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2016

Document Version:

Publisher's PDF, also known as Version of record

[Link to publication](#)

Citation for published version (APA):

Dragancea, I. V. (2016). *Neurological prognostication after cardiac arrest and targeted temperature management*. [Doctoral Thesis (compilation), Neurology, Lund]. Lund University: Faculty of Medicine.

Total number of authors:

1

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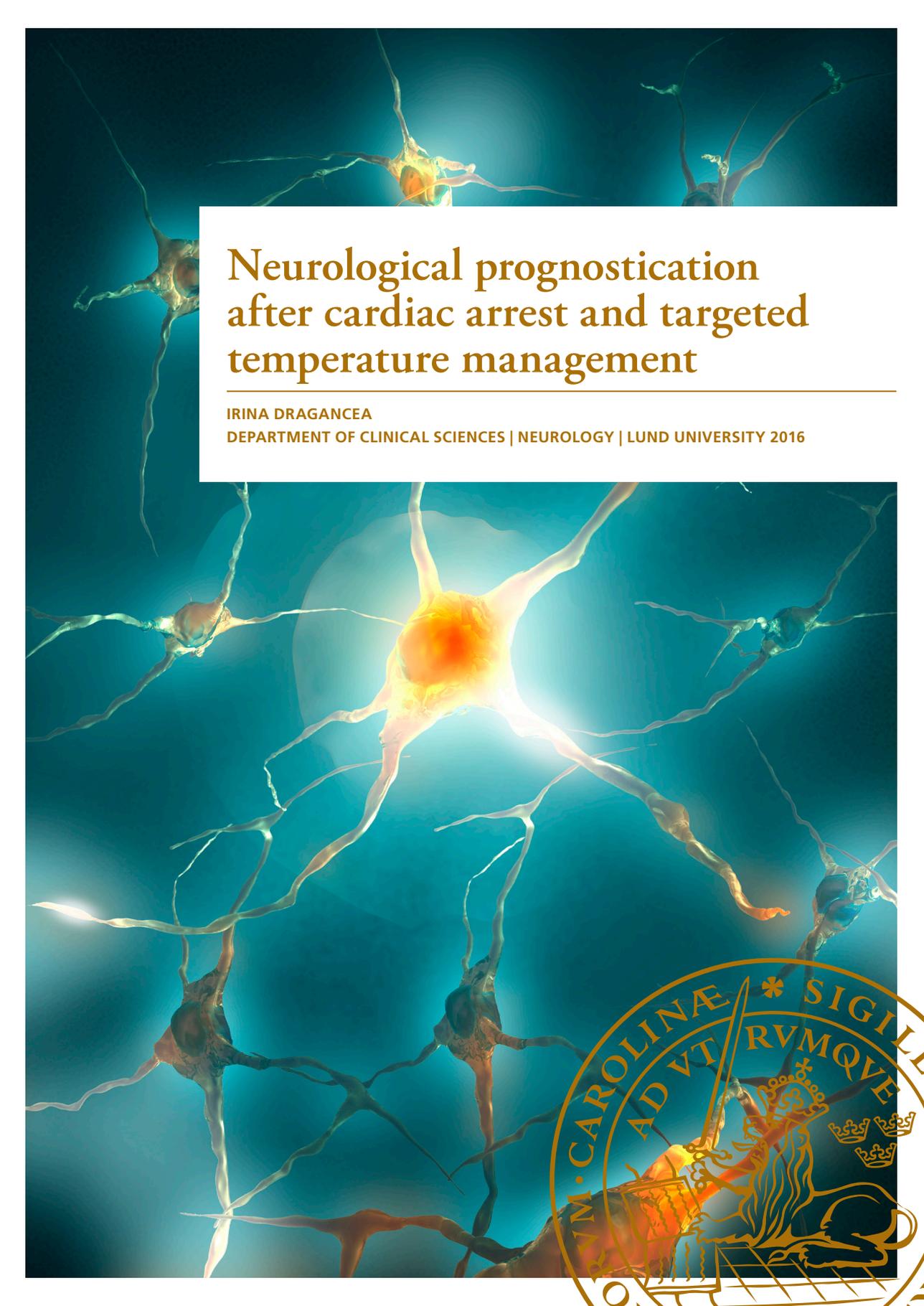
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The background of the entire page is a microscopic image of neurons. A central neuron is brightly lit with a yellow and orange glow, while other neurons are dimmer and more translucent. The axons and dendrites of the neurons are thin and branching, extending across the frame.

Neurological prognostication after cardiac arrest and targeted temperature management

IRINA DRAGANCEA

DEPARTMENT OF CLINICAL SCIENCES | NEUROLOGY | LUND UNIVERSITY 2016



Neurological prognostication after cardiac arrest and targeted temperature management

Irina Dragancea



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DOCTORAL DISSERTATION

By due permission of the Faculty of Medicine, Lund University, Sweden.
To be defended at Föreläsningssal 2, C-blocket, Skåne University Hospital,
Getingevägen 4, Lund on Friday, September 2, 2016 at 09.00 a.m.

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Organization LUND UNIVERSITY	Document name DOCTORIAL DISSERTATION	
Department of Clinical Sciences,	Date of issue September 2, 2016	
Author(s) Irina Dragancea	Sponsoring organization	
Title and subtitle Neurological prognostication after cardiac arrest and targeted temperature management		
<p>Abstract</p> <p>This thesis focuses on neurological prognostication in comatose survivors of Out-of-Hospital Cardiac Arrest (OHCA) who are admitted to an intensive care unit (ICU) after the return of spontaneous circulation (ROSC) and treated with targeted temperature management (TTM) of either 33°C or 36°C for 24 hours.</p> <p>Purpose: First, to investigate how neurological prognostication affected the decisions on withdrawal of life sustaining therapy (WLST) and the outcome of patients with OHCA and TTM; second to determine whether TTM at 33°C compared to 36°C affected the prognostic accuracy of clinical neurological findings and somatosensory evoked potentials (SSEP) in comatose patients and; third, to describe the prevalence of electrographic status epilepticus (ESE) and potential clinical and electrographic prognostic markers.</p> <p>Paper I describes the influence of TTM and delayed prognostication on the mode of death among 162 comatose cardiac arrest (CA) patient treated at an ICU between 2003-2008. We found that the majority of CA-patients treated with TTM died after WLST based on a prediction of poor neurological prognosis due to presumed severe hypoxic-ischaemic brain injury and that some young patients with a long time to ROSC became brain dead and subsequent organ donors.</p> <p>Paper II is a post hoc analysis of the TTM trial including prospectively collected data from 939 comatose adult survivors of OHCA of primary cardiac origin between 2010-2013. The aim of this paper was to determine whether different treatment temperatures (33°C vs 36°C) after resuscitation affected the prognostic accuracy of clinical neurological findings and somatosensory evoked potentials (SSEP) in comatose patients. The results were that bilateral absent pupillary or corneal reflexes and N20-peaks on SSEP were reliable markers of a poor prognosis in patients remaining comatose after TTM following OHCA and that the motor score was not a reliable predictor. The reliability of these markers did not appear to be altered by temperature and our findings do not support separate guidelines for prognostication for cardiac arrest patients treated at different targeted temperatures of either 33°C or 36°C.</p> <p>Paper III describes the prevalence of postanoxic status epilepticus (PSE) and potential clinical and electrographic prognostic markers among 127 comatose survivors of CA between 2008-2013. We found that PSE is common among comatose patients after cardiac arrest with few survivors. Potential indicators of good outcome are a continuous EEG background pattern before the onset of ESE, preserved N20-peaks on SSEP and low or moderately elevated serum neuron specific enolase (NSE) levels.</p> <p>Paper IV investigates how protocol-driven neurological prognostication affected WLST decision-making and outcome after OHCA in the TTM trial. The results suggest that different care recommendations after multimodal neurological prognostication may produce clinically important differences in length of ICU stay, survival time and outcome.</p>		
Key words neurological prognostication, brain injury, cardiac arrest, withdrawal of life-sustaining therapy		
Classification system and/or index terms (if any)		
Supplementary bibliographical information	Language English	
ISSN and key title 1652-8220	ISBN 978-91-7619-307-5	
Recipient's notes	Number of pages	Price
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Neurological prognostication after cardiac arrest and targeted temperature management

Irina Dragancea



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Lund University
Faculty of Medicine
Doctoral Dissertation 2016:81

ISBN 978-91-7619-307-5
ISSN 1652-8220

Printed in Sweden by Media-Tryck, Lund University
Lund 2016



To Cristian and Alexandra

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List of publications

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I. **Dragancea I**, Rundgren M, Englund E, Friberg H, Cronberg T. The influence of induced hypothermia and delayed prognostication on the mode of death after cardiac arrest. *Resuscitation*. 2013 Mar; 84(3):337-42.
- II. **Dragancea I**, Horn J, Kuiper M, Friberg H, Ullén S, Wetterslev J, Cranshaw J, Hassager C, Nielsen N, Cronberg T; TTM Trial Investigators. Neurological prognostication after cardiac arrest and targeted temperature management 33°C versus 36°C: Results from a randomised controlled clinical trial. *Resuscitation*. 2015 Aug; 93:164-70.
- III. **Dragancea I**, Backman S, Westhall E, Rundgren M, Friberg H, Cronberg T. Outcome following postanoxic status epilepticus in patients with targeted temperature management after cardiac arrest. *Epilepsy & Behav*. 2015 Aug; 49:173-7.
- IV. **Dragancea I**, Wise MP, Al-Subaie N, MD, Cranshaw J, Friberg H, Glover G, Kjaergaard J, Pellis T, Rylance R, Walden A, Nielsen N, Cronberg T, and the TTM trial investigators. Neurological prognostication and withdrawal of life-sustaining therapy after cardiac arrest and targeted temperature management. Manuscript.

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Abbreviations

AAN	American Academy of Neurology
ACNS	American Clinical Neurophysiology Society
ATP	Adenosine triphosphate
CA	Cardiac arrest
CT	Computed tomography
cEEG	Continuous electroencephalography monitoring
CI	Confidence intervals
CPC	Cerebral Performance Categories scale
CPR	Cardiopulmonary resuscitation
EEG	Electroencephalography
ESE	Electrographic status epilepticus
ERC	European Resuscitation Council
EMS	Emergency medical system
ESICM	European Society of Intensive Care Medicine
FPR	False positive rate
GCS	Glasgow coma scale
ICU	Intensive care unit
ILCOR	International Liaison Committee on Resuscitation
IQR	Interquartile range
MRI	Magnetic resonance imaging
N20	Cortical peak in median nerve somatosensory evoked potentials
NCSE	Non-convulsive status epilepticus
NSE	Neuron specific enolase
OHCA	Out-of-hospital cardiac arrest
PCAS	Post cardiac arrest syndrome
PEA	Pulseless electrical activity
ROSC	Return of spontaneous circulation
SSEP	Somatosensory evoked potentials
VF	Ventricular fibrillation
VT	Ventricular tachycardia
TTM	Targeted temperature management
WLST	Withdrawal of life-sustaining therapy

Background

Cardiac arrest

Epidemiology and Pathophysiology

Sudden cardiac arrest (CA) is one of the most dramatic medical emergencies, caused by the abrupt cessation of cardiac activity leading to haemodynamic collapse. Due to its immediate and often unrecognized nature, the epidemiological characteristics are difficult to determine with precision. However, estimates can be made. The annual incidence of out-of-hospital cardiac arrests (OHCA) is approximately 38-55 per 100,000 persons.¹⁻⁴ In Sweden, it is estimated that approximately 5,000-10,000 persons suffer from OCHA every year.⁵ In 2014 there were 5,127 cases of all cause OHCA treated by the emergency medical system (EMS).⁶ Overall survival from cardiac arrest is poor and fraught with complications across many organ systems due to ischaemic injury. Survival to hospital discharge varies globally from 0.2% to about 25%.^{1, 2, 4, 7, 8, 9} However, recent data suggest that both the low survival rates and rates of poor functional outcome are improving.^{10, 11} In Sweden, according to the Swedish Cardiac Arrest Registry the overall survival rate at 30 days post-arrest has doubled during the last two decades from 4.8% (1992) to 10.7% (2011).¹²

The exact mechanism of collapse in an individual patient is often impossible to establish because only a minority of patients are having their cardiac electrical activity monitored at the time of their collapse. However, in studies of patients who were monitored at the time of the incident, ventricular tachycardia (VT) or ventricular fibrillation (VF) accounted for the majority of episodes, with bradycardia or asystole accounting for nearly all of the remainder.^{13, 14} In real life, the first recorded arrhythmia in OHCA by emergency medical system (EMS) staff has served as a marker of comparison. There are four main electrical pathophysiological mechanisms leading to CA: ventricular tachycardia (VT), ventricular fibrillation (VF), asystole and pulseless electrical activity (PEA).

VF as the initially recorded rhythm is generally present in 25-50% of OHCA patients.^{4, 12, 15, 16} The most common sequence of events leading to arrhythmic sudden cardiac death is the progression of ventricular tachycardia (VT) into ventricular fibrillation (VF), often followed by asystole or pulseless electric

activity.¹³ The transition of shockable rhythms (VT/VF) to more dismal rhythms such as asystole or pulseless electric activity depends on various factors, but is highly dependent on time.¹⁷ The longer the time interval, the more likely the VT/VF degenerates to pulseless electric activity or asystole. This may explain why the survival in patients presenting with asystole or PEA is low, <5%.^{18, 19}

Aetiology

The cause of cardiac arrest is often based on a clinical judgement and is divided into cardiac causes and non-cardiac causes.¹⁷

A presumed cardiac cause has been reported in more than two thirds of OHCA.²⁰⁻²² Coronary disease was considered the underlying causes of CA in more than half of patients, according to previously autopsy studies.^{23, 24} Non-cardiac causes such as trauma, drug intoxication, near-drowning, lung diseases etc. account for approximately 18-30%.^{6, 25}

Ventricular arrhythmias (VF/VT) are most commonly the result of ischaemic heart disease.²⁶ These rhythms may also present in the setting of non-ischaemic left ventricular dysfunction, prolonged QT-interval secondary to drugs, electrolyte abnormalities, and familial syndromes of conduction abnormality (disorders in cardiac ion channels).²⁷

The most common causes of PEA are myocardial ischaemia/infarction, hypovolaemia, hypoxia, and pulmonary embolism.^{28, 29}

Cardiopulmonary resuscitation

Once cardiac arrest has occurred, the factors which determine the patient's outcome may be divided into those related to the patient, the event, the EMS system and the provided therapy. The patient related factors, such as age and co-morbidity, and the event related factors, such as witnessed collapse and cardiac rhythm, are strongly associated with outcome.³⁰ However, a high quality cardiopulmonary resuscitation remains essential to improving outcomes.³¹ A successful neurological outcome is made possible by timely interventions that can maintain some cerebral perfusion and promote the restoration of spontaneous circulation (e.g., bystander CPR and early defibrillation).^{7, 32} Moreover, the increased use of cardiac interventions^{33, 34} during the past decade and the improved post cardiac arrest care including targeted temperature management,³⁵ have contributed to an overall increase in cardiac arrest survival and neurological recovery.¹⁰⁻¹²

The chain of survival, with its four links of early recognition and call for help, early CPR, early defibrillation, and advanced post resuscitative care illustrates the interventions needed to improve survival with a good neurological outcome after cardiac arrest.³⁶

The natural course of neurological recovery

Following a few minutes of circulatory arrest all brain functions cease. Clinically, patients are comatose and often, brain stem reflexes are absent shortly after cardiac arrest. Once the circulation is re-established, the brain function will gradually recover. Since the brain stem is more resistant to anoxic-ischaemic damage than the cerebral cortex,³⁷ these patients will first regain brain stem reflexes, such as the pupillary light reflex, corneal reflexes and spontaneous breathing. The next step of recovery during unconsciousness is characterized by decerebrate or decorticate posturing, or defensive reactivity and eye-opening. After awakening, the steps of recovery comprise the recovery of verbal and motor responsiveness, eye-orientation, speech, auto-orientation, locomotor functions and finally retention and memory functions.³⁸

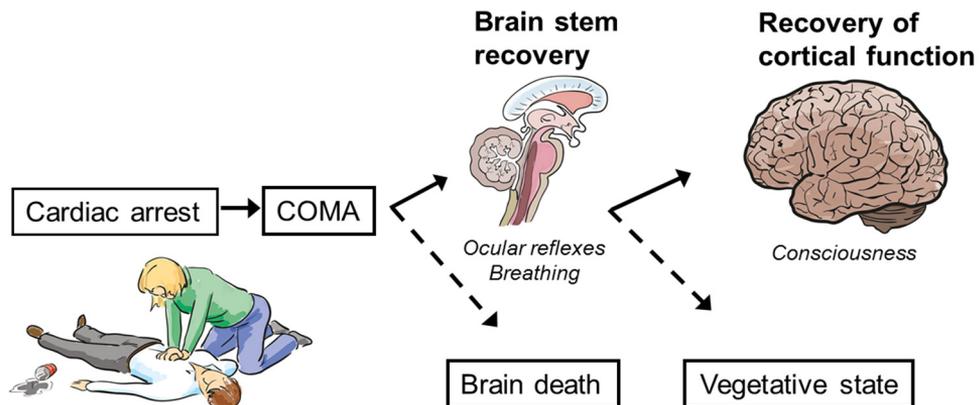


Figure 1.
The natural course of recovery after sudden cardiac arrest
Illustration by Bo Jönsson. With permission.

Post-cardiac arrest syndrome

During and after cardiac arrest, patients suffer from profound systemic ischaemia followed by reperfusion. This results in a condition termed the post-cardiac arrest syndrome (PCAS), a complex combination of pathophysiological processes including: brain injury, myocardial dysfunction, ischaemic/reperfusion response, and the precipitating disease. The concept of post-resuscitation disease as a unique and new entity was introduced by Negovsky in 1972.³⁹ The expression “post-cardiac arrest syndrome” was introduced in 2008 to describe the combination of pathophysiological processes compounding the primary condition that led to the cardiac arrest.⁴⁰

Brain injury

Brain tissue is particularly vulnerable to ischaemia, given its high metabolic demand and very limited energy resources. Neuronal death occurs within hours to days after exposure to global ischaemia.^{41, 42} Neurons within the hippocampus, neocortex, parts of the basal ganglia and the cerebellar purkinje-cells are the most sensitive to an ischaemic insult.^{37, 41}

Two main categories of neuronal cell death were described following ischaemia: neuronal necrosis and apoptosis (programmed cell death) which may occur in parallel in the same cell population.⁴³

Within about two minutes of ischaemia adenosine triphosphate (ATP) and glucose stores are depleted.^{44, 45} During these first minutes the cerebral tissue oxygen pressure also declines rapidly and reaches a zero level.⁴⁶ Anaerobic glycolysis lead to an accumulation of intracellular lactic acid and hydrogen ions (H^+), causing intracerebral acidosis.^{47, 48} After a few minutes of continued ischaemia the inhibition of ATP dependent Na/K pumps results in changes in ion gradients across the plasma membrane, leading to anoxic depolarization and the loss of the membrane potential essential for signal transduction.⁴⁹ The opening of voltage-dependent calcium channels leads to an influx of calcium and activation of calcium –dependent processes. These include the remodelling of membrane and cytoskeletal structures, signal transduction pathways and apoptosis.⁵⁰ Increased intracellular calcium levels triggers mitochondrial dysfunction that causes a further lack of energy repletion, free radical formation, release of destructive enzymes, degradation of cytoskeleton, and decreased in protein synthesis.⁵¹⁻⁵³ In addition, an increased glutamate release to the extracellular space occurs, that further enhances calcium influx via N-methyl-D-aspartate (NMDA) receptors.⁵⁴

After cerebral blood flow is restored, the increased oxygen pressure promotes the production of reactive oxygen species which may damage and compromise essential mitochondrial and cellular components.⁵⁵ Cell death continues by both apoptosis and necrosis. Cerebral vascular autoregulation is impaired and cerebral oedema may develop caused by capillary dysfunction.⁴³

Post-ischemic brain injury may be further complicated by systemic metabolic derangements such as pyrexia and hyperglycaemia. Also, seizures may occur and further increase the metabolic stress in the post-arrest phase. Clinically, brain injury in PCAS manifests as a range of neurologic deficits, including neurocognitive dysfunction, seizures, myoclonus, coma, and brain death.

Myocardial dysfunction

Myocardial dysfunction in PCAS is largely characterized by global hypokinesia and may be exacerbated by an underlying coronary artery disease or an acute coronary syndrome. Patients are usually haemodynamically unstable in the post-arrest phase, and the combination of catecholamine excess and myocardial stunning contributes to worsening of haemodynamics. A persistent low cardiac output, despite vasoactive drugs, at 24 hours post-arrest is associated with death due to multiorgan failure.⁵⁶

Clinically, this manifests as decreased cardiac output, hypotension, dysrhythmias, and sometimes cardiovascular collapse.⁴³

Systemic ischaemia/reperfusion response

The global systemic ischaemia/reperfusion response in the PCAS is mainly characterized by an activation of immunological and coagulation pathways caused by oxygen debt in the tissues, similar to sepsis. The features of this sepsis-like syndrome are vasodilation, intravascular volume depletion, impaired oxygen delivery and uptake, multiple organ failure, increased susceptibility to infection, and abnormalities in microcirculation.⁵⁷⁻⁶¹ Similarly to the patient suffering from septic shock, this ischaemia/reperfusion response in the PCAS may be reversible and responsive to early goal-directed therapy, which includes fluids, inotropes, and vasopressors.⁶²

Persistent precipitating pathology

Persistent precipitating pathology in the PCAS is related to the specific disease process that is the underlying cause for the cardiac arrest. While an acute coronary

syndrome is the common cause, others include, pulmonary disease, haemorrhage, sepsis, toxic exposures, and environmental insults. Therapies and management strategies are disease specific and must be coordinated with the management of the post-cardiac arrest neurologic, myocardial, and systemic disease processes.⁶³

Targeted temperature management

The history of induced hypothermia following cardiac arrest began in the late 1950s when a case series of four patients resuscitated from CA and treated with TTM at 30°-34°C showed good neurological recovery in all four patients.⁶⁴ In the early 1960s, Safar and colleagues recommended the use of therapeutic resuscitative hypothermia for humans after cardiac arrest.⁶⁵ At this time, it was believed that moderate hypothermia (28°-32°C) was required for brain protection. However, the resulting systemic side effects with total body cooling to temperatures below 30°C, such as shivering, vasospasm, arrhythmias and infections, caused the resuscitative hypothermia research to be halted for decades.

Previous experimental⁶⁶ and clinical studies^{67, 68} showed that fever after global ischaemia, as well as after brain injury of other causes (stroke or trauma),^{69, 70} is associated with worse outcome.

Several experimental studies performed during the 1980s showed that hypothermia (30°-34°C) had a neuroprotective effect following cardiac arrest in rodents⁷¹ and dogs.⁷²⁻⁷⁴ Among the many described mechanisms believed responsible for the neuroprotective effects of hypothermia are: a decrease in cerebral metabolism, a reduction of apoptotic mechanisms including mitochondrial dysfunction, slowing of the cerebral excitatory cascade, a decrease of the inflammatory response, reduced production of oxygen free radicals, and a decrease of vascular and membrane permeability.⁷⁵

The convergent experimental data were encouraged by two landmark clinical studies published in 2002, one randomized⁷⁶ and one quasi-randomized,⁷⁷ that compared TTM at 32°-34°C for 12-24 hours. Both studies indicated a forceful effect by TTM to improve neurological recovery,^{76, 77} and one of the studies showed a reduction in mortality.⁷⁶ However, these trials only included OHCA-patients with primary rhythm of VF or pulseless VT, they were comparatively small (275 and 77 patients), and the participating physicians were not blinded to the target temperature.

A systematic review using the GRADE-methodology found that the evidence for the clinical use of TTM of 32°-34°C is low and was associated with a substantial risk of systematic and random errors.⁷⁸

In an attempt to explore the optimal targeted temperature for management of comatose survivors of OHCA of presumed cardiac cause, two strict temperature regimes of 33°C vs 36°C were compared in a large international trial, the Targeted Temperature Management (TTM) trial, between 2010 and 2013. The main result of the TTM trial was that there were no differences in mortality or neurological outcome between the two intervention groups.⁷⁹

As a consequence, recent guidelines recommend the use of TTM between 32°-36 °C for at least 24 hours post-arrest.⁸⁰

Neurological prognostication in comatose CA survivors

Once the circulation has been re-established, evaluating the extent of brain injury is crucial for neurological prognostication. The majority of patients who are discharged alive, will ultimately obtain a good neurological function, although mild cognitive difficulties are common.⁸¹⁻⁸³ In patients who remain comatose several days after resuscitation, neurologists are often asked to assess the prognosis. The role of the neurologist is to provide as much prognostic information as possible in order to guide the treatment, inform the treating physicians and relatives about prognosis and to avoid futile treatment in patients with no chance of recovery. Post-CA prognostication is a complex process, usually charged with emotion for both physicians and relatives. During the past decade, neurological prognostication has been integrated as an important part of the post-CA care, and has moved toward a multimodal paradigm including clinical examinations combined with electrophysiological investigations, neuroimaging, and biomarkers.^{84, 85, 81, 86}

Prior studies have shown that prognostication plays a significant role in withdrawal of life-sustaining therapy (WLST).⁸⁷⁻⁹⁰ Keeping all this in mind, the clinicians are looking for evidence regarding accurate predictors and the optimal timing of prognostication, to avoid inaccurate prognosis and premature WLST.

The origin of the prognostication algorithm started in the early 1980s when Levy and colleagues published the first prognostication algorithm, the “Levy Criteria”.⁹¹ These criteria predict a patient’s long-term neurological outcome within the first few days after cardiac arrest. The algorithm basically assured no chance of regaining independence if a patient had absent pupillary reflexes at any time after cardiac arrest, or motor response no better than extension at 72 hours post-CA.

Further, in 1994, Edgren *et al.* used the control group (131 patients) from the Brain Resuscitation after Cardiac arrest Trial (BRCT) 1, to investigate whether a permanent vegetative state could be accurately predicted in comatose patients within one week after CA. The authors found that absent motor response to pain or

absent pupillary light reflexes on day 3 were invariably associated with a poor outcome. In a further multivariate analysis, the authors found that absent motor response to pain was the only independent predictor of poor outcome at >16 hours post arrest.⁹²

In 2006, a landmark review from the American Academy of Neurology (AAN) recommended a sequential algorithm to predict poor neurological outcome in comatose survivors after cardiac arrest.⁹³ According to this algorithm, the presence of myoclonus status epilepticus on day 1, the bilateral absence of the N20-response of the somatosensory evoked potentials (SSEPs) or a blood concentration of neuron specific enolase (NSE) above 33 µg/ L at days 1–3, and absent pupillary and corneal reflexes or a motor response no better than extension (Glasgow coma scale M1–2) at day 3 accurately predicted poor outcome. However, these recommendations were based on studies conducted before the introduction of TTM, which is now a standardized treatment in post-arrest coma. Moreover, the AAN algorithm did not include predictors such as electroencephalography (EEG) and imaging studies, for which the evidence was still insufficient at that time. Recent reviews have shown that these investigations can be useful adjuncts to the previous, more established, predictive indices.^{86, 94-96}

In 2013, the Swedish Resuscitation Council recommended a delayed prognostication approach at 72 hours after rewarming (4.5 days after CA), and provided helpful suggestions for early and late predictors of good and poor recovery.⁸¹

The European Resuscitation Council (ERC) and the European Society of Intensive Care Medicine (ESICM) recently issued updated guidelines on neurological prognostication after cardiac arrest, which included the four main prognostication modalities (clinical examination, electrophysiology including EEG-based predictors, biomarkers, and imaging studies) and recommended that these modalities should be combined whenever possible.⁶³

The recent ERC guidelines emphasise the need to use a multimodal strategy for prognostication as well as allowing sufficient time for neurological recovery and to enable the sedative to be cleared. The suggested prognostication strategy is to start the prognostication process at a minimum of 72 hours post-arrest in patients who are still comatose and where confounders have been excluded. Importantly, the guidelines emphasize that only ocular reflexes and SSEP are reliable marker of prognosis at that time (figure 2).⁶³

Multimodal prognostication

Accurate prediction of the neurological prognosis after cardiac arrest is critically important because these predictions are strongly associated with decisions about withdrawal of life-sustaining treatment/therapy (WLST). Prognostication tools include serial neurological examinations, serum neuron specific enolase (NSE), somatosensory evoked potentials (SSEPs), electroencephalography (EEG), brain computed tomography (CT) and magnetic resonance imaging (MRI) (figure 3). However, no single test can predict neurological outcome with complete certainty.^{96, 97} Moreover, following the introduction of TTM as a neuroprotective strategy, the reliability of different prognostic tests has been questioned.⁹⁸⁻¹⁰⁴ For this reason, the use of multiple modalities is recommended in recent ERC/ESICM guidelines, to minimize the risk of erroneous prognostications of poor outcome.⁶³

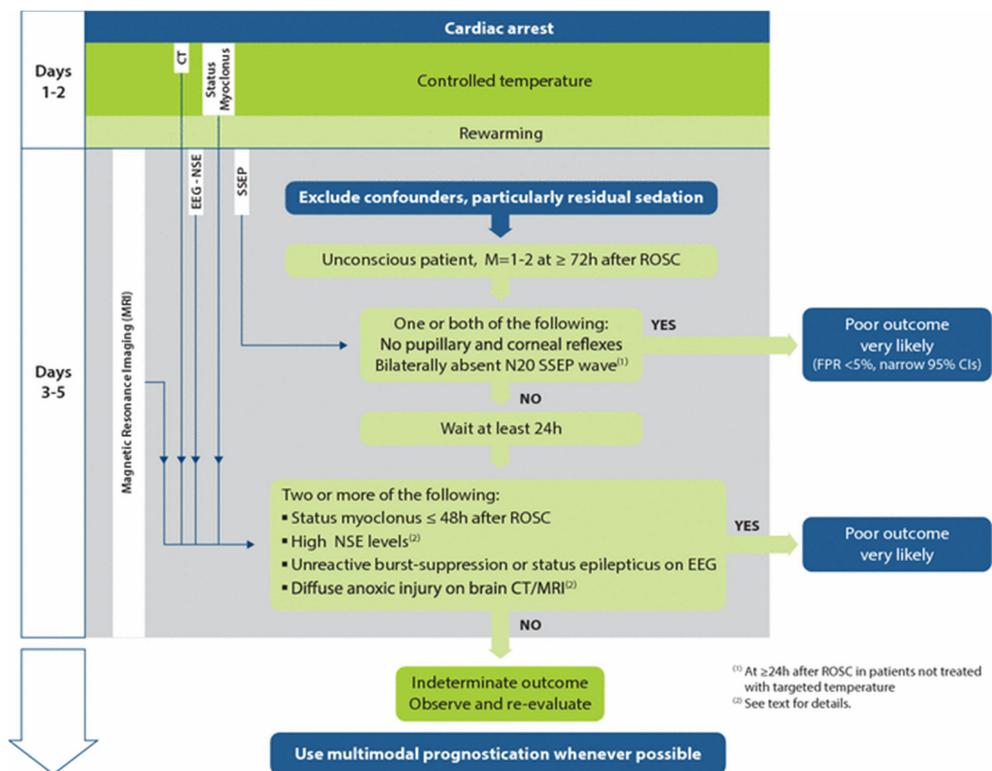


Figure 2.

Prognostication strategy algorithm

From Nolan JP, Soar J, Cariou A, *et al.* European Resuscitation Council and European Society of Intensive Care Medicine 2015 guidelines for post-resuscitation care. *Intensive care medicine* 2015;41:2039-2056. Reprinted with permission.

Clinical examination

In patients who remain comatose after the clearance of sedative drugs, an assessment of the neurological prognosis is usually performed. The findings from a clinical neurological examination constitute the foundation of the prognostic assessment since it directly evaluates the brain function and is easy to perform bedside. The neurological examination includes the testing of brainstem reflexes, motor response to painful stimuli and observation of myoclonus and other seizures.

Before the introduction of TTM, absent pupillary or corneal reflexes and absent or extensor motor response on day 3 post-arrest were found to predict poor outcome with a false positive rate of zero.^{93, 105}

In a retrospective study of 36 TTM-treated patients, the authors found that two of 14 patients with poor motor responses at 72 hours regained consciousness, whereas no patients with absent pupillary or corneal reflexes regained consciousness.⁹⁸ A larger prospective study including 111 TTM treated patients, which used the AAN algorithm for prognostication, found a high false positive rate (FPR) of 24% for motor score and a FPR of 4% for brainstem reflexes. The authors concluded that clinical tests should be interpreted with caution in TTM-treated patients.⁹⁹ In 2011, Samaniego and colleagues investigated the use of sedation and its effect on the accuracy of outcome predictors in 85 patients treated with and without TTM. The results suggested that sedation was commonly used in TTM-treated patients, making the motor score to painful stimuli and the corneal reflexes at a 72 hours-examination less reliable. In contrast, in patients who were not sedated, both predictors had a 100% specificity to predict a poor outcome.¹⁰¹

A meta-analysis by Kamps *et al.*, including 1,153 TTM-treated patients, found that a GCS-motor response of 1-2 had a high FPR for predicting poor outcome compared with bilaterally absent corneal or pupillary responses.¹⁰⁶

In 2013, two larger high-quality systematic reviews and meta-analyses regarding the reliability of clinical findings to predict poor outcomes were published. One of the studies evaluated 2,828 patients not treated with TTM.¹⁰⁷ The authors concluded that the presence of myoclonus at 24-48 hours and absence of pupillary reflex at 72 hours predicted poor outcome with 0% FPR and narrow (<10%) 95% CIs. In the other meta-analysis including 2,403 patients treated with TTM, a combination of absent pupillary and corneal reflexes combined with a motor response no better than extension after rewarming were all predictive of poor outcome.¹⁰⁸

To conclude the findings of the all these meta analyses, absent pupillary and corneal reflexes at 72 hours post-cardiac arrest seem to remain highly reliable indicators of poor outcome, whereas a poor seems to be less reliable in both non TTM-treated and TTM-treated patients. Motor response is considered the clinical sign most

affected by sedatives, opiates and neuromuscular blockade,⁹⁶ which are widely used in patients undergoing targeted temperature management.

In contrast, in a study of 72 TTM-treated patients, the presence of motor response within 24 hours after the cessation of sedation predicted a good outcome with 100% specificity.¹⁰⁹

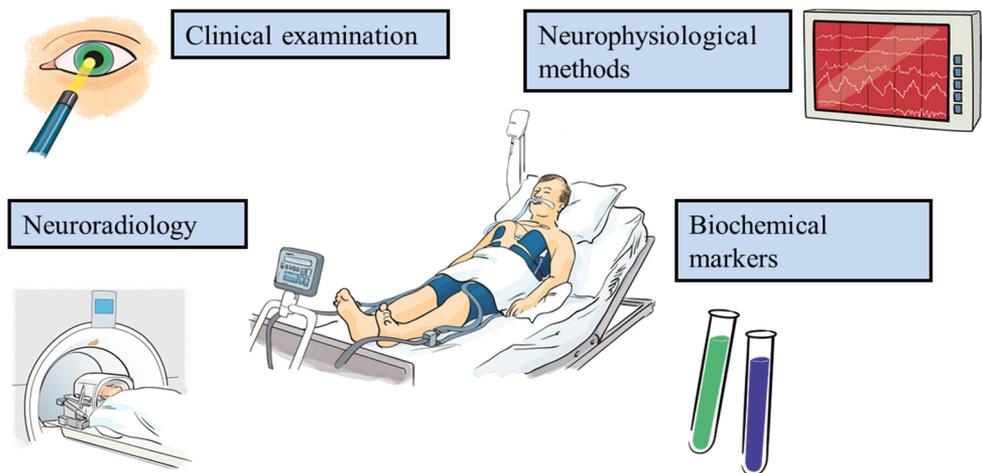


Figure 3. Neurological assessment of prognosis in comatose survivors after cardiac arrest
Prognostication methods include serial neurological examinations, neurophysiological tests (somatosensory evoked potentials, SSEPs; electroencephalography, EEG), neuroimaging (brain computed tomography, CT and magnetic resonance imaging, MRI) and measurement of biomarkers (serum neuron specific enolase, NSE).
Illustration by Bo Jönsson. With permission.

Somatosensory evoked potentials

The somatosensory-evoked potentials (SSEPs) test the integrity of the afferent sensory pathways and are elicited by electrical stimulation of the median nerve. Responses are registered over the brachial plexus (N9 potential), cervical spinal cord (N13), subcortical (N18) and over the contralateral sensory cerebral cortex (N20 potential) (figure 4). The N20-responses reflect the integrity of thalamo-cortical projections, and can only be reliably interpreted when the peripheral and spinal responses are also present. If peripheral responses are not present, this may be due to peripheral nerve damage.¹¹⁰

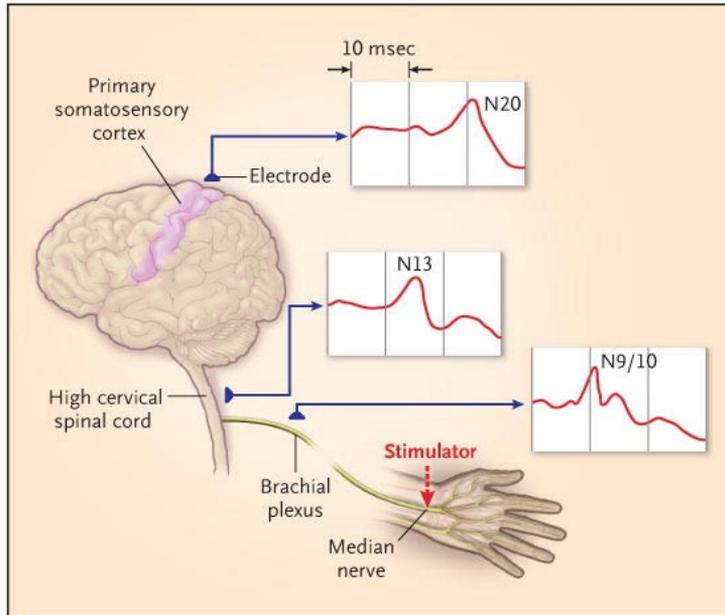


Figure 4. Somatosensory Evoked Response with Median-Nerve Stimulation
 Reproduced with permission from "Neurologic Prognosis after Cardiac Arrest" by Young GB. N Engl J Med 2009.
 Copyright Massachusetts Medical.

Bilateral absence of N20-responses has been shown to strongly correlate with poor outcome both when performing during TTM^{104, 111-113} and after rewarming.^{100, 104, 114, 115} Besides the high specificity in predicting poor outcome, SSEP has several advantages, such as being a non-invasive method and being less affected by sedation within the normal dosage range or metabolic disturbance. The N20-peaks have been reported to remain present even at a sedation level sufficient to induce an isoelectric EEG.¹¹⁰ However, SSEP's accuracy to predict good outcome has been disappointing, since only one half of the patients with poor outcome have bilaterally absent N 20.^{106, 108}

The largest study evaluating the reliability of SSEP in the prediction of poor outcome was the Prognosis in Postanoxic Coma (PROPAC) 1 study, which included 407 patients, all but 10 patients non-TTM treated. Absent N20 was found to be a reliable marker to predict poor outcome (defined as CPC 4-5), with an FPR of 0% (0-3) as early as 24 hours post-arrest.¹¹⁶ The high accuracy of SSEP seems to persist in TTM-treated patients, even if a few isolated false positive predictions have been reported.^{103, 117 118}

In a large prospective study (PROPAC II), the performance of SSEPs both during TTM and after rewarming was studied.¹⁰⁴ The authors found that three of 43 patients with bilateral absence of N20 on SSEP performed during TTM recovered, leading to a FPR of 3% (1-7). However, in a post hoc review of the false positive patients, the investigators concluded that these SSEP recordings were undeterminable due to noise.

The optimal timing of SSEP has been a matter of discussion. While some studies found that absent N20 is a reliable marker of poor prognosis even if performed during TTM,^{104, 112, 113} other studies raised concerns about early conduction of SSEP, since potential for improvement or normalisation of N20-peaks may exist over the first days post-arrest.¹¹⁹ Recent guidelines recommend using the finding of bilaterally absent N20 on SSEP after at least 72 hours after CA to predict poor outcome in comatose post-CA patients.⁸⁶

The clinician should be aware of the limitations of SSEP, including the interference effects of noise^{104, 120}, moderate to good inter-observer reliability in interpretation^{120, 121} and the low sensitivity to detect a good outcome.¹⁰⁶

Electroencephalogram

Background

EEG following CA has been studied extensively, since it allows for an immediate examination of cortical and cortical-subcortical structures. The neurons that are most sensitive to ischaemia are the cortical neurons generating the postsynaptic potentials recorded by a scalp EEG.¹²² During resuscitation, the EEG is suppressed and this pattern may persist for several hours after circulation is restored.³⁸ Recovery is then seen as an intermittent cortical background activity followed by continuous activity.^{123, 124}

EEG was used for decades to identify patterns predictive of poor outcome after cardiac arrest and to diagnose electrographic seizures or status epilepticus. While EEG is a non-invasive, inexpensive and largely available test, it is limited by the absence of a universally accepted classification system¹²⁵ and by its susceptibility to sedation¹²⁶ and metabolic conditions.⁸⁴ TTM doesn't seem to affect the prognostic ability of EEG,¹²⁷ but sedation, which are widely used during TTM, may affect the EEG background's reactivity to external stimuli.¹²⁸

EEG as prognostic tool

According to a recent survey on current practices in prognostication after CA, EEG was the most commonly used tool to assess prognosis.¹²⁹

However, the literature has been difficult to interpret due to inconsistencies in the timing of EEG recordings and the broad range of definitions of different EEG patterns between studies. A dichotomization of EEG patterns in malignant and benign pattern is often used. Among the malignant patterns described in the AAN guidelines, there are suppressed or low-voltage background $<20 \mu\text{V}$, burst suppression with generalized epileptiform activity, and generalized periodic complexes on a flat background.⁹³ In several studies, a low-voltage EEG $<20 \mu\text{V}$ background after 24 hours post-arrest in TTM-treated patients^{94, 112, 130} predicted poor outcome, but not invariably.¹²⁷ Burst-suppression can occur early after CA in survivors with good outcome,¹¹² but if a burst-suppression pattern is still present beyond 24 hours post-arrest, the prognosis is poor according to most studies both in non-TTM-treated patients¹³¹⁻¹³³ and TTM-treated patients.^{100, 104, 130, 134} However, sporadic survivors have been reported.^{135, 136} A recent routine-EEG study that used a strict definition of BS according to the ACNS terminology reported no patients with good outcome and BS after rewarming.¹³⁷

On the other hand, an early onset of continuous background during TTM or after normothermia^{115, 130, 138, 139} and reactivity of the EEG background to external stimuli⁹⁹ have been associated with good outcome.

In order to standardize the terminology of the EEG patterns, the American Clinical Neurophysiology Society (ACNS) recently published a revised version of ACNS terminology.¹⁴⁰

Using the ACNS terminology a classification of EEG patterns into highly malignant, malignant and benign has recently been proposed.¹²⁷ The highly malignant patterns are suppressed background ($<10 \mu\text{V}$), burst-suppression (suppression periods constitute $>50\%$) and continuously appearing periodic discharges on a suppressed background. Malignant EEG-patterns comprise: low-voltage, discontinuous or unreactive background; abundant periodic or rhythmic discharges; unequivocal seizure activity and reversed anterior-posterior gradient.

Since the cortical electrical activity can change with time,¹³⁹ the predictive value of EEG is probably enhanced if serial or continuous EEGs are performed over several days to assess temporal development and trends.

However, a recent study has shown that two routine EEG recordings of 20–30 min duration, within 48 hours of cardiac arrest and including stimulations for reactivity, are as informative as a continuous EEG monitoring.¹⁴¹ An exception is the postanoxic status epilepticus, in which continuous EEG recording is recommended.

The ESICM recommends EEG during TTM and within 24 hours after rewarming to rule out non-convulsive electrographic seizures in all comatose patients after CA. EEG is also suggested to assist with the prognostication of coma after CA,

particularly in patients treated with TTM. Whether cEEG has higher prognostic accuracy than intermittent EEG is still unknown.¹⁴²

Overt status epilepticus

Status epilepticus (SE) is a neurological emergency associated with an overall mortality rate of about 20%.¹⁴³ Mortality is mainly related to the secondary systemic physiologic complications such as hyperthermia, hyperkalaemia, acidosis and cardiopulmonary collapse.^{144, 145} Nonconvulsive status epilepticus (NCSE) is a heterogeneous condition with different clinical manifestations, EEG patterns and aetiology. The described prevalence of NCSE in comatose patients ranges from 5%-48%.¹⁴⁶ NCSE may be suggested clinically, but the diagnosis often requires EEG. In critically ill and comatose patients, NCSE is an under-recognized condition and the delay in diagnosis and treatment may be associated with increased mortality.

In a case series of 100 patients with NCSE of different aetiologies excluding anoxic encephalopathies, the authors found that the high mortality (18%) of NCSE correlated with the underlying aetiology, severe impairment of mental status and the development of acute complications, but not with the EEG pattern.¹⁴⁷ In a smaller study of 24 prospectively identified critically ill elderly patients (again anoxia excluded) with NCSE, 13 (54%) died.¹⁴⁸ Young *et al.* reported that 13 (57%) of 23 patients with NCSE (anoxia included) died. Seizure duration and delay to diagnosis were associated with increased mortality.¹⁴⁹

Postanoxic electrographic status epilepticus

Electrographic seizures or status epilepticus are EEG based diagnoses that occur in up to one third of comatose survivors of CA.^{112, 138, 139, 150-153} Clinically, seizures usually appear in the form of myoclonic muscle twitches in the face, trunk or extremities. Generalized tonic-clonic or focal epileptic seizures may also occur but are less common. Postanoxic status epilepticus is associated with a poor prognosis.^{114, 139, 150, 151, 154-156} However, case series have shown that a subgroup of patients may indeed recover and have a good final outcome.^{114, 138, 153, 157, 158} The reported favourable signs in survivors of PSE are the recovery of a continuous EEG background before the onset of PSE, reactive EEG background, preserved brainstem reflexes and preserved N20-peaks on SSEPs.^{114, 138, 158}

The lack of a previous consensus regarding EEG terminology and classifications has probably been important for the differences in the reported incidences of postanoxic electrographic status epilepticus between studies.⁹⁵ According to ACNS, *unequivocal* electrographic seizure activity consist of generalized spike-wave discharges at 3Hz or faster or clearly evolving discharges of any type that reach a frequency >4Hz.¹⁴⁰ However, many authors also considered other rhythmic or periodic patterns, such as generalized periodic discharges (GPDs), lateralized periodic discharges or rhythmic delta activity as seizure activity.^{138, 153, 154}

Apart from the diagnostic difficulties, the evaluation of treatment effects in PSE is also difficult, mainly due to concomitant brain injury or ongoing sedation, muscle relaxation and pain relief treatment. Moreover, the cause-effect relationship between PSE and brain injury is still an open question.

Neuroimaging

The ischaemia during CA leads to injuries especially in the grey matter areas such as the cortex, the thalami and the basal ganglia. These ischaemic injuries appear, in computed tomography (CT) imaging, as a loss of differentiation between the grey and white matter and as a generalized swelling with effacement of cortical sulci.¹⁵⁹ Some smaller cohort studies have reported that signs of reduced grey-white-matter differentiation on head CT examination may be an early predictor of poor outcome.^{160, 161} However, the prognostic value of head CT after cardiac arrest has been inconclusively investigated.

A plain/non-contrast CT scan can also provide information about structural lesions. Head CT is therefore often used to rule out non-cardiac causes of unconsciousness such as an ischaemic stroke or subarachnoid- and intracerebral haemorrhage, and to exclude contraindications for TTM.^{81, 162}

Magnetic resonance imaging (MRI) is recommended by the ERC algorithm as an additional prognostic tool, but its reliability has not been sufficiently examined.⁷⁹ Cytotoxic oedema secondary to ischaemia can be detected with diffusion-weighted sequences (DWI). Smaller studies have shown that the presence of generalized changes on DWI or fluid-attenuated inversion recovery (FLAIR) sequences within five days after CA are associated with a poor outcome.¹⁶³⁻¹⁶⁵ A recent retrospective multicentre study showed that an apparent MRI- DWI threshold of 650×10^{-6} mm²/s in $\geq 10\%$ of the total brain volume could differentiate patients with good versus poor outcome. However, this threshold had a FPR of 9% to predict poor outcome.¹⁶⁶

To conclude, although the specificity of either cranial CT or MR is insufficient to accurately predict poor outcome on their own, both methods can serve as adjunctive tools and add useful prognostic information in selected comatose patients.^{86, 96}

Biomarkers

The most commonly studied biomarker of brain injury after CA is neuron-specific enolase (NSE). NSE is an intracellular enzyme of glycolysis that is present in neurons and neuroendocrine cells.¹⁶⁷ NSE is also present in erythrocytes¹⁶⁸ and platelets,¹⁶⁹ which is a source of error with concomitant haemolysis. In the CA setting, NSE is released into the blood stream when brain injury occurs via the

damaged blood brain barrier. Cut-off levels with 0% false positive rates (FPR) for predicting poor outcome varies between studies, mainly due to differences in the laboratory assays and the time of sampling.^{170, 171} However, NSE levels above 60 µg/l at 48-72 hours post-arrest are very rarely associated with a good outcome.⁸⁶

A rise in NSE between 24 and 48 hours after CA has been reported to be indicative of a poor outcome.^{172, 173} Correspondingly, a decrease of NSE levels between 24 and 48 hours after CA was associated with good outcome.¹⁷⁴

In a recent post hoc analysis of the TTM trial, NSE levels from 686 patients measured at 24, 48, and 72 hours post-arrest were analysed. The authors found that an increase in NSE level between any two time points was associated with poor outcome regardless of TTM temperature.¹⁷⁵

Withdrawal of life-sustaining therapy and ethical aspects

The majority of patients remaining comatose due to a severe postanoxic brain injury may still survive in a vegetative state or with other severe neurological disability as long as continued intensive care is provided during the first post-arrest weeks. Consequently, the most common immediate cause of death for these patients is the withdrawal of life-sustaining therapy (WLST) such as ventilator support, and usually based on a presumption of poor neurological outcome regardless of therapy. However, in some patients without established poor neurological prognosis, ethical reasons may still justify WLST.

When dealing with ethical conflicts in the decision-making, the clinicians may consider and balance the four principles of biomedical ethics (figure 5).

These four principles were developed by Beauchamp and Childress and are: 1. *Autonomy*; 2. *Beneficence*; 3. *Non-maleficence* and 4. *Justice*.¹⁷⁶

Autonomy

The autonomy principle is usually difficult to apply after cardiac arrest, since most patients considered are comatose and, thereby have lost their ability to express their wishes. However, in some cases, the patient's wishes are known either by written document or oral directive to the relatives.

Beneficence

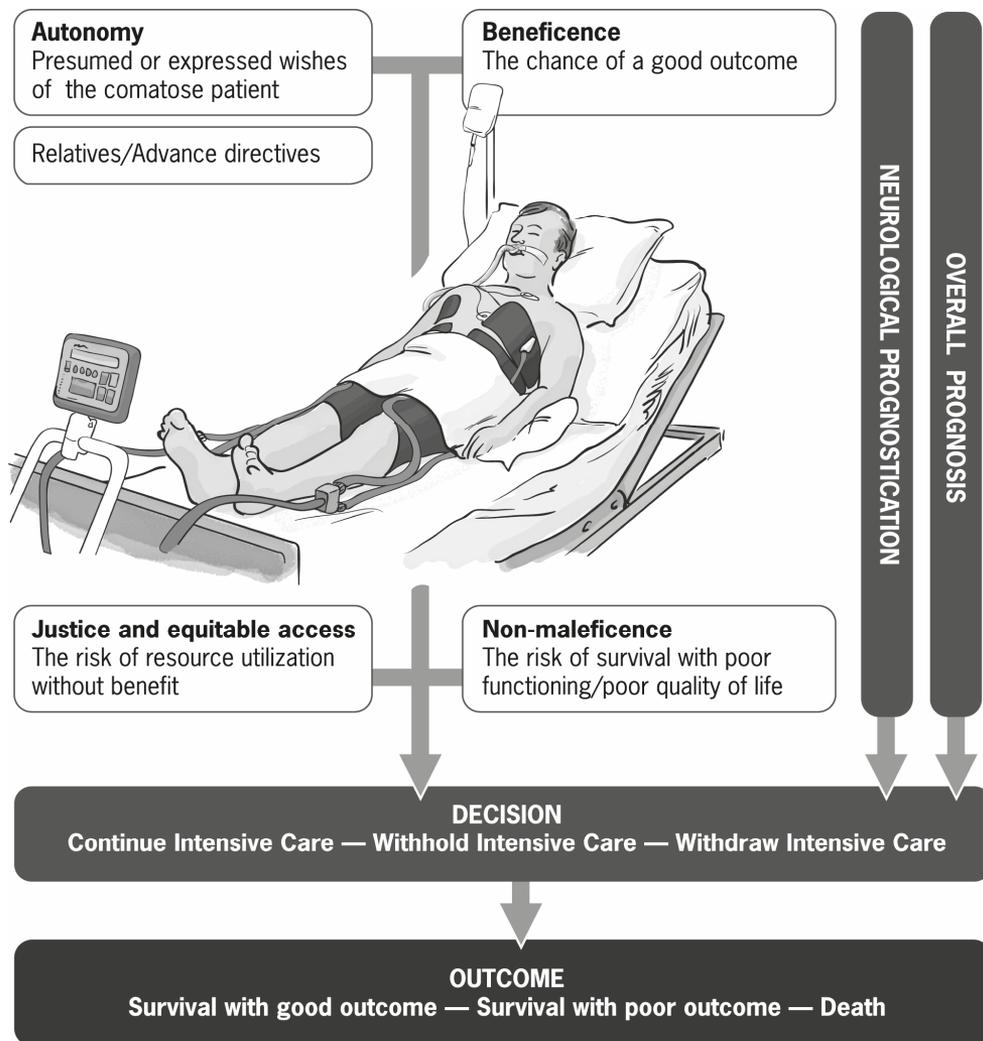
The main purpose of any treatment, including intensive care, is to be of benefit to the patient. In Sweden, it is legal to discontinue intensive care support if it is not believed of benefit for the patient. However, the practice of limiting intensive care for patients with a presumed poor outcome differs considerably between countries.¹⁷⁷

Non-maleficence

This principle has been used for centuries. For example, in the 4th century BC, Hippocrates, a physician-philosopher, directed physicians “to do good or to do no harm”.¹⁷⁸ In cardiac arrest settings, patients with severe brain injury may survive with no (vegetative state) or minimal consciousness if artificial nutrition is continued and complications treated. From the patient’s perspective, this approach may be considered an unwanted or “malicious” outcome. In countries performing neurological prognostication and WLST, survival in vegetative state (CPC 4) is nowadays very rare, but it is considerably more common in countries with other traditions or where WLST is legally prohibited.¹⁷⁹

Justice

The principle of distributive justice is applicable when resources are limited and decisions must be made about who will receive these resources. It is not uncommon that clinicians face the need to prioritize between their patients. Sometimes, it may not be ethically justified to prolong intensive care in patients with a likely poor prognosis if this, by competition, may exclude another patient for whom intensive care may be lifesaving.



Figur 5.
The four principles of biomedical ethics
The four ethical principles are balanced and informed by the results from instruments of prognostication and the patient's general medical condition. A decision on the level of care is made that will have consequences for the patient's final outcome. Illustration by Bo Jönsson. With permission.

Aims of the thesis

This thesis is focused on the neurological prognostication in comatose survivors of cardiac arrest, with the main aim of investigating the routines for prognostication and decisions on level of care. Secondary aims were to evaluate the prognostic value of a clinical neurological examination, somatosensory evoked potential and EEG in comatose survivors of cardiac arrest who received TTM. The specific aims are:

- To investigate the influence of hypothermia and delayed prognostication on the mode of death after CA.
- To describe the characteristics of patients who were declared brain dead and became organ donors.
- To determine whether targeted treatment management at 33°C compared with 36°C affected the prognostic accuracy of clinical neurological findings and somatosensory evoked potentials (SSEP) in comatose patients.
- To describe the prevalence of electrographic status epilepticus (ESE) and potential clinical and electrographic prognostic markers.
- To investigate how routines for neurological prognostication may have affected decisions on withdrawal of life sustaining therapy (WLST) in the two intervention groups.
- To describe if there are any differences between countries regarding routines for prognostication and WLST.

Material and Methods

The present thesis consists of four studies: one was based on participants in the coma project in southern Sweden between 2003 and 2008 (Paper I); two studies were based on the TTM trial participants (Paper II and IV); and one was based on patients treated after CA at the ICU of Skåne University Hospital in Lund, between 2008 and 2013 (Paper III). The materials and methods are described in detail in each paper.

Table 1.
Overview of the design of the studies included in this thesis

Paper	I	II	III	IV
Design	Single-centre, retrospective study	Pre-specified <i>post hoc</i> analysis of a prospective international multicentre study	Single-centre, retrospective study	Pre-specified <i>post hoc</i> analysis of a prospective international multicentre study
Study population	In-hospital and out-of-hospital CA-patients treated with TTM at 33°C. 2003-2008	Out-of-hospital CA patients treated with TTM of either 33°C or 36°C 2010-2013	In-hospital and out-of-hospital CA-patients treated with TTM of either 33°C or 36°C 2008-2013	Out-of-hospital CA patients treated with TTM of either 33°C or 36°C 2010-2013
Participants	N=162	N=939	N=127	N=939
Statistical analysis	Descriptive and analytic statistics (Mann–Whitney U-test with Bonferroni Corrections)	Descriptive and analytic statistics (Mann–Whitney U and Chi-squared test; sensitivity and false positive rate (1-specificity))	Descriptive and analytic statistics (Mann–Whitney U, Fischer exact test, and Chi-squared test)	Descriptive and analytic statistics (Mann–Whitney U and Chi-squared; Log-rank tests and Kaplan-Meier graphs; multiple logistic regression analysis)

Paper I

Settings and participants

This was a retrospective study of prospectively collected data on comatose survivors of cardiac arrest treated with TTM 33°C at the general ICU and thoracic ICU at Skåne University Hospital, Lund, from January 2003 to December 2008.

All adult comatose patients after CA, regardless of initial cardiac rhythm or the location of arrest, with a Glasgow Coma Scale (GCS) score <8 and without contraindications for TTM, were included. Patients were excluded from TTM if their CA was secondary to aortic dissection, intracerebral bleeding, and major trauma or if the patient was terminally ill.

Ethical permission was obtained from the Regional Ethical Review Board at Lund University (411/2004, 223/2008). Informed written consent was obtained from next-of-kin, and retrospectively from patients who recovered.

Treatment protocol

TTM at 33°C was induced using cold saline and maintained using an external cooling device or intravenous cooling. The patient's core temperature was measured in the bladder by urine catheter and maintained at $33.0 \pm 1^\circ\text{C}$ for 24 hours. The patients were sedated using propofol or midazolam and fentanyl. A non-depolarising muscle relaxant (rocuronium) was used intermittently to reduce shivering and facilitate cooling. Rewarming was active and controlled to $0.5^\circ\text{C}/\text{hour}$. At the time of normothermia, sedation was reduced or withdrawn.

Neurological prognostication

In patients not regaining consciousness, full supported treatment was continued for at least 72 hours after normothermia. At this time, a clinical neurological examination and evaluation was performed. The evaluation was based on clinical findings in combination with results from neurophysiological investigations, neuroimaging and occasionally results and trends of the biomarkers (neuron-specific-enolase, NSE). According to the guidelines, the prognosis was considered to be poor and withdrawal of intensive care was recommended if the patient was comatose with a Glasgow-Coma-Scale-motor score (GCS) of 1-2 and/or bilateral absent pupillary light reflexes or corneal reflexes and/or bilateral absence of cortical SSEP N20-peaks. Other negative prognostic markers that could be considered in

predicting poor outcome were a severely pathological EEG-pattern (flat, suppression-burst or status epilepticus not responding to treatment), an elevated NSE level ($>33 \mu\text{g/L}$) and generalized ischaemic changes on computed tomography (CT) or diffusion-weighted brain magnetic resonance imaging (MRI). In cases of uncertain prognosis the observation was prolonged. Brain death was diagnosed according to Swedish legislation by two clinical examinations, including brain-stem testing and apnoea-test, at least 2 hours apart. Post-mortem histopathological examinations were performed by a neuropathologist.

Data collection and procedure

All medical records and charts, including the results of neurological examinations, radiological investigations, continuous simplified amplitude-integrated electroencephalograms (aEEG) and conventional electroencephalograms (EEG), somatosensory evoked potentials (SSEP), biochemical markers and prescribed medical treatments were retrospectively examined systematically as well as results from *post-mortem* histopathological examinations.

The primary cause of death was classified retrospectively by an intensivist and a neurologist in consensus into 3 groups:

1. Cardiac disorders (circulatory failure despite vasoactive drugs, aortic balloon pump or heart–lung machine and new fatal arrhythmia).
2. Brain injury (hypoxic-ischaemic encephalopathy (HIE), expansive brain infarction, traumatic intracranial haemorrhage and brain death).
3. Other causes (sepsis, multi-organ failure and trauma).

The patients were evaluated using the five grade Cerebral Performance Categories (CPC) scale.¹⁸⁰ These evaluations were performed at ICU discharge, at hospital discharge and at a 6-month follow-up. Good neurological outcome was defined as CPC 1–2.

The CPC scale is a five-graded scale:

1. Good cerebral performance (conscious, alert, able to work)
2. Moderate cerebral disability (conscious, can carry out independent activities)
3. Severe cerebral disability (conscious, dependent on others for daily support)
4. Coma or vegetative state
5. Death

Outcome

The primary outcomes were cause of death and the frequency of WLST. Secondary outcomes were the characteristics of patients becoming brain dead, CPC at ICU discharge, CPC at hospital discharge and CPC at 6-month follow-up.

Papers II and IV

Settings and participants

These studies were *post hoc* analyses of the TTM trial, and both were approved by the TTM trial steering group before the data analysis.

The modified intention-to-treat population consisted of 939 adult comatose survivors of out-of-hospital CA of presumed cardiac causes, irrespective of the initial rhythm, who remained unconscious (GCS <8) after the sustained (>20 minutes) return of spontaneous circulation (ROSC). The patients were randomized 1:1 to two strict targeted temperature regimens of either 33°C or 36°C after ROSC between Nov 2010 and Jan 2013. The main exclusion criteria were unwitnessed arrests with asystole as an initial rhythm, more than four hours from ROSC to screening, persistent cardiogenic shock, pregnancy, and known CPC 3 or 4 pre-arrest.¹⁸¹

Treatment protocol

The target core temperature of either 33°C or 36°C was achieved in patients as soon as possible after randomisation. Patients were then rewarmed to 37°C 28 hours after randomisation at a maximum speed of 0.5°C per hour. All patients were intubated, mechanically ventilated and sedated throughout the 36-hour intervention period in both groups, but specific regimens were not mandated in the trial.

After the intervention period, the sedation was discontinued or tapered.

Neurological prognostication

All patients were actively treated until 72 hours after rewarming (108 hours post-arrest). Patients who then remained unconscious were neurologically assessed.^{181, 182}

A standardized protocol for prognostication and the principles for WLST was considered an important part of the trial design, in order to minimize the risk of bias due to premature withdrawal of care. The assessor of prognosis was blinded to the intervention assignment.

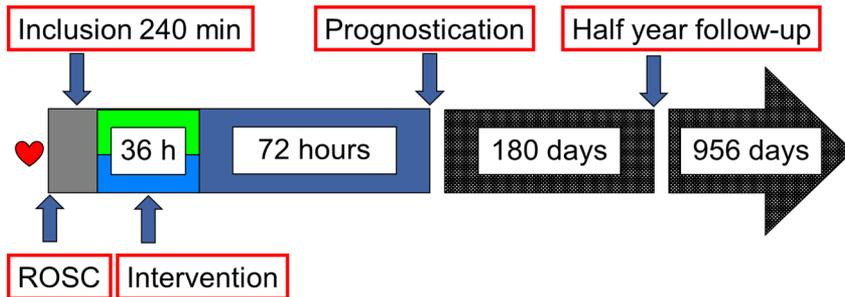


Figure 6.
The TTM study timeline

The neurological evaluation was based on the findings from a clinical neurological examination with additional support from the results of EEG and SSEP. According to the protocol, a conventional EEG should be performed at 12-36 hours after rewarming in all patients who remained unconscious. Median nerve SSEP was performed at 48-72 hours after the end of the intervention period at sites where this technology was available.

Pre-specified reasons for a poor prognosis at the time of prognostication, and allowing for WLST, were:

- 1) Persisting coma with Glasgow Coma Scale-motor response absent or extensor (GCS-M ≤ 2) at a minimum of 72 hours after the intervention period and bilateral absence of N20-peak on the median nerve SSEP after the intervention period.
- 2) Persisting coma with GCS-M ≤ 2 at minimum 72 hours after the intervention period and a treatment refractory status epilepticus (for definition of status epilepticus, see⁷⁹ Supplementary Appendix, available at NEJM.org).

Earlier WLST was allowed for the following reasons:

- 1) Brain death due to cerebral herniation and diagnosed according to national legislation.
- 2) Myoclonus status during the first 24 hours after admission and a bilateral absence of N20-peaks on median nerve SSEP after rewarming.

3) Ethical reasons

The physician performing the neurological evaluation issued one of the following recommendations:

- Continue active intensive care
- Do not escalate intensive care
- Withdraw intensive care

The final decision regarding treatment restrictions was, however, left at the discretion of the treating physician.

The clinical findings (GCS-M score, pupillary light reflex (PLR) and corneal reflexes (CR)), results from the SSEP and the recommendations regarding the level of care were systematically recorded in the electronic case report form (eCRF). Only one formal neurological evaluation of prognosis was registered in the eCRF for each patient.

Data collection and procedure

All electronic case report forms were systematically examined for information regarding the timing and findings of prognostic neurological assessments and withdrawal of life-sustaining treatment. Site investigators were contacted for clarification of incomplete or conflicting data, which were corrected accordingly.

In **paper II** the sensitivity, false positive rate (1-specificity), positive and negative value for each examination finding to predict poor outcome were calculated and presented with 95% confidence intervals.

In **paper IV** the data were analysed descriptively. A multiple logistic regression analysis model was applied to evaluate the significance of clinical findings, EEG, SSEP, head computer tomography (CT) brain and magnetic resonance imaging (MRI), as well as other standard variables like gender, age, etc., to explain the recommendation on level of care. The outcome used in the regression analysis was recommendation on level of care dichotomized to “continue active care” vs “do-not-escalate/withdraw active care”. A log-rank test was used to test the differences in survival curves between recommendation groups and Kaplan-Meier graphs were produced.

Outcome

Paper II

The primary outcomes were the accuracy (sensitivity and false positive rate) of clinical findings and SSEP to predict a poor neurological outcome assessed in a face-to-face follow-up after six months using the Cerebral Performance Category scale (CPC). Poor outcome was defined as severe disability (CPC 3), vegetative state (CPC 4) or death (CPC 5).

Paper IV

The primary outcomes were the frequency, timing and reasons of WLST. The secondary outcomes were the proportion of prognosticated patients in different countries, the ICU length and the proportion of survivors with poor neurological outcome (defined as CPC 3 and CPC 4).

Paper III

Settings and participants

The study cohort consisted of all consecutive CA patients treated at the ICU of Skåne University Hospital in Lund between January 2008 and February 2013. A subgroup of these patients were included in the TTM trial.

Treatment

All patients were treated with TTM for 24 hours. During the intervention period, including the phase of rewarming, the sedation was maintained but not protocolised. Patients with clinical seizures or ESE were treated with combinations of propofol, midazolam, fosphenytoin, valproic acid, and levetiracetam at the discretion of the treating physician. The antiepileptic treatment was not protocolised.

All patients were monitored with cEEG from arrival at the ICU, using a two-channel bipolar montage (C3–P3, C4–P4 or F3–P3, F4–P4, according to the 10–20 system), displaying both the original EEG signal and trends of amplitude-integrated EEG.

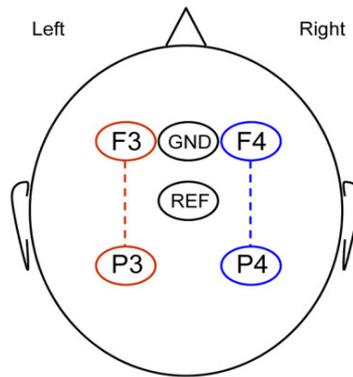


Figure 7.
Simplified electrode montage used in paper III

Data collection and procedure

Patients' charts and cEEG statements were initially screened in order to identify patients with detected or suspected ESE. Subsequently, a neurophysiologist, blinded to the patient's outcome, retrospectively reviewed the cEEG charts.

The EEG background patterns at the start of cEEG monitoring and the best background during the four hours prior to ESE debut were classified as: a) flat, b) burst-suppression, c) nearly continuous and d) continuous. ESE was defined as continuous rhythmic polyspike-/spike-/sharp-and wave or periodic discharges, with a typical frequency of ≥ 1 Hz for a minimum of 30 min or unequivocal seizures, according to the EEG terminology of the American Clinical Neurophysiology Society¹⁴⁰, recurring for at least 30 min. The duration of ESE was calculated from the first 30-minute period with ESE to the end of the last 30-minute period of ESE or to the end of monitoring if ESE was still ongoing.

All medical records, results from SSEP, and NSE levels were retrospectively examined.

The data were analysed descriptively for demographic characteristics. Comparisons between different groups were conducted and displayed in the tables.

Outcome

The primary outcome was the prevalence of postanoxic status epilepticus. Secondary outcomes were EEG patterns and clinical characteristics related to a favourable outcome.

Results

Paper I

A total of 162 patients with both in-hospital and out-of-hospital CA treated with TTM were included in the study.

Outcome

Seventy six patients (47%) survived and the majority of these (n=65, 86%) had a favourable outcome at hospital discharge (CPC 1 and CPC 2) with further improvement at 6 months.

Of the 86 patients (53%) who died during hospitalisation, 73 never regained consciousness after CA and 13 made an initial recovery but died later on. The majority of patients (67%) died during their ICU stay, at a median of 6 days after CA. One third were transferred to a medical ward and most of them died within two weeks.

Cause of death

We found that the cause of death was classified as cardiac disorders in 14 patients (16%), brain injury in 61 (71%) and other in 11 (13%).

Death due to cardiac disorders occurred earlier, at a median of two days after CA while patients with presumed brain injury as a cause of death died later, at a median of seven days after CA. Brain injury consisted of hypoxic-ischaemic brain injury in 58 patients (95%) and focal brain injury in three (5%).

Death due to other causes including multi-organ failure, sepsis, intestinal ischaemia and cervical fracture with sympathetic failure occurred later, at a median of 13 days after CA (figure 8).

Brain damage was the predominant cause of death for resuscitated patients

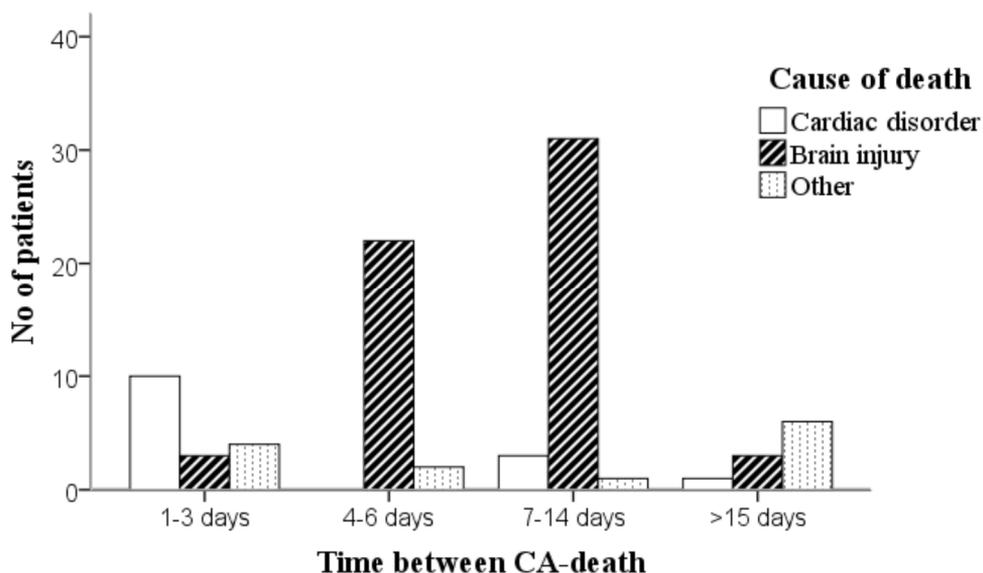


Figure 8.
Cause of death among resuscitated CA-patients

Brain injury

Hypoxic-ischaemic brain injury

The majority of these patients (54 of 58) died after multimodal neurological prognostication and a decision of withdrawal of life-sustaining therapy (WLST). The remaining four patients were declared brain dead.

In most of the patients who were neurologically prognosticated (50 of 54) the prognosis was assessed according to protocol, at 72 hours after rewarming (figure 9).

At the time point of prognostication the prognosis was considered poor in 47 of 50 patients and uncertain in three patients.

All patients receiving a poor prognosis statement had WLST. The majority (32 of 47) died during their ICU stay and 15 were transferred to the medical ward. In

patients with uncertain prognosis, the active care was prolonged by 1-5 days. All these patients died due to respiratory complications after WLST.

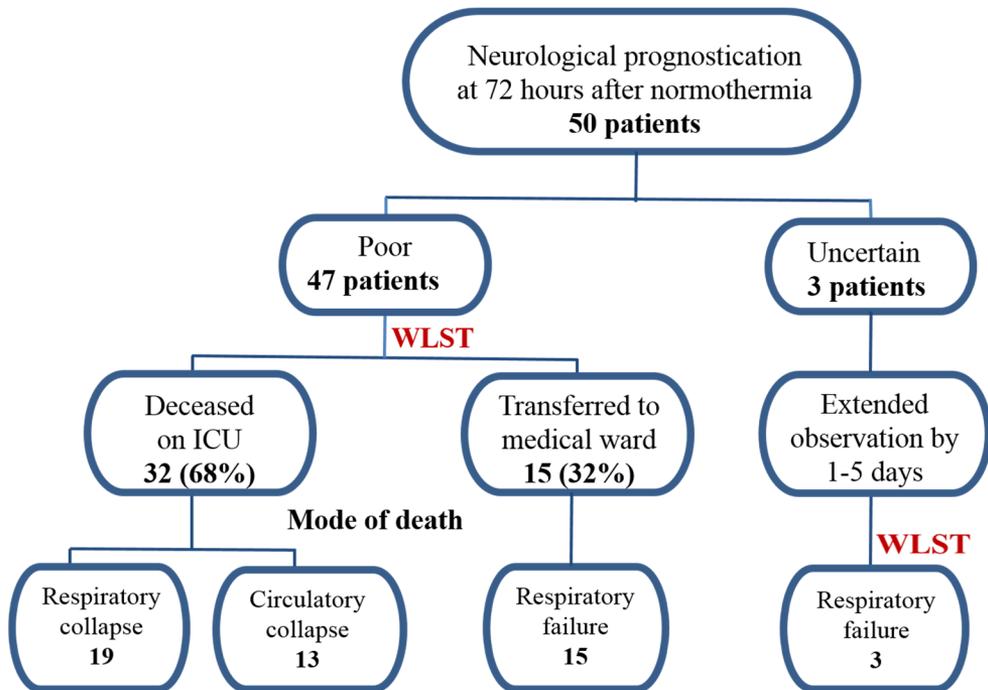


Figure 9.
Outcome of patients who were neurologically prognosticated

Focal expansive brain injury

In three patients the cause of death was focal expansive brain injury: traumatic intracranial hematoma in two patients and malignant middle cerebral artery infarction with uncal herniation in one patient.

Histopathological examination

Histopathological features of hypoxic brain injury were confirmed in 26 of 27 examined patients. Among the patients in whom the cause of death was classified as “cardiac disorder” or “other”, hypoxic-ischaemic features were seen in 3 of 4 and 1 of 1 respectively.

Paper II

The modified intention-to-treat-population of the TTM trial consisted of 939 patients: 473 assigned to 33°C and 466 to 36°C (figure 10).

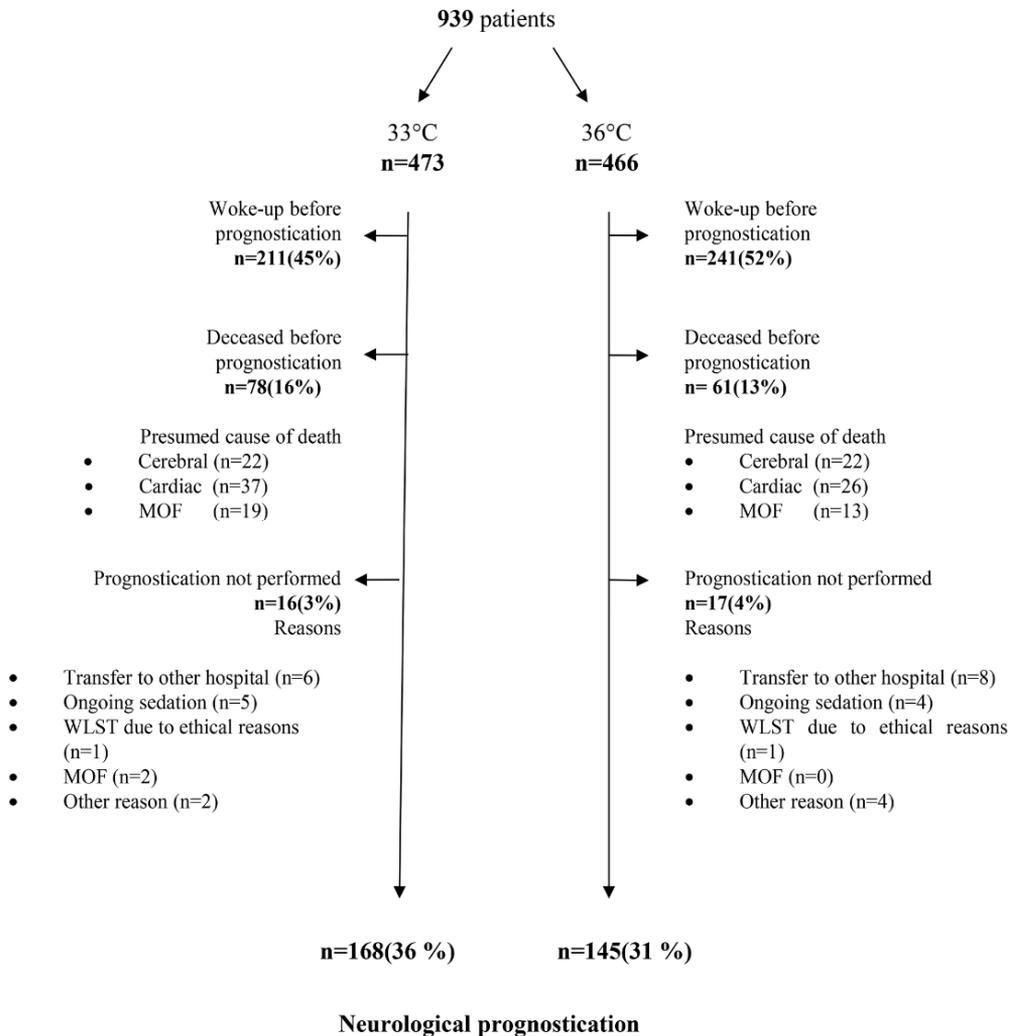


Figure 10.
Study flow chart

In total, 313 patients were neurologically evaluated, of which 168 were treated with a targeted temperature of 33°C and 145 were treated with 36°C. The median time from CA to neurological prognostication was 117 hours (5 days) and did not differ significantly between the groups ($p=0.71$, Mann-Whitney U test).

The assessment of neurological prognosis was conducted by a neurologist in 142 (45%) patients; by an intensivist in 146 (47%) patients; and by other physicians in 24 (8%) patients, similar in both groups ($p=0.67$, Chi square-test).

The recommendation from the assessor of neurological prognosis was to “continue intensive care” in 117 patients (37%), “do-not-escalate intensive care” in 55 patients (18%) and “withdraw active intensive care” in 141 (45%) patients, without significant differences between the intervention groups ($p=0.70$, Chi square-test).

Accuracy for predicting poor outcome

Glasgow coma scale motor score (GCS M)

The sensitivity of a GCS-M ≤ 2 to predict a poor neurological outcome (CPC 3-5 at six months follow-up) decreased with time after CA while the specificity increased correspondingly. We found a high false positive rate (FPR) of 40% (CI 11.7-77.0) for motor response tested within 72 hours (three days) after CA, but this also remained high at the later time intervals after CA.

Pupillary light reflexes (PLR) and corneal reflexes (CR)

The sensitivity of PLR and CR to detect poor outcome was low and decreased further with time after cardiac arrest. A higher FPR of 7.7% (CI 1.3-33.4) for PLR and CR was found in the group evaluated at 72-107 hours, due to one false prediction in PLR and one in CR respectively.

Somatosensory evoked potentials (SSEPs)

The sensitivity of SSEP was low (41% in 33°C group vs 50% in 36°C group). The FPR for bilaterally absent SSEP to predict poor outcome was 0.0% in 33°C group and 6.7% in 36°C group, the last-mentioned due to one false prediction.

Comparisons between temperature groups

Clinical findings

The comparison of the accuracy of clinical findings in predicting poor outcome between the two temperature groups did not show any statistically significant differences. The results are displayed in the table 2.

Table 2

Prediction of outcome with clinical tests. Comparison between the two interventions groups.

	Patients tested n (%)	FP n	Sensitivity % (95% CI)	P-value	FPR % (95% CI)	P-value
GCS M \leq 2				0.87		1.00
33°C	168 (100)	6	81.9 (74.6-87.5)		20.0 (9.5-37.3)	
36°C	144 (99)	3	82.7 (75.1-88.3)		17.6 (6.1-41.1)	
No pupillary light responses bilaterally				0.25		1.00
33°C	165 (98)	1	27.4 (20.5-35.5)		3.3 (0.5-16.67)	
36°C	143 (99)	0	20.6 (14.4-28.6)		0.0 (0.0-18.5)	
No corneal reflexes bilaterally				0.89		1.00
33°C	165 (98)	1	33.8 (26.4-42.2)		3.4 (0.6-17.17)	
36°C	136 (94)	0	35.3 (27.2-44.3)		0.0 (0.0-18.5)	

Data are given in numbers and percentages. Sensitivity and false positive rate (FPR) are expressed as percentage with their 95% confidence interval (CI). GCS M, Glasgow Coma Scale motor score.

SSEP was found to be a reliable prognostic marker to predict poor outcome regardless of temperature management (table 3).

Table 3

Prognostic accuracy of SSEP at 6 month follow-up (33°C versus 36° C).

	Patients tested, n, (%)	FP n	Sensitivity % (95% CI)	P-value	FPR % (CI)	P-value
Bilateral absent SSEP (N20)				0.27		0.38
33°C	110 (23)	0	41.2 (31.3-51.9)		0.0 (0.0-13.9)	
36°C	94 (20)	1	50.0 (39.0-61.0)		6.7 (1.1-29.9)	
All tested	204 (22)	1	45.3 (37.8-53.1)		2.6 (0.4-13.2)	

SSEP, somatosensory evoked potentials; CI, confidence interval; FPR, false positive rate.

Paper III

Continuous EEG

A total of 127 patients were monitored with cEEG from Jan 2008 to Feb 2013. Forty-one (32%) patients developed electrographic status epilepticus (ESE). Clinical seizures/myoclonus was present in the majority of patients with ESE (85%) compared to only 13% of the patients without ESE.

EEG background and outcome

All 25 patients (61%) with discontinuous or burst-suppression EEG background prior to the start of ESE died.

The remaining 16 patients (39%) had continuous or nearly continuous background patterns prior to the start of ESE. Four of them (25%) survived, three with CPC 1-2 and one with CPC 3 at six months.

The majority of non-survivors (35/37, 95%) died after a WLST decision.

Survivors of ESE

The four survivors developed ESE at a median of 46 hours after CA. All had preserved brainstem reflexes after rewarming, preserved N-20 peaks on SSEP and NSE level at 48 hours <40 µg/L.

Table 4
Survivors of postanoxic status epilepticus

	Patient 1	Patient 2	Patient 3	Patient 4
Age	61	69	52	54
Cause of CA	Cardiac	Cardiac	Cardiac	Cardiac
Time (min) from CA to ROSC	20	36	20	90
Time (hours) from CA to ESE diagnosis	66	43	40	49
Clinical seizures/myoclonus	Yes, after normothermia	Yes, after normothermia	No	No
EEG characteristics	Continuous background → ESE	Continuous background → ESE	Continuous background → ESE	Continuous background → ESE
Anticonvulsant drugs	Clonazepam Levetiracetam Fosphenytoin Phenobarbital	Valproic acid Levetiracetam Phenobarbital	Valproic acid Levetiracetam Fosphenytoin Phenobarbital	Valproic acid Levetiracetam Phenobarbital
ESE duration (hours)	274	132	153	253
Time from ESE (days) to ability to follow commands	20	24	Unknown	15
Length of sedation (day)	11	3,5	At least 8	14
NSE at 48 hours	20	18	25	37
Bilateral N20-peaks on SSEP	Yes	Yes	Yes	Yes
CPC at 6 months	2	3	1	2

CA=cardiac arrest. ROSC= return of spontaneous circulation. ESE=electrographic status epilepticus. EEG=electroencephalogram. NSE=neuron specific enolase. SSEP=somatosensory evoked potential. CPC=cerebral performance categories score.

Paper IV

Of the 939 patients included in the TTM study, 452 patients regained consciousness, 139 died before neurological prognostication and 313 underwent neurological prognostication. In the remaining 33 patients, prognostication was not performed, and for two patients the data were missing.

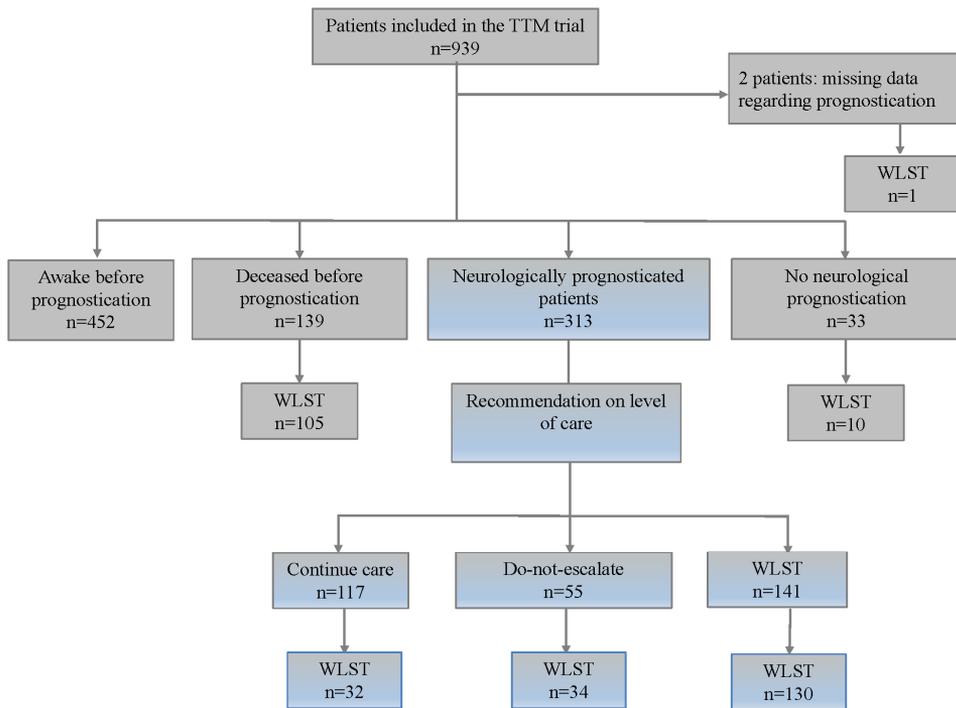


Figure 11.
Study flow chart

Neurologically prognosticated patients

At the time of prognostication, 313 patients were neurologically assessed. The recommendation was: to continue active intensive care in 117 (37%), do-not-escalate intensive care in 55 (18%) and to withdraw intensive care in 141 (45%). The frequency and combinations of prognostic tools used in order to support the recommendations are displayed in table 5.

Table 5

Tools used for neurological prognostication and recommendations on level of care

	n	Clinical findings	SSEP	EEG	CT	MR
Clinical findings	280	55	17	37	21	0
SSEP	151	17	4	9	0	1
EEG	213	37	9	11	0	0
CT	92	21	0	0	2	0
MR	13		0	0	0	0
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Clinical findings + SSEP				82	0	0
Clinical findings + EEG					30	3
SSEP+ EEG					1	2
EEG+CT						1
Clinical findings + SSEP + EEG					33	2
Clinical findings + SSEP + EEG + CT						4

For the majority of patients in the TTM trial, neurological prognosis was formulated using a multimodal approach. Our results show that clinical findings, EEG and SSEPs were most frequently involved in supporting the recommendation to continue care. Multiple logistic regression indicated that brain CT, EEG and clinical findings, when considered part of prognostication, had the strongest influence on the recommendations of “DNE” or “withdraw active intensive care”: OR 3.25 (1.7–6.19, $p < 0.001$) for CT; OR 3.04 (1.62–5.68, $p = 0.001$) for EEG; and OR 3.54 (1.5–8.35, $p = 0.004$) for clinical findings (table 6).

Table 6

Binary logistic regression including the patients who were neurologically prognosticated.

Variables	Total numbers of tests	Part of the recommendation, n, (%)		Recommendation of DNE/WAIC	
		CC n=117	DNE/WAIC n=196	Odds Ratio (95%CI)	P-value
Clinical examination	313	98 (84%)	182 (93%)	3.538 (1.500–8.345)	0.004
SSEP	172	56 (48%)	95 (48%)	0.898 (0.502–1.607)	0.719
EEG	248	67 (57%)	146 (74%)	3.035 (1.623–5.677)	0.001
CT	170	17 (15%)	75 (38%)	3.247 (1.702–6.193)	0.000
MRI	24	5 (4%)	8 (4%)	1.105 (0.281–4.346)	0.886
Age				1.036 (1.010-1.062)	0.005
Gender(female)				0.817 (0.411-1.626)	0.566
Time to ROSC				1.028 (1.012-1.044)	0.000
Initial rhythm (non-shockable)				3.200 (1.648-6.212)	0.001
Target temperature				1.126 (0.662-1.914)	0.660

A binary logistic regression model was applied to evaluate the significance of clinical findings, electroencephalography (EEG), somatosensory evoked potential (SSEP), head computed tomography (CT) and magnetic resonance imaging (MRI) and elucidate recommendations on continuing level of care. The model was adjusted for age, gender, time to return of spontaneous circulation (ROSC), initial rhythm and target temperature. The outcome was dichotomized to continue active intensive care vs do-not-escalate active intensive care or withdraw active intensive care. CC = "continue active intensive care". DNE = do-not-escalate active intensive care. WAIC = withdraw active intensive care.

Depending on the recommendation given at the time point of prognostication, further care proceeded differently.

Patients with a recommendation to continue active intensive care

Among 117 patients with a "continue care" recommendation, WLST was performed in 32 (27%), usually one to several days after prognostication. The reported reasons for WLST were: neurological futility (n=24), failing circulation (n=3), MOF (n=5), medical co-morbidity (n=1), and ethical (n=3). More than one reason could be recorded per patient. Of those patients who had WLST 31/32 died before follow-up and one survived in CPC 3. At follow-up, a total of 58 (50%) patients had died at a median of 14 days (8-36) after CA (Figure 12 B).

Patients with a do-not-escalate recommendation

A total of 55 patients received a "do-not-escalate" recommendation, 34 (62%) of whom had WLST during the first two days after prognostication. The reasons for WLST were: neurological futility (n=29), failing circulation (n=2), MOF (n=3),

medical co-morbidity (n=0), and ethical (n=4). At follow-up 51 (92%) had died at a median of eight days (6-10) after CA.

Patients with recommendation to withdraw active intensive care

Of 141 patients with a recommendation to “withdraw active intensive care”, WLST was performed in 130 (92%) of cases and in the majority of these patients (105/130, 81%) the WLST was performed on the day of prognostication. The reported reasons for WLST were: neurological futility (n=113), failing circulation (n=8), MOF (n=10), medical-comorbidity (n=5), ethical (n=13), and other (n=1) At follow-up all patients with recommendation to “withdraw active intensive care” had died except two; one who had WLST but who survived in CPC 2, one who had not WLST and survived in CPC 3. The median time to death was five days (4-8) after CA.

The Kaplan-Meier curves showed that there was a clear separation in time from recommendation to WLST, as well as from recommendation to death, between the three recommendation groups (log rank <0.001, figure 12).

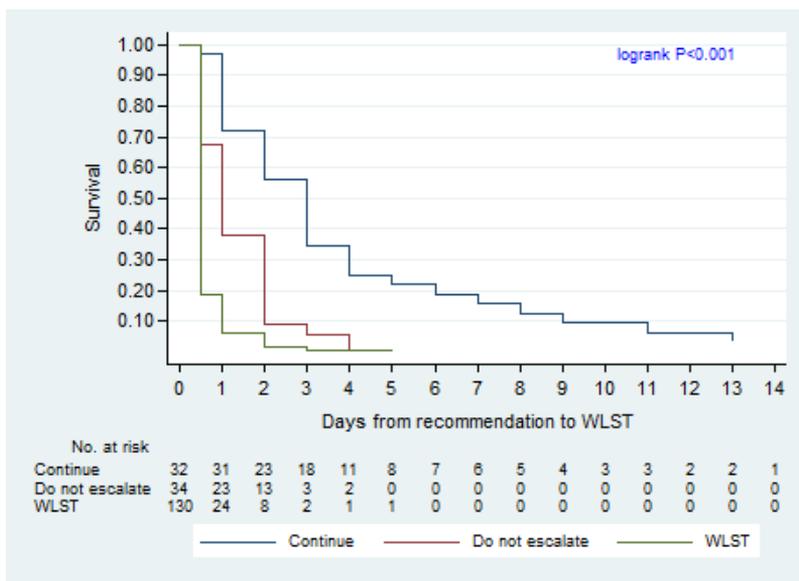


Figure 12. A. Kaplan-Meier curves showing the probability of withdrawal of life-sustaining therapy over time by recommendation on level of care.

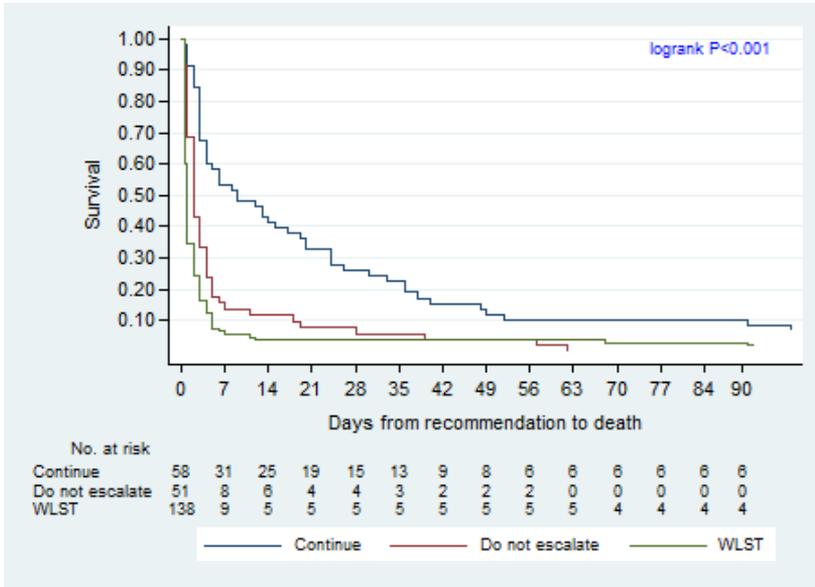


Figure 12. B.
Kaplan-Meier curves showing the probability of death over time by recommendation on level of care.

Outcome at six month follow-up for the entire study population

At six month follow-up, 447 patients had died. Of these 411 (92% of all deaths and 44% of included patients) died before hospital discharge. The recommendation of withdrawal of life-sustaining therapy preceded death in 310 (75%). WLST within 3 ICU days occurred in 87 patients (21% of in-hospital deaths), for neurological reasons including brain death in 28 patients.

The majority of the neurologically prognosticated patients died after WLST due to neurological reasons. Amongst patients dying before prognostication, WLST occurred in approximately two-thirds, mainly due to non-neurological reasons.

The predominating presumed cause of death was “cerebral” in both prognosticated patients and the entire study population (figure 13).

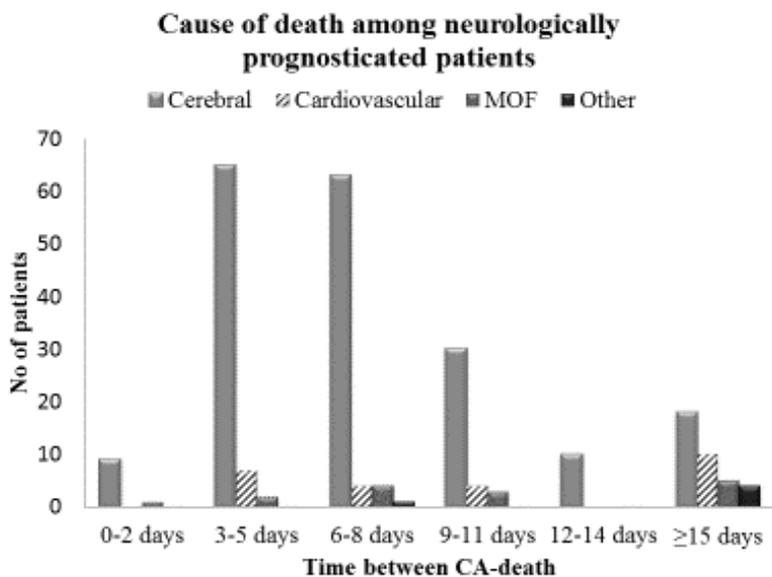


Figure 13. A.
Cause of death for neurologically prognosticated patients

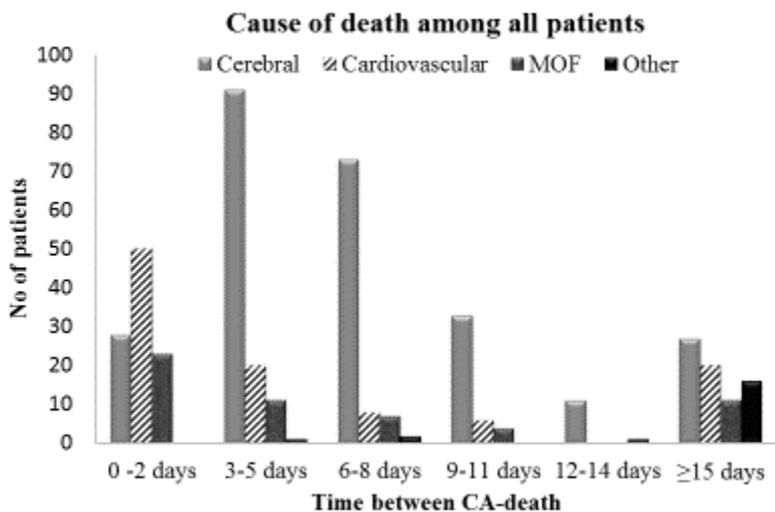


Figure 13. B.
Cause of death for all patients

Discussion

When a patient, successfully resuscitated from cardiac arrest, remains comatose, the physicians are in need of reliable methods to assess the prognosis. Early after a cardiac arrest the patient's family are grieving and prepared for the worst scenario, although the hope that their loved one will wake up is always there. An early and accurate assessment of prognosis could help minimize the false hopes and relatives' suffering, but could also enable the withdrawal of futile therapy.

In this doctoral thesis, we investigated OHCA patients treated with TTM after successful resuscitation. To put the neurological prognostication into a wider context we described how it was translated into decisions on withdrawal of life sustaining therapy, but also the mode of death among these patients (**paper I** and **IV**). In **paper II** we investigated the accuracy of clinical findings and SSEP to predict poor outcome and how their reliability was affected by the targeted temperature. In **paper III** we focused on the commonly occurring postanoxic status epilepticus (PSE) and the characteristics of patients recovering from this grave condition.

Cause of death

The overall mortality after cardiac arrest has decreased during the last decade mainly due to progress in pre hospital care^{22, 183 32} but also due to improved post cardiac arrest care, including cardiac interventions and possibly the implementation of TTM.^{33, 34, 184, 185} However, these improvements in the early phase has also led to an increased amount of patients remaining comatose due to brain injury resulting caused by global ischaemia-reperfusion. In a small number of patients the extensive swelling of a globally injured brain leads to brain death.

At our hospital, TTM was introduced in 2002-2003 and all comatose survivors of CA treated with TTM were prospectively evaluated in the multidisciplinary "coma project". **Paper I** is the first study in TTM patients focusing on the mode of death among those who died during hospitalization.

We found that brain injury was the main cause of death, accounting for 71% of all deaths. The majority of these patients died only after withdrawal of life-sustaining

therapy (WLST) based on a prediction of poor neurological outcome due to a presumption of severe hypoxic-ischaemic brain injury.

In our cohort cardiovascular mortality predominated the first 3 days while brain injury accounted for the majority of deaths after 4.5 days as a consequence of our local protocol of delayed neurological prognostication and consequent WLST.

In contrast with our findings, two large studies, the Brain Resuscitation Clinical Trial (BRCT) I¹⁸⁶ and BRCT II¹⁸⁷ conducted in the early 1980s reported that brain injury accounted for only 29% and 24% of all deaths respectively.

More recently, but still before the introduction of TTM, a study by Laver *et al.* found similar rates of death due to brain damage for their OHCA patients as we did, but significantly less for those with IHCA.¹⁸⁸ One possible reason for this might be that the praxis of “do-not-resuscitate” (DNR) orders at our hospital leads to a selection of the patients being resuscitated, excluding elderly patients with multiple illnesses, and thereby lowering post-arrest mortality due to non-neurological reasons. Our IHCA cohort was smaller, which may also be related to the use of DNR orders.

Another study by Olasveengen *et al.* including both TTM and non TTM-treated OHCA patients showed a similar rate of death due to brain injury as ours.¹⁸⁹

There is little doubt that the improved pre-hospital care and dramatic changes in the attitudes towards comatose CA patients, which have resulted in a more active intensive care, have contributed to an overall increase in survival, and the percentages of patients who are discharged with good neurological recovery.

With regard to in-hospital mortality, the shift from predominant cardiac to cerebral cause of death during the last three decades may be explained by modern cardiovascular and intensive care treatments allowing more patients to survive the first days after CA. Although a small number of patients still die early due to cardiac causes, the majority of deaths are now the result of active decisions to withdraw care due to presumed brain injury. These results emphasize the importance of absolutely reliable methods to prognosticate outcome to avoid incorrect decisions.

Brain death

Brain death occurs in a small number of patients resuscitated from CA. The most important pathophysiological mechanism of brain death is the massive swelling of a globally damaged brain tissue causing intracranial hypertension that leads further to cerebral herniation and a complete cessation of intracranial blood flow.^{190 159, 191, 192} The diagnosis of brain death is primarily based on a clinical assessment including testing of brainstem reflexes and apnoea test. However, confirmatory testing, such as cerebral angiography, head CT or MRI, EEG, SSEP and transcranial Doppler,

may be helpful to establish the diagnosis of brain death in cases when the lingering effects of sedation and analgesics cannot be ruled out or during hypothermia.

Despite being an unfavourable outcome for the individual patient, brain death creates opportunities for organ donation.^{89, 193} The 2015 American Heart Association Guidelines for Post-Cardiac Arrest Care⁸⁰ recommend that all patients who are resuscitated from cardiac arrest but who subsequently progress to brain death should be evaluated for organ donation. In **paper I**, we described the characteristics of the four patients who were declared brain dead. These patients were younger and had a longer time to ROSC. The diagnosis of brain death was based on two clinical examinations showing total loss of brain stem reflexes and positive apnoea-test, according to Swedish legislation, in combination with other confirmatory investigation. All these patients became organ donors.

Although there is a need to identify resuscitated patients who are likely to evolve towards brain death early, in order to ensure an adequate maintenance of potential organ donors, it is important to keep in mind that brain stem reflexes may be missing early after cardiac arrest and thereby the diagnosis of brain death may prove erroneous if based on clinical testing only.¹⁹⁴ To avoid this, it is important to confirm massive brain infarction, edema and tentorial herniation by neuroimaging but also to use other confirmatory tests and prolong observation in cases of uncertainties.

Neurological assessment

Accuracy of clinical findings and SSEP

In patients remaining comatose after cardiac arrest, the prediction of poor outcome (CPC 3-5) will enable the withdrawal of futile therapy. In other words, a poor neurological prognosis leads to withdrawal of care and to the death of the patient. Therefore, reliable predictors of poor outcome are necessary in order to avoid premature deaths for patients with potential to recover.

Neurological prognostication has long been based on the algorithm of Levy *et al.* from 1985, which included brain stem reflexes, motor response, verbal response and eye opening as well as the duration of coma.⁹¹ In 2005, the ERC guidelines stated that SSEP measured at 72 hours after resuscitation have a 100% specificity for poor outcome. However, the use of EEG performed between 24-48 hours was considered to have limited value.¹⁹⁵ The American Academy of Neurology (AAN) practice parameters published in 2006 issued an algorithm based on parameters (brain stem reflexes, motor response, SSEP, NSE and myoclonus status epilepticus) with a FPR of 0% tested on day 1-3 post-arrest.⁹³ However, TTM was not widely used at that

time, which is why this algorithm not necessarily would be applicable in the TTM era. Further, in the 2010 ERC guidelines it was acknowledged that among the most important developments since the 2005 ERC guidelines was the awareness of the fact that TTM challenges many traditionally established parameters.¹⁹⁶ Several studies also reported that hypothermia treatment may alter the reliability of clinical neurological findings,^{98, 100, 101, 104, 134} but not the predictive value of SSEP.^{100, 104}

Theoretically, hypothermia may affect neurological prognostication in different ways. An alleviated development of brain injury may allow patients to recover and achieve a good outcome despite an initial severe insult. Also, TTM may enhance the effects of concomitant pharmacological treatments, and make clinical testing less reliable.

However, the most crucial question has been whether the false predictive value of different prognostic markers is related to the hypothermia treatment itself or to other concomitant interventions, such as ongoing sedation.

In the TTM trial, we had a unique opportunity to examine whether the targeted temperature affected the reliability of clinical findings and SSEP. The TTM-trial showed no benefit on survival or crude neurological outcome of targeting 33°C versus 36°C and our results on prognosticators gives further support to the interpretation that the two intervention groups in this large trial behave similarly and developed an equal extent of brain injury.

In **paper II**, we demonstrated that the targeted temperature of either 33°C or 36°C had no clinically relevant influence on the predictive value of neurological findings, such as motor response or ocular reflexes. We also confirmed that SSEP is a robust instrument to predict poor neurological outcome independent of temperature treatment, and that a poor motor response (GCS-M 1-2) is compatible with good neurological outcome in a significant fraction of comatose patients. For the first time, we could show that the FPR for motor scores remained high also after delaying prognostication. Consequently, absent motor response to pain should never be used alone for predicting a poor outcome but it may be a reasonable manner to identify patients who need further evaluation to predict outcome.

In support of these neutral findings, TTM did not significantly affect the prognostic value of either NSE levels¹⁷⁵ or head CT (Moseby, personal communication) in the TTM-trial.

Our findings give some support to the theory that sedation, which is commonly used in conjunction with TTM, may be a more important factor for the decreased reliability of motor responses¹⁰¹ reported since the introduction of temperature management. Sedation may also affect other prognostic instruments such as EEG while SSEP is significantly less affected. Rare false predictions by SSEP have

anyhow been reported and noise, which may have caused our single false prediction, are a recognized cause of error.

An absence of pupillary light reflexes (PLR) at 72 hours was previously found to be the most accurate clinical predictor of a poor neurological outcome^{98, 101, 134} but in rare cases, bilateral absence of corneal reflexes (CR) was consistent with recovery.^{104, 134} In concordance with previous studies, we found that absent ocular reflexes was a reliable predictor of poor prognosis but also that it is a rare finding among patients with a poor prognosis when examined several days after the arrest.

Moreover, our findings in **paper II** do not support the use of different routines for prognostication in patients treated with TTM at 33°C or 36°C.

Optimal timing of neurological prognostication

Historically, 72 hours after cardiac arrest has been established as a suitable time of prognostication, since the process of brain damage is thought to be completed at that time for most patients.¹⁹⁷ There is also a general consensus that the specificity of different prognostic tools improves with time after the onset of postanoxic coma. Moreover, the majority of OHCA survivors with a good outcome regained consciousness within three days,^{90, 198} although late recovery may occur in some patients.^{118, 199} Thus, a later time-point will exclude some patients from prognostication and the associated risk of false predictions and WLST.

Since the introduction of TTM as a standard neuroprotective treatment, the field of prognostication has become even more complicated. TTM has been associated with larger use of sedative and paralytic agents that may delay neurological recovery and affect the optimal timing of assessment. For that reason, the AHA guidelines from 2010 recommended a delayed prognostication in TTM-treated patients.³⁵ The Swedish Resuscitation Council emphasised the needs for prolonged observation until at least 72 hours after rewarming (4.5 days after CA) to allow for recovery of all patients with a favourable prognosis and to reduce the risk of premature decision to WLST.⁸¹ Still, several recent reports show that neurological prognostication before 72 hours is common^{200, 201} and often lead to falsely pessimistic statements.⁸⁷

In paper I and III we postponed the prognostication to 72 hours after rewarming to compensate for the effects of TTM. Similarly, the TTM trial protocol (paper II and IV) recommended that prognostication should not be performed before 72 hours after the end of rewarming. Nevertheless, some patients were assessed before this time. However, a recommendation to withdraw care was made in less than half of these patients. Our results highlight that it is important not to confuse prognostication with withdrawal of life sustaining therapy.

The recent ERC-ESICM guidelines suggested that the prognostication process should not start earlier than 72 hours from the return of spontaneous circulation (ROSC) and only after major confounders, especially sedation, have been excluded.⁶³ Although the time to start prognostication was moved one step earlier compared with the TTM trial, it should be emphasised that only a bilateral absence of both the pupillary light reflexes and the corneal reflexes, or the bilateral absence of N20-peaks on SSEP were considered reliable predictors of poor outcome (FPR <5%) at this time point.

The most important development in the prognostication field has been the implementation of a multimodal approach using multiple prognostic tools.^{63, 81}

Self-fulfilling prophecy

A common and important pitfall when interpreting available evidence on prognostication following postanoxic brain injury is the so-called “self-fulfilling prophecy” bias of observational studies.⁸⁶ In these studies, clinical care is often influenced by the presence or absence of the studied factors. If treatment is withdrawn in patients with presumed negative prognostic factors, an observational study will be biased to confirm the accuracy of that prognostic finding, the “self-fulfilling prophecy”. The only way to prevent the “self-fulfilling prophecy” would be the blinding of the test results to the assessor and the provision of sufficiently life-prolonging support in patients remaining comatose after rewarming. However, both of these tasks are difficult to achieve since, for instance, clinical findings are impossible to conceal for the assessor and unlimited intensive care would give rise to ethical and financial concerns.

In the TTM trial (**paper II and IV**), a standardized and transparent protocol for prognostication and WLST was regarded as an important part of the trial design, in order to minimise the risk of the “self-fulfilling prophecy” and consequent bias.²⁰² By strictly regulating the time for prognostication and the criteria allowing for WLST, we have aimed to avoid inaccurate and immature predictions. By reporting the results of prognostication and WLST we have strived to allow a more informed interpretation of the TTM-trial results, taking the “self-fulfilling prophecy” into account. It is our interpretation that this bias has not affected the study in any significant way.

Postanoxic status epilepticus

Postanoxic status epilepticus (PSE) is a controversial diagnosis and the reported incidence is likely dependent on the classification used to differentiate these patients from those with other encephalopathic patterns. With regard to the pathophysiological aspects, it is still unknown whether electrographic seizures in patients with post-anoxic encephalopathy is merely a sign of extensive brain injury or a condition that may actually aggravate the brain injury if left untreated.⁹⁵ In a recent review the authors concluded that the dysfunction of inhibitory interneurons is a common mechanism of generalized periodic discharges.²⁰³

In general, PSE is associated with poor outcome but case series showed that some patients may still recover reasonably well, often after prolonged intensive treatment.^{114, 138, 158, 204} Evidence-based guidelines for treatment of PSE are lacking. In two surveys of neurologists published in 2010, most of the responders would initiate treatment if PSE was identified, but only one third would treat more aggressively like in overt status epilepticus.^{205, 206} Since seizure activity imposes a metabolic stress and thereby may potentially aggravate neuronal injury,²⁰⁷ treatment of clinical and electrographic seizures after CA is recommended in guidelines.²⁰⁸

A well-known issue in diagnosing PSE is the lack of a standardized electrographic definition of seizure activity but also interobserver variability in determining EEG patterns.²⁰⁹ The recent American Neurophysiological Society (ACNS) guidelines advocate a strict definition of “unequivocal” electrographic seizures but acknowledge the presence of EEG patterns belonging to the ictal–interictal spectrum.¹⁴⁰

In paper III we used a pragmatic definition of ESE and emphasized that the majority of our ESE cases would not be classified as unequivocal seizures according to ACNS. Using a continuous EEG (cEEG)-monitoring on all patients we found that postanoxic status epilepticus was a common condition that occurred in 32% of the patients. We identified two main patterns of ESE: ESE evolving from discontinuous/burst suppression background and ESE evolving from a continuous/nearly continuous background. All patients in the first category died during hospitalisation. A good outcome after PSE was found in four of the 16 patients with a continuous/nearly continuous background prior to ESE onset. All had lower NSE value, present N20-peaks on SSEP and were treated with a combination of several anti-epileptic drugs.

Neuronal death following global brain ischaemia has been associated with decreased amplitude and a slowing of background activity. Opposite, early recovery of background activity toward continuous, physiological rhythms during TTM or at normothermia^{115, 130, 138, 139} and reactivity of the EEG background⁹⁹ to external

stimuli have been associated with good outcome. In addition, patients who develop a continuous background prior to ESE onset have previously been shown to have a better outcome.^{114, 138} We can thereby speculate that an early recovery of EEG background may indicate a less injured brain, but also that background activity and epileptiform discharges are two separate pathophysiological phenomenon.

cEEG monitoring, as we used in our study, allows for detection and monitoring of epileptic activity but whether active treatment of such detected activity is beneficial or even harmful for the patients is not known. This issue may be elucidated when the results of the ongoing randomized clinical trial (TELSTAR) are released.²¹⁰

Moreover, cEEG is a useful tool to monitor the brain function after cardiac arrest allowing for assessment of the evolution of EEG patterns which may provide additional prognostic information. Importantly, we need a user-friendly standard classification of EEG patterns in order for cEEG to become a cost effective bedside brain monitoring tool for routine use.

Withdrawal of life sustaining therapy and ethical aspects

The developments in intensive care during the past decade has enabled us to maintain life in cardiac arrest patients also with a very severe brain injury. This is an outcome that very few people would wish to survive with. However, we cannot make an accurate outcome prediction earlier than 3 days after cardiac arrest.

Since the brain stem reflexes often recover, including spontaneous breathing, the patients might be extubated. By providing nutrition and treating complications, even patients with severe brain injury could survive for years in a vegetative or minimally conscious state. Therefore, in patients with a poor neurological prognosis, intensive therapy is usually considered futile and in many Western countries, WLST considered. Some physicians may feel uncomfortable deciding on WLST, whilst others would consider it unethical to continue care in patients with no chance of achieving an independent life. With regards to the four ethical principles, the patient's autonomy is difficult to assess since most patients are unable to communicate. Therefore, the clinicians have to weigh up the other three principles: "do not harm", "beneficence" and "justice". The ethical decisions are very much based on how the clinicians weigh these principles. For example, if autonomy is placed as the guiding principle then it may lead to harm or injustice. On the other hand, in rich countries, distributive justice is rarely considered, while in a low-income country, this may trump autonomy.

In the cardiac arrest settings, the majority of the patients remaining comatose and presumed to have a poor prognosis die after WLST.^{88-90, 200, 201, 211} However, it is of

great importance to note that a poor prognosis is not equal to WLST, and conversely, an assessment of potential neurological recovery does not always imply continued care. Apart from medical reasons, there are other factors that contribute to the decision on WLST, such as age, ethical reasons, the relatives' wishes, and the ICU's limited resources. Moreover, the practice of WLST may vary between countries with different traditional or religious backgrounds.¹⁷⁷

Reports that up to one third of all in-hospital deaths after CA occurred after early WLST (≤ 72 hours post-arrest) are worrying,^{87, 200, 201, 211} since the most patients are still influenced by sedation at that point and consequently, neurological prognosis is less reliable in the first days after CA.¹⁰¹

In **paper IV**, the neurological prognostication were strictly regulated regarding time-point and the criteria allowing for WLST were pre-specified. We could show that WLST due to neurological reasons preceded death in the majority of the neurologically prognosticated patients. The prevalence of WLST among patients who were not prognosticated was similar but the reasons allowing for WLST in this group were non-neurological.

Moreover we could show that our results from **paper I** regarding the prevalence of WLST, as well as cause of death were transferable to a large international cohort.

In **paper IV**, WLST in the prognosticated patients was performed at a median day six in the ICU, which is 2-3 days later than in other reports.^{90, 201} In addition, an early WLST < 72 hours occurred in only a minority of the patients suggesting that a standardized protocol for prognostication and criteria for WLST may reduce the risk of premature death. However, we acknowledge that ethical and other aspects of care may sometimes justify early WLST decisions.

Another important finding in **paper IV** was that the intensive care proceeded differently depending on the recommendation given. Most patients receiving a recommendation to “withdraw active intensive care” at the time of prognostication had WLST within one day. By contrast, the recommendation to “do-not-escalate” (DNE) or “continue care” was associated with continued ICU support for several more days. Nevertheless, a WLST decision was ultimately made in almost two-thirds of patients with a DNE recommendation and one third of the patients with a recommendation to “continue care”. Interestingly, DNE and withdraw active intensive care recommendations were associated with very similar mortality, over 90%. However, for patients receiving a DNE recommendation, our results show that the median time to death involved an additional three ICU days care, which may have ethical implications. These differences may be clinically important to patients and their relatives as well.

Recommendation to DNE and to “withdraw active intensive” care may be perceived as “end-of-life decisions” with no ethical or legal distinction between them.²¹²

As expected in a large international study the routines for neurological prognostication and WLST varied between countries with consequent differences in the prevalence of WLST, length of ICU stay and in proportions of survivors with poor neurological outcome (CPC3 and CPC4).

Limitations

In **paper I**: Because of its retrospective design all information regarding prognostication and recommendations on level of care or mode of death after withdrawal of life-sustaining therapy (WLST) is based on patients' records and charts. There was no standardized protocol for prognostication, but the local recommendations stated that prognostication should be multimodal and delayed (≥ 72 hours after rewarming). We have not been able to monitor the process of prognostication or decisions on level of care to investigate other circumstances affecting the decision of WLST that were not reported in writing. However, since the prognostication was performed at a minimum 4.5-5 days post-arrest in most patients the risk of bias due to premature WLST is considered to be low.

In **Paper II and IV**: Although the TTM-trial constitute the largest cohort of CA-patients with prospectively collected data on prognostic parameters and is the first study that compares CA-patients randomized to two temperature regimes, the TTM-trial was not primarily designed to investigate neurological prognostication. We did not investigate and collect data on the results of clinical neurological examinations repeatedly and it is essential for the interpretation that the data reported from the different intervals after CA represent separate cohorts. The majority of patients in the interval < 72 hours were selected for early prognostication due to a presumed poor prognosis (for example due to early myoclonus status or suspected brain death). This may have led to a bias exaggerating the reliability of clinical tests. Therefore the sensitivity and specificity of the clinical test < 72 hours that we found cannot be extrapolated to all unconscious patients < 72 hours after a cardiac arrest.

Since the results of SSEPs have been used in the WLST decisions we cannot exclude the risk of the "self-fulfilling prophesy". However, in our prognostic algorithm we combined the finding of absent SSEP N20-potentials with an early myoclonus status or a prolonged observation and GCS-M ≤ 2 to decrease the risk of false predictions.

The treating physician who made the decision whether to continue care, not escalate care or WLST was not bound by the recommendation of the assessor of the patient's prognosis. Although the assessor was blinded to the temperature treatment of the patient, the treating physician was aware of the temperature allocation. For patients with an uncertain prognosis at the time of prognostication, daily re-evaluation was

recommended, permitting a longer observation period for these patients. However, the details of this re-evaluation process and its effect on prognostication and outcome is unknown.

In **paper III**: We used a pragmatic definition of ESE and emphasized that the majority of our ESE cases would not be classified as unequivocal seizures according to ACNS. Moreover, we did not have any details about individual regimen of sedation but the majority of the patients were sedated with a combination of propofol/fentanyl or midazolam/fentanyl. Despite lack of treatment standardisation, most patients with ESE were treated with a combination of anticonvulsants but our study's aim was not to investigate their benefit on patients' outcome.

Conclusions

- Withdrawal of life-sustaining therapy (WLST) due to presumed severe hypoxic-ischaemic brain injury is the major cause of death in TTM-treated CA-patients
- Young patients with a long time to ROSC may become brain dead and subsequent organ donors.
- The targeted temperature management of 33°C vs 36°C had no significant influence on the predictive value of clinical findings or SSEP.
- Bilateral absent ocular reflexes or N20-peaks on SSEP were reliable markers to predict poor neurological outcome
- A poor motor score (GCS-M ≤ 2) was not a reliable predictor of poor prognosis at any time.
- Electrographic status epilepticus occurs in approximately one-third of comatose survivors of CA during ICU care and can be detected with cEEG. A minority of patients survived with good outcome after prolonged intensive care. Patients with favourable prognosis can be identified by a multimodal prognostication.
- In patients who were assessed for neurological prognosis in an international trial, WLST due to presumed brain injury predominated, while non-neurological reasons for WLST were more common among those who died prior to prognostication.
- A standardized protocol for prognostication and criteria for WLST may reduce the risk of inaccurate prognostication and premature death.
- Different care recommendations at the time of prognostication may produce clinically important differences in ICU length of stay, survival time and outcome
- The routines for neurological prognostication and WLST varied between countries.

Future directions

Neurological prognostication

In the light of modern intensive care, including TTM, the neurological prognostication remains open to research and refinement. Our studies shows how death after successful resuscitation is critically dependent on active decisions to withdraw care as a result of prognostic investigations and stress the need to develop methods and algorithms that are reliable and easy to use.

The accuracy of clinical findings and optimal timing of a neurological prognostic assessment is still debated as well as the effects of TTM and concomitant analgesedative treatment on the prognostic methods. Therefore, in future studies investigating the effect of TTM after cardiac arrest, the pharmacokinetics of sedation and neuromuscular blockers and their effects on prognostic methods should be given priority.

SSEP has been consider to be a robust predictor of poor prognosis but most of the prior studies investigating SSEPs ability to predict outcome were not blinded. In order to determine the relevance of this bias further blinded studies are warranted.

Multimodal prognostication is generally recommended but few studies have investigated the added value of different combinations of prognostic methods to predict outcome. Also, the algorithm recommended by the ERC/ESICM was never validated. Combining high-quality databases from large clinical studies will make such evaluations possible in the future facilitating further development of prognostic routines.

Withdrawal of life-sustaining therapy

Early WLST (<72 hours) is still responsible for up to one third of in-hospital mortality according to several studies and despite the lack of reliable prognostics methods during the first 3 days. To avoid premature withdrawal in routine care local well-defined protocols for prognostication with pre-specified criteria for WLST are needed.

WLST based on falsely pessimistic assumptions of the prognosis is a potential powerful source of bias in clinical cardiac arrest trials especially if the intervention is unblinded as in TTM-trials. The TTM trial was the first trial with a transparent protocol for prognostication and WLST and similar approaches will hopefully become routine in future trials.

Postanoxic status epilepticus

Postanoxic status epilepticus (PSE) is a very common condition after cardiac arrest. Continuous EEG-monitoring facilitates early detection and monitoring of treatment effects. However, we still lack knowledge whether treatment of PSE is beneficial or harmful as well as which EEG-patterns should be considered as “true epileptic activity”. Prospective studies that correlate different standardized EEG patterns, with outcome and further intervention studies in patients with PSE are clearly warranted.

Swedish summary/ Populärvetenskaplig sammanfattning

Hjärtstopp är ett ytterst allvarligt tillstånd och innebär att hjärtats pumpförmåga plötsligt upphör. Varje år drabbas ca 5000-10 000 svenskar av hjärtstillestånd och hjärt-lungräddning påbörjas hos drygt 5000 av dem. Förbättrat prehospitalt omhändertagande och avancerade behandlingsmetoder på sjukhus har gjort att allt fler patienter återfår blodcirkulation och vårdas på intensivvårdsavdelning i respirator. Trots detta är långtidsöverlevnaden efter hjärtstopp endast 11% i Sverige, baserat på registerdata.

När hjärtfunktionen har stabiliserats är hjärnskadan det största hotet och beräknas stå för två tredjedelar av dödligheten. Hjärnan är särskilt sårbar för cirkulationsstillestånd på grund av dess höga ämnesomsättning och minimala energireserver. Av de patienter som ankommer sjukhuset levande och läggs in på en intensivvårdsavdelning (IVA), överlever cirka 50%, majoriteten av dessa med inga eller lätta funktionsnedsättningar.

En sänkning av kroppstemperaturen under det första dygnet efter ett hjärtstopp har visat sig ha en skyddande effekt mot hjärnskador i tidigare studier. Fortsatt osäkerhet kring den optimala kroppstemperaturen och effekten av nedkylning ledde till att en stor internationell multicenter studie, *Target Temperature Management trial* (TTM-studien) genomfördes. Studien inkluderade 939 hjärtstoppspatienter som behandlades med temperaturkontroll vid 33°C respektive 36°C i 24 timmar. TTM-studien visade ingen skillnad i dödlighet eller svårt neurologiskt handikapp mellan de två temperaturgrupperna.

En klinisk neurologisk undersökning är hörnstenen i en prognosbedömning men viktig information fås också genom de neurofysiologiska metoderna, EEG (elektroencefalografi, registrering av hjärnans elektriska aktivitet) och SSEP (somasensoriska retnings svar; registrering av det elektriska svaret i hjärnbarken efter stimulering av en nerv i arm eller ben), neuroradiologiska undersökningar (datortomografi och magnetkameraundersökning av hjärnan), samt mätning av biokemiska hjärnskademarkörer i blodet. Temperaturbehandlingen komplicerar dock den neurologiska bedömningen eftersom patienten sövs och respiratorbehandlas under de första dagarna. Flera studier har visat att hypotermi

minskar tillförlitligheten av kliniska fynd, neurofysiologiska undersökningsmetoder och biomarkörer. Detta har skapat en osäkerhet som lett till rekommendationer om uppskjutande av prognosbedömningar.

Huvudsyftet med denna avhandling är att undersöka hur den neurologiska prognosbedömningen omsätts till beslut om avslutande av livsuppehållande behandling samt att utvärdera tillförlitligheten av kliniska och neurofysiologiska prognostiska markörer för att förutspå dålig neurologisk återhämtning hos patienter som inte vaknar efter hjärtstopp.

Mellan 2004-2008 vårdades 162 patienter på IVA/THIVA i Lund efter framgångsrik hjärt-lungräddning i samband med hjärtstopp. Samtliga patienter behandlades med kontrollerad temperatur vid 33°C i 24 timmar. Dödligheten var 53% vid utskrivning från sjukhus och 54% efter 6 månader. Bland de patienter som avled under vårdtiden var hjärnskador den dominerade dödsorsaken. Dessa patienter avled inom timmar-dagar efter att man avbrutit intensivvården baserat på en bedömning att prognosen för neurologisk återhämtning var dålig. Fyra patienter förklarades hjärndöda och samtliga blev organdonatorer.

Som en del av TTM-studien har vi analyserat tillförlitligheten av kliniska neurologiska fynd (smärtreaktion, pupill- och blinkreflexer) och bortfallna svar på SSEP-undersökning för att förespå ett dålig neurologisk utfall. Skillnader mellan temperaturgrupperna (33°/36°C) analyserades på 313 patienter. Vi fann att temperaturbehandlingen inte hade någon signifikant påverkan på det prognostiska värdet av kliniska neurologiska fynd och SSEP. Avsaknad av smärtreaktion eller stereotyp sträckmönster vid smärtstimulering var inte en tillförlitlig markör för att förespå dålig neurologisk återhämtning. Däremot var avsaknad av pupill- och blinkreflexer samt avsaknad av SSEP-svar tillförlitliga markörer för att förespå dålig neurologisk återhämtning redan 72 timmar efter ett hjärtstopp. Våra resultat visar att det inte är adekvat att använda olika riktlinjer för prognostisering beroende på om en patient behandlats med kontrollerad temperatur vid 33°C eller 36°C.

Neurologisk prognosbedömning gjordes på 313 patienter i TTM-studien. Rekommendation blev att "fortsätta intensivvård" i 37%, att "inte öka vårdnivån" i 18% och att "avsluta intensivvård" i 45%. Ett aktivt beslut om att avsluta intensivvård fattades i 196/313 patienter i median 6 dagar efter hjärtstoppet. Alla dessa patienter avled förutom 2 som överlevde med milda respektive grava neurologiska funktionsbortfall. Praxis för avbrytande av intensivvård skilde sig mellan de deltagande länderna.

Mellan 2008-2013 undersökte vi 127 medvetslösa hjärtstoppspatienter med förenklad EEG-övervakning vid IVA i Lund. Vi fann att 41 av dessa patienter utvecklade så kallat status epilepticus (långdragna epileptiska anfall) vilket var förenad med en mycket dålig prognos (37/41 avled under vårdtiden). Återhämtning

av kontinuerlig bakgrundsaktivitet på EEG före debuten av status epilepticus, låga nivåer av hjärnskademarkören neuron-specifikt enolas i blodet och bevarade SSEP-svar var faktorer som talade för en bättre prognos.

Sammanfattningsvis är det den uppkomna hjärnskadan som är den vanligaste dödsorsaken hos de patienter som återupplivats i samband med hjärtstopp och som vårdas på en intensivvårdsavdelning. Majoriteten av dessa patienter avlider under vårdtiden efter att man beslutat sig för att avbryta intensivvården efter en bedömning att prognosen för neurologisk återhämtning är dålig. Resultaten av en klinisk neurologisk undersökning tillsammans med resultat från neurofysiologiska undersökningar ger tidig information om prognosen hos patienter som är fortsatt medvetslösa efter framgångsrik återupplivning. Våra studier har visat att temperaturbehandling inte påverkar tillförlitligheten av de prognostiska metoder som vi har utvärderat.

Acknowledgements

I would like to express my deepest gratitude to everyone who has helped and supported me during my research studies. Without your support, knowledge and encouragement, this work would never have been possible. Struggling through the PhD time has been a time of both laughter and hard work.

First of all, I would like to thank my tutor and my friend, Tobias Cronberg, for introducing me to scientific work and encouraging me during all these years. For generously sharing your great scientific knowledge and never making me feel inferior. For your enthusiasm, patience, and support when times were hard and motivation sparse. You have never given up on me.

To my co-tutors: Hans Friberg, for all your encouraging words, your positive attitude and all the insightful comments; Niklas Nielsen for introducing me into the world of the TTM trial and for key discussions and important contributions to the present papers.

To Malin Rundgren, for being the foundation for my knowledge of cardiac arrest and TTM. Thank you for introducing me to the world of ICU and biostatistics. For being my supporting research-friend, always prepared with good advice.

To Elisabet Englund, my co-author, for all the kind words, support and expertise in neuropathophysiology.

To my research-friends: Erik, Gisela, Sofia and Marion for all the discussions about life, research and everything in-between.

To past and present heads of the Department of Neurology: Håkan Widner, Jesper Peterson, and Christer Nilsson for the opportunity to complete this thesis and for clinical support.

My colleagues and friends at the department of neurology for supporting me in my clinical and research journey. Thank you for all discussions on everything and for the good laughs.

To all co-authors and members of TTM steering group for all constructive comments and support.

In particular, I would like to acknowledge my co-author, Jules Cranshaw for all emails with great advices and supporting words. For your enormous dedication and wonderful contribution to review and language edit the present papers.

To my best friend Mpumi, for our lunches with lots of laughter and fun. For all your support in everything, not at least with English.

To my parents, Emilia and Dumitru, and my sister Mirela, for unconditional love and support. My dear daddy, I miss you with all my heart.

To my dear husband Cristian, for your love and endless support through all these years of too much work. You have never complained about your workload in daily routines, even when I was away or only physically present. I never felt any pressure from you during this project. I love you!

To my daughter, Alexandra, the best thing that has ever happened in my life. You have brought me only joy and love.

Financial support

This dissertation project has been made possible by generous grants from:

Swedish Heart Lung Foundation; Arbetsmarknadens försäkringsaktiebolag; AFA-Insurance Foundation ; The Swedish Research Council ; Regional research support, Region Skåne; Governmental funding of clinical research within the Swedish NHS (National Health Services) ;Thelma Zoega Foundation; Krapperup Foundation; Thure Carlsson Foundation; Hans-Gabriel and Alice Trolle-Wachtmeister Foundation for Medical Research; Skåne University Hospital; Sweden, Tryg Foundation, Denmark, and the European Clinical Research Infrastructures Network.

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Photo by Roger Lundholm

Irina Dragancea is a clinical neurologist at Skåne University Hospital Sweden. This thesis is focusing on neurological prognostication in comatose survivors of cardiac arrest. In this picture she is examining a comatose patient resuscitated from a cardiac arrest, which is an important part in the assessment of prognosis. Apart from her job she lives with her family in Södra Sandby and enjoys being out in nature, travelling and reading books.

