



# The design of the PRINCESS 2 trial: A randomized trial to study the impact of ultrafast hypothermia on complete neurologic recovery after out-of-hospital cardiac arrest with initial shockable rhythm

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## ABSTRACT

**Background** Delayed hypothermia, initiated after hospital arrival, several hours after cardiac arrest with 8-10 hours to reach the target temperature, is likely to have limited impact on overall survival. However, the effect of ultrafast hypothermia, i.e., delivered intra-arrest or immediately after return of spontaneous circulation (ROSC), on functional neurologic outcome after out-of-hospital cardiac arrest (OHCA) is unclear. In two prior trials, prehospital trans-nasal evaporative intra-arrest cooling was safe, feasible and reduced time to target temperature compared to delayed cooling. Both studies showed trends towards improved neurologic recovery in patients with shockable rhythms. The aim of the PRINCESS2-study is to assess whether cooling, initiated either intra-arrest or immediately after ROSC, followed by in-hospital hypothermia, significantly increases survival with complete neurologic recovery as compared to standard normothermia care, in OHCA patients with shockable rhythms.

**Methods/design** In this investigator-initiated, randomized, controlled trial, the emergency medical services (EMS) will randomize patients at the scene of cardiac arrest to either trans-nasal cooling within 20 minutes from EMS arrival with subsequent hypothermia at 33°C for 24 hours after hospital admission (intervention), or to standard of care with no prehospital or in-hospital cooling (control). Fever (>37,7°C) will be avoided for the first 72 hours in both groups. All patients will receive post resuscitation care and withdrawal of life support procedures according to current guidelines. Primary outcome is survival with complete neurologic recovery at 90 days, defined as modified Rankin scale (mRS) 0-1. Key secondary outcomes include survival to hospital discharge, survival at 90 days and mRS 0-3 at 90 days. In total, 1022 patients are required to detect an absolute difference of 9% (from 45 to 54%) in survival with neurologic recovery (80% power and one-sided  $\alpha=0,025$ ,  $\beta=0,2$ ) and assuming 2,5% lost to follow-up. Recruitment starts in Q1 2024 and we expect maximum enrolment to be achieved during Q4 2024 at 20-25 European and US sites.

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**Discussion** This trial will assess the impact of ultrafast hypothermia applied on the scene of cardiac arrest, as compared to normothermia, on 90-day survival with complete neurologic recovery in OHCA patients with initial shockable rhythm.

**Trial registration** NCT06025123. (Am Heart J 2024;271:97–108.)

## Background

Out-of-hospital cardiac arrest (OHCA) is a major health problem in the western world.<sup>1</sup> Only around 10% of patients with OHCA survive to discharge,<sup>1</sup> and in patients resuscitated from cardiac arrest, severe brain injury, caused by global ischemia during the arrest phase as well as reperfusion injury which begins as soon as circulation is reestablished,<sup>2</sup> is the primary cause of death.<sup>3-5</sup> Today, there are limited evidence-based neuroprotective strategies to mitigate these post-anoxic cerebral injuries and improve neurologic outcome.

Therapeutic hypothermia, also known as target temperature management (TTM), may reduce the brain damage caused by cardiac arrest.<sup>6</sup> Experimental studies suggest that the earlier hypothermia is initiated, intra-arrest or very early after reestablished circulation, the greater may the benefit be to prevent cerebral injury<sup>7-9</sup> as well as to improve survival rates.<sup>7,8,10-12</sup> In 2002, two smaller, randomized clinical trials showed improved neurologic outcome in patients with OHCA with initially shockable rhythm (e.g., ventricular fibrillation or pulseless ventricular tachycardia), when treated with hypothermia of 32°C to 34°C for 12 to 24 hours.<sup>13,14</sup> Based on these studies, TTM after cardiac arrest was recommended in international guidelines for several years.<sup>15</sup> However, in recent years, large, randomized clinical studies on a more heterogeneous OHCA population have not found any benefit in 6-months survival after therapeutic hypothermia to 33°C compared to TTM to 36°C or to normothermia with avoiding fever.<sup>16,17</sup> Thus, recommendations for temperature control changed in the fall of 2021 into actively preventing fever, instead of active hypothermia treatment.<sup>18</sup>

Despite experimental findings of the importance of early cooling, hypothermia was initiated late in the majority of previous clinical studies, after arrival to hospital and admission to the intensive care unit (ICU), and often after examinations or interventions such as CT-scan or coronary angiography. Consequently, target temperature is reached several hours (i.e., 8-10 hours) after return of spontaneous circulation (ROSC). With this delayed cooling strategy, probably due to pragmatic reasons, the optimal time window for maximal effectiveness of hypothermia might have been missed. Indeed, international guidelines still identify the potential effect of very early TTM, initiated intra-arrest or shortly after ROSC, as an important knowledge gap.<sup>18</sup>

Inducing hypothermia in patients with cardiac arrest in the prehospital setting is challenging. Rapid infusion

of cold intravenous fluids is feasible for most emergency medical systems, but has been associated with hemodynamic side effects,<sup>19-21</sup> in particular in patients with initial shockable rhythms.<sup>20</sup> Trans-nasal evaporative cooling (TNEC) is a method that can be used to induce hypothermia during cardiac arrest. The trans-nasal cooling device (RhinoChill, BrainCool Inc, Lund, SW) is a non-invasive, portable system that sprays a mixture of liquid coolant and oxygen into the upper surface of the nasal cavity through nasal catheters to rapidly cool the brain. It is designed to only take about one minute to apply. In two previous randomized studies that enrolled patients with OHCA, the PRINCE and the PRINCESS trials (overall n = 877), trans-nasal cooling with the RhinoChill device was safe and feasible to use in the prehospital setting without hemodynamic side effects. This method also significantly reduced time to target temperature.<sup>22,23</sup> In the PRINCESS trial, there was a trend towards survival with favorable neurologic outcome, defined as Cerebral Performance Category (CPC) 1 to 2, in the subgroup of patients with initial shockable rhythm, in favor of intra-arrest cooling. In the same subgroup, complete neurologic recovery defined as CPC 1, was significantly better (32.6% vs 20.0% (difference 12.6% [95% CI, 2.3%-22.9%])) in the intervention group.<sup>23</sup> Furthermore, in a recent pooled analysis of the PRINCE and PRINCESS studies, there was a significant difference in neurologic outcome (CPC 1-2) at discharge in patients with initial shockable rhythms.<sup>24</sup> In patients with non-shockable rhythm there was no difference in outcome.<sup>24</sup>

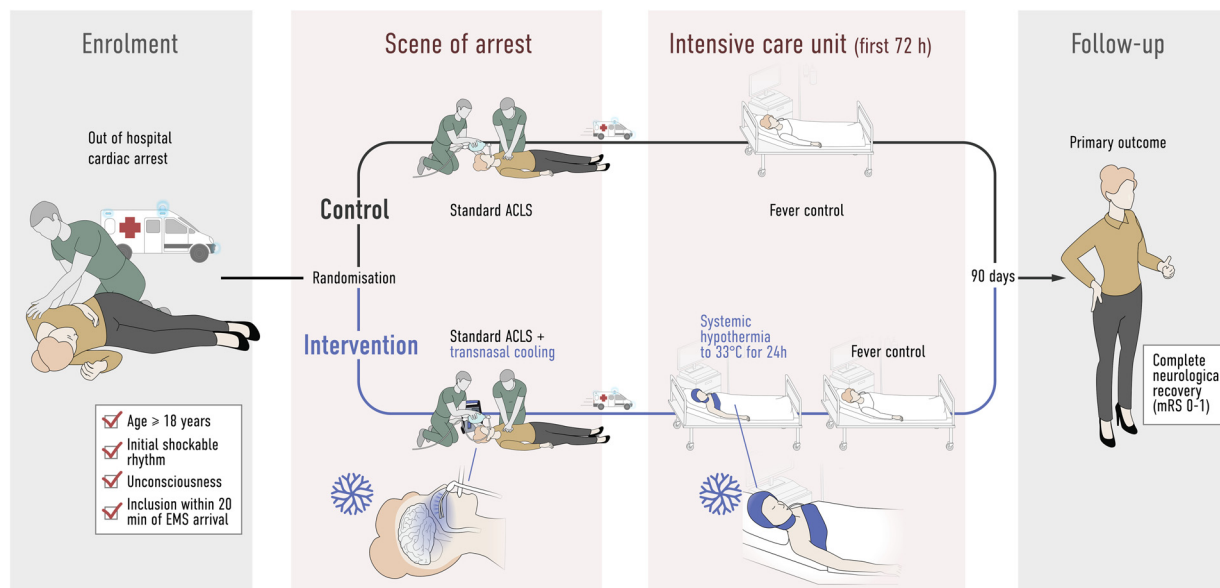
In summary, the impact of ultrafast hypothermia on survival with good neurologic function after out-of-hospital cardiac arrest is unclear, with positive indications from experimental data and from previous clinical studies. Therefore, we designed the PRINCESS 2 study which aims to evaluate the impact of ultrafast hypothermia applied on the scene of cardiac arrest, as compared to normothermia, on 90-day survival with complete neurologic recovery in OHCA patients with initial shockable rhythm.

## Methods/design

### Study design

This is an international, investigator initiated, prospective, randomized, controlled study that will be conducted by multiple prehospital emergency medical systems (EMS) and Intensive Care Units in Europe and the

**Figure 1.** Graphic study design flow chart.



United States. Patients with OHCA with initial shockable rhythms that are eligible for cardiac life support procedures will be enrolled in the study if they meet all the inclusion and no exclusion criteria. In total 1022 patients will be included.

Patients will be randomized, and thereby included in the study, at the scene of cardiac arrest, within 20 minutes from EMS arrival on scene, to either: (1) intervention: early trans-nasal evaporative cooling initiated as soon as feasible at the scene of arrest (i.e., intra-arrest or very early post ROSC), followed by subsequent systemic hypothermia at  $33 \pm 0,5^{\circ}\text{C}$  for 24 hours and fever control for 72 hours in the ICU, or (2) control: standard of care with fever control (normothermia) for 72 h in the ICU. The protocol for post resuscitation care and withdrawal of life support for patients admitted at the ICU is based on current international guidelines.<sup>25</sup> A follow up will be made at 90 days and after 1 year. See [Figure 1](#) for graphic study design flow chart. Recruitment starts in Q1 2024 and we expect maximum enrolment to be achieved during Q4 2024 at 20 to 25 European and US sites. The PRINCESS2 trial is registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov), registration number NCT06025123.

#### Inclusion/exclusion criteria

Subjects with OHCA will be screened for study eligibility by EMS personnel at the scene of arrest after the first rhythm analysis. Inclusion criteria are: age  $\geq 18$  with OHCA with initial shockable rhythm (i.e., ventricular fibrillation, pulseless ventricular tachycardia or “shock advised” by an automated external defibrillator), unconsciousness (defined as Glasgow Coma Scale  $\leq 8$ )

and inclusion within 20 minutes from EMS arrival at the scene of cardiac arrest. Exclusion criteria are: age  $\geq 80$  years, obvious non-cardiac causes of cardiac arrest (trauma, head trauma, drug overdose, severe bleeding, cerebrovascular accident, smoke inhalation, drowning, hanging, choking or burns), obviously already hypothermic (e.g., found in the snow), an obvious barrier to placing nasal catheters (i.e., nasal obstruction), a known written Do Not Attempt to Resuscitate (DNAR) order or a known terminal disease or known or clinically apparent pregnancy ([Table 1](#)).

#### Inclusion and randomization

Randomization, and thereby inclusion in the study, will be made at the scene of arrest, after screening for inclusion and exclusion criteria and after the airway is secured. At no time, screening for eligibility, or randomization, can affect quality of resuscitation, including airway management and defibrillation strategies. Randomization will be performed with permuted blocks of varied size, concealed from investigators, stratified for trial site. Each site will be given sets of sequentially numbered envelopes with randomization assignments provided in a 1:1 manner. Individual envelopes will be placed in each RhinoChill pack or in the ambulance and will be replaced as patients are enrolled. Each patient enrolled in the study will be assigned a unique trial and randomization number.

#### Blinding

Neither EMS nor hospital personnel will be blinded to treatment, since patients undergoing trans-nasal cooling

**Table 1.** Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age $\geq$ 18 years	Age $\geq$ 80 years
OHCA with initial shockable rhythm	Obvious non-cardiac causes to cardiac arrest
Unconsciousness (Glasgow coma scale $\leq$ 8)	Obvious already hypothermic (e.g., found in the snow)
Inclusion within 20 minutes from EMS arrival	Obvious barrier to placing intra nasal catheters
	A known Do Not Attempt to Resuscitate (DNAR) order or other limitations in care
	A known terminal disease
	Known or clinically apparent pregnancy

and subsequent systemic cooling are easily distinguished from those who are not. Surviving patients regaining consciousness will also be informed of which study group they are in. However, investigators, physician making the prognostication at 72 hours after cardiac arrest and the study personnel making the final neurological assessment at discharge and at the 90 days follow up will be blinded to the patient's group assignment.

#### RhinoChill device description

The RhinoChill device has previously been described in detail.<sup>22,26</sup> It is a cooling device that sprays a mixture of liquid coolant and medical grade oxygen or air through nasal catheters onto the upper surface of the nasal cavity. The coolant (perflourohexane, PFH) evaporates and absorbs heat from the tissue, thus cooling the tissue as well as the vasculature that supplies blood to the brain. Local temperatures within the nasal cavity are approximately 2°C.

The RhinoChill is CE-marked and labelled by lot and serial number where appropriate. The device contains three parts: the control unit that is attached to the medical gas source and controls the flow of coolant-gas mixture, the tubing set which delivers the coolant-gas mixture into the nasal cavity, and the 1-liter coolant bottle (Figure 2). It is designed for use both in the hospital setting (e.g., hanging on an intravenous pole) as well as in the prehospital setting, where it can be carried as a backpack that integrates an oxygen or air bottle.

The RhinoChill device will be fasten in the transporting EMS vehicles according to local guidelines.

#### Study treatment and post-resuscitation care

The specific differences between the study groups are that subjects in the intervention group will receive trans-nasal evaporative cooling initiated at the scene of arrest and subsequent systemic hypothermia treatment to  $33 \pm 0,5^\circ\text{C}$  for 24 hours at the ICU. Thereafter, patients in the intervention group will be rewarmed at a rate of no more than  $0,25^\circ\text{C}/\text{hour}$  until they reach a temperature of  $36,5^\circ\text{C}$ . Fever  $> 37,7^\circ\text{C}$  will be avoided for the first 72 hours. Patients in the control group will receive standard of care with fever control ( $\leq 37,7^\circ\text{C}$ ) for the first 72 hours (i.e., normothermia) (Figure 3). Medications and/or treatments that are considered experimental in

nature and are intended to improve outcomes after cardiac arrest are prohibited from use.

#### Resuscitation attempt

In both study groups, resuscitation attempts will follow European Resuscitation council (ERC) guidelines,<sup>27</sup> including defibrillation strategies and airway management. In patients randomized to intervention, nasal catheters will be placed and cooling initiated as soon as possible after airway management (i.e., laryngeal mask or endotracheal intubation) and randomization. Placing the catheters and starting the cooling procedure takes approximately 1 minute, and in summary, screening, including and treating a study subject will consume no more than a few minutes. Cooling will be performed with an oxygen flow of 40 L/min. Patients in the control group will receive standard Advanced Cardiovascular Life Support (ACLS). Resuscitation attempts will be continued for at least 30 minutes after advanced emergency medical personnel arrive on the scene.

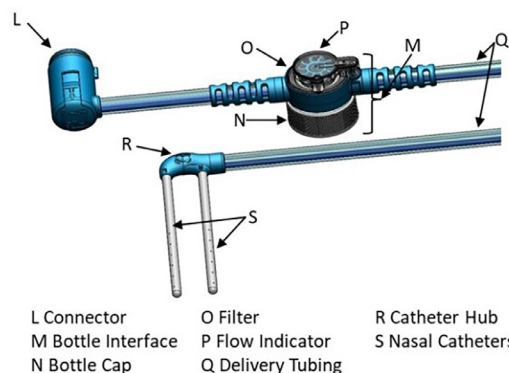
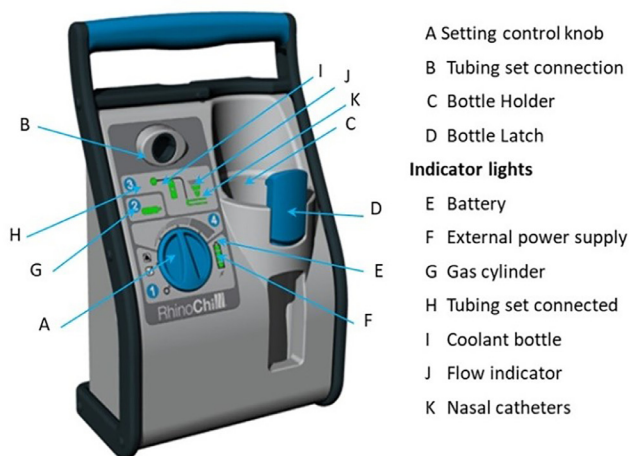
#### Pre-hospital post-resuscitation care

Sustained ROSC will in this study be defined as an organized rhythm and palpable pulse sustained for 20 minutes. Temperature will be checked via the tympanic route once an organized rhythm with palpable pulse is achieved. If a patient randomized to cooling wakes up after ROSC, to the degree that prehospital extubation or removal of laryngeal mask is possible, trans-nasal cooling will be discontinued. Bolus doses of sedation administered intravenously will be given only if needed. During transportation to hospital, the oxygen supply in the transport vehicle will be used for continued RhinoChill cooling. Normal transport routines will be used for patients in the control group. All patients will otherwise receive standard post resuscitation care. Infusions with chilled iv fluids or cold packs in the prehospital setting will not be allowed for any patients included in the study.

#### In-hospital post-resuscitation care

Except for the TTM, all subjects enrolled in the study will undergo standard post resuscitation treatment upon hospital arrival according to ERC guidelines 2021.<sup>25</sup> For the intervention group, trans-nasal evaporative cooling will be continued until systemic cooling is initiated in the Emergency department or ICU. If diagnostic measures or treatments are performed before ICU admission, trans-nasal cooling will be continued during these procedures

**Figure 2.** The RhinoChill device.



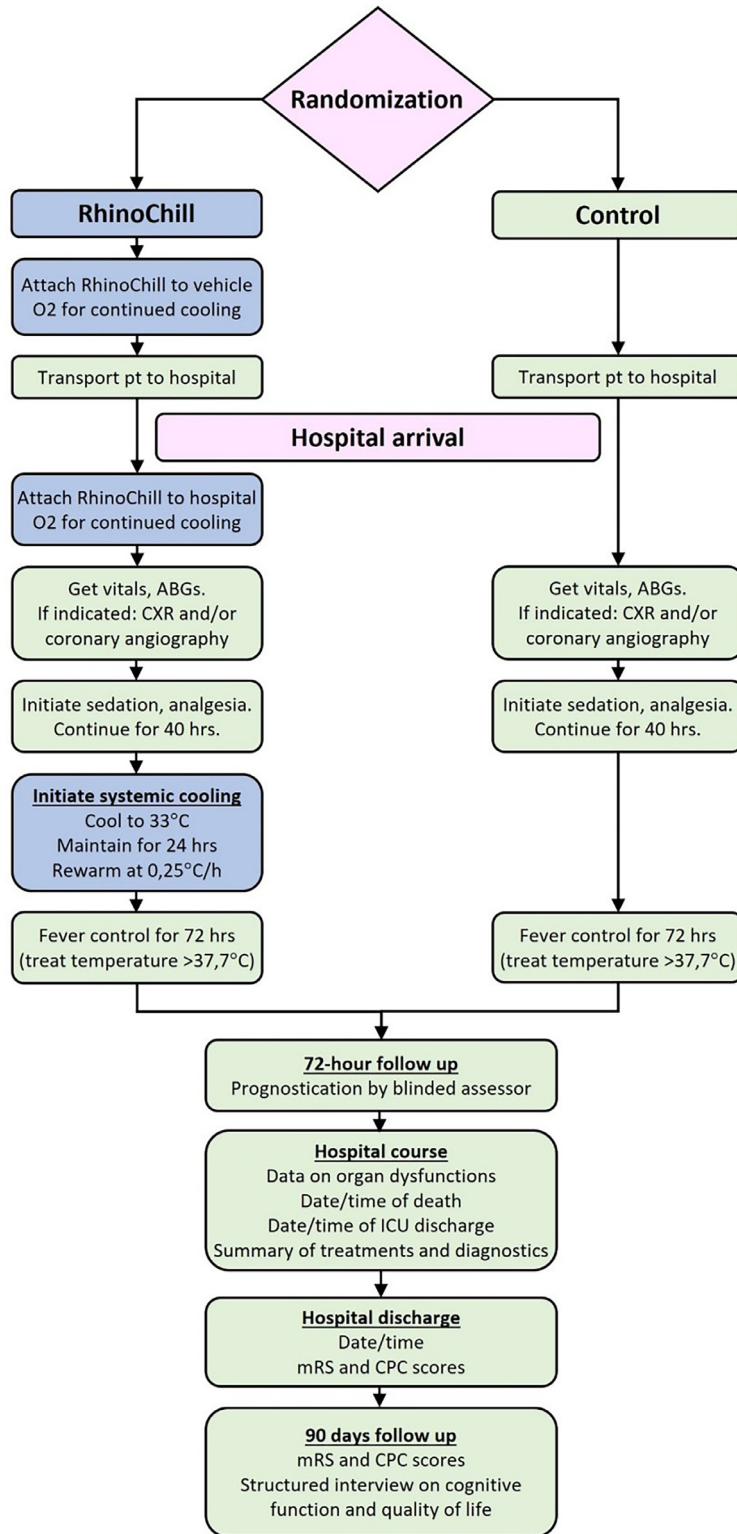
and during intra hospital transports. For all patients, a systemic temperature probe (i.e., bladder or esophageal) will be placed as soon as possible after arrival, and core temperature recorded. Vital signs, level of consciousness, ECG and other standard diagnostic measures including arterial blood gases will be recorded. Decisions of diagnostic measures prior to ICU admission, such as coronary angiography or CT scan, will be made according to local protocols and guidelines.

Systemic cooling of patients in the intervention group will be started as soon as possible. Either surface cooling systems or intravascular cooling systems can be used, according to local protocols. Once systemic hypothermia is initiated, the RhinoChill device will be turned off, but nasal catheters will be left in place for the first 3 hours as intermittent activation of the RhinoChill device may be considered if the core temperature does not approach target temperature. Patients in the intervention group will be cooled to a target temperature of  $33 \pm 0,5^{\circ}\text{C}$ , and this temperature will be maintained for 24 hours. Thereafter, patients will be rewarmed at a rate of no more than  $0,25^{\circ}\text{C/h}$  until core temperature reaches  $36,5^{\circ}\text{C}$ . Temperatures (core and tympanic) will be registered every 20 minutes until target temperature is reached, thereafter once per hour during the maintenance phase. Shivering will be assessed using The Bedside Shivering Assessment Scale (BSAS)<sup>28</sup> and treated with buspirone, magnesium, clonidine, meperidine, increased sedation or, if needed, neuromuscular blocking agents. In both study groups, fever, defined as core body temperature  $>37,7^{\circ}\text{C}$ , will be avoided for the first 72 hours from cardiac arrest by using antipyretics or, if necessary, cooling devices.

To facilitate a comparison between the two study groups, all patients will be sedated for 40 hours after randomization (i.e., phases of induction, maintenance and rewarming). Short acting drugs and opioids will be recommended, according to international guidelines. Neuromuscular blockage will not be used routinely, but only in cases of severe shivering during TTM. A deep sedation, defined as a Richmond Agitation-Sedation Scale (RASS)<sup>29</sup> of minus 4 (no response to voice, but movement to physical stimulation) will be targeted.

Targets for respiration and circulation will follow the ERC guidelines.<sup>25</sup> Ventilator settings will be adjusted to normoxia (arterial saturation of 94%-98%,  $\text{paO}_2$  of 10-13 kPa) and normocapnia ( $\text{pCO}_2$  of 4,5-6 kPa), with tidal volumes of 6 mL/kg to 8 mL/kg. Mean arterial blood pressure (MAP) should be kept  $>65$  mmHg, and a normal lactate and urinary output  $>0,5$  ml/kg/h will be targeted. Insufficient MAP will be treated with crystalloid fluids in case of hypovolemia, and/or with vasopressor drugs. In patients with ST-elevation presenting on 12 lead ECG, emergent cardiac catheterization evaluation (and PCI if required) will be performed. In patients without ST-elevation, but with a high probability of acute coronary occlusion emergent cardiac catheterization will also be considered. Echocardiographic examinations will, if feasible, be made after 24 hours and 72 hours respectively, to measure left ventricular ejection fraction (LVEF). Troponin and NTproBNP will be registered at different time points. ECMO (including ECPR) or other mechanical circulatory support such as intra-aortic balloon pump (IABP) or Impella will be used if needed, according to local guidelines.

**Figure 3.** Study flow diagram.



In case of clinical convulsions electroencephalography (EEG) is recommended to diagnose electrographic seizures and monitor treatment effects. Treatment will follow recommendations from ERC guidelines using levetiracetam or sodium valproate as first-line antiepileptic drugs, in addition to sedative drugs.

#### **Prognostication and withdrawal of care**

All patients included in the study still submitted to the ICU after  $\geq 72$  hours will be subject to standardized prognostication. The prognostication will be performed by a physician (neurologist, intensivist or other specialist experienced in prognostication after cardiac arrest) blinded to group allocation, and will be based on the ERC and European Society for Intensive Care Medicine recommendations. Clinical examination including assessment of brainstem reflexes and response to pain and other stimuli will be mandatory for the prognostication, as will a diagnostic electroencephalogram (EEG) between 36 and 72 hours from randomization in all patients still comatose at this point. Neuron-Specific Enolase (NSE) levels, Brain CT, Brain MRI and somatosensory evoked potential (SSEP) will be optional. Prognostication might be delayed due to factors such as residual sedation, or practical reasons such as weekends or national holidays. The result of the prognostication will be the answer to the question “does this patient fulfil the study criteria for a likely poor neurological outcome” categorized as “YES” or “NO”. The assessment will be recorded in the Case Report Form (CRF) and will be communicated to the treating physician, but no recommendations of withdrawal of life support or continued care will be made.

Study criteria for a likely poor neurologic outcome, evaluated at the earliest at 72 hours from randomization, is an unconscious patient with absent or extensor motor response to pain with no confounders (e.g., sedation) AND at least two of the following:

- Bilaterally absent pupillary and corneal reflexes
- Bilaterally absent SSEP N20-responses
- Diffuse anoxic brain injury on CT or MRI
- Documented status myoclonus within 48 hours of randomization
- High levels of serum NSE ( $>60\mu\text{g/L}$  at 48 hours and/or 72 hours)
- An EEG with a highly malignant pattern and without any observed reactivity to sound or pain. Patterns that are considered highly malignant are:
  1. Suppressed background (amplitude  $<10$  mV, 100% of the recording) without discharges.
  2. Suppressed background with superimposed continuous periodic discharges.
  3. Burst-suppression (periods of suppression with amplitude  $<10$  mV constituting 50% of the recording) without discharges.
  4. Burst-suppression with superimposed discharges.

All patients will be actively treated for 72 hours or more. The exemptions will be participants in whom further treatment is considered unethical due to irreversible organ failure, documented medical comorbidity, or other reasons. The reason for withdrawal of life-sustaining therapy (WLST) must be documented comprehensively in the CRF. Participants in whom brain death is established are also exempted, however this will be defined as death and not WLST.

Any decision to withdraw active intensive care will be made by the treating physicians, together with the patient's relatives or legal surrogates, as required by local legislation. The reasons for WLST will be documented in the CRF.

#### **Data collection**

Data will be reported in the different stages of the study; prehospital, emergency department, ICU, discharge and follow up at 30 and 90 days as well as one year. Data will be recorded in electronic CRF's (RED-Cap, Vanderbilt University, Nashville, TN, USA). Prehospital data include time of collapse, location, time of emergency call, time of arrival of first and second emergency medical team, brief patient characteristics (i.e., gender, age), time of randomization and resuscitation parameters such as bystander CPR, time of first defibrillation, time and method of established airway, use of mechanical compression device, time of ROSC, if ROSC occurred onsite, if any new cardiac arrest occurred after ROSC and time of departure from scene with patient. For the intervention group, time of initiation of trans-nasal cooling will be recorded, and for both groups tympanic temperature at ROSC. Device related adverse events and technical issues leading to interruption of cooling will be documented in the CRF, and serious adverse events will also be reported directly to regional or national investigators.

After hospital admission early post-resuscitation parameters such as first registered vital functions, ECG, arterial blood gas, neurologic assessment and core and tympanic temperatures will be recorded. At the ICU, sequential organ failure assessment (SOFA) score is recorded at arrival and once a day for the first three days. Known comorbidities prior to cardiac arrest, estimated pre-arrest mRS and Clinical Frailty Scale (CFS), maximum levels of troponin T or I (depending which is routinely used at the different sites) will also be documented, as well as neuron-specific enolase (NSE) at 24, 48, and 72 hours. For the intervention group, the systemic cooling procedure including method, timing of initiation, termination of cooling with the RhinoChill, target temperature, termination and reaching normothermia will be recorded. The occurrence of fever  $>37,7$  °C will be documented in both groups. At discharge from ICU, a summary of ICU measures will be collected, such as angiography and revascularization, organ support such as ECMO, intra-

aortic balloon pump, Impella, continuous renal replacement therapy (CRRT), adverse events (severe and moderate bleeding according to Gusto criteria), sepsis or septic shock (according to the 3rd international consensus definitions for sepsis and septic shock), arrhythmia resulting in hemodynamic compromise (bradycardia with need for pacing, ventricular tachycardia or ventricular fibrillation), new cardiac arrest, cardiogenic shock requiring inotropes or mechanical support, device related complications).

### Follow-up

Overall survival will be reported at discharge, 30 days, 90 days and after 1 year. The formal primary outcome follow-up with blinded outcome assessor will take place at 90 days from cardiac arrest (as close as possible to 90 days from cardiac arrest, but not before 90 days). Participants, and if possible, a close relative, will be invited to a clinic visit, but follow-up is also possible via telephone. The subjects will be assessed according to the modified Rankin Scale (mRS),<sup>30</sup> the Cerebral Performance Category (CPC) scale,<sup>31</sup> and will fill in an EQ-5D-5L<sup>32</sup> questionnaire. mRS is a scale on neurologic outcome ranging from 0 to 6, where mRS 0 means no neurologic disabilities, and mRS 6 equals death.<sup>30</sup> mRS 0-1 corresponds to CPC 1 (no or minimal neurologic disabilities). Since 2018, mRS is the recommended measure of neurologic outcome after cardiac arrest.<sup>33</sup> The EQ-5D-5L is a standardized measure of health-related quality of life consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), and a VAS scale of overall self-reported health.<sup>32</sup> The outcome-assessor could be a physician, research nurse, psychologist or similar, and will be provided with a written manual with guidelines for performing questionnaires and assessments. If needed, training sessions will be provided by the trial coordinating team.

For patients who died in the hospital, cause of death (cerebral, cardiac, multi-organ failure, infection, other) will be recorded, as well as prognostic methods used for withdrawal of life sustaining therapies, whether the patients died in the ICU or hospital ward, when intensive care was terminated and if the patient fulfilled the study criteria for poor outcome.

### Study outcomes

#### Primary outcome

- Survival with complete neurologic recovery at 90 days, defined as mRS 0-1

#### Secondary outcomes

- Sustained ROSC and admitted alive
- Survival at hospital discharge
- Modified Rankin scale 0 to 3 at hospital discharge
- Survival at 90 days
- Modified Rankin scale 0 to 3 at 90 days

### Tertiary outcomes

- 1-year survival
- Modified Rankin scale 0 to 1 at 1 year
- Distribution of CPC scores at 90 days
- Health economy related outcomes
- Quality of life EQ5D at 90 days
- Distribution of mRS at 90 days
- Hospital free days alive at 90 days

### Safety endpoints

- Adverse events, including device related, occurring within 24 hours of enrolment
- The composite serious adverse event (SAE) rate from the time of patient randomization through the first seven days of hospitalization (see specified in section below)
- New cardiac arrest prior to hospital admission

### Statistical analysis

#### Power calculation

This study is powered to detect clinically significant changes in survival with complete neurologic recovery (mRS 0-1) at 90 days from cardiac arrest. Sample size calculation was based on the preceding clinical trials as the PRINCESS trial<sup>23</sup> and other recent trials in OHCA such as TTM2.<sup>17</sup> In the PRINCESS trial, the survival rate with CPC 1 to 2 at 90 days in VF-patients was 34.8% vs 25.9% and in CPC 1 at 90 days 32.6% vs 20%. Among patients with VF admitted alive, the survival with CPC 1 to 2 at 90 days was 57.8% vs 44.9% and in CPC 1 at 90 days 54.2% vs 33.6%.

As the study population in PRINCESS 2 will be a combination of patients included intra-arrest and early post ROSC the base line survival with CPC 1 that corresponds to mRS 0 to 1 is assumed to be 45%. To show an absolute difference of 9% (from 45% to 54%) a sample size of 483 patients in each study group (total 966 patients) is required to detect a statistically significant difference using a one-sided alpha of 0.025 and a beta of 0.2 (80% power). To adjust for 1 interim analysis (Haybittle-Peto) after 40% inclusion (approximately 400 patients), with 1 test of efficacy and 1 test of futility the sample size is inflated to 996 patients. In addition, an estimated 2.5% lost to follow up would give in total 1022 study patients.

#### Analysis

Descriptive statistics will be calculated for all performance, safety, demographic, and baseline variables. Means, standard deviations, and ranges will be used to describe continuous measurements, counts and percentages to describe categorical parameters. Differences between variables associated at different time points will be evaluated using an appropriate comparative statistic. Data from the two treatment groups will be analyzed for treatment effect. A 2-sided *P*-value less than .05 will be considered statistically significant.

Outcome analyses will be performed as Intention to treat (ITT). Secondary analyses will also be performed ac-



ording to “modified Intention to treat” where post randomization data on the patients that appear will restrict or imply limitations in the care, such as existing DNAR or severe comorbidities that upon admission to hospital will lead to restrictions in care and interrupt the study intervention, as well as “per protocol” and “as treated” for all randomized patients. No imputed values will be used for patients for whom data is not available.

Stratified analyses will be performed for patients where cooling is started intra-arrest versus post-ROSC; if cooling was started within 20 minutes from the cardiac arrest vs after 20 minutes; men vs women; above median age vs equal or below median age; patients receiving bystander CPR vs not receiving bystander CPR; patients receiving ECPR vs not receiving ECPR; STEMI vs non-STEMI. The statistical analysis plan can be found in the supplementary material (S1).

#### Substudies

Several predefined substudies, such as in ECPR patients and in health economics, will be performed with additional data compared to the core CRE. Participation on these sub studies and others will not be mandatory for study sites. These sub-studies will be presented at clinicaltrial.gov.

#### Consent/ethics

Patients eligible for this study will be unable to provide their consent prior to inclusion as they will be comatose. Subjects of the study face a life-threatening condition, and early cooling with the RhinoChill device has shown improved rates of complete neurologic recovery in this group of patients.<sup>23</sup> In total, 877 OHCA patients have been studied in randomized trials with the RhinoChill device without any major safety concerns,<sup>22,23</sup> and it is therefore expected that the potential benefit of using the RhinoChill device in this population outweighs the risks. The subjects next of kin will be informed of the patient’s study participation as soon as practical, and subjects regaining normal neurologic function will be informed about their study participation and asked for their written consent to use their data and to be included in further follow up.

Ethical consideration for treating subjects without their express consent will be in accordance with the World Medical Association Helsinki Declaration of 1964, as revised at the 59th General Assembly in Seoul in 2008. Local Ethics Committees have approved the study for eligible patients (Swedish Ethical Review Authority—reference number 2022-02446-01, Ö62-2002/3.1). Other participating study sites will apply for ethical approval separately.

#### Data safety management

The study monitoring will be coordinated by the study sponsor according to the trial monitoring plan. The frequency of on-site monitoring will depend on compliance

with the protocol, number of patients included and data handling. At minimum there will be a pre-trial initiation meeting, mandatory monitoring once during the trial period and once inclusion has finished.

Individual Site Investigators shall maintain all study-related correspondence, the investigator’s copy of the CRFs, device disposition records, information on Ethics Committee approvals, all patient records and signed informed consent forms for a minimum of five years from publication or according to specific country/institutional regulations. Data will then be de-identified and archived for a total of at least 10 years from publication according to the regulations of the study sponsor (Karolinska Institutet).

Data on safety will be provided to the steering committee at regular time intervals, which will depend upon the rate of patient enrolment and relevant safety issues. Independent analyses of serious adverse events will be performed and adjudicated if the frequency or nature of serious adverse events warrants it.

#### Pilot phase

The PRINCESS2 trial design differ from the prior PRINCESS study in several ways. Therefore, we will perform and publish a pilot study during first phase of the main trial, with the purpose of ensuring that the study intervention will be performed with high quality according to protocol at each study site. The pilot phase will comprise the first 100 patients of the main study and aims to assess feasibility and adherence to treatment protocol (intervention and control) including the subgroup of patients treated with ECPR. If certain study sites or certain patient groups are identified with low adherence to protocol, measures will be taken to intensify training and monitoring to improve quality of intervention. No primary or secondary endpoints will be analyzed in the pilot phase study.

#### Safety and futility analysis

An interim analysis for safety and futility will be performed by an external Data and Safety Monitoring Committee (DSMC) after the first 400 patients have provided primary endpoint data. Conditional power for meeting the primary endpoint will if needed, be computed at that time, and if the interim results do not correspond to the primary endpoint, termination of the study for futility will be considered. Early stopping for efficacy reasons will only be considered if major outcome differences are seen between the groups according to the Haybittle rule with a p-value  $\leq 0.001$ . The DSMC will be able to request additional data if they find it necessary.

## Discussion

Despite experimental findings of the neuroprotective benefits of early cooling,<sup>7-12</sup> the majority of clinical studies on hypothermia after OHCA have initiated cooling

late, after hospital arrival and often after interventions and diagnostics such as coronary angiography and CT-scans. As a result, target temperature was reached several hours after ROSC. One might argue that with this delayed cooling strategy the underlying pathophysiology of ischemia and reperfusion may not have been adequately addressed and the optimal time window for maximal effectiveness of hypothermia might have been missed. None of the studies leading to important changes in international guidelines on post-resuscitation care; the TTM<sup>16</sup> and TTM2<sup>17</sup> trials, the HACA<sup>13</sup> or the Bernard<sup>14</sup> trials have really answered the question of whether very early cooling, initiated already at the scene of arrest, is beneficial in patients with OHCA. The predecessor of the trial described here, the PRINCESS trial, did however start trans-nasal evaporative cooling intra-arrest at the scene of arrest but showed no significant neurologic improvement in the whole group of OHCA-patients, although, in the subgroup of patients with initially shockable rhythm, complete recovery, defined as CPC 1, was significantly better in the intervention group.<sup>23</sup>

The rationale behind the PRINCESS 2 trial is to confirm the promising results of early trans-nasal cooling observed in OHCA patients with initial shockable rhythms in the PRINCESS trial and to evaluate the effects on complete neurologic survival. The PRINCESS2 trial differ from the PRINCESS study in some important aspects; only patients with initially shockable rhythms will be included, inclusion can be made both intra-arrest and early post-ROSC (with a maximum of 20 minutes from EMS arrival), and the control group will be normothermic with fever control for the first 72 hours, which is the current standard of care. The protocol for post-resuscitation care and withdrawal of care is also more comprehensive than in the PRINCESS study. Lastly, the primary outcome will be complete neurologic recovery at 90 days, defined as mRS 0 to 1. The rationale for including only subjects with initial shockable rhythms is based on the findings in the PRINCE and PRINCESS trials, and that a first rhythm of ventricular fibrillation or pulseless ventricular tachycardia is a strong indicator for cardiac etiology and improved outcome.<sup>34</sup> The study population in PRINCESS2, with initial shockable rhythms, witnessed arrest, limited in age and short EMS times, will also be similar to the populations studied in both the HACA<sup>13</sup> and Bernard<sup>14</sup> studies. The reason for including patients both intra-arrest and post-ROSC is to be able to include all patients comatose from OHCA with initial shockable rhythms, not only those still pulseless at inclusion and thereby with longer ROSC times. We believe this will make the trial more generalizable, and also more pragmatic and feasible. Stratified analyses will be made on patients cooled pre- and post-ROSC, but this study is not powered to detect differences between these groups. The rationale behind changing the primary outcome from favorable

neurologic outcome (CPC 1-2) to complete neurologic recovery (mRS 0-1) is that findings in the PRINCESS trial that indicated that significantly more patients in the intervention group had full neurologic recovery, and we believe that this is the optimal target for treatment strategies for cardiac arrest—survival without any significant disabilities. The measure of neurologic function is changed from the Cerebral Performance Category scale to modified Rankin Scale as this is in line with current recommendations.<sup>35</sup>

The major strength of the study design of the PRINCESS2 trial is that there is a protocol for the whole chain of resuscitation and post-resuscitation care, including a protocol for neurologic prognostication and withdrawal of care. Another strength is the large sample size. The blinding of outcome assessors, prognosticators and investigators is also a strength. Limitations include the fact that EMS and hospital personnel cannot be blinded to treatment as the use of the cooling devices is clearly visible.

In summary, the important knowledge gap still remains of whether very early initiation of hypothermia, started at the scene of arrest, will improve survival with good neurologic outcome in patients with initial shockable rhythms. The PRINCESS2 trial will address this knowledge gap. If found to improve neurologic outcome, early prehospital trans-nasal cooling may be considered to be used as a neuroprotective strategy in OHCA.

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## CRediT authorship contribution statement

**Emelie Dillenbeck:** Methodology, Writing - original draft, Visualization, Project administration. **Jacob Holtenberg:** Conceptualization, Methodology, Writing - review & editing, Project administration. **Michael Holzer:** Methodology, Writing - review & editing, Project administration. **Hans-Jörg Busch:** Methodology, Writing - review & editing, Project administration. **Graham Nichol:** Conceptualization, Methodology, Writing - review & editing. **Peter Radsel:** Methodology, Writing - review & editing, Project administration. **Jan Belohlavec:** Methodology, Writing - review & editing. **Ervigio Corral Torres:** Methodology, Writing - review & editing. **Esteban López-de-Sa:** Methodology, Writing - review & editing. **Fernando Rosell:** Methodology, Writing - review & editing. **Giuseppe Ristagno:** Methodology, Writing - review & editing. **Sune Forsberg:** Conceptualization, Methodology, Writing - re-

view & editing, Project administration. **Filippo Annoni:** Methodology, Writing - review & editing, Project administration. **Leif Svensson:** Conceptualization, Methodology, Writing - review & editing, Project administration. **Martin Jonsson:** Methodology, Writing - review & editing, Project administration, Software. **Denise Bäckström:** Methodology, Writing - review & editing, Project administration. **Mikael Gellerfors:** Methodology, Writing - review & editing, Project administration. **Akil Awad:** Methodology, Writing - review & editing, Project administration. **Fabio S Taccone:** Conceptualization, Methodology, Writing - review & editing, Project administration. **Per Nordberg:** Conceptualization, Methodology, Writing - review & editing, Project administration, Funding acquisition.

## Conflicts of Interest

Dr Hollenberg reports grants from Swedish Heart and Lung Foundation and Healthcare Region of Stockholm. Dr Holzer reports honoraria for lectures from Becton Dickinson and honoraria for consulting from Zoll Medical Austria. Dr Nichol reports the following disclosures: Abiomed Inc., Danvers, MA. Emergency Care Core for Trial of Impella in Patients with STEMI and Cardiogenic Shock (RECOVER IV), PI. ZOLL Medical Corp., Chelmsford, MA. Multidimensional Study of Oxygenation in Early Post-Resuscitation (MOSER), PI. Vapotherm Inc., Exeter, NH. Vapotherm Device for Rapid Cooling Study (VOS), Co-PI. ZOLL Circulation Inc., San Jose, CA. Better Resuscitation with Supersaturated Oxygen (BASSO) Study, Co-PI. CPR Therapeutics Inc., Putney, VT. Consultant. Heartbeam Inc., Santa Clara, CA. Consultant. Invero Health LLC, Montville, NJ. Consultant. Kestra Medical Technologies Inc., Kirkland, WA. Consultant. Orixha Inc, Saint Cyr Au Mont d'Or, France, Consultant. BrainCool AB, Lund, Sweden, Consultant. Dr Belohlavec reports being consultant for Abiomed, Getinge, Xenios. Dr Lopez-de-Sa reports research grants from AstraZeneca AB, Merck Sharp & Dohme, Novartis, ZOLL Circulation, Inc and Speakers Bureau: BD (Becton, Dickinson and Company), Daiichi Sankyo, Rovi, Servier, ZOLL Circulation, Inc. Dr Taccone reports receiving lecture fees from BD and ZOLL. Dr Nordberg reports grants from Swedish Heart and Lung Foundation and Healthcare Region of Stockholm. No other disclosures were reported.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.ahj.2024.02.020](https://doi.org/10.1016/j.ahj.2024.02.020).

## References

1. Gräsner JT, Lefering R, Koster RW, et al. EuReCa ONE-27 nations, ONE Europe, ONE registry: a prospective one month

- analysis of out-of-hospital cardiac arrest outcomes in 27 countries in Europe. *Resuscitation* 2016;105:188–95.
2. Sekhon MS, Ainslie PN, Griesdale DE. Clinical pathophysiology of hypoxic ischemic brain injury after cardiac arrest: a “two-hit” model. *Crit Care* 2017;21:90.
3. Laver S, Farrow C, Turner D, Nolan J. Mode of death after admission to an intensive care unit following cardiac arrest. *Intensive Care Med* 2004;30:2126–8.
4. Witten L, Gardner R, Holmberg MJ, et al. Reasons for death in patients successfully resuscitated from out-of-hospital and in-hospital cardiac arrest. *Resuscitation* 2019;136:93–9.
5. Lemiale V, Dumas F, Mongardon N, et al. Intensive care unit mortality after cardiac arrest: the relative contribution of shock and brain injury in a large cohort. *Intensive Care Med* 2013;39:1972–80.
6. Froehler MT, Geocadin RG. Hypothermia for neuroprotection after cardiac arrest: mechanisms, clinical trials and patient care. *J Neurol Sci* 2007;261:118–26.
7. Nozari A, Safar P, Stezoski SW, et al. Critical time window for intra-arrest cooling with cold saline flush in a dog model of cardiopulmonary resuscitation. *Circulation* 2006;113:2690–2696.
8. Nozari A, Safar P, Stezoski SW, et al. Mild hypothermia during prolonged cardiopulmonary cerebral resuscitation increases conscious survival in dogs. *Crit Care Med* 2004;32:2110–2116.
9. Kuboyama K, Safar P, Radovsky A, et al. Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: a prospective, randomized study. *Crit Care Med* 1993;21:1348–58.
10. Abella BS, Zhao D, Alvarado J, et al. Intra-arrest cooling improves outcomes in a murine cardiac arrest model. *Circulation* 2004;109:2786–91.
11. Zhao D, Abella BS, Beiser DG, et al. Intra-arrest cooling with delayed reperfusion yields higher survival than earlier normothermic resuscitation in a mouse model of cardiac arrest. *Resuscitation* 2008;77:242–9.
12. Wang H, Barbut D, Tsai MS, et al. Intra-arrest selective brain cooling improves success of resuscitation in a porcine model of prolonged cardiac arrest. *Resuscitation* 2010;81:617–21.
13. Hypothermia after Cardiac Arrest Study G. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002;346:549–56.
14. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002;346:557–63.
15. Deakin CD, Nolan JP, Soar J, et al. European Resuscitation Council guidelines for resuscitation 2010 Section 4. Adult advanced life support. *Resuscitation*. 2010;81:1305–52.
16. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N Engl J Med* 2013;369:2197–206.
17. Dankiewicz J, Cronberg T, Lilja G, et al. Hypothermia versus normothermia after out-of-hospital cardiac arrest. *N Engl J Med* 2021;384:2283–94.
18. Soar J, Nolan JP, Andersen LW, et al. Temperature Management in Adult Cardiac Arrest Consensus on Science with Treatment Recommendations [Internet] Brussels, Belgium: International Liaison Committee on Resuscitation (ILCOR) Advanced Life Support Task Force; 2021 August 30. Available from: <http://ilcor.org>.

19. Kim F, Nichol G, Maynard C, et al. Effect of prehospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest: a randomized clinical trial. *JAMA* 2014;311:45–52.
20. Bernard SA, Smith K, Finn J, et al. Induction of therapeutic hypothermia during out-of-hospital cardiac arrest using a rapid infusion of cold saline: the RINSE trial (rapid infusion of cold normal saline). *Circulation* 2016;134:797–805.
21. Debaty G, Maignan M, Savary D, et al. Impact of intra-arrest therapeutic hypothermia in outcomes of prehospital cardiac arrest: a randomized controlled trial. *Intensive Care Med* 2014;40:1832–42.
22. Castrén M, Nordberg P, Svensson L, et al. Intra-arrest transnasal evaporative cooling: a randomized, prehospital, multicenter study (PRINCE: pre-ROSC IntraNasal cooling effectiveness). *Circulation* 2010;122:729–36.
23. Nordberg P, Taccone FS, Truhlar A, et al. Effect of trans-nasal evaporative intra-arrest cooling on functional neurologic outcome in out-of-hospital cardiac arrest: the PRINCESS randomized clinical trial. *Jama* 2019;321:1677–85.
24. Taccone FS, Hollenberg J, Forsberg S, et al. Effect of intra-arrest trans-nasal evaporative cooling in out-of-hospital cardiac arrest: a pooled individual participant data analysis. *Crit Care* 2021;25:198.
25. Nolan JP, Sandroni C, Böttiger BW, et al. European Resuscitation Council and European Society of Intensive Care Medicine guidelines 2021: post-resuscitation care. *Intensive Care Med* 2021;47:369–421.
26. Nordberg P, Taccone FS, Castren M, et al. Design of the PRINCESS trial: pre-hospital resuscitation intra-nasal cooling effectiveness survival study (PRINCESS). *BMC Emerg Med* 2013;13:21.
27. Soar J, Böttiger BW, Carli P, et al. European Resuscitation Council Guidelines 2021: adult advanced life support. *Resuscitation* 2021;161:115–51.
28. Badjatia N, Strongilis E, Gordon E, et al. Metabolic impact of shivering during therapeutic temperature modulation: the Bedside Shivering Assessment Scale. *Stroke* 2008;39:3242–7.
29. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002;166:1338–44.
30. Rankin J. Cerebral vascular accidents in patients over the age of 60. II. Prognosis. *Scott Med J* 1957;2:200–15.
31. Jennett B, Bond M. Assessment of outcome after severe brain damage. *Lancet* 1975;1:480–4.
32. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med* 2001;33:337–43.
33. Haywood K, Whitehead L, Nadkarni VM, et al. COSCA (core outcome set for cardiac arrest) in adults: an advisory statement from the International Liaison Committee on Resuscitation. *Resuscitation* 2018;127:147–63.
34. Sasson C, Rogers MA, Dahl J, Kellermann AL. Predictors of survival from out-of-hospital cardiac arrest: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes* 2010;3:63–81.