RR, 1.00 [95% CI, 0.93–1.08]). None of the prespecified subgroups (sex, age <65 years, interval <25 minutes from CA to ROSC, initial rhythm, and shock on admission), showed improved functional outcome with a lower target temperature. Patient-reported quality of life was almost identical in the intervention and control group (mean EQ-5D-5L score: 74 [33 °C] versus 75 [<37.5 °C], not significant.). Of note, 46% of the patients in the normothermia group received device-based cooling (31% with an intravascular device and 69% with a surface device). In summary, the results of the TTM2 trial imply a low likelihood of any meaningful clinical improvement with hypothermia at 33 °C for 28 hours compared with targeted normothermia at <37.8 °C.26

The HACA trial, although underpowered for detecting a mortality difference, found a survival benefit for patients with ventricular fibrillation or ventricular tachycardia. The RCTs that followed, which were adequately powered for mortality, could not reproduce these results. Furthermore, the Bernard et al and the HACA trial from 2002, as well as the HYPERION trial, which was published 2019, have found improved neurological function with hypothermia, but the TTM2 trial did not reproduce these results. In accordance with this, the extensive functional outcome analyses based on the TTM1 trial population, after a follow-up of 6 months, showed no benefit for a lower targeted temperature. The quality of evidence put forward by both TTM trials is high, despite the above-mentioned limitations and contradicts the more promising preclinical data of the past.22

**IMPACT OF THE COOLING TECHNIQUE**

Cooling for therapeutic hypothermia or normothermia can simply be achieved by placing ice packs on the patient’s neck, torso, and proximal limbs, or by using fans and adapting the ambient temperature. In the ICEREA (Clinical and Economical Interest of Endovascular Cooling in the Management of Cardiac Arrest) trial, Deye et al compared the efficacy and precision of these surface cooling techniques to a modern intravascular cooling catheter device in 400 adults suffering OHCA of presumed cardiac cause, with shockable and nonshockable initial rhythms (Table 1). The study protocol defined a target temperature of 33 °C for 24 hours, followed by controlled active rewarming at a rate of <0.5 °C per hour, in the endovascular device group and passive rewarming in the control group. A similar proportion of patients reached the target temperature in both groups, but patients managed with an endovascular device had a significantly shorter delay from cooling initiation to achieving the 33 °C target (71 versus 10.0 hours, P<0.0001). In the maintenance phase, the mean time with a deviation of >1 °C from the target temperature, was also lower in the endovascular group (1.0 versus 5.5 hours, P<0.0001), whereas the time to reach 37 °C after the 24-hour hypothermia period was the same (9.0 versus 9.1 hours, P=0.70). All 3 cases of accidental hypothermia, <30 °C, occurred in the external cooling group. A particular focus of the study was the nursing workload with both temperature management approaches. The external cooling devices required significantly more time dedicated to the temperature management method (38.0 versus 10.0 minutes, P<0.0001), but also an increased overall
nursing workload, evaluated by the paramedical time spent per patient and collected during the temperature management phase (530.0 versus 428.5 minutes, \( P=0.033\)). However, the physician workload was not investigated, but will surely rise when implant of a jugular or femoral vein cooling catheter is needed. The proportion of patients with favorable neurological function (CPC 1–2) after 28 days (36.0% versus 28.4%, \( P=0.107\)) as well as the overall survival rate after 3 months was not significantly different between groups (41.9% versus 38.1%, \( P=0.44\)). Improvement of outcome at day 90 in favor of the endovascular group did not reach significance (\( P=0.07\)).

This was replicated by another smaller RCT, comparing intravascular temperature management (n=23) to a gel-pad cooling system (n=22). The odds ratio (OR) for survival to discharge (internal versus external cooling) was 1.96 (95% CI, 0.59–6.86), and discharge with a favorable neurological outcome (CPC 1–2) was similar (OR, 1.49 [95% CI, 0.39–5.65]). On protocol adherence, the authors found significantly more incidences of undercooling <33 °C in the external device group (\( P=0.01\)), and rebound hyperthermia was also more common when compared with the intravascular temperature management group (\( P=0.02\)).

Modern systems for extracorporeal life support contain a temperature regulation module to implement temperature management in patients suffering prolonged circulatory failure. Pang et al assessed outcomes in a small group of individuals (n=21) in whom extracorporeal life support was initiated within 45 minutes after CA (90.5% IHCA). Survival to hospital discharge was 33.3% and 18.2%, in patients receiving targeted hypothermia at 34 °C and targeted normothermia at 37 °C, respectively, for 24 hours (\( P=0.4\)). Other outcome parameters (ie, 6-month survival and favorable neurologic outcome) were also similar between the 2 groups.

Overall, an endovascular temperature management strategy compared with basic external cooling is superior in terms of the initial cooling speed and temperature stability in the maintenance phase. Unfortunately, this does not result in better survival or improved functional outcomes.

**IMPACT OF HYPOTHERMIA INITIATION TIMING**

The preclinical data on early intra-arrest hypothermia have been promising, and timely initiation of temperature management has a sound pathophysiological rationale. A study by Bernard et al focused on preadmission TTM versus standard prehospital care by randomizing 234 individuals who suffered OHCA with VF as initial rhythm (Table 1). In the intervention group, 2000 mL of cold Ringer’s lactate solution was administered intravenously after ROSC during transport, followed by a bolus of 10 to 20 mL/kg upon arrival at the hospital. In comparison with the control group (cooling after hospital admission), the prehospital intervention resulted in a lower core temperature at admission, but not in a higher rate of patients discharged home or to a rehabilitation facility (47.5% versus 52.6%, \( P=0.43\)). In a subsequent much larger RCT with similar design, Kim et al randomized 1359 patients to receive prehospital induced hypothermia using up to 2000 mL of ice-cold saline (4 °C) delivered by paramedics versus hypothermia induction upon arrival at the hospital. They found no significant difference in survival to discharge in the correlative subgroup of patients with initial VF (62.7% versus 64.3%, \( P=0.69\)). The authors also included 776 patients with initial rhythm other than VF in their primary analysis. Survival to discharge was 19.2% in the intervention group receiving prehospital temperature management and 16.3% in the control group (\( P=0.30\)). The composite probability of full neurological recovery and mild impairment with and without prehospital temperature management was 57.5% and 61.9%, respectively, in the VF subgroup (\( P=0.69\)), and 14.4% and 13.4%, respectively, in the non-VF subgroup (\( P=0.30\)). After 3 months, the overall proportion of patients with CPC 1 to 2 was 59% and 58% (\( P=0.70\)) and mRS score of 0 to 2 was 50% and 49% (\( P=0.35\)). Survivors of the initial event from both the early and delayed temperature management group had a similar chance of 1-year survival (87% versus 84%, \( P=0.42\)).

For the RINSE (Rapid Infusion of Cold Normal Saline) trial, 618 patients received a rapid infusion of 30 mL/kg boluses of cold fluid during resuscitation if ROSC was not achieved despite defibrillation and intravenous adrenaline application. The intervention and control group both were cooled to a core temperature of 33 °C after admission. Survival to hospital discharge was 10.2% in the early temperature management group and 11.4% in the control group (\( P=0.71\)), but the immediate effects of intra-arrest initiation of hypothermia were rather inimical to the resuscitation efforts. Patients receiving cold fluids required CPR for longer, after emergency medical services’ arrival (22.6 versus 20.0 minutes, \( P=0.01\)), and a higher total epinephrine dose (6.5 versus 5.9 mg, \( P=0.006\)). Most importantly, significantly fewer patients reached ROSC if a shockable rhythm was present initially in the intervention group, showing potential harm in prehospital cooling (41.2% versus 50.6%, \( P=0.03\)). Moreover, the rate of suspected pulmonary edema was significantly higher in the intervention group (10.0% versus 4.5%, \( P<0.001\)). Both findings led to a general recommendation against the use of cold intravenous fluids in the preclinical setting to commence temperature management after/during OHCA.
A trial by Debaty et al used neuron-specific enolase as a biomarker for brain damage in 245 adults randomly assigned to prehospital intra-arrest hypothermia or conventional care. Twenty-four hours after the event onset, patients with OHCA in the intervention group had a median neuron-specific enolase blood concentration of 96.7 μg/L compared with 97.6 μg/L in the control group (P=0.64). Survival to 1 month and 1 year was similar in both groups as well (5.7% versus 4.1%, P=0.73 and 4.1% versus 4.1%, P=0.99, respectively).

In the clinical trial by Scales et al, including 585 patients with OHCA, the authors found that early temperature management did not lead to more patients reaching the target temperature (rate of target temperature [32 °C–34 °C] reached: 30% [prehospital cooling] versus 25% [standard care] [P=0.22]). Survival to discharge, as well as good neurological outcome at discharge, were not different in both groups (33% versus 32%, P=0.88 and 29% versus 26%, P=0.37).

Maybe the detrimental effects of intravenous delivery of large volumes of cold fluids have counterbalanced the benefit of early attainment of target temperature in the above-mentioned trials. Against this background, it is important to analyze those trials in which the concept of achieving rapid prehospital cooling using an intranasal device was investigated, considering the promising preclinical data on local instead of systemic cooling of the brain. In 2010, Castrén et al sought to investigate this concept in a prospective safety and efficacy trial (n=200) for the first time. Emergency medical services were equipped with a portable intranasal cooling device that achieves central nervous heat absorption by evaporating liquid perfluorocarbon inside the nasal cavities. The catheters can be inserted rapidly into the nostrils, even during an ongoing resuscitation. The median interval from collapse to trananasal cooling initiation was 26 minutes, whereas systemic temperature management after hospital admission was initiated after 113 minutes in the control group. The time to reach a target temperature of 34 °C was also shorter using the intranasal cooling device. However, the number of patients successfully resuscitated was similar in the device and the control group (37.6% versus 42.6%, P=0.48) as was survival to hospital discharge and survival with good neurologic function (CPC 1–2) (43.8% versus 31.0%, P=0.26 and 34.3% versus 21.4%, P=0.21, respectively).

The PRINCESS (Prehospital Resuscitation Intra Nasal Cooling Effectiveness Survival Study) trial, a mortality-powered RCT published by Nordberg et al, confirmed these results. Of note, patients in both groups received CPR by emergency medical services personnel for a median time of 9 minutes after CA, and 40% presented with an initial shockable rhythm. Although the median temperature at hospital admission and time to reach the target core temperature was significantly lower in the transnasal cooling group (34.6 °C versus 35.8 °C, P<0.001; 105 versus 182 minutes, P<0.001), survival with favorable neurological outcome after 3 months was 16.6% and 13.5%, respectively (P=0.25).

Thus, transnasal evaporative intra-arrest cooling, compared with conventional care, did not result in a significant improvement in survival with good neurologic outcome, and intra-arrest transnasal cooling, in general, has not affected clinically relevant neuroprotection. Consequently, it was not incorporated into clinical practice.

Overall, in a prehospital setting, cooling devices need to fulfill the high demands of out-of-hospital emergency situations including easy handling, safe and fast application, and high efficacy, without jeopardizing other life-saving interventions. An effect on mortality and neurological outcome of preclinical temperature management strategies could not be shown to date, and the evidence from the above-mentioned trials does not support the early routine use of prehospital temperature management. Instead, the RINSE trial demonstrated harm resulting in significantly fewer patients achieving ROSC when prehospital infusion of ice-cold saline was delivered during ongoing resuscitation efforts.

**IMPACT OF HYPOTHERMIA DURATION**

In most studies, temperature management was implemented for 24 hours; however, prospective data explicitly focusing on temperature management duration are limited. One study, by Kirkegaard et al, was conducted to evaluate targeted hypothermia at 33 °C for 48 and 24 hours after OHCA (Table 1). The intervention period was followed by controlled rewarming to reach 37 °C at a rate of 0.5 °C per hour. The majority of participants received an intravascular cooling device in both groups. Sedation was used until rewarming was complete. Favorable neurologic function after 6 months was assessed using the CPC score, which reached a value of 1 to 2 in 69% of patients treated with TTM for 48 hours and 64% in patients treated for 24 hours (P=0.33). Survival to 6 months was similar in both groups (27% versus 34%, P=0.19). As expected, the average ICU length of stay was prolonged in the 48-hour temperature management group. Ninety-seven percent and 91% of patients assigned to receiving temperature management for 48 and 24 hours, respectively, experienced at least 1 adverse event (P=0.03).

Without additional survival benefit and higher risk of complications, temperature management for 48 hours can be seen as inferior to shorter durations. The ICECAP (Influence of Cooling Duration on Efficacy in Cardiac Arrest Patients) trial (NCT04217551)
is currently recruiting patients with an estimated study completion date of 2025 and an estimated enrollment of 1800 participants. The study is designed to determine the optimal duration (eg, 12, 24, or 48 hours) of temperature management on good neurologic outcome and to ascertain whether the development of a duration response curve can be effective in a wider population of CA survivors using an adaptive subject-allocation approach.

**IMPACT OF TARGET TEMPERATURE**

The TTM1 trial showed that there is no additional neuroprotective benefit for patients undergoing temperature management with a lower target temperature at 33 °C as compared with more mild hypothermia at 36 °C. Whether more precise temperature settings lead to improved outcomes has been addressed in the FROST-I (Finding the Optimal Cooling Temperature After Out-of-Hospital Cardiac Arrest) trial by Lopez-de-Sa et al in 2018 (Table 1). One hundred fifty OHCA survivors with shockable initial rhythms were randomized into 3 groups to receive targeted hypothermia at 32 °C, 33 °C, and 34 °C, respectively, for 24 hours. Temperature control was performed using an intravascular cooling device inserted into the femoral vein. Controlled rewarming was limited to 0.1 to 0.2 °C per hour, followed by a period of targeted normothermia, which was then maintained until 50 hours after starting temperature management. Favorable neurologic outcome, defined as a mRS score of ≤3 at 90 days, was observed in 63.3% of patients assigned to the 32 °C group, 68.2% in the 33 °C group, and 65.1% in the 34 °C group, without a significant difference. Ninety-day all-cause mortality was similar between all groups at 30.8%, 26.5%, and 28.5%, respectively.

Most of the relevant RCT protocols determined a constant target temperature of 33 °C in the intervention arm, which was then compared with a control group treated with targeted normothermia of 36.5 °C to 37.5 °C.

**Complications associated with therapeutic hypothermia bleeding**

In the HACA trial, the proportion of patients with any complication did not differ significantly between the hypothermia and the normothermia group (P=0.7), although bleeding occurred numerically more often in the hypothermia group. In the second major RCT from 2002, a crude analysis of adverse events did not reveal any relevant differences between the intervention and control group. During the ICU stay, Nielsen et al observed uncontrolled bleeding in 2.2% of patients in the 33 °C group and 1.3% in the 36 °C group (P=0.45). Overall, 93% (33 °C group) and 90% (36 °C group) of patients experienced at least 1 serious adverse event during their ICU stay (P=0.086), which lasted a median of 124 hours in the 33 °C group and 117 hours in the 36 °C group. In patients with a nonshockable initial rhythm, enrolled in the HYPERION trial, the rate of severe bleeding within 7 days after CA was equal in both groups (5.6% versus 5.7%, P=0.97). In the TTM2 trial, the incidence of bleeding was 5% in both the targeted hypothermia and control group (P=0.81). Additional data by Kirkegaard et al indicate a shorter temperature management duration, of 24 hours to be favorable compared with 48 hours as it relates to the risk of severe bleeding (1% versus 4%, P=0.03) and overall complications (91% versus 97%, P=0.03).

**Infection**

In the HACA trial, pneumonia and sepsis occurred more often in the hypothermia group without reaching significance. The number of patients experiencing pneumonia, severe sepsis, and septic shock was similar between the 2 groups of the TTM1 trial (52% versus 46%, P=0.089; 10% versus 10%, P=0.92; 4.8% versus 5.4%, P=0.63, respectively). In the HYPERION trial, the rate of bacteremia was similar in both groups as well (4.2% versus 3.7%, P=0.76). In the FROST-I trial, there were fewer infections in the 32 °C group, with a significantly lower incidence of respiratory infections (P=0.012). In the TTM2 trial, the incidence of pneumonia (36% versus 35%, P=0.75) and sepsis (11% versus 9%, P=0.23) was comparable between the 2 groups.

**Arrhythmias**

Lethal or long-lasting arrhythmia occurred numerically more often in the HACA trial’s hypothermia group. Bernard et al reported similar rates of supraventricular and ventricular arrhythmias between the 2 groups in the TTM1 trial, as did Lascarrou et al in the HYPERION trial (12.3% versus 10.4%, P=0.48). On the contrary, in the TTM2 trial population, relevant arrhythmias requiring pacing or CPR were detected more frequently in the targeted hypothermia group (24% versus 16%, P<0.001). One case of hemodynamically relevant bradycardia occurred in the intervention group.

**Device-related complications**

Temperature management was accomplished exclusively using cool packs and other external devices in the early trials from 2002. The authors of both RCTs, however, did not specify device-related complications. In the subsequent TTM1 trial, bleeding from
catheter insertion sites occurred in 9.2% of patients in the 33 °C group and in only 6.1% in the 36 °C group (P=0.076). Intravascular devices were used in a similar proportion of patients, which may indicate a lower target temperature to trigger this adverse effect. 41 In the HYPERION trial, device-related complications were also not evaluated. 27 Dankiewicz et al reported 3 cases of venous thromboembolism, classified as potential unexpected serious adverse events, which may be related to use of an intravascular cooling device. The TTM2 trial protocol also defined blistering or skin necrosis related to external cooling as a prespecified serious adverse event. This occurred in 10 out of 927 patients in the targeted hypothermia group and 5 out of 922 patients in the control group (P=0.21). 26 Studies dedicated to exploring the differences between internal versus external cooling methods provide more detailed information on device-related complications. Although being more effective and precise than cooling with external devices, Deye et al found higher rates of complications related to intravascular cooling catheters including minor insertion site complications (44% versus 29%), catheter colonization and infection (39% versus 26%), and lower limb ischemia (3.5% versus 0%). 38 Notably, all 3 instances of accidental deep hypothermia <30 °C occurred with external cooling. About systemic adverse events, the risk of cardiac arrhythmias and seizures appears to be similar using intravascular or external cooling approaches. 31 In both studies by Castrén et al and the PRINCESS trial, the use of an intranasal cooling device was associated with a low probability of serious adverse events. Serious nose bleeding occurred rarely, cases of pneumocephalus/periorbital emphysema resolved spontaneously, and the overall prevalence of adverse events was comparable. 28, 43

COMPLICATIONS RELATED TO LARGE-VOLUME COLD FLUID APPLICATION

Most RCTs conducted to evaluate prehospital hypothermia initiated temperature management by intravenous infusion of up to 2000 mL of ice-cold Ringer’s lactate solution or normal saline. Although not unanimously, this approach has been described as harmful rather than beneficial. Kim et al observed higher rates of re-arrest (26% versus 21%, P=0.008) and radiographic evidence of pulmonary edema (41% versus 30%, P<0.001), necessitating more frequent use of diuretics as compared with standard prehospital care. 39 Furthermore, Bernard et al found a 9.6% lower likelihood for ROSC in patients with an initial shockable rhythm who received cold saline during CPR. The RINSE trial also reproduced the finding of a higher risk of pulmonary edema with cold saline infusion (10.0% versus 4.5%, P<0.001), 53 which subsequently led to a recommendation against the use of intravascular temperature management strategies in the field. 10, 14 and the design of transnasal cooling devices.

Conclusively, lower target temperatures may be detrimental to recovery, especially when rapid intravascular application of cold fluids are used for temperature control. The largest and most recent RCT additionally suggests a significant risk for arrhythmias with targeted hypothermia. 26 Whether this complication is secondary to electrolyte imbalances is unclear and needs to be evaluated in substudies and future trials.

PRACTICAL IMPLICATIONS AND FUTURE DIRECTIONS

The 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care as well as the European Resuscitation Council and European Society of Intensive Care Medicine guidelines on postresuscitation care published in March 2021, generally recommend temperature management for all patients suffering OHCA and IHCA. 10, 14 (Table 2). A recommendation for temperature management is given for patients with an initial nonshockable or shockable rhythm who remain in an unresponsive state after ROSC. The strong recommendation for the use of temperature management in OHCA survivors proposed by the American societies is mainly based on the HYPERION and HACA trials, as well as the data published by Bernard et al in 2002. Because there is no RCT dedicated to IHCA survivors with a shockable rhythm to date, a derivative recommendation for temperature management also based on the results of the HYPERION trial, which included patients with IHCA, is proposed for this subgroup. In comparison, the European guidelines lowered their temperature management recommendations only for patients suffering OHCA with a nonshockable rhythm, but otherwise they coincided with their counterpart. In view of the TTM1 trial results, both agree that a target temperature of 32 °C to 36 °C should be selected and maintained for at least 24 hours. On early temperature management initiation in the prehospital setting, a strong recommendation against the use of cold intravenous fluids is given based on the findings, showing a significant risk of pulmonary edema and increased failure to achieve ROSC in the RINSE trial.

The data published by Dankiewicz et al in June 2021 contradict parts of these recommendations. In the TTM2 trial, patients suffering OHCA did not benefit from targeted hypothermia as compared with normothermia with a target core temperature of <37.5 °C in
terms of mortality and neurologic function. Considering the higher risk for clinically relevant arrhythmias, a target temperature of 32 °C to 34 °C may not be suitable for this patient cohort. Here, current guidelines differ, with a wide range for target temperatures (32 °C versus 33 °C versus 34 °C versus 35 °C versus 36 °C), which has led to great variance in hospitals’ standard operating procedures. They should be advised to incorporate the results of the TTM2 trial to streamline the temperature selection process by narrowing the target range to, for example 36 °C, or even allow for temperature above 36 °C, while preventing fever >37.8 °C. Also, the general importance of active temperature management in patients with CA should be emphasized because the recommendation of targeted normothermia may lead to a less attentive surveillance and treatment of fever in clinical practice.50,51

The TTM2 trial subgroup of individuals, with a non-shockable initial rhythm, had the same relative risk of poor neurological function with targeted hypo- and normothermia in patients with assumed CA because of cardiac origin. Findings from both the TTM2 and HYPERION trials indicate no additional benefit in terms of overall survival. The most recently published meta-analysis, including 10 randomized controlled studies with 4218 patients, finally concluded that no form of hypothermia (mild, moderate, deep) would lead to an improvement in functional outcomes or survival compared with targeted normothermia but could be associated with increased complications.52 The updated TTM algorithm of the cardiac ICU of the University Hospital of Munich, incorporating the evidence of the TTM2 trial, is summarized in Figure 3. Here, the only subpopulation excluded in the TTM2 trial (ie, patients

| Table 2. Principal Guidelines on Temperature Management |
|-----------------------------------------------|
| Recommendation | AHA Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care (2020) | ERC and European Society of Intensive Care Medicine guidelines (2021) | Supporting evidence from randomized trials |
|-----------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-----------------------------------------------|
| TTM for adults who do not follow commands after ROSC from OHCA with initial nonshockable rhythm | 1 B-R Weak Very low-quality evidence HYPERION 2019 (+) [27]; TTM2 2021 (+) [26] | | |
| TTM for adults who do not follow commands after ROSC from OHCA with initial shockable rhythm | 1 B-R Strong Low-quality evidence HACA 2002 (+) [44]; Bernard et al 2002 (+) [45]; TTM2 2021 (+) [26] | | |
| TTM for adults who do not follow commands after ROSC from IHCA with initial nonshockable rhythm | 1 B-R Weak Very low-quality evidence HYPERION 2019 (+) [27] | | |
| TTM for adults who do not follow commands after ROSC from IHCA with initial shockable rhythm | 1 B-NR Weak Very low-quality evidence No randomized data available | | |
| Selection and maintenance of constant target temperature between 32 °C and 36 °C | 1 B-R Strong Moderate-quality evidence TTM 2013 (+) [41] and substudies (+) [35,40]; FROST-I 2018 (+) [29]; TTM2 2021 (+) [26] | | |
| TTM maintenance of at least 24h | 2a B-NR Weak Very low-quality evidence Kirkegaard et al 2017 (+) [30] | | |
| Active prevention of fever in patients in a coma after TTM | 2b C-LD Weak Very low-quality evidence No randomized data available | | |
| Recommendation against routine use of rapid infusion of cold IV fluids for prehospital cooling of patients after ROSC | 3 A Strong Moderate-quality evidence Scales et al 2017 (-) [32]; RINSE 2016 (-) [33]; Debaty et al 2014 (-) [38]; Kim et al 2014 (-) [39]; Bernard et al 2010 (-) [42] | | |

Current AHA Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care (published in 2020) and the ERC and European Society of Intensive Care Medicine guidelines (published in 2021) on postresuscitation care with corresponding class of recommendation and supporting evidence from randomized trials. It is important to consider that the TTM2 trial results have not been incorporated in both yet; thus, its results are considered only in square brackets. AHA indicates American Heart Association; FROST-I, Finding the Optimal Cooling Temperature After Out-of-Hospital Cardiac Arrest; HACA, Hypothermia After Cardiac Arrest; HYPERION, Hypothermia After Cardiac Arrest With Nonshockable Rhythm; IHCA, in-hospital cardiac arrest; OHCA, out-of-hospital cardiac arrest; RINSE, Rapid Infusion of Cold Normal Saline; ROSC, return of spontaneous circulation; TTM, targeted temperature management; and TTM2, Targeted Hypothermia Versus Targeted Normothermia After Out-of-Hospital Cardiac Arrest.
with concomitant asystole as initial rhythm and unwitnessed CA) may undergo temperature management at 33 °C.

To briefly summarize the available data, targeted hypothermia at 32 °C to 34 °C does not improve survival after OHCA compared with targeted normothermia. An additional benefit of target temperatures <36 °C, however, is unlikely when temperature management is initiated after hospital admission. Intravascular temperature management using large-volume fluid delivery during/after CA in the field can be harmful and jeopardize resuscitation efforts. The positive effects of temperature management on neuroprotection are possibly mainly achieved by preventing hyperthermia. However, sufficient randomized data on fever prevention versus targeted normothermia and temperature management after targeted hypothermia/normothermia in the acute phase are not available yet, and further trials are urgently needed.

CONCLUSIONS

The basis of recommendations for therapeutic hypothermia in patients with CA because of shockable rhythm arose from 2 underpowered trials performed 20 years ago using closed envelope randomization and no standardized neurologic prognostication or palliation. Unfortunately, 2 decades later, mild hypothermia does neither lower mortality nor improve neurological outcome in patients after CA in the largest RCT performed to date. The remaining questions would be: (1) Is there is a need for any sedation in these patients? (2) How to treat patients suffering IHCA? (3) What is the optimal duration of temperature management and supportive care? (4) What is the ideal test for neurological monitoring and prognostication? Fever prevention seems to be the last important therapeutic target remaining after numerous RCTs on temperature management. However, because tolerating fever was not and will never be an option, there might be no need for further trials on this. Finally, guidelines should rapidly incorporate the findings of the TTM2 trial and simplify recommendations to standardize temperature management in everyday clinical practice primarily targeting fever prevention.

ARTICLE INFORMATION

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Acknowledgments
The authors thank L. De Lange for proofreading the article. All ethical standards were met during the writing and submission of this correspondence.

Sources of Funding
None.

Disclosures
Drs Peters, Scherer, and Petzold received speaker honoraria from AstraZeneca outside the submitted work. Dr Orban has received
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