Department of Clinical Science and Education,
Södersjukhuset
Karolinska Institutet, Stockholm, Sweden

ASPECTS OF INTENSIVE CARE AFTER CARDIAC ARREST

Akil Awad

Stockholm 2023

Published by Karolinska Institutet.
Printed by Universitetsservice US-AB, 2023

ISBN 978-91-8016-936-3
Cover illustration: Created by Jari Radros

Aspects of intensive care after cardiac arrest

Thesis for Doctoral Degree (Ph.D.)

By

Akil Awad

The thesis will be defended in public in the Aula at Södersjukhuset, Stockholm
May 5, 2023 at 09:00 a.m.

Principal Supervisor:
Per Nordberg,
Associate Professor, M.D.
Karolinska Institutet
Department of Clinical Science
and Education, Södersjukhuset
Center for Resuscitation Sciences

Co-supervisor(s):
Mattias Ringh,
Associate Professor, M.D.
Karolinska Institutet
Department of Clinical Science
and Education, Södersjukhuset
Center for Resuscitation Sciences

Eva Joelsson-Alm,
Associate Professor, R.N.
Karolinska Institutet
Department of Clinical Science
and Education, Södersjukhuset
Division of Anesthesiology and
Intensive care

Jens Olson, M.D., Ph.D
Karolinska Institutet
Department of Clinical Science
and Education, Södersjukhuset
Division of Cardiology

Opponent:
Markus Skrifvars
Professor, M.D.
Helsinki University
Department of Anaesthesiology
Division of Intensive Care

Examination Board:
Malin Rundgren,
Associate Professor, M.D.
Lund University
Department of Clinical Sciences
Division of Anesthesiology and Intensive Care

Emma Larsson,
Associate Professor, M.D.
Karolinska Institutet
Department of Physiology and Pharmacology
Division of Anesthesiology

Magnus Settergren,
Associate Professor, M.D.
Karolinska Institutet
Department of Medicine
Unit of Cardiology

To my grandmother, Helena

Popular science summary of the thesis

Annually, around 6000 people suffer from out-of-hospital cardiac arrest (OHCA) in Sweden and only around 10% survive. Apart from cardiopulmonary resuscitation (CPR) and early defibrillation of an initial shockable rhythm, it has been difficult to find treatments that can increase survival rates after cardiac arrest. The aim of the work in this thesis was to investigate prehospital and in-hospital treatments after cardiac arrest and how they affect patient outcomes.

Three of the studies in the thesis explored different aspects of cooling treatment (therapeutic hypothermia), which since the beginning of the 2000s has been a common treatment in intensive care units (ICUs) after cardiac arrest. The reason for cooling is that hypothermia may protect the brain from damage caused by cardiac arrest. The standard target temperature for the cooling treatment was initially 33 °C, but in a study published in 2013 (the *TTM trial*) 36 °C was proposed as target temperature. We found that the proportion of patients in Sweden receiving hypothermia treatment after OHCA decreased after publication of the TTM trial and that it did not have any significant effect on survival.

In the second study, which is a sub-analysis of the international PRINCESS trial, we compared cooling through the nasal cavity, started by the emergency medical services <20 minutes after the cardiac arrest, with cooling started after hospital admission. The results showed that for patients with shockable rhythms, early cooling was associated with better neurological outcome.

In another study, we compared two different cooling methods, intravenous cooling versus surface cooling (i.e., via a cooling suit), in patients that had survived OHCA and were cooled to 33 °C after hospital arrival. This is a sub-analysis of the international *TTM 2 trial*. We analysed almost 900 patients and found that intravenous cooling, compared with surface cooling, was associated with better cooling performance (cooling was faster and more precise) and better neurological outcome.

Oxygen is a cornerstone in cardiac-arrest treatment. It is well known that low levels of oxygen can be harmful. In the fourth study, we wanted to investigate if too much oxygen (hyperoxemia) after cardiac arrest can be harmful. We linked patient data from four different Swedish patient registries for the period 2010–2021 and analysed almost 10,000 patients that had survived cardiac arrest and were admitted to a Swedish ICU. Oxygen values were measured +/- 1 hour from ICU admission. We found that hyperoxemia after cardiac arrest is associated with a lower survival rate. This association was stronger the higher the oxygen level.

Abstract

Background

Cardiovascular disease, and in particular cardiac arrest with the subsequent associated brain injury, is the most common cause of death in many countries. Annually, around 6000 people suffer from Out-of-Hospital Cardiac Arrest (OHCA) in Sweden and only around 10% survive to hospital discharge. Apart from early cardiopulmonary resuscitation (CPR) and defibrillation, it has been difficult to find interventions that can increase survival in OHCA, in particular in the post-resuscitation phase.

Methods and results

Study I. A national observational retrospective study, evaluating the adherence to Targeted Temperature Management (TTM) guidelines in Sweden after the publication of the TTM trial, and if the change in targeted temperature level (from 33 °C to 36 °C) influences 6-month survival. In total, 2899 OHCA patients were included, and of those, 1038 were treated by means of TTM. The proportion of patients with initial shockable rhythm receiving any TTM, i.e., following international guidelines, decreased after publication of the TTM trial (from 70.5% to 54.5%). There was no difference in 6-month survival between the TTM33 (47.2%) and the TTM36 (47.3%) groups (adjusted odds OR 1.12, 95% CI 0.80–1.56).

Study II. A sub-analysis of the PRINCESS trial, in which 677 OHCA patients were randomized to trans-nasal intra-arrest cooling initiated by the emergency medical services (EMS) or cooling started after hospital arrival. In this sub-analysis, the association between early initiation of intra-arrest cooling and neurological outcome was evaluated. Early cooling (intervention group, n=150) was defined as cooling initiated ≤ 20 minutes from collapse, and these patients were propensity score-matched with comparable controls (n=150). The primary outcome was survival with good neurological outcome (defined as Cerebral Performance Category [CPC] 1–2) at 90 days. The proportion of cases with CPC 1–2 at 90 days was 23.3% in the intervention group vs. 16% in the control group (OR 1.92, 95% CI 0.95–3.85). In patients with shockable rhythm the corresponding figures were 50.9% (intervention) vs. 29.8% (control) (OR 3.25, 95% CI 1.06–9.97).

Study III. A nationwide observational retrospective study, evaluating the association between different levels of hyperoxemia at Intensive Care Unit (ICU) arrival after cardiac arrest, and 30-day survival. Partial oxygen pressure (PaO_2) was recorded in a standardized way at ICU admission (± one hour). Hyperoxemia was defined as mild (13.4–20 kPa), moderate (20.1–30 kPa), severe (30.1–40 kPa) or extreme (>40 kPa). Normoxaemia was defined as PaO_2 8–13.3 kPa and hypoxemia as PaO_2 <8 kPa. In total,

9735 patients were included. Of these, 44.6% were hyperoxemic, 44.8% were normoxaemic and 10.5% were hypoxemic. Compared with the normoxemia group, the adjusted risk ratios (RRs) for 30-day survival in the hyperoxemia groups were: mild 0.91 (95% CI 0.85–0.91), moderate 0.88 (95% CI 0.82–0.95), severe 0.79 (95% CI 0.7–0.89), and extreme 0.68 (95% CI 0.58–0.79).

Study IV. A post-hoc analysis of the TTM2 trial, in which 1900 resuscitated OHCA patients were randomized to either hypothermia (TTM of 33 °C) or normothermia (<37.8 °C) groups for 28 hours. This sub-analysis was carried out to evaluate if there is any association between the cooling method used, i.e., intravascular (IC) vs. surface cooling (SFC), in the TTM 33°C group, and neurological outcome. The primary outcome was survival with good neurological outcome (defined as modified Rankin scale [mRS] result of 0–3) at six months. In total, 876 patients were included in this study, in which 30% were treated by means of IC and 70% by SFC. At six months, after propensity score matching, 53.0% of the patients in the IC group and 42.3% of the patients in the SFC group were alive, with mRS scores of 0–3 (OR 1.5, 95% CI 1.05–2.15). The IC group demonstrated better cooling speed and precision compared with the SFC group.

Conclusions

After publication of the TTM trial, fewer OHCA patients in Sweden received any TTM and this change of practice did not affect six-month survival among patients who underwent TTM.

In the PRINCESS trial, intra-arrest cooling started within 20 minutes of arrest, compared with cooling started after hospital admission, was not associated with a significantly better neurological outcome. In the subgroup with shockable rhythms, early cooling was associated with better neurological outcome.

Among resuscitated OHCA patients, hyperoxaemia at ICU admission, compared with normoxemia, was associated with lower 30-day survival. The association was stronger in connection with higher PaO_2 levels.

In OHCA patients in the TTM2 trial treated by means of TTM 33 °C, intravascular cooling, compared with surface cooling, was associated with better cooling performance and better neurological outcomes after six months.

List of scientific papers

I. Abazi L, Awad A, Nordberg P, Jonsson M, Taccone FS, Wickerts CJ, Svensson L, Hollenberg J, Ringh M, Forsberg S
Long-term survival in out-of-hospital cardiac arrest patients treated with targeted temperature control at 33 degrees C or 36 degrees C: A national registry study.
Resuscitation. 2019;143:142-7

II. Awad A, Taccone FS, Jonsson M, Forsberg S, Hollenberg J, Truhlar A, Ringh M, Abella BS, Becker LB, Vincent JL, Svensson L, Nordberg P
Time to intra-arrest therapeutic hypothermia in out-of-hospital cardiac arrest patients and its association with neurologic outcome: a propensity matched sub-analysis of the PRINCESS trial.
Intensive Care Med. 2020.

III. Awad A, Nordberg P, Jonsson M, Hofmann R, Ringh M, Hollenberg J, Olson Joelsson-Alm E
Hyperoxemia after reperfusion in cardiac arrest patients – A potential dose-response association with 30-day survival.
Crit Care. 2023;27(1):86

IV. Awad A, Dankiewicz J, Jonsson M, Hollenberg J, Ringh M, Nielsen N, Nordberg P
Intravascular versus surface cooling in out-of-hospital cardiac arrest patients receiving hypothermia after hospital arrival - a post hoc analysis of the TTM2 trial.
Manuscript

Scientific paper not included in the thesis

Dankiewicz J, Cronberg T, Lilja G, Jakobsen JC, Levin H... Awad A, et al. *Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest*.
New England Journal of Medicine. 2021;384(24):2283-94.

CONTENTS

LIST OF ABBREVIATIONS

AED	Automated External Defibrillator
AHA	American Heart Association
CA	Cardiac Arrest
CCI	Charlson Comorbidity Index
CDR	Cause of Death Register
CI	Confidence Interval
$CMRO_2$	Cerebral Metabolic Rate of Oxygen
CPC	Cerebral Performance Category
CPR	Cardiopulmonary Resuscitation
CRF	Case Report Form
EMS	Emergency Medical Service(s)
ERC	European Resucitation Council
GCS	Glascow Coma Scale
IC	Intravascular Cooling
ICU	Intensive Care Unit
IHCA	In-hospital Cardiac Arrest
mRS	modified Rankin scale
NPR	National Patient Register
O_2	Oxygen
OHCA	Out-of-Hospital Cardiac Arrest
OR	Odds Ratio
PEA	Pulseless Electrical Activity
SpO_2	Peripheral Oxygen saturation
PaO_2	Partial arterial Oxygen pressure
$PbtO_2$	Cerebral Oxygen tension
PCAS	Post-Cardiac Arrest Syndrome
ROS	Reactive Oxygen Species
ROSC	Return Of Spontanous Circulation
SAPS-3	Simplified Acute Physiology Score-3

SCD	Sudden Cardiac Death
SFC	Surface Cooling
SIR	Swedish Intensive Care Registry
SRCR	Swedish Registry for Cardiopulmonary Resuscitation
TNEC	Trans-Nasal Evaporative Cooling
TTM	Targeted Temperature Management
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

1 RATIONALE

Cardiovascular disease is the leading cause of death globally and according to estimations from the WHO it accounts for more than 30% of all deaths worldwide (1). A large proportion of these deaths are due to out-of-hospital cardiac arrest (OHCA). Despite the progress made in recent decades in the management of cardiac arrest, mortality is still high. In many countries, less than 10% of OHCA patients survive to hospital discharge in cases where the emergency medical services (EMS) started cardiopulmonary resuscitation (CPR) (2). Major knowledge gaps remain, not least regarding post-resuscitation care, where it has been difficult to find evidence-based treatments that increase survival (3).

2 BACKGROUND

2.1 Historical glance

According to legend, the Greek courier Pheidippides ran from Marathon to Athens in 490 BC to announce the Athenians victory over the Persians in the Battle of Marathon. At arrival he shouted "We are victorious!" and shortly afterwards collapsed and died; a case of cardiac arrest (4).

Throughout history, scientists have been fascinated by "apparent death" and methods to treat it. In 1792, James Curry published his book "Popular Observations of Apparent Death from Drowning, Suffocation etc" (5). Based on animal studies and clinical observations he distinguished between treatable apparent death and the subsequent development of absolute death. Furthermore, Curry introduced an early version of external defibrillation. By using two electrodes, one over the lower left chest and one above the clavicle, he managed to resuscitate two patients who apparently seemed to be dead (6).

In 1868, John Hill described a sternal compression technique (twelve compressions/minute) that restored circulation in apparently dead patients with no carotid pulse (7). The effectiveness of external chest compression was confirmed by several studies in the late nineteenth century but was outcompeted by internal (open chest) heart massage during the first half of the twentieth century (6).

William Kouwenhoven is often regarded as the founder of modern CPR. For several decades he studied the effect of chest compression and electric current on the fibrillating heart (6). In 1960, together with his colleagues Knickerbocker and Jude, he published a milestone article in the Journal of the American Medical Association, where 14 of 20 cardiac-arrest patients survived after receiving cardiac resuscitative measures (8).

Four years earlier, Paul Zoll and colleagues described a case series in which patients with ventricular fibrillation (VF) regained normal rhythm after receiving external defibrillation (9). These findings, in combination with development the mouth-to-mouth breathing technique by Peter Safar and colleagues (10, 11), laid the foundation of modern CPR.

2.2 Definitions

Cardiac arrest usually occurs suddenly and if untreated leads to inevitable death. There are several definitions of cardiac arrest, but one commonly used is "the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation" (12). When cardiac arrest occurs outside a hospital, it is referred to as out-of-hospital cardiac arrest (OHCA). This thesis is focused primarily on OHCA.

A commonly used term in this context is sudden cardiac death (SCD), which is defined as "an unexpected death without obvious extracardiac cause, occurring with a rapid witnessed collapse, or if unwitnessed, occurring within 1 hour after onset of symptoms" (13).

2.3 Incidence

The reported incidence numbers differ both between and within countries, and therefore the exact incidence of OHCA is unknown (14). A rough estimate is that every year a total of 356 000 people in the US and more than 400 000 in Europe suffer from OHCA in cases where EMS started CPR (2, 15). According to a recent study, the overall incidence of EMS-treated OHCA in 28 European countries was 56/100 000 person-years, and similar results have been reported from the US and Australia (2). In 2021, there were around 5900 EMS-treated OHCA cases in Sweden (16).

2.4 Survival rates

In a large prospective European study, the overall rate of survival to hospital discharge in OHCA patients in whom CPR was started was 8% (2). Among patients with an initial shockable rhythm, 24% survived to hospital discharge, while only 3% of patients with a non-shockable rhythm survived to this timepoint. According to a recent meta-analysis, including 141 studies, the overall survival rate to hospital admission was 22% and to hospital discharge, 8.8% (17). Interestingly enough, a substantial difference in survival to hospital discharge was seen between continents (Oceania 16.2%, Europe 11.7%, North America 7.7%, Asia 4.5%). However, some of these differences may have been a result of varying quality of the registers. In Sweden, 11% of EMS-treated OHCA patients survived to hospital discharge in 2021 (16).

2.5 Aetiology

Historically, different ways of reporting patient variables and the CPR situation made it challenging to compare results from different cardiac arrest studies. In the light of this, a consensus opinion (the Utstein template) was published 1991 in order to report OHCA in a more uniform way (18). It quickly became widespread and has been updated several times (19). According to the template the aetiology of OHCA can be divided into medical and non-medical causes. Furthermore, the medical causes can be divided into cardiac and non-cardiac causes. An overview of aetiologies (not intended to be exhaustive) is shown in Table 1.

Table 1. Causes of OHCA

Medical		**Non-medical**
Cardiac	Non-cardiac	
Ischaemic heart disease -Acute myocardial infarction -Chronic ischemic cardiomyopathy -Non-arteriosclerotic coronary disease Cardiomyopathies -Acute or chronic heart failure -Dilated cardiomyopathy -Hypertrophic cardiomyopathy -Infiltrative cardiomyopathy -Arrhythmogenic cardiomyopathy (ARVC) Primary electrical abnormalities -Long QT-syndrome -Brugada syndrome -Wolf–Parkinson–White syndrome -CPVT* Valvular heart disease Pericardial tamponade Myocarditis Congenital heart disease	Hypovolaemia Pulmonary embolism Intracerebral bleeding Electrolyte disturbances Hypoglycaemia Septic chock Aortic dissection Lung disease (hypoxemia) -Chronic obstructive pulmonary disease (COPD) -Pneumonia	Trauma Drug overdose Drowning Asphyxia Hypothermia Intoxication Electrocution

Adapted from Riva (20). *Catecholaminergic polymorphic ventricular tachycardia

The most frequent cause of OHCA is cardiac disease, in particular ischaemic heart disease, but the exact incidence is not known (21). In three prospective cohort studies it was estimated that around 60–65% cases of OHCA were due to cardiac causes (22-24). According to some studies, up to 70–80% of patients with sudden cardiac death (SCD) have an underlying coronary heart disease (25-27). However, this does not prove that it was the cause of the cardiac arrest.

A large autopsy study revealed that 32% of the OHCA cases had coronary disease as the leading cause of death (22). In a recent randomized trial including OHCA patients with an initial shockable rhythm, return-of-spontaneous circulation (ROSC) and no ST-elevation on the ECG, 64.5% of these patients had coronary artery disease, and percutaneous coronary intervention (PCI) was performed in 33% of the patients randomized to immediate coronary angiography (28). Interestingly enough, only 13.6% had an acute unstable lesion and 3.4% had acute thrombotic occlusion.

Finding out the aetiology of cardiac arrest is important in order to provide the most effective treatment. In practice, however, it is challenging for EMS providers to make the correct diagnosis, as the patient data is sparse in out-of-hospital settings. If the aetiology of an OHCA is unknown, which is often the case, the latest guidelines advise that EMS providers should report it as a presumed cardiac cause (19). Inevitably, this introduces a risk of cardiac aetiology being overestimated in EMS reports.

2.6 Risk factors

Given the fact that cardiac disease is the predominant cause of OHCA, known cardiovascular risk factors such as hypertension, age, smoking, diabetes mellitus, hyperlipidaemia, lower socioeconomic status and male sex increase the risk of SCD (29, 30).

Among patients with known cardiac disease there are subgroups with a markedly elevated one-year risk of SCD (e.g., previous cardiac arrest or sustained ventricular arrythmias, recent myocardial infarction, low ejection fraction, and some inherited arrhythmic disorders), but these patients constitute only a minority of all OHCA cases in society (29, 31). On the other hand, approximately 50% of patients with SCD do not have any previous known cardiac disease and another 30% are patients with known cardiovascular disease but considered as a “low-risk subgroup” (29). This makes it complex to create a SCD prediction model for the general population (31).

2.7 Predictors of survival

There are several known factors that affect the probability of surviving OHCA. These can be categorized into patient-related factors (e. g. age, comorbidity, sex, socioeconomic status), event-related factors (e.g. initial rhythm, witness status, bystander CPR, agonal breathing) and system-related factors (e.g. time to CPR, time to defibrillation, dispatcher-assisted CPR) (21). Some predictors are stronger than others and several are interdependent and not easy to fully separate (e.g. time to EMS arrival influences the first recorded rhythm).

What several of the predictors reflect is how incredibly important it is that treatment, in particular CPR and defibrillation, is started early (32). For every minute CPR is delayed in cases of witnessed OHCA with an initial shockable rhythm, survival decreases by 7–10% (33). Some of the most important predictors are discussed below.

2.7.1 First recorded rhythm

The first recorded ECG in cardiac arrest can be divided into shockable rhythms (ventricular fibrillation [VF] or pulseless ventricular tachycardia [VT]) or non-shockable rhythms (asystole or pulseless electrical activity [PEA]).

The true proportions of the different rhythms at the initial phase of OHCA is impossible to know, since most patients are not monitored, and untreated VF can quickly deteriorate to asystole (often after a period of decreasing amplitude of VF) (34). In a study of patients wearing an ambulatory ECG-monitoring device, 84% of those who experienced SCD had initial ventricular tachyarrhythmia, most often VF secondary to sustained VT (35). Although the patient cohorts are not directly comparable, this is in strong contrast to the finding that only 20–30% of OHCA patients had VT/VF as the first recorded rhythm (by EMS) in Sweden during the last decade (36). This highlights the crucial importance to initiate treatment as soon as possible.

The presence of an initial shockable rhythm is the single strongest predictor of survival in OHCA, and according to a meta-analysis it increases the probability of survival almost threefold (37).

It is important to distinguish asystole from PEA, since the former is associated with significantly worse prognosis than the latter (36). In patients with asystole as the first recorded rhythm the prognosis is very dismal; in several studies around 1% or less survive to hospital discharge (38-40). Furthermore, in patients with an initial non-shockable rhythm who survive, neurological outcome is more favourable in cases of PEA compared with asystole (38, 39).

PEA consists of a heterogeneous group of causes (e.g. hypovolaemia, pulmonary embolus, asphyxia, trauma) with varying prognosis (41). In Sweden, the proportion of

cases of PEA as the first recorded rhythm has increased in recent decades and survival rates have increased fivefold, today reaching almost 5% as regards 30-day survival (40). In an Australian study, 6% of PEA patients survived to hospital discharge (38). In practice, it can be a diagnostic challenge for healthcare professionals, as PEA can range from a motionless heart (so-called "electromechanical dissociation") to a well-pumping heart with profound hypotension due to hypovolaemia or septic shock. Conclusions about prognosis should be avoided until the aetiology is established.

2.7.2 Witness status

A witnessed cardiac arrest is defined as "a cardiac arrest that is seen or heard by another person or is monitored" and is a predictor of increased survival in OHCA (19). For natural reasons, a witnessed collapse is associated with an earlier start of treatment and an increased chance of VT/VF as the first recorded rhythm, but it has also been proven to be an independent predictor (42, 43). According to a large registry study, the chance of survival in OHCA doubled if the collapse was witnessed (43). The small subgroup of OHCA cases that are witnessed by the EMS, in contrast to lay persons, seem to have an even better prognosis (44).

2.7.3 Bystander CPR

Bystander CPR is defined as "CPR performed by a person who is not responding as part of an organized EMS to a cardiac arrest. It my may be compression only or compressions with ventilation" (19). As with witness status, the occurrence of bystander CPR is associated with other predictors, but is independently associated with increased survival in OHCA (44). In two Scandinavian cohorts it increased the likelihood of survival two- to fourfold (44, 45).

2.7.4 Location

Most OHCAs occur at home, at least two thirds according to several studies, and collapse at this location is associated with worse outcome (43, 46, 47). The reason for this is probably multifactorial. When an OHCA occurs outside the home it is more often witnessed, the likelihood of bystander CPR is higher, the time to EMS-arrival is shorter, the patients are younger and the proportion of cases of initial shockable rhythm is higher (43, 47, 48).

2.7.5 Age

Although associated with several other predictive factors, advanced age has been shown to be an independent risk factor of worse outcome after OHCA (43, 49, 50). After adjusting for other risk factors, age is substantially less predictive and one should be aware of the risk of a "self-fulfilling prophecy" when life-sustaining therapies are withdrawn early after ROSC by the clinician (50, 51).

2.7.6 Sex

Men account for more than two thirds of OHCA cases (36, 52). Compared with men, females have significantly lower crude survival rates (53, 54). This may be explained by the fact that females experiencing OHCA are older, more often at home, less often witnessed and receive bystander CPR less often (53, 54). After adjusting for confounders, the difference in survival is no longer apparent and, in some subgroups, even higher in females (54, 55).

2.8 Neurological outcome

Since the brain is very susceptible to damage after cardiac arrest, it is important not only to measure survival rates but also assess the neurological function of surviving patients.

Only a minority of OHCA patients surviving to hospital discharge have severe neurological impairment (56). According to a recent study, 47% returned to full-time work and another 23% returned to work with reduced working hours (57). On the other hand, mild cognitive impairment and symptoms such as fatigue, depression, and decreased problem-solving capacity are very common, including among survivors who return to work (57).

For many years the Cerebral Performance Category (CPC) has been the most commonly used neurological outcome measure after cardiac arrest (58). According to this scale CPC 1–2 is considered as a good neurological outcome, while CPC 3–5 is regarded as a poor outcome (Table 2). According to critics, use of the CPC has limited ability to differentiate between mild and moderate brain injury (58). In recent years, the Modified Rankin Scale (mRS) has been increasingly used in cardiac arrest to evaluate neurological status and is recommended as a part of the latest Utstein template (59). If necessary to dichotomize, mRS 0–3 is often labelled as a good neurological outcome, while mRS 4–6 is considered as poor outcome (Table 3). There are additional neurological tests on the horizon, e.g. the Glasgow Outcome Scale Extended (GOS-E), which may become more used in the future (60).

Table 2. Cerebral Performance Categories (58)

CPC 1	Conscious, alert, able to work and lead a normal life. May have minor psychologic or neurologic deficits (mild dysphasia, non-incapacitating hemiparesis, or minor cranial nerve abnormalities).
CPC 2	Conscious. Sufficient cerebral function for part-time work in a sheltered environment or independent activities of daily life (dressing, travel by public transportation, food preparation). May have hemiplegia, seizures, ataxia, dysarthria, or permanent memory or mental changes.
CPC 3	Conscious. Dependent on others for daily support (in an institution or at home with exceptional family effort). Has at least limited cognition. This category includes a wide range of cerebral abnormalities, from patients who are ambulatory but have severe memory disturbances or dementia precluding independent existence, to those who are paralyzed and can communicate only with their eyes, as in the "locked in" syndrome.
CPC 4	Unconscious. Unaware of surroundings, no cognition. No verbal and/or psychologic interaction with environment.
CPC 5	Brain dead, circulation preserved.

Table 3. The Modified Rankin Scale (58)

mRS 0	No symptoms.
mRS 1	No significant disability. Able to carry out all usual activities, despite some symptoms.
mRS 2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
mRS 3	Moderate disability. Requires some help, but able to walk unassisted.
mRS 4	Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
mRS 5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
mRS 6	Dead.

3 TREATMENT

In order to understand the rationale behind different treatment strategies and the "chain of survival" in OHCA, a certain understanding of the pathophysiology of brain damage during and after cardiac arrest is needed. To fully cover this and all aspects of treatment is beyond the scope of this thesis. The focus of this project is on some aspects of intra-arrest and post-resuscitation care, in particular, therapeutic hypothermia and oxygen treatment.

3.1 Pathophysiology

Anoxic brain injury due to cerebral hypoperfusion is the main reason for death and disability after cardiac arrest (3). If ROSC is achieved, the reperfusion phase is associated with several cellular mechanisms that can lead to further neuronal damage several days after the arrest, also called "post-resuscitation encephalopathy" (61). The cerebral pathophysiology is complicated and not fully understood (61). Some of the known features will be briefly discussed below.

As soon as four minutes after cerebral hypoperfusion, ATP depletion and failure of several ion pumps begins (62). This leads to several cytotoxic events (e.g. lipolysis, release of glutamate, activation of certain proteases, increased intracellular calcium concentration) with secondary cellular necrosis (61, 63). Lipolysis leads to an accumulation of free fatty acids, in particular arachidonic acid (61). Furthermore, the ischaemia phase leads to inflammation with a complicated cytokine cascade, which appears to have both protective and harmful effects (64).

Early in the reperfusion phase, in the transition from anaerobic to aerobic metabolism, an excessive amount of oxygen radicals is generated (e.g. from arachidonic acid) which, among other things, leads to peroxidation of phospholipids with damage of cell membranes (65). This peroxidation starts within 15 minutes and can continue for more than three days (65). Almost immediately after ROSC, autoregulation of the cerebral blood blow is disturbed (61). Initially, there is a brief period (15–30 min) of hyperaemia, which is followed by prolonged hypoperfusion. After 90 minutes, cerebral blood flow can decrease to around 50% of normal and this disturbance of autoregulation can last for up to 12 hours (66). The phenomenon above, together with other mechanisms, can lead to delayed neuronal damage several days after the primary insult (61).

In addition to brain injury, whole-body hypoperfusion-reperfusion in cardiac arrest can trigger activation of a number of pathophysiological pathways (e.g. an immense inflammatory response) effecting several organ systems (67). To cover all aspects of these pathophysiological cascades is beyond the scope of this thesis and is discussed in detail elsewhere (67). In short, the clinical picture can mimic sepsis syndrome in

several ways and is often termed post-cardiac arrest syndrome (PCAS) (68). Organ-supportive intensive care unit (ICU) action (e.g. use of vasopressors/inotropes) is often needed during the first days after ROSC (69).

3.2 Chain of survival

The "chain of survival" was adopted by the American Heart Association (AHA) in 1991 and is a well-established concept in cardiac-arrest care that illustrates measures to increase survival at different phases after collapse (70). The steps are:

1. Early recognition and call for help
2. Early CPR
3. Early defibrillation
4. Post resuscitation care

Figure 1:

Nolan et al. (71)

The deleterious pathophysiology discussed in the previous section is very time-dependent and every minute of hypoperfusion matters (61). For natural reasons, the number of patients susceptible to intervention decreases with every step in the chain. Therefore, it is not surprising that there is most evidence supporting the first steps in the chain (3, 13, 72-75). The main focus of this thesis is on the later steps in the chain, in particular, early advanced life support and post-resuscitation care.

3.2.1 Early recognition and call for help

Early recognition includes identification of symptoms preceding the cardiac arrest (e.g. chest pain or shortness of breath) plus symptoms of the actual cardiac arrest, most importantly unresponsiveness and abnormal breathing (75). This enables the EMS to arrive sooner, which in turn both reduces the risk of the symptoms developing into cardiac arrest (e.g. by means of rapid and effective treatment of myocardial infarction) and in the case of collapse, decreases the time to start of CPR (75). Together, this leads to a better chance of survival (37, 76).

3.2.2 Early CPR

An early start of bystander CPR can increase the likelihood of survival severalfold (73, 77-79). This includes both compressions together with ventilation (if the bystander has CPR training) or "compression-only CPR" (if the bystander does not have CPR training or is unwilling to perform rescue breaths) (45, 80). There may be several physiological explanations for this, most importantly that CPR provides a certain degree of circulation to both the brain and coronary arteries (75). This, in turn, can prolong the time before brain injury occurs, and also prolong the time before VT/VF deteriorates to asystole, action which may increase the chance of successful defibrillation (73, 75, 79). If bystander CPR is provided, the corresponding benefit to survival is 3–4% per minute, highlighting the importance of early CPR (32, 73, 81).

3.2.3 Early defibrillation

In cardiac arrest with an initial shockable rhythm, early defibrillation is crucial in order for the victim to survive (75). Survival can be as high as 70% in OHCA patients with initial VT/VF treated with a public automated external defibrillator (AED) (82). The outcome is substantially better if CPR is started within five minutes of collapse and it is estimated that for every minute of delay to defibrillation the probability of survival (to hospital discharge) decreases by approximately 10% (32).

3.2.4 Early advanced life support and post resuscitation care

The list of all potential advanced life support and post-resuscitation care measures is long and is discussed in more detail elsewhere (3, 60). Although several of these measures have demonstrated promising results in animal studies it has been difficult to find treatments that improve patient-centered outcomes (e.g. hospital discharge with favourable neurological status) in clinical studies (72, 74).

In short: once brain injury and post-cardiac arrest syndrome is established, it is very challenging to halt further organ damage (72). However, there are some potential post-resuscitation measures that have shown promising results, especially in the early phase after ROSC (72). Some of these are of special interest in this thesis and will be discussed below.

3.3 Therapeutic hypothermia

There is no universally accepted definition of fever. A historically often used definition of "fever of unknown origin" is >38.3 °C (83). Others have proposed 37.7 °C as the upper limit of normal temperature (84-86).

Fever is common in the first days after cardiac arrest and several studies have demonstrated that it is associated with worse outcome (87, 88). There are no RCTs concerning comparison of no fever control with normothermia after cardiac arrest, and therefore it is unknown whether fever actually causes brain injury or merely is a marker of already established brain damage (89). Nevertheless, the latest international guidelines recommend avoidance of fever in comatose survivers after cardiac arrest, at least for the first 72 hours (3).

Core body temperature affects the brain in several ways. It is known that the cerebral metabolic rate of oxygen ($CMRO_2$) is reduced by approximately 6% per degree °C and this is associated with several complicated biochemical processes that may be important as regards brain damage after cardiac arrest (90-92). For instance, induced hypothermia decreases the onset of anoxic cell depolarisation, it reduces accumulation of excitatory amino acids (e.g. glutamate) and supresses the formation of free radicals (92, 93). In experimental studies, hypothermia has been associated with decreased leakiness of the blood-brain barrier, less brain oedema, higher cerebral oxygen tension, a lower lactate/pyruvate ratio, less programmed cell death and decreased inflammation (92-95). On the other hand, this reduction in inflammation was not seen in a more recent clinical trial (96).

Deep hypothermia is routinely used for neuroprotection in cardiothoracic surgery and it is well known that patients who have suffered from accidental hypothermia with secondary prolonged cardiac arrest can survive with minimal neurological sequelae (97, 98). In these examples hypothermia precedes hypoperfusion of the brain, which is important to distinguish from the usual cardiac arrest scenario, where hypothermia is induced *after* circulatory arrest.

It leaves us with the question: is therapeutic hypothermia (recently renamed targeted temperature management [TTM]) initiated after cardiac arrest neuroprotective? A proposed definition of mild therapeutic hypothermia is 34.0 °C–35.9 °C, moderate therapeutic hypothermia 32.0 °C–33.9 °C and deep therapeutic hypothermia <32 °C (99). Since the side-effects (e.g. coagulopathy, immunosuppression, arrythmias) are substantially more pronounced in connection with deep hypothermia compared with mild–moderate hypothermia, the majority of clinical trials conducted have concerned the latter (89, 99). Results from animal studies are promising, while results from clinical studies have been more divergent (72). Of note, all conducted TTM trials have been on

patients that are commatose (often defined as Glascow coma scale ≤8) after ROSC (72), and the evidence provided is restricted to this subset of patients.

3.3.1 Animal studies

According to a recent meta-analysis, which included 181 studies with a range of different animals and different hypothermia strategies, TTM after cardiac arrest seems to be benificial as regards most of the tested outcomes (mortality, neurobehavioural, histological) (100). The greatest benefit was seen when hypothermia was initiated early, preferably intra-arrest or within 15 minutes after ROSC (100, 101). However, most studies have been of low–medium quality and there are very few studies on gyrencephalic species, and especially on comorbid animals, which makes translation to humans difficult (100).

3.3.2 Intra-arrest & prehospital hypothermia – clinical studies

Several RCTs have investigated the effect of administration of cold intravenous (iv) crystalloid fluids during CPR (102, 103) or immediately after ROSC (104-107) in cases of OHCA. Overall, there was no significant difference in survival, but in some of the trials the group that received cold iv fluids had higher rates of rearrest (107) or lower rates of ROSC (in patients with an initial shockable rhythm) (102). Current guidelines advise against using large amounts of cold iv fluids immediately after ROSC (3).

One way to more selectively cool the brain intra-arrest without adding intravenous volume is through trans-nasal evaporative cooling (TNEC) (108, 109). The method is portable and is suitable for use in pre-hospital settings. It cools surrounding structures in the nasopharynx, which causes the brain to cool via the large vessels and via conductivity. The inert cooling liquid perfluorohexane evaporates to cooling gas which is delivered through nasal catheters (108). This method has been used in two RCTs where witnessed OHCA patients were randomized during CPR to receive either TNEC during CPR or standard care (including therapeutic hypothermia at hospital after ROSC) (110, 111). In both studies the intervention group reached target temperature (32 °C–34 °C) faster. In the larger study (the *PRINCESS* trial), some interesting trends were observed in the prespecified patient outcomes (in favour of the intervention group), but these were not statistically significant (111). In *post hoc* analyses, in the subgroup of patients with initial shockable rhythm, the intervention group showed significantly better survival with complete neurological recovery (CPC 1 at 90 days) (111).

3.3.3 Post resuscitation hypothermia- clinical studies

In 2002, one RCT and one quasi-RCT demonstrated favourable survival and neurological outcome in OHCA patients with an initial shockable rhythm treated by means of TTM (32 °C–34 °C for 12–24 hours) compared with standard care (112, 113). After this, TTM with a goal temperature 32–34 °C became standard treatment in comatose patients with OHCA and ROSC. In 2013, in the TTM trial, standard TTM at 33 °C was compared with higher TTM at 36 °C, and there was no difference in survival rates nor neurological outcome at six months between the two strategies (56). Nor did the subsequent TTM2 trial, including 1900 patients (with ROSC after OHCA) that were randomized 1:1 to hypothermia (≤33 °C) and normothermia (defined as ≤ 37.8 °C) groups, demonstrate any difference in survival or neurological outcome at six months. After these publications, the latest guidelines recommend normothermia over hypothermia in comatose patients after cardiac arrest, although targeting at 32–36 °C may be considered for selected patients(114).

In the HYPERION-trial from 2019, which included both OHCA and in-hospital cardiac arrest (IHCA) patients, resuscitated comatose patients with an initial non-shockable rhythm were randomized to TTM with a goal temperature of either 33 °C or 37 °C for 24 hours (115). The intervention group (TTM 33 °C) had a significantly higher rate of survival with favourable neurological status (defined as CPC 1–2) at 90 days. This difference in outcome was mainly seen in patients with IHCA (115). In a more recent trial, which included 249 IHCA patients, there was no significant difference in outcomes between the hypothermia and normothermia group (116).

In landmark trials, one in 2002 (112, 113), and in the more recent HYPERION trial (115), some patients in the control group developed fever, which, after the TTM trials, raised the question of whether the beneficial effect seen in connection with hypothermia was simply due to having managed to avoid fever.

3.4 Oxygen treatment

Oxygen (O_2) can have a double-edged effect during and after cardiac arrest. Cerebral oxygen tension ($PbtO_2$) can drop to almost zero within minutes after cardiac arrest, which quickly can lead to irreversible hypoxic injuries (117, 118). $PbtO_2$ is dependent on both brain perfusion and PaO_2. By delivering a high fraction of inspired oxygen (FiO_2) during high-quality CPR it is possible to achieve almost pre-arrest levels of $PbtO_2$ (117-119). In cases where ROSC is achieved, $PbtO_2$ increases several-fold and if high amounts of O_2 are delivered during this phase supranormal arterial oxygen pressure (PaO_2), so called hyperoxemia, occurs (117, 118).

The impact of hyperoxemia on pathophysiology following cardiac arrest is not fully understood, but the key mechanism is the formation of reactive oxygen species (ROS),

which directly or indirectly leads, for example, to mitochondrial damage, excitotoxicity, loss of ion gradients, cerebral vasoconstriction and increased inflammation, all of which can result in brain damage (120-124). This pathophysiology starts within 15 minutes of reperfusion and seems to be accelerated by higher levels of hyperoxaemia (125, 126).

What is abnormal PaO_2? A frequently used definition for hypoxemia is PaO_2<8 kPa (60 mmHg), for normoxemia PaO_2 8–13.3 kPa (60–100 mmHg) and for hyperoxemia PaO_2>13.3 kPa (100 mmHg) (127, 128). To further complicate matters, in several clinical studies hyperoxaemia has been defined as PaO_2 >40 kPa (300 mmHg), mainly based on results from animal studies (129). But as so often when concerning physiological parameters, there is no commonly accepted, unambiguous definition available. In this case, it is more about a continuum of oxygen content without clear defining limits. This is important to have in mind when interpreting the results of clinical trials on the subject.

The results of several animal studies suggest that hyperoxaemia, especially PaO_2 >40 kPa, is harmful during the first few hours after ROSC (120-122). Clinical studies show more divergent results (127, 129, 130). There are no RCTs concerning comparison of different O_2-treatment strategies during CPR, while there are a few RCTs on comparison of different strategies in the post-resuscitation phase (131-136).

In a recently published study (the EXACT trial), resuscitated unconscious OHCA patients were randomized to either a lower (90–94%) or higher (98–100%) peripheral O_2 saturation (SpO_2) target in pre-hospital settings. Although the study was stopped earlier than planned due to the Covid pandemic, the lower target group had a clear but statistically nonsignificant trend towards lower survival and significantly more hypoxic events. This study highlighted the challenge of conducting a randomized study on this research question in a prehospital setting. First of all, most often it is not possible to analyse arterial blood gases (PaO_2) in this setting. Furthermore, pulse oximetry is often unreliable (due to vasoconstriction, for example), and it is difficult to measure SpO_2 levels in a safe manner outside hospital. Another randomized trial was stopped early because a large proportion of the control group (SpO_2 goal 90–94%) had an episode of hypoxia (defined as SpO_2 <88%) (133).

A handful of RCTs have been carried out to compare different O_2-target strategies in unconscious and mechanically ventilated ICU patients (135, 137-139). In general, there was no difference in patient-centered outcomes and only one of the studies specifically concerned OHCA patients. Of note, in all the studies the "liberal" O_2 groups had PaO_2 levels around 14–15 kPa, i.e. mild hyperoxaemia. In a real-world clinical setting, a substantial proportion of patients have significantly higher PaO_2 levels (129). Furthermore, since it can take several hours (due to time-consuming measures such as intra-hospital transfers, X-rays, coronary catheterization, etc.) until a patient arrives in the ICU, randomization and intervention were most often performed several hours after

ROSC. So far, there has been no RCT carried out to compare different O_2-target strategies in the period between leaving the emergency room to ICU arrival, a vulnerable phase for the brain where abnormal O_2 levels could possibly affect the pathophysiological process.

In a recent systematic review, including more than 30 observational studies, it was concluded that the majority of the studies conducted on the subject suffer from a high risk of bias (129). The study designs were rather heterogeneous, not least in regard to when and for how long oxygen levels were measured. For this reason, pooled analysis was not performed (129). In most studies hyperoxemia was defined as PaO_2 >40 kPa (300 mmHg). In some studies, early hyperoxia was associated with significantly worse outcomes (140, 141), while others did not find this association (128, 142-144). Although most studies had point estimates favouring normoxia over hypo-/hyperoxemia, the majority did not reach statistical significance (129).

Current European Resuscitation Council (ERC) guidelines recommend that 100% oxygen should be administered during CPR, and if ROSC is achieved, the aim should be arterial blood saturation of 94–98%, but the level of evidence for these recommendations is weak (3). There is a need for further studies on this subject in order to close this important knowledge gap.

4 AIMS

The overall aim of this work was to study aspects of optimal post-resuscitation care after OHCA with a focus on therapeutic hypothermia and hyperoxemia.

Specific aims of the study:

1. To study the adherence to targeted temperature management (TTM) guidelines in Sweden after publication of the TTM trial and to compare six-month survival between patients treated by means of TTM at 33 °C and at 36 °C.

2. To study the association between early initiation of trans-nasal evaporating intra-arrest cooling and neurological outcome in OHCA.

3. To study the association between different levels of hyperoxaemia in the reperfusion period after cardiac arrest, and 30-day survival.

4. To compare cooling performance and neurological outcomes in patients treated by means of intravascular cooling versus surface cooling for targeted temperature management at 33 °C after OHCA.

5 METHODS

5.1 Overview of study designs

	Study I	Study II	Study III	Study IV
Design	Observational retrospective study	Sub-analysis of a randomized controlled trial	Observational retrospective study	Sub-analysis of a randomized controlled trial
Data sources	- SIR - SRCR - NPR - CDR	Study - CRF	- SIR - SRCR - NPR - CDR	Study - CRF
Numbers	n=2899	n=300	n=9735	n=876
Years	2010-2016	2010-2018	2010-2021	2017-2020
Inclusion criteria	OHCA, ROSC, mechanically ventilated	Witnessed OHCA	OHCA or IHCA, ROSC, mechanically ventilated	OHCA, ROSC, unconscious
Statistical methods	-Multiple logistic regression -Propensity score matching	Propensity score matching	Multivariable modified Poisson regression	Propensity score matching
Outcomes	6-month survival	Survival with CPC 1–2 at 90 days	30-day survival	Survival with mRS 0–3 at 6 months

Table 4. Overview of design, study population, data sources and methods in Studies I–IV

SIR, Swedish Intensive Care Registry; SRCR, Swedish Registry for Cardiopulmonary Resuscitation; NPR, National Patient Register; CDR, Cause of Death Register; CRF, Case Report Form

5.2 Studies I and III; observational cohort studies

5.2.1. Study design, population, data sources and statistical methods

In these observational studies, data from four different Swedish registers were used; SIR, SRCR, NPR and CDR. In both studies, cardiac-arrest patients with sustained ROSC, admitted to an ICU and mechanically ventilated were found in SIR. This data was merged with data from SRCR to obtain information about the cardiac arrest, and with NPR data to obtain information about comorbidities and survival status.

5.2.2 The Swedish Intensive Care Registry (SIR)

The SIR is a national quality ICU registry founded in 2001 containing a large amount of ICU-related patient data such as diagnoses, physiological parameters and interventions (145). The coverage has increased over the years and in 2021 all 83 Swedish ICUs reported to the SIR (146).

It is mandatory for all ICUs to report to the SIR the score according to the Simplified Acute Physiology Score-3 (SAPS-3) system. SAPS-3 is a risk-adjustment system for critically ill patients used in many countries (e.g. Sweden) and it includes, for example, physiological parameters (e.g. lowest PaO_2) collected ±1 hour from ICU arrival (147). According to the latest annual report from SIR, the coverage rate for SAPS-3 was 97% (146) but of note, a SAPS-3 score is reported even if there are missing variables (missing variables are filled in as "normal" in the model). According to a study examining the prevalence of missing physiological data reported in SAPS-3 in Sweden in 2011–2014, 11% of physiological data were missing (more common as regards low-risk admissions and survivors) and one or more variables were missing in 41% of admissions (148). The most common missing variables were oxygenation (25% missing) and bilirubin (21%). The proportion of missing data in the SAPS-3 system seems to have decreased; last year around 30% of the data on reported admissions had one or more missing variable (149). To date, it has not been validated how well the variables in SAPS-3 reported to the SIR match real-world values.

5.2.3 The Swedish Registry for Cardiopulmonary Resuscitation (SRCR)

The SRCR was started in 1990 for OHCA and in 2005 for IHCA and it includes patients in whom CPR was started (16). It contains cardiac-arrest-related data in accordance with Utstein guidelines (150). The coverage has increased over the years and since 2010 all hospitals and EMS-providers in Sweden report to the SRCR.

Initially, the data was reported manually on paper, but since 2008 it has been reported electronically via a web-based system. The registry contains three parts. First, pre-hospital cardiac arrest data (e.g. location of arrest, witnessed status, bystander CPR, first recorded rhythm, defibrillation, administration of drugs etc.) reported by the EMS crew. Second, in-hospital data (e.g. interventions) most often reported by an experienced nurse. Third, data on Patient-Reported Outcome Measures (PROMs) has been collected since 2013 and is usually conducted through a telephone call/follow-up visit 3–6 months after cardiac arrest.

Until 2010, the coverage for OHCA was estimated to be 70–100% and after that almost 100% (151). The coverage for IHCA is lower than for OHCA, but the exact figure is unknown. The coverage for PROM has varied over the years and not all hospitals report PROM.

5.2.4 The National Patient Register (NPR) and Cause of Death Register (CDR)

The NPR and the CDR are run by the Swedish National Board of Health and Welfare and they collect individual patient data based on Swedish social security numbers. They include patient data on comorbidities, cause of hospital admission, hospital interventions and date of death, for example (152). The registers have almost 100% coverage and the NPR has included all in-patient care in Sweden since 1978. According to the results of investigations, 85–95% of the diagnoses in the NPR are valid (153).

5.2.5 Study I

The aim of this study was to investigate the adherence to targeted temperature management (TTM) guidelines in Sweden after publication of the TTM trial and to compare six-month survival between patients treated by means of TTM at 33 °C and at 36 °C.

Adult OHCA patients with ROSC, who were admitted to an ICU unconscious (Glasgow Coma Scale [GCS] ≤8), mechanically ventilated and recorded in the SIR between January 2010–March 2016 were eligible for inclusion. Information on whether or not the patient received TTM was collected from the SIR, but since the SIR defined all types of TTM as "active hypothermia", with no discrimination between TTM 33 °C and TTM 36 °C, a survey was sent to all the ICUs (n=69). The survey included the question: Have you changed from TTM 33 °C to TTM 36 °C when treating OHCA patients and if so, at what date was this change implemented in your hospital? According to the date the patient was admitted to the ICU and answers from the survey, patients receiving active hypothermia were classified into either the TTM33 or TTM36 group. The primary outcome was 6-month survival.

Statistical methods

Categorial variables were presented as counts and proportions, and continuous variables as medians and quartiles. To test baseline differences, the chi-square test for categorial variables, and Wilcoxon's rank-sum test for continuous variables were used. To test if there was a difference in survival between the TTM33 and the TTM36 group, binary logistic regression analysis was performed as well as propensity score matching. The logistic regression analysis was adjusted for age, gender, location, bystander CPR, witnessed status, Charlson comorbidity index (CCI) and SAPS-3 score. The same variables were included in the propensity score calculation (1:1 nearest neighbour).

5.2.6 Study III

The aim of this study was to evaluate the association between different levels of hyperoxemia at ICU arrival after cardiac arrest, and 30-day survival. Adult OHCA and IHCA patients who were admitted to an ICU, mechanically ventilated and recorded in the SIR between January 2010–March 2021 were eligible for inclusion. Partial oxygen pressure (PaO_2) was collected from the SAPS-3 score (± one hour from ICU arrival) registered in the SIR and the patients were divided into groups based on this PaO_2 value. Normoxaemia was defined as PaO_2 8–13.3 kPa and hypoxaemia as PaO_2 <8 kPa. Hyperoxaemia was defined as mild (13.4–20 kPa), moderate (20.1–30 kPa), severe (30.1–40 kPa) and extreme (>40 kPa). The primary outcome was 30-day survival.

Statistical methods

Categorial variables were presented as counts and proportions. Continuous variables were presented as means and standard deviations, or medians and quartiles. The normoxaemia group was used as a reference group and the other groups were compared with this group. To handle missing data, multiple imputation was performed under the assumption of missing at random. Relative risks (RRs) and 95% confidence intervals (CIs) were estimated using multivariate modified Poisson regression adjusted for age, sex, bystander CPR, witnessed status, initial shockable rhythm, CCI, SAPS-3 score, location and EMS-response time.

5.3 Studies II and IV; sub-analyses of randomized controlled trials

Study design, population, data sources and statistical methods

Both these studies are sub-analyses of randomized controlled trials (RCTs) with the study CRF from the respective studies as the data source.

5.3.1 Study II

In the PRINCESS trial, 677 bystander-witnessed OHCA patients were randomized during CPR to either intra-arrest trans-nasal evaporative cooling (TNEC) initiated by EMS or cooling started after hospital arrival. In both groups, patients admitted alive to the hospital received systemic TTM with a targeted temperature of 32–34 °C for 24 hours.

The aim of this prespecified sub-study of the PRINCESS trial was to evaluate the association between early initiation of TNEC and neurological outcome. Early cooling (intervention) was defined as cooling initiated ≤20 minutes (median time to initiation of cooling in the main trial) since collapse, and these patients were propensity score-matched with comparable patients in the control group. The primary outcome was survival with good neurological outcome, defined as CPC 1–2, at 90 days.

Statistical methods

Patients in the early cooling group were (1:1) propensity score-matched with patients in the control group using nearest neighbour (caliper width 0.2) to balance covariates between the groups. The used variables in the propensity score calculations were: "time to randomization", gender, age, weight, aetiology, bystander CPR, initial rhythm, study site. Conditional logistic regression was used for the outcome analyses.

5.3.2 Study IV

In the TTM2 trial, 1900 OHCA patients with ROSC and GCS scores ≤8 were randomized to either hypothermia (TTM 33 °C) or normothermia (<37.8 °C) for 28 hours. It was up to each hospital to choose the cooling method. The aim of this sub-study of the TTM2 trial was to evaluate the association between the chosen cooling method, i.e., intravascular cooling (IC) or surface cooling (SFC), in the hypothermia group, and outcomes. The primary outcome was survival with good neurological outcome, defined as mRS score 0–3, at six months. Secondary outcomes included six-month survival and cooling performance.

Statistical methods

Propensity score matching (1:1) using nearest neighbour with caliper width 0.2 was used to find corresponding patients in the IC and SFC group and to balance covariates between the groups. Variables included in the propensity score calculation were sex, age, initial rhythm, time to ROSC, location, frailty score, witnessed status, bystander CPR and CCI score. Supplementary analysis using both frequentist and Bayesian multilevel logistic regression was performed.

5.4 Ethical considerations

All studies in this doctoral project were approved by regional ethics boards (EPN/EPM). The diary numbers for the different studies are:

Study 1: 2016/172-31
Study 2: 2010/383-32 (in addition to 2009/57-31/3)
Study 3: 2022-01450-02 (in addition to 2021-01165, 2018/2193-32 and 2016/172-31)
Study 4: 2017/622 (in addition to 2017/36 and 2015/228)

All studies in this doctoral project included unconscious cardiac arrest patients. Some ethical issues are the same for all studies, while others differ depending on the study design. A cornerstone in the Declaration of Helsinki is informed consent from the person that is studied, preferably *before* inclusion. This is especially important in experimental studies. A general ethical problem when studying cardiac-arrest patients is the fact that the vast majority of them are unconscious at the time of inclusion (many cardiac-arrest studies include only unconscious patients), which makes it very challenging to obtain informed consent before inclusion. On the other hand, some argue that it is *unethical* to avoid research on critically ill patients merely because of the fact that they are unconscious. How can the care of future cardiac-arrest patients be improved if research is not allowed on unconscious patients?

This ethical dilemma is not unique to cardiac-arrest patients. For instance, a large proportion of patients treated in the ICU are in the same position. Historically, this has made it more difficult to conduct research on ICU-treated patients. There are different ways to handle this question.

In the best of all possible worlds, informed consent would always be collected in advance, for instance when patients are in contact with the healthcare system for another reason. There are several problems with this approach. Firstly, it is very resource- and time-consuming, since it would require an enormous amount of consent documentation, especially if the disease in question is fairly uncommon. This

problem could partly be solved by asking for general consent (e.g. "I agree to participate in ICU-related research if I were unable to give informed consent before inclusion"). On the other hand, this approach raises a new ethical dilemma: is a "general consent" of this sort ethically valid if the patient is not informed about the details of these hypothetical studies?

Another way is to ask next of kin for consent until (if ever) the patient is able to make a decision. In recent decades, this approach has been commonly used in experimental studies on ICU-treated patients. One could question the validity of this type of consent, perhaps even more if the relative says no, especially if the research question is on interventions that already are a part of standard treatment in many institutions (e.g. when comparing different goal temperatures with targeted temperature management after cardiac arrest). This method was used in sub-study 2 in this doctoral project.

A third way is presumed consent and that the patient has the possibility to withdraw when (if ever) they are able make a decision. When using this approach, next of kin are often informed (but not asked for consent) that the patient is included in a study. An argument for this approach is that relatives generally do not have enough medical knowledge to make a well-informed decision regarding the research question, or the patient's attitude towards participation. On the other hand, using this method implies that no one needs to give consent in cases where patients die before they wake up, and according to some, this, the absence of any consent, is problematic. This method has been used in sub-study 4 in this doctoral project.

Observational studies (like sub-studies 1 and 3) are associated with somewhat different ethical considerations compared with experimental studies. When patients are not exposed to any experimental intervention *per se*, many argue that informed consent is less relevant, especially if the intervention is already part of standard treatment and the participants are somehow anonymized. This, of course, does not mean that consent is irrelevant.

Of prime importance, a person's right to self-determination should always be highly valued, and in most Swedish registers there is an opportunity for anyone to leave the register if they actively ask for it. Secondly, a great deal of personal data is sensitive and if misused the consequences can be devastating. Although many registers are anonymized, there are often possible ways of breaking that anonymization using identification keys. Furthermore, even if anonymization can be guaranteed at an individual level, collection of data without informed consent at a group level can also be problematic, for instance when it comes to ethnicity, sexual orientation, religion, political views etcetera.

In sub-studies 1 and 3 in this doctoral project we collected data from four Swedish registries: the SIR, the SRCR, the NPR and the CDR. These registries, like most others in Sweden, have collected patient information without individual informed consent. Instead, members of the public have received more general information that their patient data may be used for research purposes. The data is pseudo-anonymized (there is a code key), and in our studies the key is destroyed after three months. The results are based on group analysis of historical data and this has not affected the treatment that patients received. Thorough and well-motivated applications are needed in order to convince both the Swedish Ethical Review Authority and respective register-holders to allow collection and research on data from the Swedish registries. Although the individual patients did not benefit from participating in the studies there is some public benefit (after publication of the studies), which hopefully will outweigh the relatively small downsides for the participants.

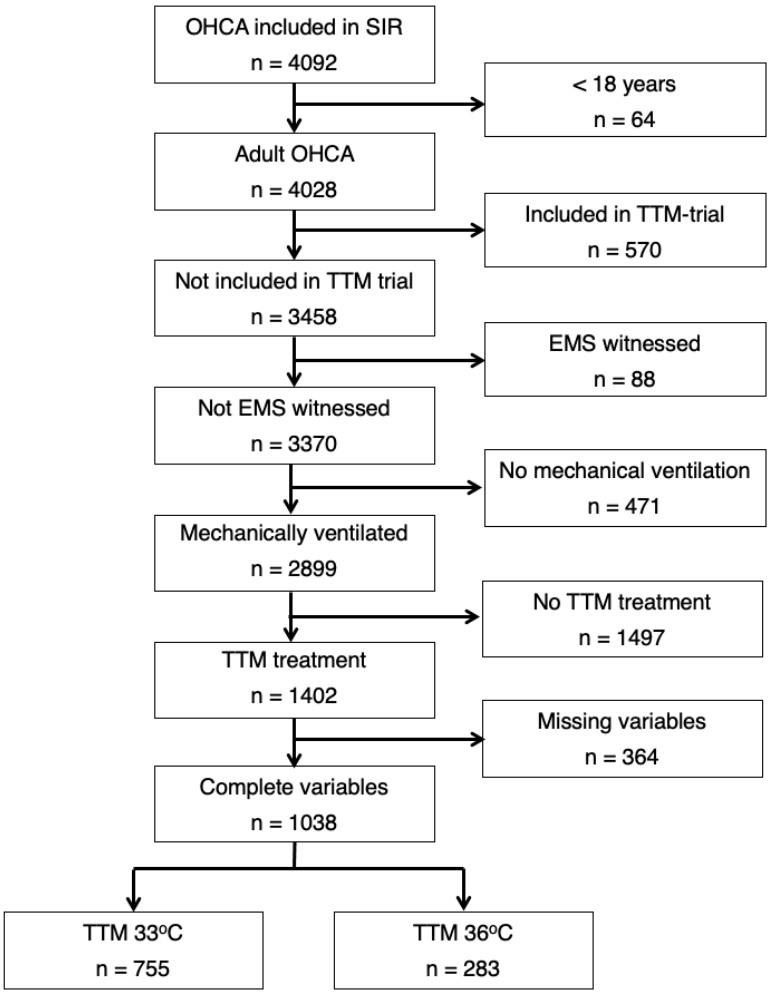
6 RESULTS

6.1. Study 1 –Changes in hypothermia management in OHCA patients after the publication of the TTM trial and its effect on survival

Study population

In total, 4092 OHCA patients were found in the SIR during the study period. After exclusion, 2899 patients were included in the analysis. Of these, 1402 (48%) were treated by means of TTM and after exclusion of patients with missing variables, 1038 patients (median age 66, 75% men, 65% shockable rhythm) were included in the survival analysis. Of these, 755 (73%) patients underwent TTM33°C and 283 (27%) patients underwent TTM36°C.

Figure 2. Study I. Flow of patients.

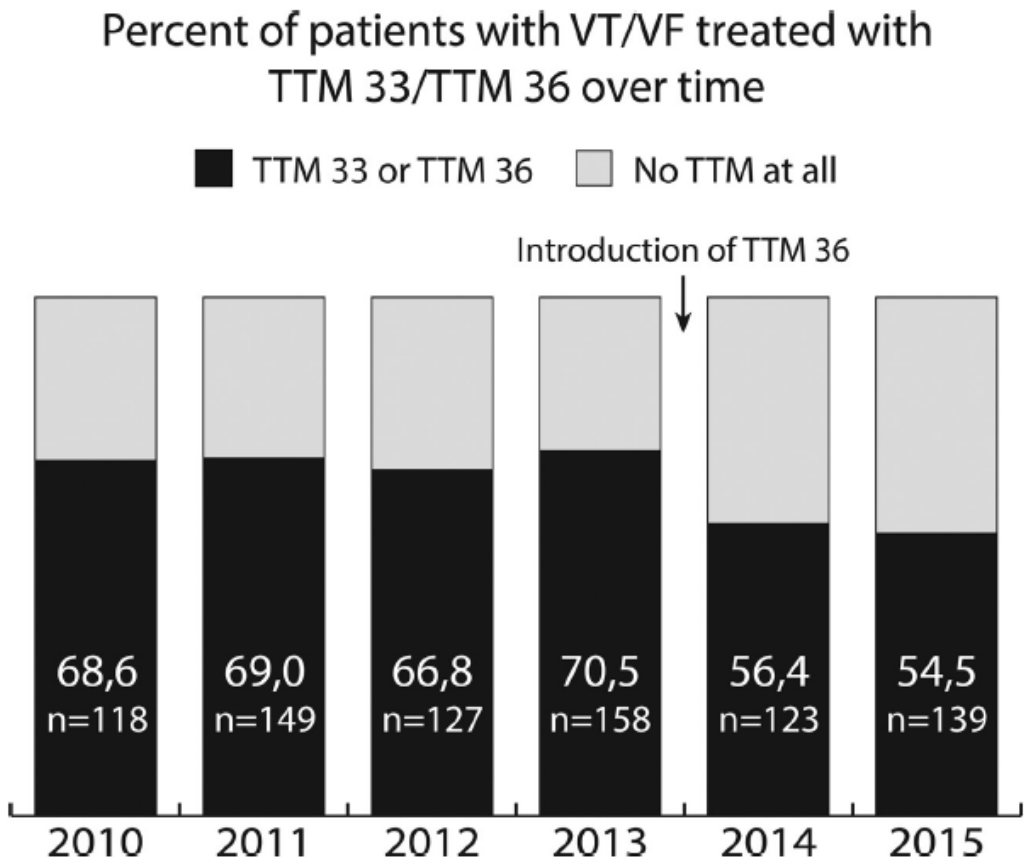


Abazi L, Awad A et al. Resuscitation.(154) Reprinted with permission from Elsevier.

Main results

After publication of the TTM trial, the majority of ICUs in Sweden changed targeted temperature management from 33 °C to 36 °C within a couple of months. At the end of the study period, all but one ICU (68/69) had changed. The proportion of patients receiving any TTM decreased significantly (p for trend <0.001) after publication of the TTM trial; from 70.5% to 54.5% in patients with initial shockable rhythm and from 41.3% to 26.7% in patients with non-shockable rhythm.

Figure 3. Proportion of patients with initial shockable rhythm treated with any TTM in Sweden between 2010 and 2015.



Abazi L, Awad A. et al.(154) Reprinted with permission from Elsevier.

There was no difference in 6-month survival between the TTM33°C group (47.2%) and the TTM36°C (47.3%) group (adjusted OR 1.12, 95% CI 0.8–1.56). After propensity score analysis, 52.7% in the TTM33°C group and 47.3% in the TTM36°C group were alive at six months. The difference was larger (in favour of the TTM33°C group) in patients with initial shockable rhythm, but this was not statistically significant.

6.2 Study 2 – The effect of early initiation of trans-nasal cooling on neurological outcome in OHCA patients

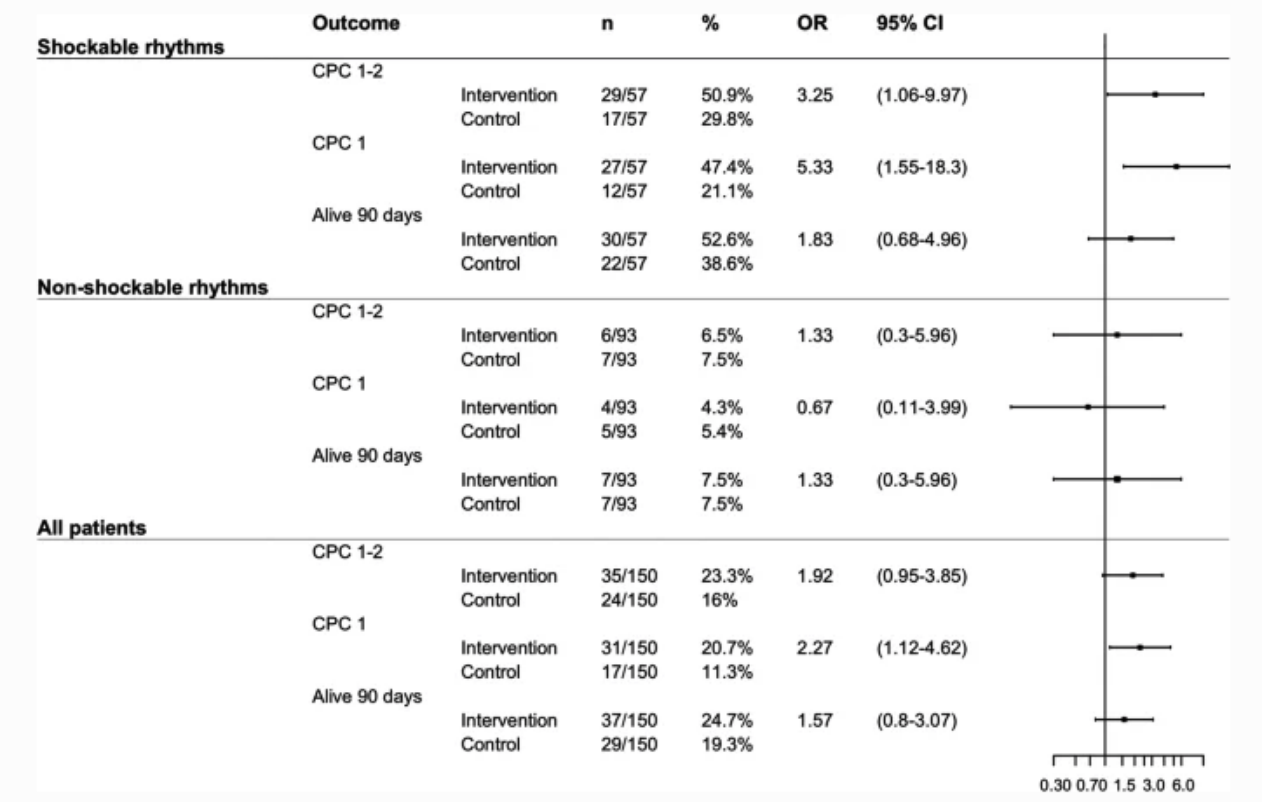
Study population

Of 677 patients included in the PRINCESS trial, 343 were randomized to intra-arrest trans-nasal evaporating cooling (TNEC). Among these, TNEC was initiated ≤20 minutes after collapse in 156 patients. Of these, 150 patients (intervention) were included in the propensity score matching analysis and compared (1:1) with 150 patients (control) in the group where cooling was initiated after hospital arrival. The median age was 65 years, 76% were men and 38% had initial shockable rhythm. The baseline characteristics were balanced in the two groups; e.g., in both groups the median time from collapse to randomization was 13 minutes.

Main results

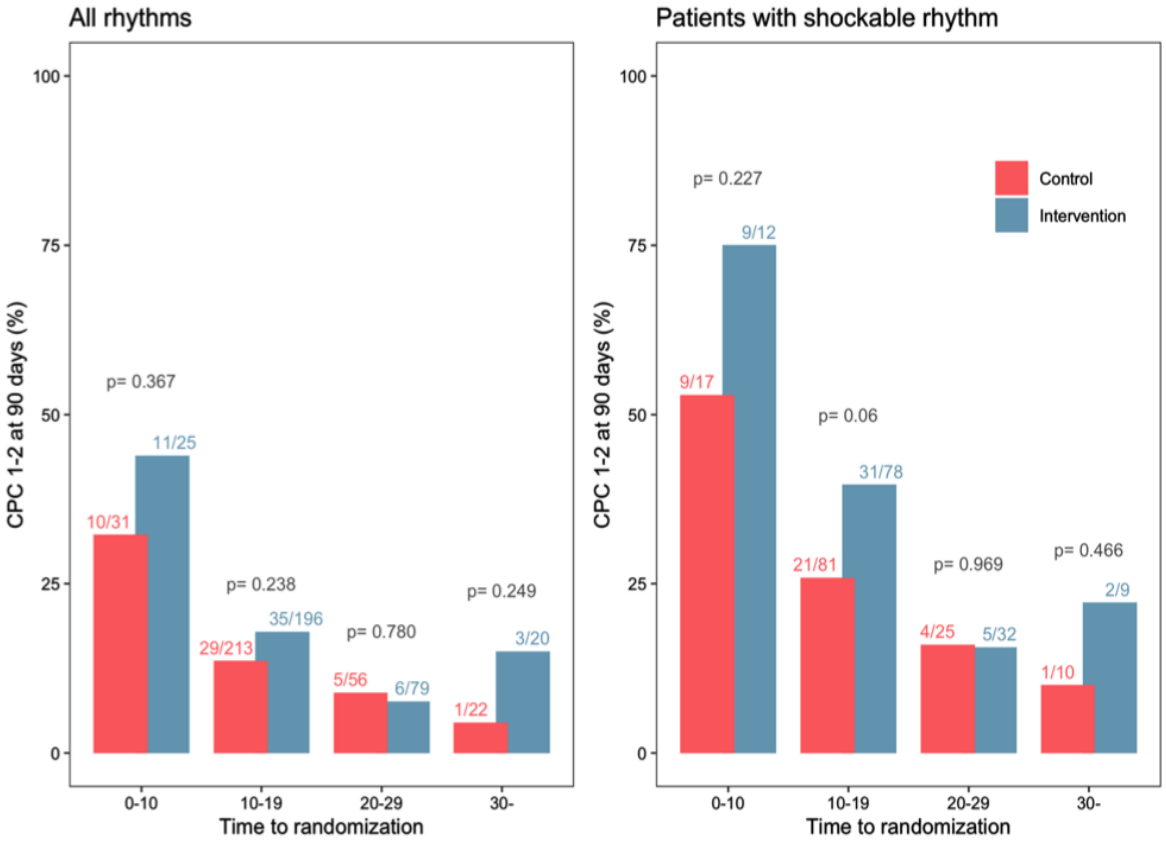
The time to goal temperature (<34 °C) was significantly shorter in the intra-arrest cooling group (median 95 vs. 157 minutes, p<0.001) while the rate of ROSC was similar in both groups: 51.3% in the intervention group vs. 48.6% in the control group (p=0.64). There was no significant difference in the primary outcome (CPC 1–2 at 90 days): 23.3% in the intervention group vs. 16% in the control group (OR 1.92, 95% CI 0.95–3.85). In the subgroup with an initial shockable rhythm, there was a significant difference: 50.9% in the intervention group vs. 29.8% in the control group (OR 3.25, 95% CI 1.06–9.97). The difference was greater as regards complete neurological recovery (defined as CPC 1): 47.4% in the intervention group vs. 21.1% in the control group (OR 5.33, 95% CI 1.55–18.3). In the subgroup with non-shockable rhythm there was no significant difference in any of the outcomes.

Figure 4. Primary and secondary outcomes after propensity score matching.



Awad A. et al. (155). Reprinted with permission from Springer.

Figure 5. Survival with CPC 1–2 at 90 days depending on time from randomization.



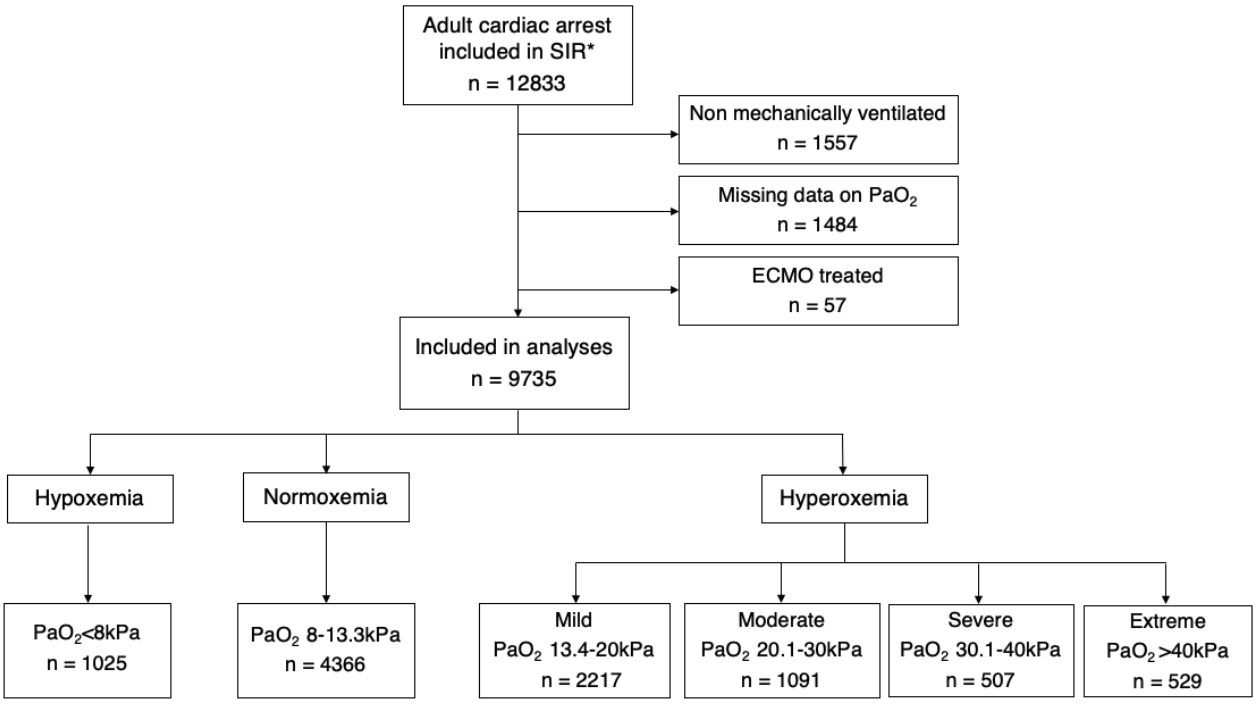
Awad A et al (155). Reprinted with permission from Springer.

6.3 Study 3 – Association between hyperoxemia after cardiac arrest and survival

Study population

In total, 12,833 cardiac-arrest patients were found in the SIR during the study period and 9735 (7733 OHCA and 5100 IHCA) patients were included in the analysis. Of these, 44.6% were hyperoxaemic, 44.8% were normoxaemic and 10.5% were hypoxaemic. Among patients with hyperoxaemia, 2217 were classified as mild hyperoxaemia, 1091 as moderate hyperoxaemia, 507 as severe hyperoxemia and 529 as extreme hyperoxemia.

Figure 6. Study III. Flow of patients.

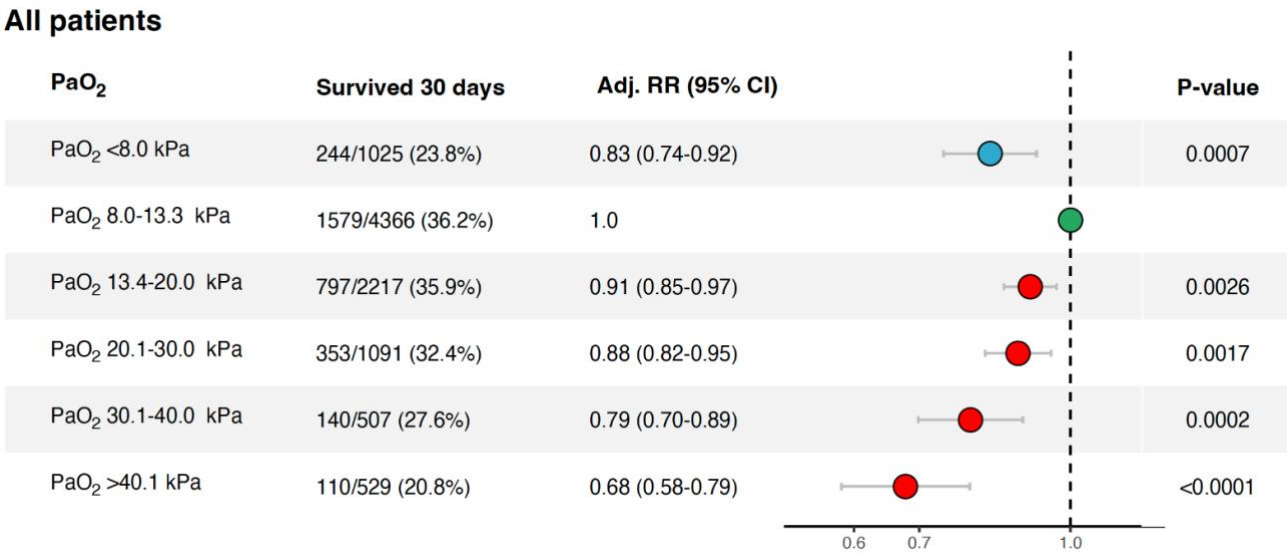


Awad et al (156).Reprinted with permission from Springer.

Main results

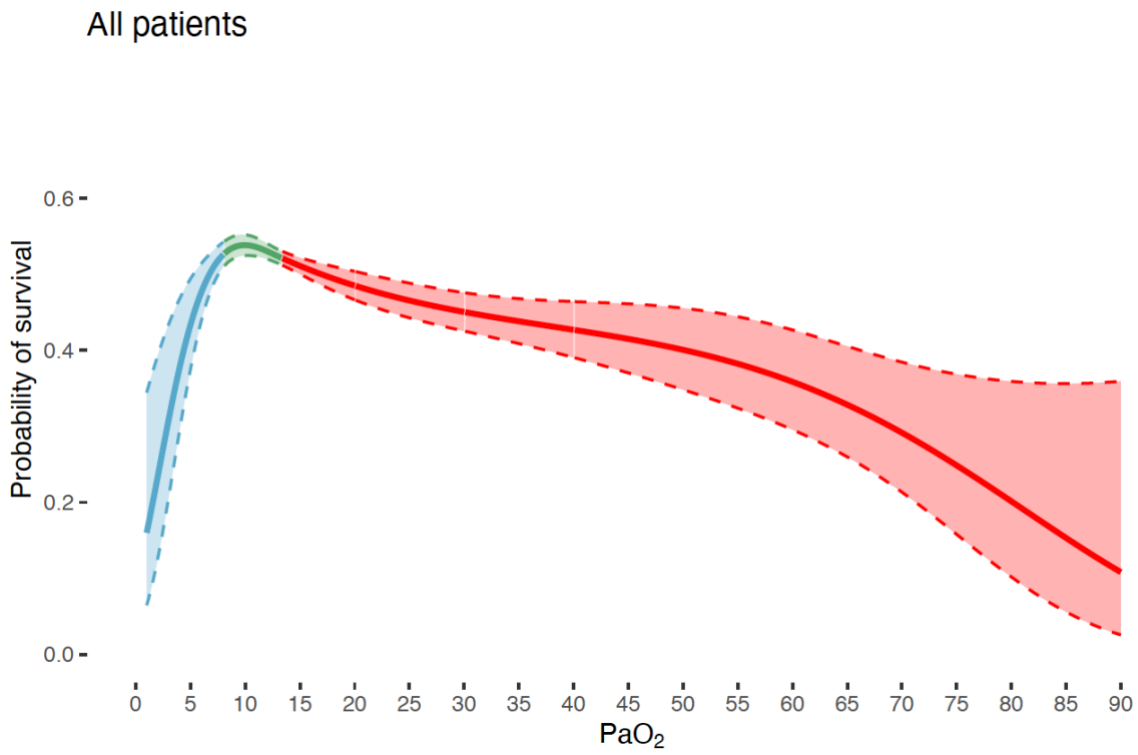
In the whole study population, the rates of 30-day survival were 32.2% in the hyperoxaemia group, 36.2% in the normoxemia group and 23.3% in the hypoxemia group. In patients with hyperoxemia, survival rates were successively lower with higher pO_2-levels. Compared with the normoxia group (reference group), the adjusted RRs as regards 30-day survival were: mild hyperoxemia, 0.91 (95% CI 0.85–0.97), moderate hyperoxaemia, 0.88 (95% CI 0.82–0.95), severe hyperoxemia 0.79 (95% CI 0.7–0.89), and extreme hyperoxemia, 0.68 (95% CI 0.58–0.79). The adjusted RR for the hypoxaemia group, compared with the normoxemia group, was 0.83 (95% CI 0.74–0.92). A similar pattern was seen in both OHCA and IHCA patients.

Figure 7. Adjusted relative risk (RR) as regards 30-day survival in different O_2 groups compared with the normoxaemia group.



Adjusted for sex, age, witnessed status, bystander CPR, initial rhythm, Charlson comorbidity index, SAPS-3 score, response time, location. Reprinted with permission from Springer, Awad et al (156).

Figure 8. Adjusted predicted 30-day survival with PaO_2 (kPa) as a continuous variable.



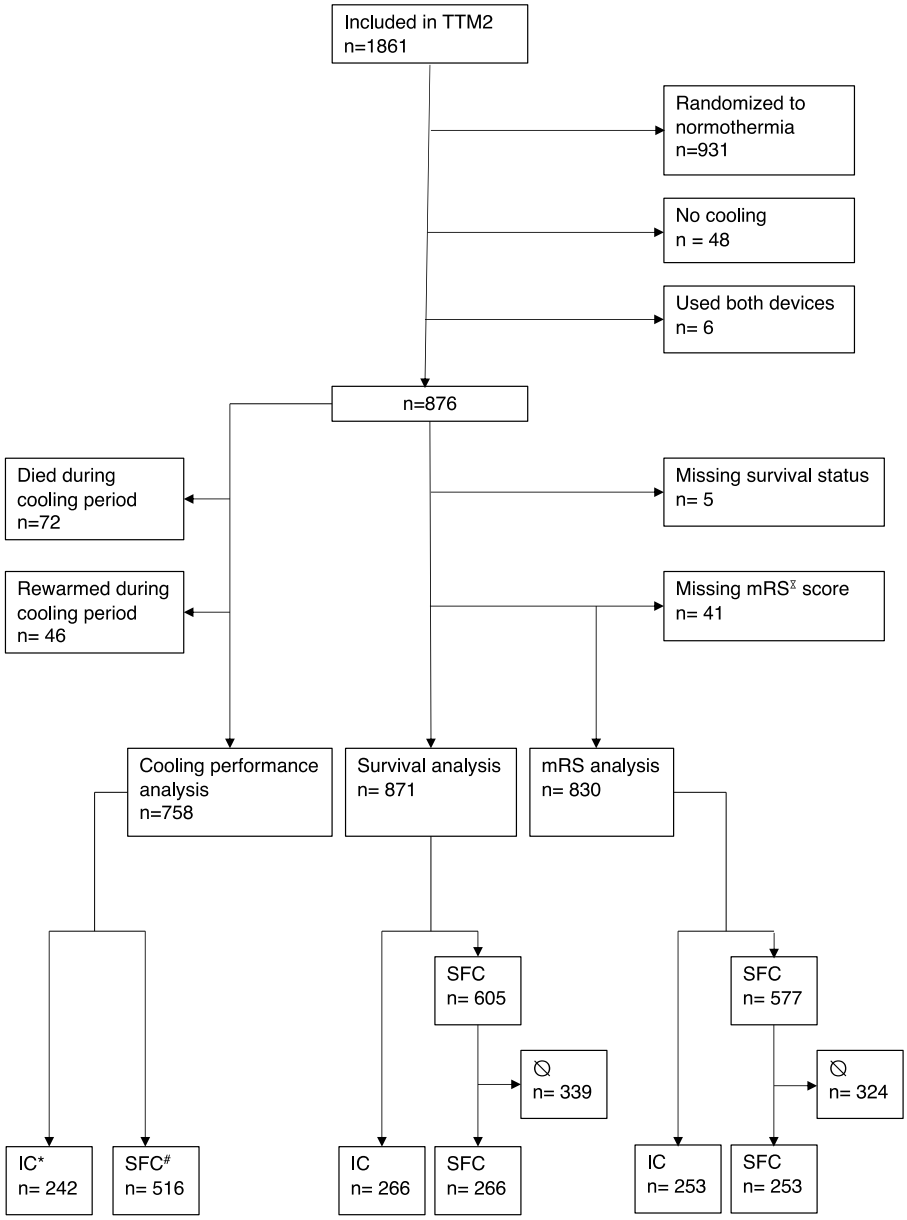
Adjusted for sex, age, witnessed status, bystander CPR, initial rhythm, Charlson comorbidity index, SAPS-3 score, response time, location. Dotted lines indicate 95% confidence intervals. Reprinted with permission from Springer, Awad et al (156).

6.4 Study 4 – Cooling performance and neurological outscomes in OHCA patients receiving intravascular versus surface cooling

Study population

Of 1900 patients included in the TTM2 trial, 925 were randomized to TTM33°C, of which 876 were included in this sub-study. Of those, 30% received intravascular cooling (IC) and 70% received surface cooling (SF). Twenty-five (41%) of the hospitals used IC in at least one patient and 53 (87%) of the hospitals used SFC in at least one patient. Most centres that had both cooling methods had a clear tendency to use one or the other of them. The mean age of the patients was 64; 80% were men and 74% had an initial shockable rhythm. Most baseline characteristics were similar in the two groups.

Figure 9. Study IV. Flow of patients.



⃠ Not included in propensity score matching.

Patient outcomes and cooling precision

At six months, after propensity score matching, 134/253 (53%) patients in the IC group vs. 107/253 (43.1%) patients in the SFC group were alive, with mRS scores of 0–3 (OR 1.5, 95% CI 1.03–2.48), and 152/266 (57.1%) in the IC group vs. 134/266 (50.4%) in the SFC group were alive (OR 1.3, 95% CI 0.93–1.81).

A larger proportion of patients in the IC group vs. the SF group reached targeted temperature (≤33.5 °C) within four hours from randomization (66.5% vs. 49.6%, p<0.001) and within eight hours (93% vs. 87%, p<0.024). The median time to reach ≤33.5°C was approximately three hours in the IC group vs. 4 hours in the SFC group.

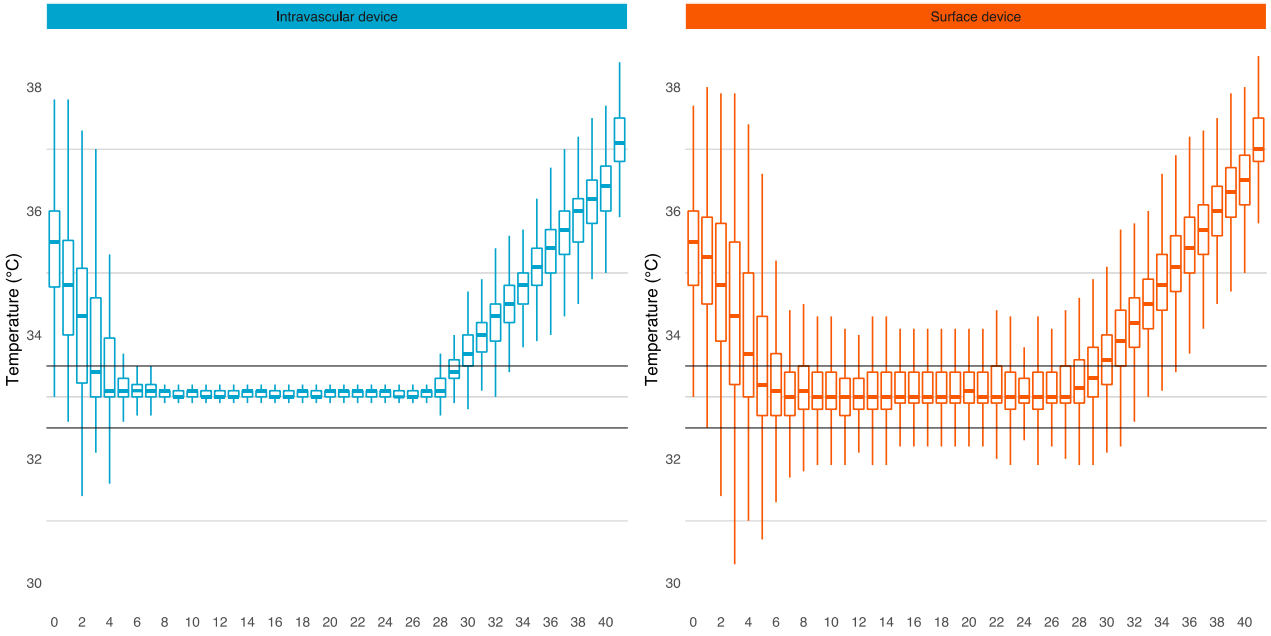
Temperature variability was significantly higher in the SFC group; more patients in the SFC group had at least one episode of overcooling (70.8% vs. 20.9%, p<0.001) and more patients in the SFC group has at least episode of post-TTM fever (21.5% vs. 8.7%).

Figure 10. Outcomes and cooling precision for intravascular vs surface devices.

	Intravascular cooling	**Surface device cooling**	**p value**
Patient centred outcomes			
Survival with mRS* 0-3 at 180 days after propensity score matching#, no. (%)	134 (53.1) OR 1.5 (95% CI 1.05-2.15)	107 (43.1)	0.03
Survival at 180 days after propensity score matching#, no (%)	152 (57.1) OR 1.3 (95% CI 0.93-1.81	134 (50.4)	0.13
Cooling performance			
Number of patients reaching target temperature within 4 hours from randomization (%)	161 (66.5)	256 (49.6)	<0.001
Number of patients reaching target temperature within 8 hours from randomization	225 (93.0)	449 (87.0)	0.024
Number of patients with at least one episode of overcooling (%)	52 (20.9)	390 (70.8)	<0.001
Proportion of temperature measurements out of range (%)	19.7	43.4	<0.001
Mean temperature deviation among measurements out of range (^{0}C)	0.9	1.0	<0.001
Cumulative temperature deviation (proportion x mean deviation)	17.8	43.6	<0.001
Number of patients with at least one episode of post-TTM fever (%)	21 (8.7)	111 (21.5)	<0.001

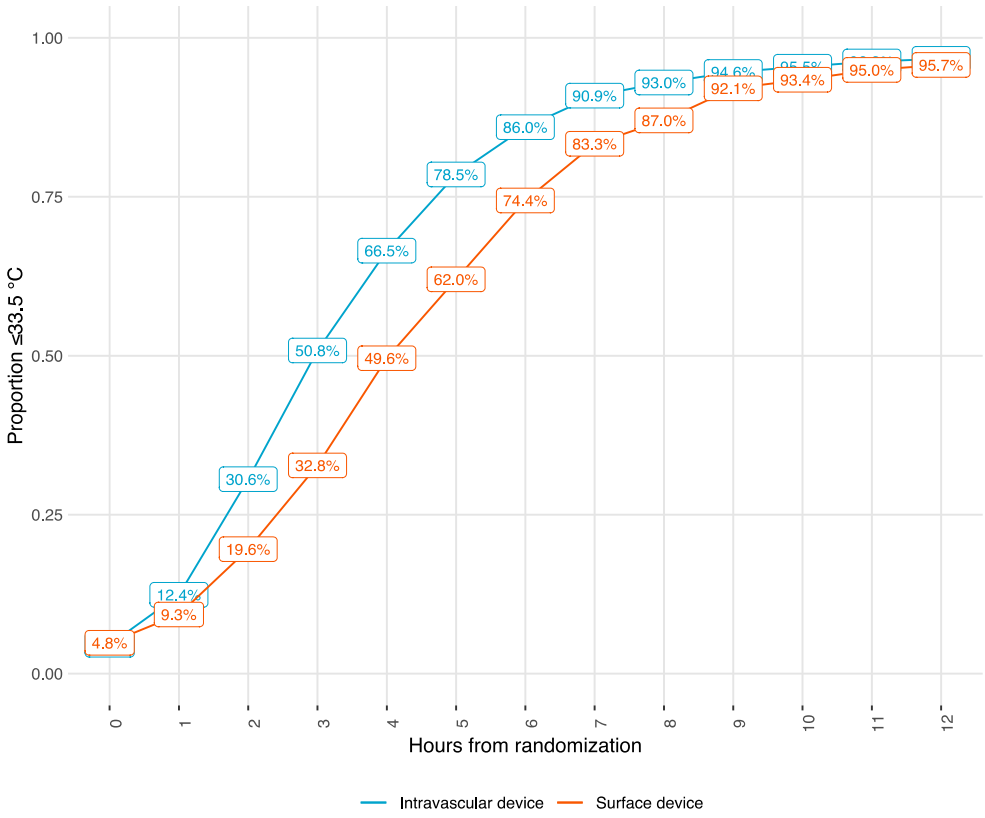
*Modified Rankin Scale 0-3 #Propensity score matching including age, sex, initial rhythm, frailty score, time to ROSC, witnessed status, bystander CPR, location, Charlson comorbidity score

Figure 11. Patient temperatures over the intervention period.



Median and interquartile temperatures in intravascular (blue) and surface (red) cooling groups during the intervention period. Hours from randomization on the x-axis

Figure 12. Proportions of patients reaching target temperature within 12 hours in the IC versus the SFC group.



7 DISCUSSION

7.1 Maind findings

The fact remains: the prognosis after OHCA is still poor and the evidence for interventions in the post-resuscitation phase remains low. However, the main finding in this work is that there are several aspects in post-resuscitation care that may influence the outcomes, especially neurological outcomes. We have demonstrated that:

1. Early initation (<20 minutes from collapse) of intra-arrest TNEC, compared with cooling started after hospital arrival, in patients with shockable rhythm, is associated with better neurological outcome.
2. Intravascular cooling, compared with surface cooling, in patients in whom targeting is 33 °C after cardiac arrest is associated with better cooling performance and better neurological outcome
3. Both hyperoxemia (in a potential dose-dependent way) and hypoxaemia, compared with normoxemia, early after cardiac arrest, is associated with worse neurological outcome.

Since all these findings come from registries or sub-analyses of RCTs, and which all are observational studies, we can only draw conclusions about associations and *not* about causality. As with all observational studies, biases and residual confounding cannot be completely excluded. Nevertheless, these findings raise important questions and can be stepping stones to future studies.

Furthermore, we have demonstrated that after publication of the TTM trial, most hospitals in Sweden almost immediately changed targeted temperature (from 33 °C to 36 °C) in OHCA patients receiving therapeutic hypothermia, that the proportion of OHCA patients receiving any TTM decreased, and that 6 month-survival was not affected in patients undergoing TTM.

7.2 Why is it difficult to find evidence for interventions in the post resuscitation phase after cardiac arrest?

"Time is brain" in cardiac arrest. As discussed above, the detrimental pathophysiology after cardiac arrest is very time-dependent and every minute of hypoperfusion matters. After a certain period of ischaemia, brain cells, not least neurons, can be beyond saving, and in such situations all interventions may be ineffective. This could possibly explain why early initiation of TNEC was associated with better neurological outcome in VT/VF patients (with probably a shorter period of hypoperfusion), versus PEA/asystole patients, in Study II. On the other hand, in the HYPERION trial, which included only PEA/asystole patients, TTM 33 °C led to higher rates of survival with CPC scores of 1–2

(115). However, it should be mentioned that this was largely driven by the IHCA group, in which systemic cooling can be started earlier than in OHCA patients.

The challenge is to pinpoint the group of patients that have enough neurons that can be saved in order for them to survive with favourable neurological function, without "overtreating" too many patients. To save as many patients as possible, we will inevitably treat some beyond saving and this overtreatment comes with ethical and health economic dilemmas.

A similar dilemma arises in a research context when choosing inclusion criteria. Broad inclusion criteria (e.g., including cardiac arrests with all initial rhythms and including non-witnessed cardiac arrests) increases the study inclusion rate, leads to a more heterogeneous study population and potentially greater generalizability. On the other hand, if an effect is found in only one subgroup (e.g., patients with VT/VF, early intra-arrest cooling or intravascular cooling), this effect may be diluted by another subgroup showing no effect or even harm (e.g. patients with PEA/asystole, late initiation of cooling or surface cooling) and the final result may not be significant. The question is whether or not it is realistic to find significant evidence for an intervention in the post-resuscitation phase in an unselected and heterogeneous cardiac-arrest population. It partly depends on what we define as a clinically significant difference and how large can we make clinical trials, both from an ethical and economic standpoint. Nevertheless, it is a consideration that those undertaking future studies must take into account.

7.3 Similarities between cardiac arrest trials and ICU trials in general

In general, resuscitated cardiac-arrest patients are treated in ICUs. Difficulties to find evidence-based interventions that increase survival are not unique to cardiac-arrest patients, and represent a general problem for almost all ICU-related treatments. Despite a large number of conducted trials, very few "positive" ICU RCTs have been carried out when using survival as the primary outcome. ICU patients are complex, heterogeneous and often suffer from multi-organ failure, which makes it difficult to find interventions which on their own can affect survival. Furthermore, prognoses for ICU patients can differ greatly, which has implications as regards trial results. Some ICU patients will survive regardless of trial intervention, while others will die despite intervention. If these patients are included in analysis, this will dilute the observed effect on the group that may benefit from the intervention in question. The challenge is to identify which patients are hanging in balance and may benefit from the intervention in question, both in clinical practice and in studies.

7.4 Should we use survival or neurological outcome as the primary outcome in cardiac arrest studies?

There are several arguments for having survival as the primary outcome when studying cardiac-arrest patients. First, it is a robust and arguably the most objective patient-centred outcome. Second, it is relatively easy to follow up. Third, it is easy to use when comparing different studies. Although survival will always be an important outcome in cardiac arrest, it is not always need the best one. An alternative is to use neurological status as the primary outcome.

The brain is the most vulnerable organ in cases of cardiac arrest, and several of the interventions (e.g., therapeutic hypothermia) tested in the post-resuscitation phase have primarily been aimed at protecting the brain. This could explain why RCTs demonstrating a positive effect of therapeutic hypothermia have done so primarily in connection with neurological outcome and not survival (112, 113, 115). The same pattern can be seen in Studies II–IV in this thesis. Therefore, one could argue that neurological status should be the primary outcome in most cardiac-arrest studies, but this brings its own challenges, e.g., to define "good neurological outcome".

7.5 What is good neurological outcome?

There is no clear answer to this question. As mentioned previously, for many years a CPC score of 1–2 has been used as a definition of good neurological outcome after cardiac arrest, but this has been criticised for its limited ability to differentiate between mild and moderate disability. Therefore, the mRS (with 0–3 defined as good neurological outcome) has been increasingly used over the years and is also recommended in the latest Utstein template (59). A limitation of the mRS is that it was primarily developed for evaluating neurological status after stroke, and has been associated with substantial inter-rater variability (157). There are new neurological tests on the horizon, e.g., the Glasgow Outcome Scale-Extended (GOS-E), but there will always be a risk of subjectivity and inter-rater variability when it comes to neurological scales. Furthermore, different patients will estimate "good" neurological status in different ways. One patient with CPC 2 may rate it as high quality of life, while another patient with the same score may rate it as low. Therefore, it may be of value to use "complete" neurological recovery (e.g., CPC 1 or mRS 0–1) as an outcome measure in future studies. Of note, in the PRINCESS trial and in Study II, the difference between groups (in favour of the intra-arrest cooling group) was larger in connection with CPC 1 than CPC 1–2. No matter which scales or definitions will be used in future studies, it is of importance to take these questions into consideration, and if possible, to involve patient representatives when designing studies.

7.6 Are there risks in adopting results from new studies immediately?

In Study I we demonstrated that most Swedish hospitals changed targeted temperature (33 °C to 36 °C) in OHCA patients receiving TTM only months after publication (November 2013) of the TTM trial, even before international guidelines were changed in 2015. In the 2015 guidelines, targeted temperature was changed from 32–34 °C to 32–36 °C, but the strength of the recommendation to use TTM after OHCA was unchanged; strong recommendation for patients with VT/VF and weak recommendation for patients with PEA/asystole (72). Despite this, the proportion of patients receiving any TTM decreased in 2014–2016 (among both VT/VF and PEA/asystole patients), which we interpret as lower adherence to guidelines. It is unknown if this trend was a coincidence or a consequence of the TTM trial. Perhaps some interpreted TTM 36 °C as "no intervention"? If so, it would be a misinterpretation of the TTM trial (the TTM 36 °C group were actively cooled). Fortunately enough, this did not have any significant impact on six-month survival in our cohort (158). On the other hand, another "before and after study" demonstrated increased frequency of fever and slightly worse survival rates in OHCA patients after publication the TTM trial (159). Even though the more recent TTM2 trial did not demonstrate any difference between TTM 33 °C vs. normothermia (<37.8 °C), this information was not available during the period 2014–2016.

7.7 Should we give up therapeutic hypothermia after cardiac arrest?

After publication of the TTM2 trial one may ask: should we give up therapeutic hypothermia after cardiac arrest? Why expose patients to hypothermia, with its costs and potential side-effects, when normothermia seems to be just as good? The answer to this should be both yes and no. If it refers to the way most hospitals have used hypothermia during the last few decades, e.g., cooling initiated several hours after ROSC in relatively unselected cardiac arrest patients, the answer is probably yes. However, as seen in Studies II and IV in this thesis, for example, there are several aspects of cooling after cardiac arrest which should be further investigated before we can come to a conclusion.

To date, the TTM2 trial was a well-conducted and by far the largest (n=1900) RCT concerning therapeutic hypothermia after OHCA. It was a pragmatic study including all rhythms, allowing randomization up to three hours after arrest, and it was up to every participating centre to choose the cooling method. In the hypothermia group, the median time from arrest to randomization was 136 minutes and the median time from randomization to <34 °C was three hours. These cooling rates are similar to those in most previous trials (56, 115, 160, 161) and probably reflect clinical practice in centres with experience of hypothermia. It leaves us with the question: is it possible and/or of value to initiate cooling and reach hypothermia faster?

From both animal studies and a physiological standpoint it is reasonable to believe that the earlier cooling is initiated (and hypothermia reached), the better. However, this has been difficult to demonstrate in clinical studies. In the PRINCESS trial, there was no statistically significant difference in main outcomes between initiation of intra-arrest TNEC vs. systemic cooling started after hospital arrival in the whole study population. However, as we demonstrated in Study II, there was an association between early initiation (<20 minutes) of TNEC in patients with initial VF/VT and improved neurological outcome. Although the results from this sub-analysis should be interpreted with caution, it is hypothesis generating and motivating future intra-arrest cooling studies.

Moreover, there are no large RCTs in which different advanced cooling methods with temperature feed-back loops have been compared. According to the results of meta-analyses (162-164) and Study IV, intravenous cooling, compared with surface cooling, is associated with better neurological outcome. Whether this difference is causal and whether this potential effect is large enough to motivate therapeutic hypothermia vs. normothermia is up to future studies to answer.

Furthermore, therapeutic hypothermia after IHCA is not well studied. To date, there is only one RCT concerning therapeutic hypothermia focused on IHCA. This study (the HACA in-hospital trial) could not demonstrate any significant difference in outcomes between the hypothermia and normothermia group. On the other hand, in the HYPERION trial, including both OHCA and IHCA patients, the observed difference in the primary outcome (CPC 1–2) was largely driven by the IHCA group. Although this was only a subgroup analysis, it warrants further studies. Since IHCA patients are already in hospital, there is a potential to initiate systemic/advance cooling more rapidly than in OHCA patients.

In addition to the above, there are further aspects of therapeutic hypothermia after cardiac arrest that have not been fully explored (e.g., optimal duration of hypothermia), and before we give up cooling, it should be tested under optimal conditions among different subgroups of patients.

7.8 Therapeutic hypothermia is difficult to blind; is it a problem?

Since most cardiac-arrest patients receiving therapeutic hypothermia are unconscious, it is usually not difficult to blind them to the intervention. Furthermore, in most RCTs on the subject, the people assessing outcomes and the statisticians have been unaware of the trial-group assignment. However, it is very difficult to blind the health professionals involved in patient care to the intervention. First, it is almost impossible to blind the patient's body temperature. Second, it is practically impossible to blind the health professionals initiating cooling intervention. Third, even if the person initiating the intervention is not one of the health professionals taking care of the patients, it is usually

difficult to hide the cooling method (e.g., ice packs, surface cooling or intravenous cooling). This introduces a risk of performance bias. For example, patients enrolled in prehospital intervention may receive longer CPR compared with the control group, or patients receiving systemic hypothermia may receive better/worse ICU-care compared with those in the control group. Biased ICU-care can be particularly problematic in cardiac-arrest patients, since early withdrawal of life-supporting therapies is a common cause of death after cardiac arrest (165, 166). Since most patients in whom life support is withdrawn will die, there is a risk of self-fulfilling prophecy (166). Furthermore, it can be challenging to blind the intervention to relatives (e.g., when visiting the ICU) for the same reasons as for health professionals, and this may introduce a bias if the relatives reveal this to the patient (if they wake up) or are involved in the neurological follow-up.

7.9 When does intensive care after cardiac arrest start?

The short answer is: immediately after collapse. There is no universal definition of intensive care, but usually it is advanced healthcare supplied in the ICU after hospital arrival. However, in a time-critical condition such as cardiac arrest, every minute counts and advanced care must be provided immediately. This may include high-quality CPR, defibrillation, airway management, ventilation, administration of oxygen, administration of drugs, therapeutic hypothermia, blood-pressure targets, extracorporeal membrane oxygenation (ECMO) and percutaneous coronary intervention (PCI). For an OHCA patient, it can take several hours from collapse to ICU arrival (due to transport, time in the emergency room, X-ray, PCI etc.) and suboptimal care during this period could affect the pathophysiological processes. This is highlighted by the results of Studies II and III, which to a large extent focus on the period before ICU-arrival.

7.10 Why do results from observational studies vs. randomized clinical trials on hyperoxaemia after cardiac arrest differ?

As mentioned previously, observational studies on hyperoxemia after cardiac arrest are heterogeneous and show divergent results. In most of them, hyperoxaemia has been defined as PaO_2 >40 kPa, and according to pooled results in a meta-analysis (129), hyperoxaemia, compared with normoxemia, seems to be harmful. In the few RCTs specifically concerned with the study of oxygen levels after cardiac arrest (135, 136), hyperoxaemia was not harmful. Of note, the "liberal" oxygen groups had PaO_2 levels of around 15 kPa, which is significantly lower than the definition of hyperoxaemia used in most observational studies. In Study III in this thesis, we demonstrated that hyperoxemia, compared with normoxemia, was associated with worse 30-day survival in a dose-dependent way. We did not find a definitive cut-off point for worse outcomes, but it seems to be somewhere around PaO_2 >20 kPa, this also being above the levels seen in the RCTs. Furthermore, there is always a risk of the Hawthorne effect (i.e.,

modification of behaviour in response of being observed) in RCTs, which in general can contribute to differences seen in observational studies vs. RCTs (167).

7.11 Is it ethical to randomize resuscitated cardiac arrest patients to more extreme hyperoxemia levels?

Although based on low-grade evidence, consecutive ERC guidelines have recommended that hyperoxaemia should be avoided in cardiac-arrest patients with ROSC (3, 72). The dose-response association seen in Study III supports these guidelines and although previous studies have shown mixed results, there is not a single cardiac-arrest study suggesting that more extreme PaO_2 levels are beneficial. Therefore, the question is: would it be reasonable to randomize patients to more extreme PaO_2 levels (e.g., >20 kPa)? Probably not. It would be hard to initiate such a study from an ethical standpoint. Instead, this is probably a question where we must settle for well-conducted observational studies.

7.12 Future perspectives

In summary, we still lack convincing evidence-based interventions for cardiac-arrest patients in the post-resuscitative phase. Does this mean that it does not matter how we treat the patients in this critical phase? Of course not. As Dr. Carl Sagan said, "Absence of evidence is not evidence of absence".

We as a scientific community must continue to develop the way we conduct our studies, and, as demonstrated in this thesis, there are several aspects of post-resuscitative care that may influence the outcome of the patient and are worth following up. Some of the knowledge gaps in care after cardiac arrest that ought to be addressed in future studies are:

- Is early intra-arrest TNEC in VT/VF patients neuroprotective?
- Is intravasular cooling, compared with surface cooling, neuroprotective?
- What is the optimal ventilation and oxygenation strategy after ROSC?
- What is the optimal blood-pressure target after ROSC?
- Does the duration of therapeutic hypothermia matter?
- Is fever after cardiac arrest harmful?
- Is intra-arrest ECMO benificial for some subgroups of patients?

8 CONCLUSIONS

Study I

After publication of the TTM trial, most Swedish hospitals almost immediately changed targeted temperature (from 33 ^{O}C to 36 ^{O}C) in resuscitated OHCA patients. The proportion of patients that received any TTM decreased, and this was not associated with any change in six-month survival in patients who did undergo TTM.

Study II

In the whole study population, early (<20 minutes) initiation of intra-arrest TNEC, compared with systemic cooling started after hospital arrival, was not associated with improved neurological outcome. In the subgroup of patients with initial shockable rhythms, early intra-arrest TNEC was associated with improved neurological outcome.

Study III

In this nationwide cohort study with resuscitated OHCA patients, hyperoxaemia at ICU admission, compared with normoxaemia, was associated with worse 30-day survival. The association was stronger in connection with higher PaO_2 levels.

Study IV

In this sub-study of the TTM2 trial, including resuscitated OHCA patients who had undergone TTM33^{O}C, intravascular cooling, compared with surface cooling, was associated with better cooling performance and improved neurological outcome at six months.

9 SAMMANFATTNING PÅ SVENSKA

Årligen drabbas ca 6000 personer i Sverige av hjärtstopp utanför sjukhus (*eng* out-of-hospital cardiac arrest, *OHCA*). Trots att överlevnaden ökat genom åren är prognosen fortfarande dålig, endast ca 10% överlever. Utöver att starta hjärtlungräddning och använda hjärtstartare så tidigt som möjligt har det varit svårt att hitta evidensbaserade behandlingar som ökar överlevnaden efter hjärtstopp. Syftet med denna avhandling var att studera olika behandlingsalternativ i vården efter hjärtstopp.

Tre av studierna i denna avhandling har utforskat olika aspekter av kylbehandling (terapeutisk hypotermi), som ges på intensivvårdsavdelning (IVA) och som i flera decennium varit en vanlig behandling efter hjärtstopp. Hjärnskador är den vanligaste dödsorsaken efter hjärtstopp och huvudsyftet med kylbehandlingen är att försöka minska hjärnskadorna.

Till en början kyldes alla patienter till 33°C men 2013 publicerades en internationell studie (*TTM*-studien) som inte kunde påvisa någon skillnad i patientöverlevnad då man jämförde 33°C mot 36°C. I denna avhandlings första studie undersökte vi vilka konsekvenser TTM-studien fick för OHCA patienter i Sverige. Vi fann att andelen patienter som fick hypotermibehandling efter hjärtstopp minskade de första åren efter publikationen (vilket stred mot de då aktuella riktlinjerna) men att detta inte ledde till någon signifikant skillnad i patientöverlevnad.

I denna avhandlings andra studie, som är en subanalys till den internationella *PRINCESS*-studien, undersökte vi hur det gick för OHCA patienter som fick tidig kylbehandling via näshålan (startat av ambulanspersonal inom 20 minuter från hjärtstoppet) jämfört med OHCA patienter där man startade kylbehandling på sjukhuset. Vi fann att bland patienter med ”defibrillerbar” första rytm (dvs en hjärtrytm som kan behandlas med hjärtstartare) var tidig kylbehandling via näshålan associerat med bättre neurologiskt patientutfall.

I en annan studie, som är en subanalys till den internationella *TTM2*-studien, ville vi jämföra två olika kylmetoder: intravenös kylning kontra ytkylning (via kyldräkt). Nästan 900 OHCA patienter som hade överlevt hjärtstoppet och som skulle kylas till 33°C ingick i vår studie. Vi fann att intravenös kylning presterade bättre (snabbare kylning och mindre temperaturvariation) och var associerat med bättre neurologiskt patientutfall.

Syrgas är en hörnsten i hjärtstoppsbehandlingen och det är välkänt att syrebrist är skadligt. Vi har i en studie undersökt om för mycket syrgas (hyperoxemi) efter hjärtstopp kan vara skadligt. Genom att koppla ihop data från fyra olika svenska register för åren 2010-2021 har vi kunnat undersöka nästan 10000 hjärtstoppspatienter som återupplivats och vårdats på IVA. Vi fann att hyperoxemi efter hjärtstopp är kopplat till sämre överlevnad och detta var tydligast för patienterna med högst syrgashalt i blodet.

10 ACKNOWLEDGEMENTS

I would like to express my deepest gratitude to everyone who supported me during my time as a PhD student and who made this thesis possible; in particular:

Per Nordberg, my main supervisor. You have been a great mentor, role model and friend over the years. When we first met about 10 years ago, you inspired be to become a cardiologist and later to start doing research. I have great respect for your calmness, your kindness and your great knowledge, both in terms of research and clinical work. You have been a support when I needed it and allowed me to gradually grow and take on more responsibility. I can´t think of a better supervisor and I´m eternally grateful for our collaboration!

Jens Olson, my co-supervisor. The smartest doctor I know and the person I most often call when I need help with a cardiology-related question. I appreciate our discussions and your wise input into our studies.

Eva Joelsson Alm, my co-supervisor. Thanks for your wisdom and for your broad knowledge in scientific thinking, not least for registry-based research. It´s been a pleasure to have you in our team.

Mattias Ringh, my co-supervisor. A very skilled and pragmatic clinician and researcher. I appreciate your ability to highlight the essentials and your sense of humour.

Martin Jonsson, for your invaluable statistical and analytical support. This would not have been possible without your help. I really appreciate your perspective on research (and football) and I learn something new every time we have a discussion.

To all my fellow researchers at the Centre for Resuscitation Science, not least *Jacob Hollenberg* (head of the Centre), *Leif Svensson* (founder of the Centre) and Mårten Rosenqvist (founder of the Centre). Many years of hard work, determination and enthusiasm have laid the foundation for this fantastic research group, something many of us are grateful for.

To *Per Tornvall* (clinical research leader and prefect at KI SöS), for your generous support and for creating a good research atmosphere. *Robin Hofmann* (co-author and clinical research leader at the Cardiology department), for your encouraging words and for being so dedicated.

To all my colleagues at the Cardiology, Anaesthesiology and ICU departments. You (together with our patients) are the reason why Södersjukhuset is the world's best workplace! Special thanks go to my senior colleagues *Nikolas Lambiris* and *Brian Cleaver,* for all the supervision, wisdom and for being my role models as clinical doctors.

To my bosses (*Raffaele Scorza, Eva Stråât, Eva Sjöblom Printz, Annette Grip, Marie Fahlgren-Brodin,, Marco Schuster, Emma Jerkegren Olsson* and *Stephan Serenius*) over the years, for being so supportive and making it possible to combine my clinical work with research.

Emma Blick Nordqvist, *Johanna Kämpe* and *Erik Nyberg Bååth*, for your positive energy in general and for your invaluable help with the dissertation party (that is, if I pass).

To all the research nurses, especially *Mia Henning*, *Anna-Sofia (Fia) Hallberg Börjesson* and *Malin Hedberg*.

To secretaries *Marie Strand, Anne-Lie Larsson, Anette Boban, Åsa Sthén, Patrizia Pierazzi Engvall* and *Mi-Ri Yu*. You must be tired of all my questions and e-mails, but I´m very grateful for your tireless support.

My dear friends *Niki Radros*, *Jari Radros, Kasra Vali, Emma Lindstöm, Svava Steiner* and *Christian Tranchell*. For all the love and laughs over the years and for always being there for me. Special thanks go to *Jari* for illustrating the cover of this thesis.

To *Frida Ottosson, Daniel Lindberg* and to my family-in-law, *Charlotta Prytz Hedström*, *Per Hedström*, *Johanna Hedström Knös* and *Johan Knös*. Thanks for all the encouraging support over the years. I´m happy that you have become part of our family.

My siblings, *Rami* and *Nadia*. For all your love and support.

My mother. For always putting us first and for the sacrifices you made. For always making me feel loved and for always believing in me.

My wonderful wife, *Josefin Hedström*. For being so wise, empathetic and encouraging. For all your support when it felt difficult. For sharing your life with me. This wouldn´t have been possible without you.

11 REFERENCES

1. WHO. Cardiovascular diseases 2017 [updated 17-05-17. Available from: https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds).

2. Gräsner JT, Wnent J, Herlitz J, Perkins GD, Lefering R, Tjelmeland I, et al. Survival after out-of-hospital cardiac arrest in Europe - Results of the EuReCa TWO study. Resuscitation. 2020;148:218-26.

3. Nolan JP, Sandroni C, Böttiger BW, Cariou A, Cronberg T, Friberg H, et al. European Resuscitation Council and European Society of Intensive Care Medicine guidelines 2021: post-resuscitation care. Intensive Care Med. 2021;47(4):369-421.

4. Gaieski DF, Goyal M. History and current trends in sudden cardiac arrest and resuscitation in adults. Hosp Pract (1995). 2010;38(4):44-53.

5. J C. Popular Observations on Apparent Death from Drowning, Suffocation etc. . London Law. 1792.

6. Hurt R. Modern cardiopulmonary resuscitation--not so new after all. J R Soc Med. 2005;98(7):327-31.

7. JD H. Observations on some of the dangers of chloroform in surgical practice, and successful mode of treatment. . Br J Dent Sci. 1868;11:355-8.

8. Kouwenhoven WB, Jude JR, Knickerbocker GG. Closed-chest cardiac massage. Jama. 1960;173:1064-7.

9. Zoll PM LA, Gibson W, Paul MH and Norman LR. Termination of ventricular fibrillation in man by externally applied electrical counterchock. . N Engl J Med. 1956;176:727-32.

10. Safar P EL, Elam JO. . A comparison of mouth-to-mouth and mouth-to-airway methods of artificial respiration with the chest-pressure arm-lift methods. . N Engl J Med. 1958;258:671-7.

11. P S. Mouth-to-mouth Anestesiology 1957;18:904-6.

12. Jacobs I, Nadkarni V, Bahr J, Berg RA, Billi JE, Bossaert L, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries. A statement for healthcare professionals from a task force of the international liaison committee on resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa). Resuscitation. 2004;63(3):233-49.

13. Fishman GI, Chugh SS, Dimarco JP, Albert CM, Anderson ME, Bonow RO, et al. Sudden cardiac death prediction and prevention: report from a National Heart, Lung, and Blood Institute and Heart Rhythm Society Workshop. Circulation. 2010;122(22):2335-48.

14. Berdowski J, Berg RA, Tijssen JG, Koster RW. Global incidences of out-of-hospital cardiac arrest and survival rates: Systematic review of 67 prospective studies. Resuscitation. 2010;81(11):1479-87.

15. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circulation. 2019;139(10):e56-e528.

16. HLR-rådet. HLR-registret årsrapport 2021 2022 [Available from: https://registercentrum.blob.core.windows.net/shlr/r/SHLR-rsrapport-med-data-fr-n-2021-B1x0F0cFGs.pdf.

17. Yan S, Gan Y, Jiang N, Wang R, Chen Y, Luo Z, et al. The global survival rate among adult out-of-hospital cardiac arrest patients who received cardiopulmonary resuscitation: a systematic review and meta-analysis. Crit Care. 2020;24(1):61.

18. Cummins RO, Chamberlain DA, Abramson NS, Allen M, Baskett PJ, Becker L, et al. Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the Utstein Style. A statement for health professionals from a task force of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council. Circulation. 1991;84(2):960-75.

19. Perkins GD, Jacobs IG, Nadkarni VM, Berg RA, Bhanji F, Biarent D, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the Utstein Resuscitation Registry Templates for Out-of-Hospital Cardiac Arrest: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Circulation. 2015;132(13):1286-300.

20. Riva G. Survival after different forms of bystander cardiopulmonary resuscitation in out-of-hospital cardiac arrest: Thesis for doctoral degree, Karolinska Institutet 2019.

21. Myat A, Song KJ, Rea T. Out-of-hospital cardiac arrest: current concepts. Lancet. 2018;391(10124):970-9.

22. Tseng ZH, Olgin JE, Vittinghoff E, Ursell PC, Kim AS, Sporer K, et al. Prospective Countywide Surveillance and Autopsy Characterization of Sudden Cardiac Death: POST SCD Study. Circulation. 2018;137(25):2689-700.

23. Hawkes C, Booth S, Ji C, Brace-McDonnell SJ, Whittington A, Mapstone J, et al. Epidemiology and outcomes from out-of-hospital cardiac arrests in England. Resuscitation. 2017;110:133-40.

24. Geri G, Passouant O, Dumas F, Bougouin W, Champigneulle B, Arnaout M, et al. Etiological diagnoses of out-of-hospital cardiac arrest survivors admitted to the intensive care unit: Insights from a French registry. Resuscitation. 2017;117:66-72.

25. Zipes DP, Wellens HJ. Sudden cardiac death. Circulation. 1998;98(21):2334-51.

26. Spaulding CM, Joly LM, Rosenberg A, Monchi M, Weber SN, Dhainaut JF, et al. Immediate coronary angiography in survivors of out-of-hospital cardiac arrest. N Engl J Med. 1997;336(23):1629-33.

27. Farb A, Tang AL, Burke AP, Sessums L, Liang Y, Virmani R. Sudden coronary death. Frequency of active coronary lesions, inactive coronary lesions, and myocardial infarction. Circulation. 1995;92(7):1701-9.

28. Lemkes JS, Janssens GN, van der Hoeven NW, Jewbali LSD, Dubois EA, Meuwissen M, et al. Coronary Angiography after Cardiac Arrest without ST-Segment Elevation. N Engl J Med. 2019;380(15):1397-407.

29. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Heart Rhythm. 2018;15(10):e73-e189.

30. Reinier K, Thomas E, Andrusiek DL, Aufderheide TP, Brooks SC, Callaway CW, et al. Socioeconomic status and incidence of sudden cardiac arrest. Cmaj. 2011;183(15):1705-12.

31. Deo R, Norby FL, Katz R, Sotoodehnia N, Adabag S, DeFilippi CR, et al. Development and Validation of a Sudden Cardiac Death Prediction Model for the General Population. Circulation. 2016;134(11):806-16.

32. Larsen MP, Eisenberg MS, Cummins RO, Hallstrom AP. Predicting survival from out-of-hospital cardiac arrest: a graphic model. Ann Emerg Med. 1993;22(11):1652-8.

33. Ibrahim WH. Recent advances and controversies in adult cardiopulmonary resuscitation. Postgrad Med J. 2007;83(984):649-54.

34. Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. N Engl J Med. 2001;345(20):1473-82.

35. Bayés de Luna A, Coumel P, Leclercq JF. Ambulatory sudden cardiac death: mechanisms of production of fatal arrhythmia on the basis of data from 157 cases. Am Heart J. 1989;117(1):151-9.

36. HLR-rådet. HLR-regisret, årsrapport 2019. 2020 [updated 2020-09-19. Available from: https://www.hlr.nu/hjart-lungraddningsregistrets-arsrapport-2018/.

37. 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(1):63-81.

38. Andrew E, Nehme Z, Lijovic M, Bernard S, Smith K. Outcomes following out-of-hospital cardiac arrest with an initial cardiac rhythm of asystole or pulseless electrical activity in Victoria, Australia. Resuscitation. 2014;85(11):1633-9.

39. Fukuda T, Ohashi-Fukuda N, Matsubara T, Doi K, Kitsuta Y, Nakajima S, et al. Association of initial rhythm with neurologically favorable survival in non-shockable out-of-hospital cardiac arrest without a bystander witness or bystander cardiopulmonary resuscitation. Eur J Intern Med. 2016;30:61-7.

40. Bergström M, Schmidbauer S, Herlitz J, Rawshani A, Friberg H. Pulseless electrical activity is associated with improved survival in out-of-hospital cardiac arrest with initial non-shockable rhythm. Resuscitation. 2018;133:147-52.

41. Myerburg RJ, Halperin H, Egan DA, Boineau R, Chugh SS, Gillis AM, et al. Pulseless electric activity: definition, causes, mechanisms, management, and research priorities for the next decade: report from a National Heart, Lung, and Blood Institute workshop. Circulation. 2013;128(23):2532-41.

42. Stiell IG, Wells GA, Field B, Spaite DW, Nesbitt LP, De Maio VJ, et al. Advanced cardiac life support in out-of-hospital cardiac arrest. N Engl J Med. 2004;351(7):647-56.

43. Herlitz J, Engdahl J, Svensson L, Angquist KA, Young M, Holmberg S. Factors associated with an increased chance of survival among patients suffering from an out-of-hospital cardiac arrest in a national perspective in Sweden. Am Heart J. 2005;149(1):61-6.

44. Hollenberg J, Herlitz J, Lindqvist J, Riva G, Bohm K, Rosenqvist M, et al. Improved survival after out-of-hospital cardiac arrest is associated with an increase in proportion of emergency crew--witnessed cases and bystander cardiopulmonary resuscitation. Circulation. 2008;118(4):389-96.

45. Wissenberg M, Lippert FK, Folke F, Weeke P, Hansen CM, Christensen EF, et al. Association of national initiatives to improve cardiac arrest management with rates of bystander intervention and patient survival after out-of-hospital cardiac arrest. Jama. 2013;310(13):1377-84.

46. Iwami T, Hiraide A, Nakanishi N, Hayashi Y, Nishiuchi T, Uejima T, et al. Outcome and characteristics of out-of-hospital cardiac arrest according to location of arrest: A report from a large-scale, population-based study in Osaka, Japan. Resuscitation. 2006;69(2):221-8.

47. Eisenburger P, Sterz F, Haugk M, Scheinecker W, Holzer M, Koreny M, et al. Cardiac arrest in public locations--an independent predictor for better outcome? Resuscitation. 2006;70(3):395-403.

48. Herlitz J, Eek M, Holmberg M, Engdahl J, Holmberg S. Characteristics and outcome among patients having out of hospital cardiac arrest at home compared with elsewhere. Heart. 2002;88(6):579-82.

49. Herlitz J, Svensson L, Engdahl J, Gelberg J, Silfverstolpe J, Wisten A, et al. Characteristics of cardiac arrest and resuscitation by age group: an analysis from the Swedish Cardiac Arrest Registry. Am J Emerg Med. 2007;25(9):1025-31.

50. Terman SW, Shields TA, Hume B, Silbergleit R. The influence of age and chronic medical conditions on neurological outcomes in out of hospital cardiac arrest. Resuscitation. 2015;89:169-76.

51. Beesems SG, Blom MT, van der Pas MH, Hulleman M, van de Glind EM, van Munster BC, et al. Comorbidity and favorable neurologic outcome after out-of-hospital cardiac arrest in patients of 70 years and older. Resuscitation. 2015;94:33-9.

52. Blom MT, Oving I, Berdowski J, van Valkengoed IGM, Bardai A, Tan HL. Women have lower chances than men to be resuscitated and survive out-of-hospital cardiac arrest. Eur Heart J. 2019;40(47):3824-34.

53. Lei H, Hu J, Liu L, Xu D. Sex differences in survival after out-of-hospital cardiac arrest: a meta-analysis. Crit Care. 2020;24(1):613.

54. Goto Y, Funada A, Maeda T, Okada H, Goto Y. Sex-specific differences in survival after out-of-hospital cardiac arrest: a nationwide, population-based observational study. Crit Care. 2019;23(1):263.

55. Adielsson A, Hollenberg J, Karlsson T, Lindqvist J, Lundin S, Silfverstolpe J, et al. Increase in survival and bystander CPR in out-of-hospital shockable arrhythmia: bystander CPR and female gender are predictors of improved outcome. Experiences from Sweden in an 18-year perspective. Heart. 2011;97(17):1391-6.

56. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, et al. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. N Engl J Med. 2013;369(23):2197-206.

57. Lilja G, Nielsen N, Bro-Jeppesen J, Dunford H, Friberg H, Hofgren C, et al. Return to Work and Participation in Society After Out-of-Hospital Cardiac Arrest. Circ Cardiovasc Qual Outcomes. 2018;11(1):e003566.

58. Rittenberger JC, Raina K, Holm MB, Kim YJ, Callaway CW. Association between Cerebral Performance Category, Modified Rankin Scale, and discharge disposition after cardiac arrest. Resuscitation. 2011;82(8):1036-40.

59. Nolan JP, Berg RA, Andersen LW, Bhanji F, Chan PS, Donnino MW, et al. Cardiac Arrest and Cardiopulmonary Resuscitation Outcome Reports: Update of the Utstein Resuscitation Registry Template for In-Hospital Cardiac Arrest: A Consensus Report From a Task Force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia). Resuscitation. 2019;144:166-77.

60. Wilson JT, Pettigrew LE, Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. J Neurotrauma. 1998;15(8):573-85.

61. Froehler MT, Geocadin RG. Hypothermia for neuroprotection after cardiac arrest: mechanisms, clinical trials and patient care. J Neurol Sci. 2007;261(1-2):118-26.

62. Krause GS, White BC, Aust SD, Nayini NR, Kumar K. Brain cell death following ischemia and reperfusion: a proposed biochemical sequence. Crit Care Med. 1988;16(7):714-26.

63. Neumar RW, Hagle SM, DeGracia DJ, Krause GS, White BC. Brain mu-calpain autolysis during global cerebral ischemia. J Neurochem. 1996;66(1):421-4.

64. Zheng Z, Yenari MA. Post-ischemic inflammation: molecular mechanisms and therapeutic implications. Neurol Res. 2004;26(8):884-92.

65. Sakamoto A, Ohnishi ST, Ohnishi T, Ogawa R. Relationship between free radical production and lipid peroxidation during ischemia-reperfusion injury in the rat brain. Brain Res. 1991;554(1-2):186-92.

66. Beckstead JE, Tweed WA, Lee J, MacKeen WL. Cerebral blood flow and metabolism in man following cardiac arrest. Stroke. 1978;9(6):569-73.

67. Nolan JP, Neumar RW, Adrie C, Aibiki M, Berg RA, Böttiger BW, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A Scientific Statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; the Council on Stroke. Resuscitation. 2008;79(3):350-79.

68. Girotra S, Chan PS, Bradley SM. Post-resuscitation care following out-of-hospital and in-hospital cardiac arrest. Heart. 2015;101(24):1943-9.

69. Kang Y. Management of post-cardiac arrest syndrome. Acute Crit Care. 2019;34(3):173-8.

70. Cummins RO, Ornato JP, Thies WH, Pepe PE. Improving survival from sudden cardiac arrest: the "chain of survival" concept. A statement for health professionals from the Advanced Cardiac Life Support Subcommittee and the Emergency Cardiac Care Committee, American Heart Association. Circulation. 1991;83(5):1832-47.

71. Nolan J, Soar J, Eikeland H. The chain of survival. Resuscitation. 2006;71(3):270-1.

72. Nolan JP, Soar J, Cariou A, Cronberg T, Moulaert VR, Deakin CD, et al. European Resuscitation Council and European Society of Intensive Care Medicine Guidelines for Post-resuscitation Care 2015: Section 5 of the European Resuscitation Council Guidelines for Resuscitation 2015. Resuscitation. 2015;95:202-22.

73. Perkins GD, Handley AJ, Koster RW, Castrén M, Smyth MA, Olasveengen T, et al. European Resuscitation Council Guidelines for Resuscitation 2015: Section 2. Adult basic life support and automated external defibrillation. Resuscitation. 2015;95:81-99.

74. Soar J, Nolan JP, Böttiger BW, Perkins GD, Lott C, Carli P, et al. European Resuscitation Council Guidelines for Resuscitation 2015: Section 3. Adult advanced life support. Resuscitation. 2015;95:100-47.

75. Olasveengen TM, Semeraro F, Ristagno G, Castren M, Handley A, Kuzovlev A, et al. European Resuscitation Council Guidelines 2021: Basic Life Support. Resuscitation. 2021;161:98-114.

76. Takei Y, Nishi T, Kamikura T, Tanaka Y, Wato Y, Kubo M, et al. Do early emergency calls before patient collapse improve survival after out-of-hospital cardiac arrests? Resuscitation. 2015;88:20-7.

77. Waalewijn RA, Tijssen JG, Koster RW. Bystander initiated actions in out-of-hospital cardiopulmonary resuscitation: results from the Amsterdam Resuscitation Study (ARRESUST). Resuscitation. 2001;50(3):273-9.

78. Holmberg M, Holmberg S, Herlitz J. Factors modifying the effect of bystander cardiopulmonary resuscitation on survival in out-of-hospital cardiac arrest patients in Sweden. Eur Heart J. 2001;22(6):511-9.

79. Hasselqvist-Ax I, Riva G, Herlitz J, Rosenqvist M, Hollenberg J, Nordberg P, et al. Early cardiopulmonary resuscitation in out-of-hospital cardiac arrest. N Engl J Med. 2015;372(24):2307-15.

80. Riva G, Ringh M, Jonsson M, Svensson L, Herlitz J, Claesson A, et al. Survival in Out-of-Hospital Cardiac Arrest After Standard Cardiopulmonary Resuscitation or Chest Compressions Only Before Arrival of Emergency Medical Services: Nationwide Study During Three Guideline Periods. Circulation. 2019.

81. Valenzuela TD, Roe DJ, Cretin S, Spaite DW, Larsen MP. Estimating effectiveness of cardiac arrest interventions: a logistic regression survival model. Circulation. 1997;96(10):3308-13.

82. Ringh M, Jonsson M, Nordberg P, Fredman D, Hasselqvist-Ax I, Håkansson F, et al. Survival after Public Access Defibrillation in Stockholm, Sweden--A striking success. Resuscitation. 2015;91:1-7.

83. Petersdorf RG, Beeson PB. Fever of unexplained origin: report on 100 cases. Medicine (Baltimore). 1961;40:1-30.

84. Mackowiak PA, Wasserman SS, Levine MM. A critical appraisal of 98.6 degrees F, the upper limit of the normal body temperature, and other legacies of Carl Reinhold August Wunderlich. Jama. 1992;268(12):1578-80.

85. Dankiewicz J, Cronberg T, Lilja G, Jakobsen JC, Bělohlávek J, Callaway C, et al. Targeted hypothermia versus targeted Normothermia after out-of-hospital cardiac arrest (TTM2): A randomized clinical trial-Rationale and design. Am Heart J. 2019;217:23-31.

86. Obermeyer Z, Samra JK, Mullainathan S. Individual differences in normal body temperature: longitudinal big data analysis of patient records. Bmj. 2017;359:j5468.

87. Bro-Jeppesen J, Hassager C, Wanscher M, Soholm H, Thomsen JH, Lippert FK, et al. Post-hypothermia fever is associated with increased mortality after out-of-hospital cardiac arrest. Resuscitation. 2013;84(12):1734-40.

88. Leary M, Grossestreuer AV, Iannacone S, Gonzalez M, Shofer FS, Povey C, et al. Pyrexia and neurologic outcomes after therapeutic hypothermia for cardiac arrest. Resuscitation. 2013;84(8):1056-61.

89. Donnino MW, Andersen LW, Berg KM, Reynolds JC, Nolan JP, Morley PT, et al. Temperature Management After Cardiac Arrest: An Advisory Statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Circulation. 2015;132(25):2448-56.

90. McCullough JN, Zhang N, Reich DL, Juvonen TS, Klein JJ, Spielvogel D, et al. Cerebral metabolic suppression during hypothermic circulatory arrest in humans. Ann Thorac Surg. 1999;67(6):1895-9; discussion 919-21.

91. Busija DW, Leffler CW, Pourcyrous M. Hyperthermia increases cerebral metabolic rate and blood flow in neonatal pigs. Am J Physiol. 1988;255(2 Pt 2):H343-6.

92. Gunn AJ, Thoresen M. Hypothermic neuroprotection. NeuroRx. 2006;3(2):154-69.

93. Drury PP, Gunn ER, Bennet L, Gunn AJ. Mechanisms of hypothermic neuroprotection. Clin Perinatol. 2014;41(1):161-75.

94. Nagel S, Su Y, Horstmann S, Heiland S, Gardner H, Koziol J, et al. Minocycline and hypothermia for reperfusion injury after focal cerebral ischemia in the rat: effects on BBB breakdown and MMP expression in the acute and subacute phase. Brain Res. 2008;1188:198-206.

95. Donadello K, Su F, Annoni F, Scolletta S, He X, Peluso L, et al. The Effects of Temperature Management on Brain Microcirculation, Oxygenation and Metabolism. Brain Sci. 2022;12(10).

96. Bro-Jeppesen J, Kjaergaard J, Wanscher M, Nielsen N, Friberg H, Bjerre M, et al. The inflammatory response after out-of-hospital cardiac arrest is not modified by targeted temperature management at 33 °C or 36 °C. Resuscitation. 2014;85(11):1480-7.

97. Gega A, Rizzo JA, Johnson MH, Tranquilli M, Farkas EA, Elefteriades JA. Straight deep hypothermic arrest: experience in 394 patients supports its effectiveness as a sole means of brain preservation. Ann Thorac Surg. 2007;84(3):759-66; discussion 66-7.

98. Walpoth BH, Walpoth-Aslan BN, Mattle HP, Radanov BP, Schroth G, Schaeffler L, et al. Outcome of survivors of accidental deep hypothermia and circulatory arrest treated with extracorporeal blood warming. N Engl J Med. 1997;337(21):1500-5.

99. Polderman KH, Herold I. Therapeutic hypothermia and controlled normothermia in the intensive care unit: practical considerations, side effects, and cooling methods. Crit Care Med. 2009;37(3):1101-20.

100. Olai H, Thornéus G, Watson H, Macleod M, Rhodes J, Friberg H, et al. Meta-analysis of targeted temperature management in animal models of cardiac arrest. Intensive Care Med Exp. 2020;8(1):3.

101. Marion DW, Leonov Y, Ginsberg M, Katz LM, Kochanek PM, Lechleuthner A, et al. Resuscitative hypothermia. Crit Care Med. 1996;24(2 Suppl):S81-9.

102. Bernard SA, Smith K, Finn J, Hein C, Grantham H, Bray JE, 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(11):797-805.

103. Debaty G, Maignan M, Savary D, Koch FX, Ruckly S, Durand M, et al. Impact of intra-arrest therapeutic hypothermia in outcomes of prehospital cardiac arrest: a randomized controlled trial. Intensive Care Med. 2014;40(12):1832-42.

104. Kim F, Olsufka M, Longstreth WT, Jr., Maynard C, Carlbom D, Deem S, et al. Pilot randomized clinical trial of prehospital induction of mild hypothermia in out-of-hospital cardiac arrest patients with a rapid infusion of 4 degrees C normal saline. Circulation. 2007;115(24):3064-70.

105. Kämäräinen A, Virkkunen I, Tenhunen J, Yli-Hankala A, Silfvast T. Prehospital therapeutic hypothermia for comatose survivors of cardiac arrest: a randomized controlled trial. Acta Anaesthesiol Scand. 2009;53(7):900-7.

106. Bernard SA, Smith K, Cameron P, Masci K, Taylor DM, Cooper DJ, et al. Induction of therapeutic hypothermia by paramedics after resuscitation from out-of-hospital ventricular fibrillation cardiac arrest: a randomized controlled trial. Circulation. 2010;122(7):737-42.

107. Kim F, Nichol G, Maynard C, Hallstrom A, Kudenchuk PJ, Rea T, 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(1):45-52.

108. Boller M, Lampe JW, Katz JM, Barbut D, Becker LB. Feasibility of intra-arrest hypothermia induction: A novel nasopharyngeal approach achieves preferential brain cooling. Resuscitation. 2010;81(8):1025-30.

109. Yu T, Barbut D, Ristagno G, Cho JH, Sun S, Li Y, et al. Survival and neurological outcomes after nasopharyngeal cooling or peripheral vein cold saline infusion initiated during cardiopulmonary resuscitation in a porcine model of prolonged cardiac arrest. Crit Care Med. 2010;38(3):916-21.

110. Castren M, Nordberg P, Svensson L, Taccone F, Vincent JL, Desruelles D, et al. Intra-arrest transnasal evaporative cooling: a randomized, prehospital, multicenter study (PRINCE: Pre-ROSC IntraNasal Cooling Effectiveness). Circulation. 2010;122(7):729-36.

111. Nordberg P, Taccone FS, Truhlar A, Forsberg S, Hollenberg J, Jonsson M, 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(17):1677-85.

112. HACA-group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. The New England journal of medicine. 2002;346(8):549-56.

113. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. The New England journal of medicine. 2002;346(8):557-63.

114. Sandroni C, Nolan JP, Andersen LW, Böttiger BW, Cariou A, Cronberg T, et al. ERC-ESICM guidelines on temperature control after cardiac arrest in adults. Intensive Care Med. 2022;48(3):261-9.

115. Lascarrou JB, Merdji H, Le Gouge A, Colin G, Grillet G, Girardie P, et al. Targeted Temperature Management for Cardiac Arrest with Nonshockable Rhythm. N Engl J Med. 2019.

116. Wolfrum S, Roedl K, Hanebutte A, Pfeifer R, Kurowski V, Riessen R, et al. Temperature Control After In-Hospital Cardiac Arrest: A Randomized Clinical Trial. Circulation. 2022;146(18):1357-66.

117. Imberti R, Bellinzona G, Riccardi F, Pagani M, Langer M. Cerebral perfusion pressure and cerebral tissue oxygen tension in a patient during cardiopulmonary resuscitation. Intensive Care Med. 2003;29(6):1016-9.

118. Cavus E, Bein B, Dörges V, Stadlbauer KH, Wenzel V, Steinfath M, et al. Brain tissue oxygen pressure and cerebral metabolism in an animal model of cardiac arrest and cardiopulmonary resuscitation. Resuscitation. 2006;71(1):97-106.

119. Nelskylä A, Skrifvars MB, Ångerman S, Nurmi J. Incidence of hyperoxia and factors associated with cerebral oxygenation during cardiopulmonary resuscitation. Resuscitation. 2022;170:276-82.

120. Dell'Anna AM, Lamanna I, Vincent JL, Taccone FS. How much oxygen in adult cardiac arrest? Crit Care. 2014;18(5):555.

121. Hazelton JL, Balan I, Elmer GI, Kristian T, Rosenthal RE, Krause G, et al. Hyperoxic reperfusion after global cerebral ischemia promotes inflammation and long-term hippocampal neuronal death. J Neurotrauma. 2010;27(4):753-62.

122. Pilcher J, Weatherall M, Shirtcliffe P, Bellomo R, Young P, Beasley R. The effect of hyperoxia following cardiac arrest - A systematic review and meta-analysis of animal trials. Resuscitation. 2012;83(4):417-22.

123. Watson NA, Beards SC, Altaf N, Kassner A, Jackson A. The effect of hyperoxia on cerebral blood flow: a study in healthy volunteers using magnetic resonance phase-contrast angiography. European journal of anaesthesiology. 2000;17(3):152-9.

124. Floyd TF, Clark JM, Gelfand R, Detre JA, Ratcliffe S, Guvakov D, et al. Independent cerebral vasoconstrictive effects of hyperoxia and accompanying arterial hypocapnia at 1 ATA. Journal of applied physiology (Bethesda, Md : 1985). 2003;95(6):2453-61.

125. Singer M, Young PJ, Laffey JG, Asfar P, Taccone FS, Skrifvars MB, et al. Dangers of hyperoxia. Crit Care. 2021;25(1):440.

126. Alva R, Mirza M, Baiton A, Lazuran L, Samokysh L, Bobinski A, et al. Oxygen toxicity: cellular mechanisms in normobaric hyperoxia. Cell Biol Toxicol. 2022:1-33.

127. Wang CH, Chang WT, Huang CH, Tsai MS, Yu PH, Wang AY, et al. The effect of hyperoxia on survival following adult cardiac arrest: a systematic review and meta-analysis of observational studies. Resuscitation. 2014;85(9):1142-8.

128. Ebner F, Ullen S, Aneman A, Cronberg T, Mattsson N, Friberg H, et al. Associations between partial pressure of oxygen and neurological outcome in out-of-hospital cardiac arrest patients: an explorative analysis of a randomized trial. Crit Care. 2019;23(1):30.

129. Holmberg MJ, Nicholson T, Nolan JP, Schexnayder S, Reynolds J, Nation K, et al. Oxygenation and ventilation targets after cardiac arrest: A systematic review and meta-analysis. Resuscitation. 2020;152:107-15.

130. Llitjos JF, Mira JP, Duranteau J, Cariou A. Hyperoxia toxicity after cardiac arrest: What is the evidence? Ann Intensive Care. 2016;6(1):23.

131. Kuisma M, Boyd J, Voipio V, Alaspää A, Roine RO, Rosenberg P. Comparison of 30 and the 100% inspired oxygen concentrations during early post-resuscitation period: a randomised controlled pilot study. Resuscitation. 2006;69(2):199-206.

132. Thomas M, Voss S, Benger J, Kirby K, Nolan JP. Cluster randomised comparison of the effectiveness of 100% oxygen versus titrated oxygen in patients with a sustained return of spontaneous circulation following out of hospital cardiac arrest: a feasibility study. PROXY: post ROSC OXYgenation study. BMC Emerg Med. 2019;19(1):16.

133. Young P, Bailey M, Bellomo R, Bernard S, Dicker B, Freebairn R, et al. HyperOxic Therapy OR NormOxic Therapy after out-of-hospital cardiac arrest (HOT OR NOT): a randomised controlled feasibility trial. Resuscitation. 2014;85(12):1686-91.

134. Bray JE, Hein C, Smith K, Stephenson M, Grantham H, Finn J, et al. Oxygen titration after resuscitation from out-of-hospital cardiac arrest: A multi-centre, randomised controlled pilot study (the EXACT pilot trial). Resuscitation. 2018;128:211-5.

135. Schmidt H, Kjaergaard J, Hassager C, Mølstrøm S, Grand J, Borregaard B, et al. Oxygen Targets in Comatose Survivors of Cardiac Arrest. N Engl J Med. 2022;387(16):1467-76.

136. Bernard SA, Bray JE, Smith K, Stephenson M, Finn J, Grantham H, et al. Effect of Lower vs Higher Oxygen Saturation Targets on Survival to Hospital Discharge Among Patients Resuscitated After Out-of-Hospital Cardiac Arrest: The EXACT Randomized Clinical Trial. Jama. 2022.

137. Mackle D, Bellomo R, Bailey M, Beasley R, Deane A, Eastwood G, et al. Conservative Oxygen Therapy during Mechanical Ventilation in the ICU. N Engl J Med. 2020;382(11):989-98.

138. Gelissen H, de Grooth HJ, Smulders Y, Wils EJ, de Ruijter W, Vink R, et al. Effect of Low-Normal vs High-Normal Oxygenation Targets on Organ Dysfunction in Critically Ill Patients: A Randomized Clinical Trial. Jama. 2021;326(10):940-8.

139. Semler MW, Casey JD, Lloyd BD, Hastings PG, Hays MA, Stollings JL, et al. Oxygen-Saturation Targets for Critically Ill Adults Receiving Mechanical Ventilation. N Engl J Med. 2022.

140. Kilgannon JH, Jones AE, Shapiro NI, Angelos MG, Milcarek B, Hunter K, et al. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. Jama. 2010;303(21):2165-71.

141. Roberts BW, Kilgannon JH, Hunter BR, Puskarich MA, Pierce L, Donnino M, et al. Association Between Early Hyperoxia Exposure After Resuscitation From Cardiac Arrest and Neurological Disability: Prospective Multicenter Protocol-Directed Cohort Study. Circulation. 2018;137(20):2114-24.

142. Ebner F, Riker RR, Haxhija Z, Seder DB, May TL, Ullén S, et al. The association of partial pressures of oxygen and carbon dioxide with neurological outcome after out-of-hospital cardiac arrest: an explorative International Cardiac Arrest Registry 2.0 study. Scandinavian journal of trauma, resuscitation and emergency medicine. 2020;28(1):67.

143. Bellomo R, Bailey M, Eastwood GM, Nichol A, Pilcher D, Hart GK, et al. Arterial hyperoxia and in-hospital mortality after resuscitation from cardiac arrest. Crit Care. 2011;15(2):R90.

144. Humaloja J, Litonius E, Efendijev I, Folger D, Raj R, Pekkarinen PT, et al. Early hyperoxemia is not associated with cardiac arrest outcome. Resuscitation. 2019.

145. SIR. [updated 2021-08-12. Available from: https://www.icuregswe.org/en/about-sir/organization/.

146. SIR. Årsrapport 2021 [updated 2022-03-17. Available from: https://www.icuregswe.org/globalassets/arsrapporter/arsrapport_2021.pdf.

147. Metnitz PG, Moreno RP, Almeida E, Jordan B, Bauer P, Campos RA, et al. SAPS 3--From evaluation of the patient to evaluation of the intensive care unit. Part 1:

Objectives, methods and cohort description. Intensive Care Med. 2005;31(10):1336-44.

148. Engerström L, Nolin T, Mårdh C, Sjöberg F, Karlström G, Fredrikson M, et al. Impact of Missing Physiologic Data on Performance of the Simplified Acute Physiology Score 3 Risk-Prediction Model. Crit Care Med. 2017;45(12):2006-13.

149. SIR. Utdataportalen: SIR; [Available from: https://portal.icuregswe.org/utdata/sv/report/q2.saps3-poang.

150. Langhelle A, Nolan J, Herlitz J, Castren M, Wenzel V, Soreide E, et al. Recommended guidelines for reviewing, reporting, and conducting research on post-resuscitation care: the Utstein style. Resuscitation. 2005;66(3):271-83.

151. Strömsöe A, Svensson L, Axelsson Å B, Claesson A, Göransson KE, Nordberg P, et al. Improved outcome in Sweden after out-of-hospital cardiac arrest and possible association with improvements in every link in the chain of survival. Eur Heart J. 2015;36(14):863-71.

152. Patientregistret. [updated 2019/05/20. Available from: https://www.socialstyrelsen.se/en/statistics-and-data/registers/register-information/the-national-patient-register/.

153. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC public health. 2011;11:450.

154. Abazi L, Awad A, Nordberg P, Jonsson M, Taccone FS, Wickerts CJ, et al. Long-term survival in out-of-hospital cardiac arrest patients treated with targeted temperature control at 33 degrees C or 36 degrees C: A national registry study. Resuscitation. 2019;143:142-7.

155. Awad A, Taccone FS, Jonsson M, Forsberg S, Hollenberg J, Truhlar A, et al. Time to intra-arrest therapeutic hypothermia in out-of-hospital cardiac arrest patients and its association with neurologic outcome: a propensity matched sub-analysis of the PRINCESS trial. Intensive Care Med. 2020.

156. Awad A, Nordberg P, Jonsson M, Hofmann R, Ringh M, Hollenberg J, et al. Hyperoxemia after reperfusion in cardiac arrest patients: a potential dose-response association with 30-day survival. Crit Care. 2023;27(1):86.

157. Wilson JT, Hareendran A, Hendry A, Potter J, Bone I, Muir KW. Reliability of the modified Rankin Scale across multiple raters: benefits of a structured interview. Stroke. 2005;36(4):777-81.

158. Abazi L, Awad A, Forsberg S. Reply to: Monitoring outcomes after cardiac arrest: All resuscitated patients matter. Resuscitation. 2020;146:272.

159. Salter R, Bailey M, Bellomo R, Eastwood G, Goodwin A, Nielsen N, et al. Changes in Temperature Management of Cardiac Arrest Patients Following Publication of the Target Temperature Management Trial. Crit Care Med. 2018;46(11):1722-30.

160. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med. 2002;346(8):549-56.

161. Kirkegaard H, Søreide E, de Haas I, Pettilä V, Taccone FS, Arus U, et al. Targeted Temperature Management for 48 vs 24 Hours and Neurologic Outcome After Out-of-Hospital Cardiac Arrest: A Randomized Clinical Trial. Jama. 2017;318(4):341-50.

162. Calabró L, Bougouin W, Cariou A, De Fazio C, Skrifvars M, Soreide E, et al. Effect of different methods of cooling for targeted temperature management on outcome after cardiac arrest: a systematic review and meta-analysis. Crit Care. 2019;23(1):285.

163. Matsumoto S, Kuno T, Mikami T, Takagi H, Ikeda T, Briasoulis A, et al. Effect of cooling methods and target temperature on outcomes in comatose patients resuscitated from cardiac arrest: Systematic review and network meta-analysis of randomized trials. Am Heart J. 2022;256:73-84.

164. Bartlett ES, Valenzuela T, Idris A, Deye N, Glover G, Gillies MA, et al. Systematic review and meta-analysis of intravascular temperature management vs. surface cooling in comatose patients resuscitated from cardiac arrest. Resuscitation. 2020;146:82-95.

165. May TL, Ruthazer R, Riker RR, Friberg H, Patel N, Soreide E, et al. Early withdrawal of life support after resuscitation from cardiac arrest is common and may result in additional deaths. Resuscitation. 2019;139:308-13.

166. Noordergraaf GJ, Venema A. On prognostication and withdrawal of life sustaining treatment after cardiac arrest: Does the "thin gray line" between life and death (too often) wear white? Resuscitation. 2019;139:356-8.

167. Sedgwick P, Greenwood N. Understanding the Hawthorne effect. Bmj. 2015;351:h4672.