

INDUCED HYPOTHERMIA AFTER CARDIAC ARREST

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2010

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Cover illustration: Bengt Mattsson, 2003

Lund University
Faculty of Medicine
Doctoral Dissertation Series 2010:47

ISSN 1652-8220

ISBN 978-91-86443-62-7

Printed by **MEDIA-TRYCK**, Lund 2010

“Never mind manoeuvres, always go at 'em!”

Vice admiral Horatio Lord Nelson

*“What is wanted is not the will to believe, but the wish to find out,
which is its exact opposite”*

Bertrand Russell

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ORIGINAL PAPERS

This thesis is based on results reported in the following papers, which will be referred to in the text by their Roman numerals.

I. Nielsen N, Sandhall L, Scherstén F, Friberg H, Olsson SE. *Successful resuscitation with mechanical CPR, therapeutic hypothermia and coronary intervention during manual CPR after out-of-hospital cardiac arrest*. Resuscitation. 2005;65:111-113.

II. Nielsen N, Hovdenes J, Nilsson F, Rubertsson S, Stammet P, Sunde K, Valsson F, Wanscher M, Friberg H. *Outcome, timing and adverse events in therapeutic hypothermia after out-of-hospital cardiac arrest*. Acta Anaesthesiologica Scandinavica. 2009;53:926-934.

III. Rundgren M, Karlsson T, Nielsen N, Cronberg T, Johnsson P, Friberg H. *Neuron specific enolase and S-100B as predictors of outcome after cardiac arrest and induced hypothermia*. Resuscitation. 2009; 80: 784-789.

IV. Nielsen N, Sunde K, Hovdenes J, Nilsson F, Riker R, Rubertsson S, Stammet P, Friberg H. *Adverse events and their relation to mortality after out-of-hospital cardiac arrest and therapeutic hypothermia*. Submitted for publication.

V. Nielsen N, Friberg H, Gluud C, Herlitz J, Wetterslev J. *Hypothermia after cardiac arrest should be further evaluated– systematic review of randomised trials with meta-analysis and trial sequential analysis*. Submitted for publication.

VI. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Hassager C, Hovdenes J, Kjaergaard J, Rubertsson S, Rundgren M, Valsson F, Wanscher M, Åneman A, Friberg H. *Target temperature management after out-of-hospital cardiac arrest – a randomised, parallel groups, assessor blinded clinical trial. Rationale and design of the TTM-trial*. Manuscript.

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ABSTRACT

This thesis is based on studies of the clinical use of induced hypothermia as an intervention to reduce mortality and neurological impairment after cardiac arrest.

After the publication of two trials indicating benefit of induced hypothermia, we developed a registry to assess outcome, possible adverse events and conduct of induced hypothermia when this intervention was implemented in a clinical population of cardiac arrest patients.

Approximately half of the patients admitted to intensive care after out-of-hospital cardiac arrest survive and few patients have severe residual neurological impairment.

The timing of hypothermia (early versus late induction of hypothermia and achievement of target temperature) was not associated to outcome.

Adverse events were common, but only sustained hyperglycaemia and anticonvulsants administered for seizures were associated with increased mortality. Bleeding and infections were more common for patients having invasive procedures performed, but these adverse events were not associated with increased mortality.

In a study of biomarkers of brain damage, neuron specific enolase was superior to S-100B as a predictor of a poor outcome.

In a systematic review with meta-analyses and trial sequential analyses we conclude that the accumulated evidence for induced hypothermia is associated with substantial risks of systematic errors and the quality of the evidence is low. Trial sequential analyses indicate that the required information size to establish firm conclusions is not yet reached. Thus, we still do not know if induced hypothermia is beneficial, neutral or harmful for cardiac arrest patients

Accordingly, clinical equipoise exists with respect to induced hypothermia and we therefore propose a randomised trial with the design based on the findings in this thesis.

INTRODUCTION

1. Cardiac arrest.

Cardiac arrest is in most cases a natural ending of life. The cessation of blood circulation will lead to death. Cardiac arrest may however arrive prematurely, suddenly and unexpectedly, and medical therapies can in some cases restore the function of the heart and help avoiding the otherwise inevitable outcome. “Death is not a moment, it is a protracted pathophysiological process.” This quote from the late Peter Safar, father of modern resuscitation, pushed a wedge into a previously closed concept of cardiac arrest and implied that this process could be stopped or reversed.

Most people would say that death is the moment when the last breath has expired and the heart stops, but this is not true in a biological sense. Cellular ion pumps continue to keep cell membrane potentials intact as long as there are energy stores left, sustaining life in these tissues until the last membrane potential is equalized and the tissue is no longer resuscitable. The tissue is dying. The human brain with its high metabolism and low energy stores will go through this process in minutes and the brain will succumb when oxygen tension is low, energy stores are depleted, and waste products have reached critical levels. These minutes between the circulatory collapse and the moment when the brain is permanently injured represent a window of opportunity for a resuscitation effort.

Death is probably best understood as a moment and not a process – it is inherently discontinuous and instantaneous. Thus, death is an irreversible biological phenomenon and it separates alive from dead (Bernat 1998). According to the Swedish law, and many other legal systems in the world, death has occurred when the functions of the brain have irrevocably ceased to exist, and then the patient will be declared dead in a legal sense. A non-beating heart and absent breathing may be used as indirect criteria for declaring someone dead, conditional on the indisputable knowledge that the brain will be extinct minutes after the circulation has stopped.

In this context it is therefore tempting to modify the quote from Dr Safar to: “*Dying* is a protracted pathophysiological process.” A patient resuscitated from cardiac arrest has not returned from the dead, nor returned from death, but returned from dying – at least temporarily.

1.1 Types of cardiac arrest

Cardiac arrests are mainly categorised as arrests occurring at the hospital (in-hospital cardiac arrests) and outside the hospital (out-of-hospital cardiac arrests). In-hospital arrests are aetiologically different, the patients are suffering from acute or chronic diseases causing hospitalisation and the demographics and outcome is clearly different (Herlitz et al. 2000). In addition, the causes of mortality differ between these groups. Of patients with restored circulation that die during hospitalisation, a vast majority have a neurological cause of death in the out-of-hospital group, while the mortality in the in-hospital cardiac arrest patients is attributed to more diverse causes (Laver et al. 2004). Therefore out-of-hospital and in-hospital populations are not fully comparable. In this thesis the focus will be on out-of-hospital cardiac arrests.

Furthermore, cardiac arrest is usually divided in categories depending on what type of arrhythmia the heart presents at first electrocardiographic recording (ECG), often referred to as initial rhythm or first monitored rhythm. This information is only available when there has been an ambulance or emergency medical services (EMS) crew at the scene, and thus data on incidence are derived from selected populations (Engdahl et al. 2002).

There are four main categories of initial rhythms causing pulseless cardiac arrest: non-perfusing ventricular tachycardia (VT), ventricular fibrillation (VF), pulseless electrical activity (PEA) that previously was denoted electromechanical dissociation (EMD), and asystole. The first two are often grouped together. There may be a continuum between the different rhythms, since a ventricular fibrillation that continues over time will diminish in amplitude and progress into asystole. The same is true for PEA. However, this transformation may be rather slow and in some materials the rhythm was still VF in 40 % of the patients 20 minutes after the cardiac arrest (Holmberg et al. 2000).

VF is defined as an electrical chaos with rapid uncoordinated depolarisation and repolarisation throughout the heart muscle. The incidence of VF as an initially recorded rhythm after out-of-hospital cardiac arrest of a cardiac cause has been reported to be approximately 40 % (Lombardi et al. 1994; Cobb et al. 2002; Rea et al. 2004; Herlitz et al. 2005). The estimated incidence of VF at the time of the cardiac arrest has though been speculated to be as high as 80-90 % (Holmberg et al. 2000) since the rhythm may have deteriorated to asystole when the first ECG is recorded (Waalewijn et al. 2002). In a Swedish material the incidence of patients found in VF has decreased over the last decades (Herlitz et al. 2004).

PEA is defined as a state of non-detectable central or peripheral pulses and an electrographic rhythm other than VT, VF or asystole. Echocardiography and invasive blood pressure recordings have indicated that there may be myocardial movement and small pressure gradients even when the clinical diagnosis is PEA,

and therefore the border between severe cardiogenic shock and PEA may be hard to define (Bocka et al. 1988; Paradis et al. 1992; Engdahl et al. 2002).

Asystole is defined as no pulses and no electrical activity on ECG. It is a sign of a dead or dying heart and the overall chance of survival may be as low as 1 % (Hallstrom et al. 2007). In some materials the incidence of asystole, as an initial rhythm, is over 50 % and concomitant with the decrease in VF, the incidence of asystole has increased (Herlitz et al. 2004). However, the selected group of patients with asystole who are successfully resuscitated and brought to hospital have a higher chance of survival and this is especially the case for asystole of a presumed cardiac cause.

VF and VT are often classified as shockable rhythms since they may be defibrillated by an electrical DC-shock, while asystole and PEA are classified as non-shockable rhythms. An initial shockable rhythm is associated with better survival than a non-shockable rhythm (Herlitz et al. 2005).

1.2 Causes of cardiac arrest

A cardiac cause is presumed to be the aetiology in over 80 % of all out-of-hospital cardiac arrests in whom resuscitation is attempted, as shown in a large material from Scotland (Pell et al. 2003). However there may be an overrating of a cardiac aetiology because of low autopsy rates (Kuisma et al. 1997). The major cardiac cause of arrest is coronary disease, presumably with plaque rupture and acute thrombus formation leading to myocardial ischaemia triggering the rhythm disturbance. Acute myocardial ischaemia has been reported to account for the majority of all cardiac arrests. In autopsy studies acute coronary processes were discovered in more than half of the patients (Davies et al. 1984; Farb et al. 1995). The most frequent cardiac and non-cardiac causes for cardiac arrest are listed in Table 1.1.

Table 1.1. Aetiology of cardiac arrest

Cardiac causes of cardiac arrest	Non-cardiac causes of cardiac arrest
Ischaemic coronary disease	Trauma
Non-atherosclerotic coronary disease	Bleeding and hypovolaemia
Cardiomyopathy	Pulmonary embolism
Valvular disease	Drug overdose, suicide
Inflammatory or infiltrative myocardial disease	Suffocation, hanging
Congenital disease	Submersion
Primary diseases in conductive system	Malignancy
	Lung disease

Adapted after Engdahl, Resuscitation 2002 (Engdahl et al. 2002)

1.3 Epidemiology of cardiac arrest

In a European material the incidence of cardiac arrest is reported to be approximately 40 per 100,000 inhabitants per year, where resuscitation is attempted (Atwood et al. 2005). In a similar study from the United States the incidence was 54 per 100,000 per year (Rea et al. 2004) and these numbers have recently been confirmed (Nichol et al. 2008). The incidence increases with age and is higher for men than women (Engdahl et al. 2002). In 25-40 % of the arrests where resuscitation is attempted, return of spontaneous circulation (ROSC) is achieved and many of these patients are hospitalised alive (Langhelle et al. 2003; Herlitz et al. 2006). In a North-American material, 40 % of the out-of-hospital cardiac arrest victims transported to hospital were admitted to hospital (Callaway et al. 2010).

Over 90 % of patients hospitalised alive are unconscious and need intensive care treatment with mechanical ventilation and active hemodynamic support, but some patients with a poor prognosis or terminal illnesses may be admitted to regular wards without active support. Conscious patients are often admitted to coronary care units (Herlitz et al. 2003).

The overall survival rate for out-of-hospital cardiac arrest patients varies considerably, probably due to how data are reported, selection bias and also because of the varying configuration of EMS systems. The choice of denominator is crucial and unfortunately not standardised. In an American report the overall survival was 1 % (Lombardi et al. 1994) and in a Norwegian small study, including only patients admitted via the emergency helicopter, the survival was 23 % (Herlitz et al. 1999). The best estimates indicate a survival of about 6 % (de Vreede-Swagemakers et al. 1997) but for patients where resuscitation is attempted the overall survival in Europe was 11 %, with a 21 % survival for patients with initial VT/VF (Atwood et al. 2005). In the United States the overall survival was 8 % (Rea et al. 2004; Nichol et al. 2008) with an 18 % VT/VF survival (Rea et al. 2004).

For patients hospitalised alive the survival also varies considerably between hospitals and regions with rates from 34% to 56 % (Bottiger et al. 1999; Herlitz et al. 2003; Langhelle et al. 2003; Herlitz et al. 2006; Carr et al. 2009), and select materials may present even higher survival rates (Wolfrum et al. 2008). However, in a multivariate analysis, hospital characteristics were not associated to final outcome (Callaway et al. 2010).

The rate of persistent neurological deficits also show great variability (Kuisma et al. 1997; Jorgensen et al. 1998; Bottiger et al. 1999; Bunch et al. 2003) and the long term outcome with intact neurology has been reported to be around 70 % (Graves et al. 1997; Tiainen et al. 2007; Cronberg et al. 2009).

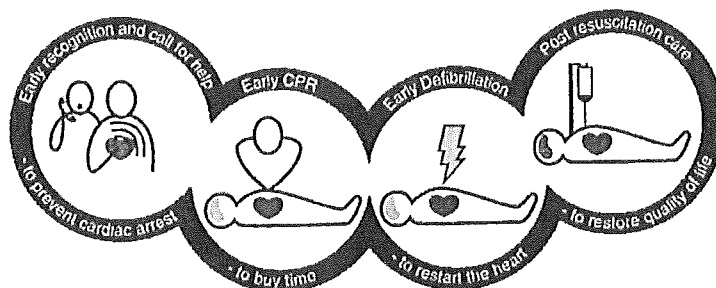
Reported five year survival among patients who were discharged alive from hospital varies between 40 and 79 % (Dickey et al. 1991; Bunch et al. 2003;

Engdahl et al. 2003; Pell et al. 2006). It has been suggested that the long-term prognosis for out-of-hospital cardiac arrest patients discharged alive from hospital does not differ from patients hospitalised for acute myocardial infarction without cardiac arrest (Engdahl et al. 2001).

1.4 Cardiopulmonary Resuscitation

The time between arrest and ROSC is characterised by a no-flow period before cardiopulmonary resuscitation (CPR) is attempted and a low-flow period when the circulation is artificially upheld by chest compressions. After successful ROSC the reperfusion period commences. The chain of survival for a patient with a cardiac arrest includes early recognition of the problem, bystander CPR with chest compressions and lung inflations, electrical therapies with defibrillation of the uncoordinated electrical activity of the heart, delivery of therapeutic drugs and a well functioning and standardised post resuscitation care (Figure 1).

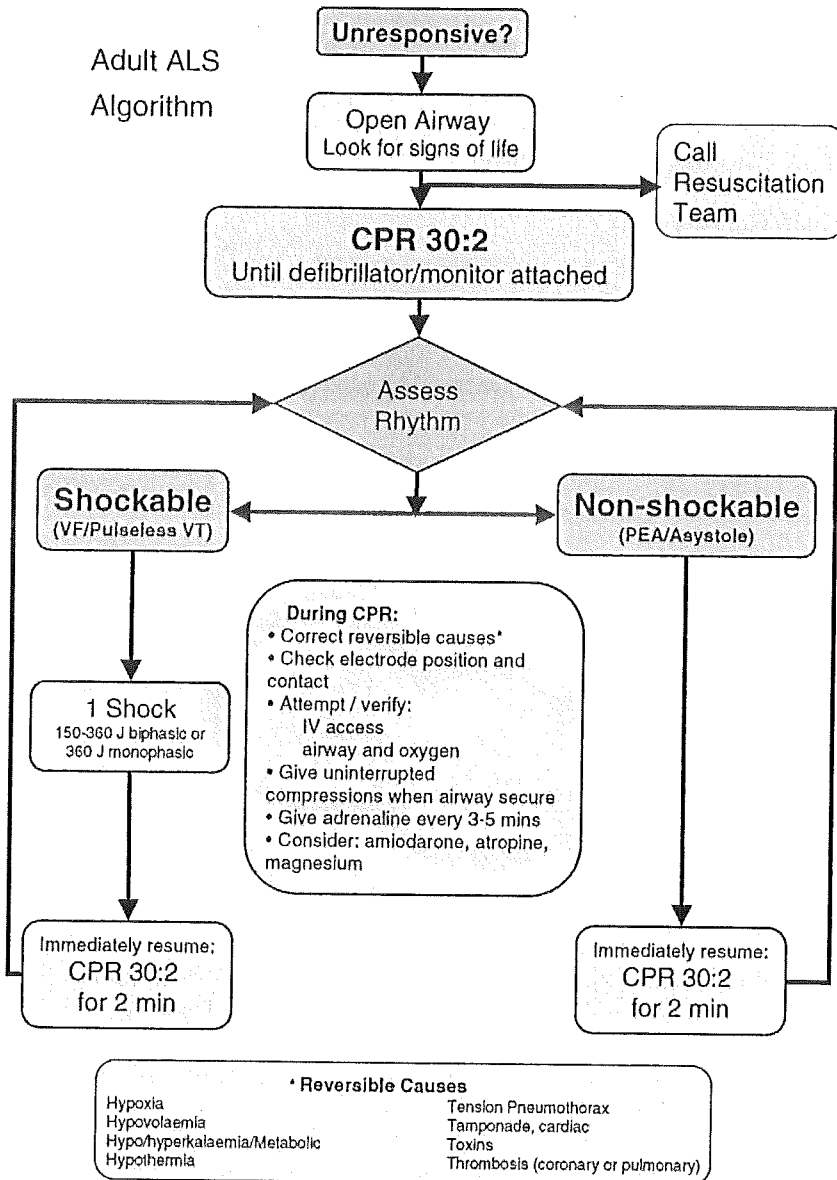
Figure 1 The Chain of Survival.



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The resuscitation phase is divided into basic life support (chest compressions, lung inflations and in special circumstances defibrillation) and advanced life support with defibrillation, devices to secure the airway and deliver efficient ventilation, vascular access and drug delivery. For the advanced life support algorithm, see Figure 2. The chance of a successful ROSC is declining with increasing length of the no-flow and low-flow periods. One predictor of a subsequent good outcome is if the cardiac arrest is witnessed, and the chance of survival increases two or three fold if immediate bystander CPR is performed (Holmberg et al. 2001; Herlitz et al. 2005). Also early defibrillation is important. Immediate CPR and defibrillation within the first minutes after cardiac arrest have led to survival rates of 49-75 % and the chance of surviving to hospital discharge diminishes with every minute delay with defibrillation (Handley et al. 2001).

Figure 2. The algorithm for advanced life support.



Lung inflations and chest compressions

When the heart arrests the oxygen delivery to critical organs (brain and heart) is abruptly halted. This is more of a circulatory problem than a ventilatory problem. Therefore it is suggested that CPR in adult cardiac arrest victims should start with chest compressions to restore the circulation and to deliver the still saturated blood to the organs. However, if the arrest is prolonged, ventilation of the lungs must also commence at some time point.

The ventilation of the patient in cardiac arrest should be significantly reduced compared to normal ventilation, to match the reduced blood flow through the lungs with lower net oxygen uptake. Further, a reduced ventilation will increase venous return to the heart through lower intrathoracic pressures, minimise the risk of gastric distension and vomiting and, perhaps most important, reduce interruptions of adequate chest compressions (Handley et al. 2001).

Moreover, to overcome the problem with reluctance and hesitation to start mouth-to-mouth ventilation, there has been suggestions that lay-people do chest compressions only, which for cardiac arrest with only a few minutes from arrest to start of CPR may be equally beneficial during the first minutes (Bohm et al. 2007). Compression only-CPR is shown to be superior to no CPR at all, when waiting for the arrival of medical expertise (Becker et al. 1997). However, when the emergency medical service arrives, proper ventilation must start. In the advanced life support guidelines a secure and protected airway is recommended, preferably with endotracheal tube and bag ventilation. Other types of artificial airways, like combi-tubes, laryngeal tubes and laryngeal masks, with varying ability to protect the airway from abdominal regurgitation, may also be used (Nolan et al. 2005). The pre-hospital placement of endotracheal tubes is associated with prolonged interruptions of CPR (Wang et al. 2009), which might be unfavourable. The optimal artificial airway for the pre-hospital setting is not known.

There have been various methods to artificially replace heart activity during cardiac arrest through history, where thoracotomy with open heart massage is the most spectacular, however readily used prior to the invention of closed chest massage-chest compressions. Direct massage to the heart produces better coronary perfusion than standard CPR (Boczar et al. 1995) and may still be used during and after thoracic surgery, in trauma situations and when the heart arrests during abdominal surgery.

Closed chest compressions were discovered in the 1950s (Kouwenhoven et al. 1960) and presented in the "ABCs of Resuscitation" by Peter Safar in 1957 (Safar 1989). Chest compressions produce a blood circulation by direct compression on the heart and also by changes in intrathoracic pressure. During CPR the systolic pressure can reach 70-90 mm Hg during optimal conditions but the diastolic pressure remains low, and thus the mean arterial pressure rarely exceeds 40 mm Hg (Paradis et al. 1989). This may result in a minor, but sometimes sufficient, perfusion to the brain through the carotid and vertebral

arteries and also to the heart through the coronary circulation. At the best, the circulation will reach about one third of normal resting values. However, this critical blood flow may be sufficient to minimise brain injury and may also increase the likelihood for the heart to restart.

Many of the recommendations for the mode of delivery of chest compressions are derived from animal experiments. It is suggested that the compressions should be continued with as few interruptions as possible, at a pace of approximately 100 per minute, that they should be performed in the centre of the chest on the lower part of the sternum with a depth of 4-5 cm and with allowance of a full recoil of the chest when pressure is released. With an unprotected airway and when there is only one rescuer present there must be alternations between compressions and ventilations.

Animal data suggest that the former ratio of 15 compressions to 2 ventilations may be insufficient and computer simulations have shown an optimal ratio of 30 to 2 (Handley et al. 2001). However, when the airway is intubated, compressions and ventilations could be performed simultaneously with a ventilation rate of 10 breaths per minute and the compression rate of 100 per minute. The implementation of 30:2 compared to 15:2 have reduced no-flow times and thus improved the delivery of CPR (Hostler et al. 2007). An increased fraction of chest compressions is associated with improved outcome in a clinical observational study (Christenson et al. 2009).

Active compression decompression and mechanical compressions

Different adjuncts and devices to enhance delivery of CPR have been proposed. The theory that active decompressions during the chest recoil phase increased CPR efficacy was implemented in the Cardio-pump® with a suction cup attached to the chest, lifting the chest during decompression. This active decompression leads to a decreased intrathoracic pressure increasing venous return, and the device is associated with increased cardiac output leading to increased coronary and cerebral perfusion pressures (Shultz et al. 1994). However meta-analysis of randomised trials have failed to prove long-term effects on survival (Lafuente-Lafuente et al. 2004).

There are several products applying automated mechanical compressions and one combines active compression-decompression with automaticity; the Lund University Cardiac Arrest System (LUCAS®). This is a gas-driven system that enables prolonged CPR, and combined with a Boussignac endotracheal tube with a high flow of oxygen it may provide both a sufficient cardiac output and oxygenation of the blood (Steen et al. 2005). Most of the data are derived from animal experiments, and pilot randomised trials did not suggest improved outcome (Axelsson et al. 2006; Axelsson et al. 2009). However, a large-scale trial is under way (Rubertsson, personal communication).

Defibrillation

Cardiac arrest often starts with VF when the coordinated electrical activity governed by the rhythm generating nodes (most often the sinus node in the atrium) for various reasons (ischaemia, old ischaemic “scars”, electrolyte disturbances etc) has been replaced by an electrical chaos in the myocardium. With an electrical current of sufficient power the myocardium may be simultaneously depolarised and the normal rhythm-generating centre can restore coordination of heart activity through the conductive system. The delivery of an electrical shock is called an attempt to defibrillate. Defibrillation is when fibrillation stops, or better defined as the absence of ventricular fibrillation 5 seconds after the electrical shock (Deakin et al. 2005). Electrical therapy leading to defibrillation is one of very few proven interventions that increases survival after cardiac arrest when the initial rhythm is ventricular fibrillation (Auble et al. 1995).

Early attempts to defibrillate have been shown to be important for survival, and the chance of a subsequent good outcome declines with 7 -10 % per minute if defibrillation is not attempted in the absence of bystander CPR and with 3-4 % per minute when CPR is performed (Larsen et al. 1993; Valenzuela et al. 1997; Waalewijn et al. 2001). Earlier guidelines have emphasized attempts of early defibrillation.

There is evidence that CPR before an attempt to defibrillate is superior in achieving ROSC in the experimental setting (Menegazzi et al. 2003; Rittenberger et al. 2007). This strategy is also associated with increased survival when the ambulance response times exceeded five minutes (Wik et al. 2003).

Guidelines also stress the importance of uninterrupted ongoing CPR and to continue compressions directly after the delivery of an electrical shock. A palpable pulse rarely reappears directly after successful defibrillation (Rea et al. 2005), and repeated checking for pulse will increase no-flow periods (van Alem et al. 2003).

It is suggested that ongoing CPR when ROSC is achieved does not increase the risk for a new arrest (Hess et al. 2005). However, a recent report suggests that early resumption of chest compressions indeed increases the risk of recurrent VF (Berdowski et al. 2010).

Drugs

Vasopressor drugs (e.g. adrenaline) have been administrated in the cardiac arrest scenario for many years, and they are advocated in guidelines mainly based on expert opinions and animal experiments, showing increased coronary and cerebral perfusion pressures. There has previously been no human randomised placebo controlled trial indicating a survival benefit of any vasopressor.

The use of the anti-arrhythmic drug amiodarone is recommended for refractory VT/VF, but studies have only suggested short-term benefit of survival to hospital admission (Dorian et al. 2002). Intravenous magnesium is indicated only when the VF is of a Torsade-de-point type or if severe hypomagnesaemia is confirmed or suspected (Allegra et al. 2001).

Atropine is indicated only for asystole and PEA with concomitant electrographic bradycardia but is not supported by any studies.

The use of buffer solutions is not recommended for cardiac arrest, unless associated with hyperkalaemia or intoxication with tricyclic antidepressants (Nolan et al. 2005).

In a large multicenter randomised trial on thrombolysis during resuscitation there was no difference in survival (Bottiger et al. 2008).

For many years, adrenaline and other drugs have been recommended as essential parts of advanced life support, but a recent study suggested no difference in mortality if resuscitative drugs were delivered or not. The authors though state that the study possibly was somewhat underpowered to detect small, but maybe clinically important, differences (Olasveengen et al. 2009) but clinical equipoise for intervention trials on drug delivery during CPR was indeed demonstrated.

When to stop resuscitation attempts

The maximum duration of a resuscitation attempt is impossible to define and it is only touched upon in guidelines. There are no sufficiently strong predictors of mortality or survival in the acute cardiac arrest scenario and therefore clear guidelines on this ethically challenging topic are lacking.

There are many variables that may predict a subsequent poor outcome (see below) but used on their own they lack in sensitivity, specificity and predictive value. They may also have been tested and been predictive on a population level, but nevertheless reveal very little information for the individual patient.

2. The brain, brain metabolism and cerebral ischaemia

The adult human brain constitutes about 2 % of the total body weight, but it receives about 15 % of the cardiac output and it consumes about 20 % of all oxygen in resting conditions. These values reflect the metabolic demand and the high oxygen consumption of the brain. The brain has a metabolism seven to eight times the average metabolism of the rest of the body tissues. In moments of intense brain activity the metabolic activity can further increase manifold.

The brain consists of neurons and supportive glial tissue. Most of the energy expenditure takes place in the neurons, mainly to keep homeostasis of cell membranes with ion pumps transporting sodium and calcium to the outside of the

cell membrane and potassium and chloride to the inside. Every time a neuron fires an action potential, these electrolytes pass through the membranes, leading to increased ion pump activity, in order to restore the resting potential and to rebuild the proper concentration gradients.

Most body tissues can manage without oxygen and nutrient supply for several minutes and up to hours. They rely on stored nutrients, for instance in the form of glycogen, and use anaerobic metabolism partially breaking down glucose or glycogen without reacting with oxygen. This pathway is 18 times less efficient, but it provides the cells with energy in moments of distress or extra needs, when there is an imbalance between supply and demand (e.g. stopped breathing, insufficient blood circulation, athletic sprints or short distance swimming) (Guyton et al. 2000).

The brain has a very limited anaerobic capacity and the amount of stored nutrients is very scarce. Therefore, the activity and function of the neurons rely on a moment-by-moment supply of oxygen and glucose from the blood.

Cerebral ischaemia is defined as a severe reduction, or total loss, of blood flow to the brain leading to fast oxygen and glucose deprivation. A symptom of the speedy mechanisms is that ischaemia leads to unconsciousness in 5 to 10 seconds (Rossen et al. 1943). Cerebral tissue oxygen tension is declining rapidly and reaches a zero level after about 2 minutes (Cavus et al. 2006). The cessation of mitochondrial oxidative phosphorylation leads to a rapid decline in levels of brain tissue adenosine triphosphate (ATP), which is the common energy currency in living organisms (Ljunggren et al. 1974; Nordstrom et al. 1978). After few minutes of dense ischaemia, ion gradients across plasma membranes can no longer be upheld and anoxic cellular depolarisation ensues (Hansen 1985). In conjunction with this sudden enhancement of ion permeability, a massive release of neurotransmitters (glutamate and other excitatory amino acids) is observed, which may lead to excitotoxicity (Benveniste et al. 1984; Hagberg et al. 1985). The deleterious cell environment is further deranged during ischaemia by an increase in intracellular calcium concentrations and also accumulation of lactate and hydrogen ions leading to intracellular acidosis (Siesjo 1988; Kristian et al. 1998).

If the brain ischaemia is of short duration, the cellular homeostasis, the mitochondrial respiration and the energy levels will be restored. However, if the ischaemia is prolonged, homeostasis may only be partially or transiently restored when the tissue is reperfused, and if the ischemia lasts for hours there is very little reversibility seen, if any. The consequence is necrosis (Kalimo et al. 1977).

A successful restoration of circulation will lead to reperfusion of the injured tissue. Different regions of the brain may not be equally affected. Certain areas of the brain, like the CA-1 (*CA=cornu ammonis, shaped as the horn of Amun*) region of the hippocampus and thalamic structures, are more susceptible to anoxic brain damage (Blomqvist et al. 1985; Bottiger et al. 1998). The rising oxygen tension facilitates the production of reactive oxygen species (free radicals), which may

aggravate the damage during the ischaemic period (Sakamoto et al. 1991). ATP energy levels are restored, and the cell will then have the opportunity to launch cell mechanisms to engage the ischaemic damage, activating both damaging as well as repairing processes. Modified gene expression, inflammation and apoptosis mechanism play pivotal roles (Siesjo 1988; Bottiger et al. 1998; Wieloch et al. 2001; Wieloch 2002).

The post-ischaemic period is complicated by hyperthermia induced by generation of pyrogens in the brain, but also by hyperthermia secondary to a global systemic inflammation (Adrie et al. 2002) and infection in the clinical intensive care setting. Fever occurring during the first 48 hours after global ischemia may be detrimental (Coimbra et al. 1996; Bottiger et al. 2008), accelerating the damaging processes, and is in considerable disfavour of an optimal cerebral metabolic rate of oxygen (Erecinska et al. 2003).

3. Post cardiac arrest syndrome

When the brain and the body are circulated with blood after complete ischaemia and successful resuscitation, a unique pathophysiological state begins that affects multiple body organs. This was recognised by Dr Negovsky in the 1970s as the post resuscitation disease (Negovsky 1972). In 2008 the International Liaison Committee on Resuscitation published a statement about this physiological state, proposing a change of the name from post resuscitation disease to the post cardiac arrest syndrome (Nolan et al. 2008). The reason for this change was that resuscitation nowadays is used for a broader panorama of shock states and that post resuscitation would imply that the resuscitative act is over. On the contrary, an even more intense period of resuscitation begins after ROSC and when the patient is admitted to hospital.

The post cardiac arrest syndrome must be appreciated in the context of the disease that caused the arrest and possible comorbidities. There are three main components of the post cardiac arrest syndrome apart from the persistent precipitating pathologies and diseases mentioned above: post-cardiac arrest brain-injury, post cardiac arrest myocardial dysfunction and global systemic ischaemia /reperfusion response (often called a sepsis-like syndrome (Adrie et al. 2002) with a similar clinical pattern as the Systemic Inflammatory Response Syndrome (SIRS) (Bone et al. 1992)). The severity of these components is of course related to the magnitude of the ischaemia and the cause of the arrest as well as the patients' prearrest state of health, and may also vary between individuals.

3.1 Post cardiac arrest brain injury

For out-of hospital cardiac arrest patients admitted to hospital the mortality varies between approximately 50 % and 70 %, and there are reports that the cause of death, in about 70 % of the cases, is due to brain injury (Laver et al. 2004; Olasveengen et al. 2009). As mentioned above, the cascade of deleterious mechanisms during the reperfusion period is complex, and there is selective vulnerability in different regions of the brain. The observed pathology evolves over days with a delayed neuronal death implicating an extended therapeutic window for neuroprotective interventions.

There are two important aspects of the post cardiac arrest phase: first, physiological disturbances may further increase the vulnerability of the injured brain and cause secondary brain injury and, second, there may be interventions that could protect from or reverse the unfavourable processes.

Possible physiological factors that may affect the final outcome with respect to brain injury may be for instance mean arterial pressure, cerebral perfusion pressure, blood flow and oxygen delivery, in a situation when the auto regulation of the cerebral blood flow is disturbed and the brain may be prone to oedema (Sundgreen et al. 2001). The optimal targets for these parameters are not known, but it may be reasonable to expect that hypotension, hypertension and severe blood loss are deleterious.

Electrolytes and blood glucose may also be of importance, but again, the optimal targets are not known (Losert et al. 2008).

Seizures are common in the post cardiac arrest phase and they are probably both a consequence of and a cause of brain damage. Seizures have been associated with an increased mortality (Langhelle et al. 2003; Rossetti et al. 2007; Rossetti et al. 2009). To date there are no trials evaluating the potential beneficial effect of aggressive treatment of seizures after cardiac arrest, but there are case-reports where patients with seizures have survived with intact neurology (Hovland et al. 2006; Sunde et al. 2006).

Elevated body temperature is common after cardiac arrest and is associated with increased mortality (Takino et al. 1991; Takasu et al. 2001; Zeiner et al. 2001; Langhelle et al. 2003). These observational data on survival from cardiac arrest populations in the pre-hypothermia era suggest odds ratios for a poor outcome of 2.7; 95 % Confidence Interval (CI) 1.2-6.2 for temperatures >37.8 °C (Langhelle et al. 2003) and 2.26; 95 % CI 1.24-4.12 for every degree higher than 37 °C (Zeiner et al. 2001), but whether the elevated temperatures caused the decrease in survival or were just a marker of severe brain injury could not be clarified.

Also there are concerns with microcirculation and ischaemia-induced coagulopathy/coagulation that may further hamper brain function, especially with cardiac arrests with no-flow periods of more than 15 minutes, as indicated in

animal experimental studies (Fischer et al. 1996; Bottiger et al. 1997). However, the TROICA-trial with thrombolysis during attempts to resuscitate did not increase 30-day survival (Bottiger et al. 2008).

3.2 Post cardiac arrest myocardial dysfunction

The post cardiac arrest myocardial dysfunction may also contribute to mortality in patients admitted to hospital after cardiac arrest. There is no typical scenario in circulatory performance after ROSC, and patterns from cardiogenic shock to high-output states may be present. The risk for an unstable circulation after ROSC increases with prolonged periods of VF (Menegazzi et al. 2008). Elevated blood pressure and tachycardia may be effects of exogenous and endogenous catecholamines from the CPR-phase (Rivers et al. 1994). If myocardial dysfunction appears it may be detected early in the post ROSC period (Kern et al. 1996). The lowest cardiac output is often seen after six to eight hours after the arrest and usually an improvement is seen at 24 to 48 hours. Recovery is often seen 72 hours after the arrest for survivors (Kern et al. 1996; Laurent et al. 2002).

Of course these patterns are blunted by pharmacological treatments with vasopressors and inotropes in the clinical setting, and therefore much information is derived from animal experimental studies. The myocardial dysfunction is responsive to medical therapies but the effect on survival is not yet evident. However, strategies with reperfusion of occluded coronary vessels are associated with increased survival (see below).

3.3 Systemic ischaemia-reperfusion response

The ischaemia during the cardiac arrest and the partial reperfusion during CPR followed by full reperfusion after ROSC are associated with an oxygen debt in the peripheral tissues and concomitant elevation of waste products. This may cause an activation of immunological and coagulatory pathways leading to a situation that is similar to what is seen in sepsis caused by microbes. This sepsis/SIRS like syndrome features a similar clinical picture as sepsis with vasodilatation/vasoplegia, the need for intravascular volume, disturbed oxygen delivery and uptake, organ dysfunction and increased risk of infections (Cerchiari et al. 1993; Adrie et al. 2002; Adams 2006). Even if not proven in clinical trials, there might be physiological reasons to counteract and treat these pathologies as early as possible.

4. Post cardiac arrest intensive care

More than 90 % of patients hospitalised alive after out-of-hospital cardiac arrest are unconscious and need intubation, mechanical ventilation and sedation (Herlitz et al. 2003). The optimal treatment includes a multi-disciplinary team of caregivers. Much of the initial care is similar to any other critically ill patient category with attention to airway and breathing, oxygenation and vital parameters, and also to other concomitant intensive care treatments with standard indications, as for instance for renal replacement therapy.

However, there are certain areas of special concern attributed to cardiac arrest patients including interventions aimed at the cause of arrest, neuroprotective strategies and prognostication. The neuroprotective strategies involving temperature control will be discussed below. There have been randomised trials evaluating various potentially neuroprotective drugs and substances as calcium blockers, corticosteroids, diazepam, magnesium and thiopental without improved outcomes (1986; Jastremski et al. 1989; Roine et al. 1990; 1991; Longstreth et al. 2002).

4.1 Cardiac and coronary care

Immediate revascularisation for patients with cardiogenic shock is beneficial for long-term survival (Hochman et al. 1999). As described above coronary artery disease is present in the majority of patients with out-of-hospital cardiac arrest, and acute myocardial infarction is the most common cause of sudden cardiac death. There are a number of reports indicating a beneficial effect of early revascularisation also after cardiac arrest both in the pre-hypothermia and hypothermia era (Spaulding et al. 1997; Knafelj et al. 2007; Sunde et al. 2007; Werling et al. 2007; Reynolds et al. 2009). However, all of these findings are based on observational studies.

Even if the overall mortality is higher for patients referred for revascularisation after cardiac arrest, compared to those without cardiac arrest, the mortality after surviving the acute phase is similar between the groups. In a recent study, the long-term survival with intact neurology was as favourable as 87 % in the cardiac arrest group (Lettieri et al. 2009).

4.2 Standardised intensive care treatment

As previously mentioned, cardiac arrest is a time sensitive disease where delay of various interventions may cause permanent damage and fatality. There are indications that a standardised pro-active treatment strategy following strict guidelines tailored to the needs and capacities of the individual institution may be

beneficial for the final outcome (Sunde et al. 2007; Rittenberger et al. 2008). These strategies include attention to physiological parameters, temperature management, coronary care, aggressive treatment of electrolyte and metabolic parameters to safe target values, and they also include protocols for treatment of seizures and standardised prognostication and withdrawal strategies. As protocolised care has been proven to increase survival in general intensive care there is a rationale for this strategy (Kern et al. 1999).

4.3 Prognostication

Post cardiac arrest brain damage spans from very subtle defects in memory to persistent coma and vegetative states. It is reasonable to try to find prognostic tools to define the patients who will benefit from prolonged, expensive and in many aspects stressful intensive care treatment. However, when relating to an individual patient the demands on such prognostic tools are enormous; as a next of kin or an attending physician there is no margin for false prediction of a poor outcome if this would lead to premature and erroneous withdrawal of life support. Hence, it is always more tempting to continue the care and increase the observation time, even if it may impose great stress and more anguish to the patient and relatives and will increase costs for hospitals and society. On the other hand, delayed actions to withdraw futile care may increase the proportion of patients in a vegetative state.

Many centres have had poor practice principles to guide length of observation periods for patients not immediately regaining consciousness after cardiac arrest, and to some extent therapeutic nihilism has prevailed. The newly awakened interest for cardiac arrest patients, triggered by the randomised trials of hypothermia (HACA-study-group 2002, Bernard et al. 2002), has in many aspects changed this practice. Therefore there is a great need to define robust prognostic tools to guide the controversial issues of whether to withdraw or sustain life support. Also, the introduction of hypothermia in itself may disable the use of prognostication tools developed in the pre-hypothermic era.

The main approaches to prognostication are based on demographic and cardiac arrest parameters, clinical neurological evaluation, electrophysiological and neuroimaging methods, and blood markers of brain damage.

The advent of induced hypothermia has raised certain concern about the reliability of neurological prognostic tests, since deep sedation, muscle relaxation and delayed development of pathophysiological processes may affect the test results, and a conservative approach has been advocated (Nolan et al. 2008). Moreover, a multi modal approach to prognostication is probably wise combining information from multiple investigations and making a final decision no earlier than after 72 hours after the arrest in unsedated, non-hypothermia treated patients

and 72 h after rewarming in hypothermia treated patients (Cronberg et al, unpublished).

Demographic and cardiac arrest parameters

The time from arrest to start of CPR and time from arrest to ROSC, reflecting the magnitude of the ischaemic insult, are two of the most important predictors of the subsequent outcome after cardiac arrest. Other important predicting factors are whether the arrest is witnessed or not, if by-stander CPR is performed, the response time for emergency medical services, the age of the victim and the level of consciousness/coma at admission to hospital. Retention of neurological function, including being conscious and able to obey verbal commands, is obviously a good sign. Conversely, being comatose and unresponsive without preserved neurological function predicts a poor outcome, but it has limited absolute prognostic value. Further, the initial rhythm presented is of importance, where an initial rhythm of VT/VF and concurrent acute myocardial infarction with ST-elevation is a marker of a good outcome compared to asystole and PEA. Also level of blood glucose, pH and core temperature at admission are important as well as a previous history of diabetes (Herlitz et al. 2003; Langhelle et al. 2003; Skrifvars et al. 2003; Herlitz et al. 2005; Nolan et al. 2007; Carr et al. 2009).

Clinical neurological evaluation

The clinical neurological bedside examination is a widely used and universally available prognostic tool. The best predictive power is found in the absence of pupillary and corneal reflexes and absent brain stem reflexes or a Glasgow Coma Scale motor score of ≤ 2 at 72 hours after the cardiac arrest in unsedated patients (Zandbergen et al. 1998; Wijdicks et al. 2006; Zandbergen et al. 2006).

Neurophysiological and neuroimaging methods

The most evaluated neurophysiological tests are electroencephalogram (EEG) and somatosensory evoked potentials (SSEP).

There are EEG patterns associated with a poor outcome where burst suppression, generalized suppression and periodic complexes on a flat background are the most prominent (Wijdicks et al. 2006). Effects of sedation on the EEG pattern and also amplitude attenuation by hypothermia are valid concerns when using information from EEG. EEG provides valuable information, but when used alone it is not sufficient to defend a prognosis. Recently the use of bed-side amplitude integrated EEG was shown to be useful in hypothermia treated patients where patterns of seizure activity, burst suppression and a flat EEG were

associated with a poor outcome and a continuous background pattern suggested a subsequent good outcome (Rundgren et al. 2006).

The so far most promising strategy is to evaluate SSEP, as early as 24 hours after the cardiac arrest, where a bilaterally absent N20 wave is highly associated with a poor outcome (false positive rate 0 %; 95 % CI 0 to 3 %) (Zandbergen et al. 2006). However, a presence of the N20 waveform was on the contrary not predictive of a good outcome. This SSEP strategy is best evaluated for unsedated, non-hypothermia treated cardiac arrest patients and information how the SSEP should be interpreted in hypothermia treated patients will hopefully be presented in a pending Dutch study (PROPAC 2). In a sub study of the HACA-trial (HACA-study-group 2002) 60 patients randomly assigned to hypothermia or control were evaluated with SSEP. A bilateral absence of the N20 wave were 100 % associated with a poor outcome in both patients treated with hypothermia and those who were not (Tiainen et al. 2005), and thus hypothermia did not seem to influence the interpretation of the test. There are suggestions that SSEP alone is better than clinical neurological evaluation (Zandbergen et al. 2006) but that is more of an academic interest, since there is no reason why an SSEP should rule out the performance of a clinical examination. In contrast, it highlights that clinical neurological tests are unreliable in the first hours and days of cardiac arrest coma.

There are two reports on hypothermia treated patients that indicate a possible prognostic tool in the Bispectral Index (BIS), which is an easy and widely available technology (Seder et al. 2009; Stammers et al. 2009). BIS provides a dimensionless number between 0 and 100 where 0 reflects no activity on EEG and 100 is a typical awake person. BIS is intended to be used for measuring depth of general anaesthesia.

Magnetic Resonance Imaging (MRI) and especially Computed Tomography (CT) are useful for evaluation of intracranial pathologies as stroke and bleedings that may obscure the clinical picture. It is reasonable to propose that all patients who do not regain consciousness should have a CT or MRI performed, however there are no controlled trials of these modalities for prognostication of the cardiac arrest patient.

Serum markers of brain damage

The most investigated serum markers of brain damage are the astroglial protein S-100B and the neuron cytoplasmatic enzyme neuron specific enolase (NSE). Both markers are hampered by the lack of standardised methods for laboratory analysis, which may be the reason for the diverse cut-off levels that have been proposed as indicative of a poor outcome. These markers have been evaluated for cardiac arrest patients before the use of hypothermia (Martens et al. 1998; Rosen et al. 1998; Schoerhuber et al. 1999; Bottiger et al. 2001; Rosen et al. 2001; Hachimi-Idrissi et al. 2002; Meynaar et al. 2003; Zandbergen et al. 2006).

There are also three studies where hypothermia treated patients are evaluated (Tiainen et al. 2003; Hachimi-Idrissi et al. 2005; Oksanen et al. 2009). All available studies are quite small and heterogeneous in populations, design and findings; strong inferences should probably be cautioned against. However, when more thoroughly evaluated and used together with other prognostic tools, these markers may prove to be useful.

Neuron specific enolase is a glycolytic enzyme found intracellularly in neurons, but also in other cells of neuroectodermal origin. It is also present in platelets and erythrocytes limiting its usefulness when blood samples have been haemolysed.

S-100B is a calcium binding protein found in astroglia and Schwann cells, i.e. in the supporting tissue surrounding neurons. It is also present in oligodendrocytes, in plexus choroideus but also extracerebrally.

The half-life of these proteins are 30 hours for NSE and 30 minutes for S-100B, and thus their temporal profiles are markedly different.

4.4 Adverse events and complications

Adverse events such as pneumonia and other infections, arrhythmias, hyperthermia/fever, seizures and electrolyte and metabolic disorders occur commonly among intensive care patients, and especially for comatose patients treated after resuscitation from cardiac arrest (Jorgensen et al. 1998; Zeiner et al. 2001; Langhelle et al. 2003; Skrifvars et al. 2003; Tsai et al. 2005). Several of these factors have been related to a poor outcome (Zeiner et al. 2001; Langhelle et al. 2003; Skrifvars et al. 2003). These events may be related to factors that precipitate the cardiac arrest, the severity of the cardiac arrest and the magnitude of the ischaemic insult, disturbances in myocardial function but also factors related to the intensive care treatment itself. As the comatose cardiac arrest victim is a very critically ill patient, it is expected that many adverse events will occur since mechanical ventilation, invasive procedures and multipharmacy are necessary ingredients of the treatment. Many of the events may not be possible to foresee and prevent but could be treated, while a standardised and protocolised care could possibly help preventing other.

After the introduction of hypothermia as a treatment for cardiac arrest patients, adverse events in the post cardiac arrest period have received more attention. Questions have been raised whether the incidence, the spectrum and severity of adverse events have changed after the implementation of hypothermia. Hypothermia itself may affect many physiological processes with altered electrolyte regulation, insulin secretion and activity with subsequent glucose disturbances, coagulopathy and response to infections. In addition hypothermia treatment in itself requires deeper sedation, prolonged mechanical ventilation and

also neuromuscular blockade, which may further increase the risk for adverse events.

5. Long-term prognosis

As previously described, less than 10 % of cardiac arrest patients survive. However, for the selected group of patients, which is admitted to intensive care units, approximately one third and up to more than one half of the patients survive. In recent years numerous publications report a survival to hospital discharge around 50 %.

For patients discharged from hospital, survival with a good neurological outcome varied in one study between 70 % and 90 % (Langhelle et al. 2003) and in a large database from the United Kingdom with over 6000 patients, 68 % presented a good neurological outcome according to the Cerebral Performance Category Scale, numbers similar to other studies (Graves et al. 1997; Cronberg et al. 2009). However, the numbers do change over time and the best time point to evaluate outcome is not fully established but a perspective of at least six months seems appropriate. Patients severely ill and still in a comatose state at hospital discharge have a high probability of dying and patients in a CPC category of 2 and 3 may improve during the first months or die (Arrich et al. 2009).

Neurological sequelae may constitute a great handicap (Edgren et al. 1994; Jorgensen et al. 1998) and for patients with pre-arrest employment, few patients had returned to previous work with full employment, one half were on sick-leave and the rest worked part time at six months after the arrest (Cronberg et al. 2009). This study of hypothermia treated cardiac arrest patients, also showed that mild cognitive impairment was common, but despite this mild impairment the survivors had a high level of functioning as reflected in CPC scores of 1 or 2 in 50 of 52 patients. Also, their quality of life was good. Memory deficits and frontal lobe dysfunction were the most prominent neurological impairments. The spectrum and prevalence of these impairments were similar to what have been found in patients not treated with hypothermia (Graves et al. 1997) as well as with other hypothermia treated cardiac arrest patient groups (Madl et al. 2004; Tiainen et al. 2007).

In a recent study the CPC at hospital discharge was significantly improved following the implementation of hypothermia, but significant improvement in survival, cognitive status or quality of life could not be detected at long-term follow-up. However, in this study, the baseline outcome was better than seen in other comparable studies (Bro-Jeppesen et al. 2009).

6. Induced hypothermia

6.1 Thermoregulation

Humans are homeotherms and they attempt to maintain a constant body temperature despite fluctuations in environmental temperature. There is no single body temperature that can be considered normal and there are reported variations in baseline body temperature between 36 °C to over 37.5° C. Also, there are inconsistencies where to measure core temperature (rectally, orally, oesophageally etc) and reported normal ranges fluctuate accordingly. The average normal temperature range is normally considered to be 36.7 °C to 37.0 °C, when measured orally. When the rate of heat production is greater than the loss, there will be a net heat accumulation in the body and vice versa when the heat loss is greater than the production.

Heat is one of the main by-products of metabolism and proportional to the metabolic rate of the body. Most of the body heat is generated in the liver, the brain, the heart and in skeletal muscles. There is a basal heat generation level that may be increased manifold when necessary or as a by-product by other processes. The heat from the body organs is conducted to the skin and it is then transferred from the skin to the surrounding environment. An efficient barrier to the latter procedure is body insulation by fat and subcutaneous tissue and of course by clothing.

The main physical processes that dissipate heat from the body to the environment are:

Radiation

All objects radiate infrared heat rays. If the body temperature is greater than the temperature of the surrounding, a greater quantity of heat is radiated from the body than to the body. In normal room temperature about 60 % of the heat loss from the body at rest is dissipated by radiation.

Conduction

Conduction is the phenomenon of heat exchange between two objects adjacent to each other. Conduction to other objects is under normal conditions quite limited but may increase substantially if the body is submerged into water or if placed on a cold floor. However, conduction to the air constitutes around 10 to 20 % of the normal heat loss. The kinetic energy of the skin molecules will spread to the air molecules, increasing their velocity. This transfer is self-limited when the velocities are levelled out, unless the heated air is transported from the body surface and is replaced by unheated air (i.e. convection).

Convection

Convection is the exchange of heat because of a current of a flowing medium (e.g. air and water). First, the heat is conducted from the body to the medium and then the convective current will transport the heat away. A body submerged in running water or experiencing heavy wind will be exposed to strong convective forces. Even in a room without apparent air movement the heated air adjacent to the body will rise (compare, hot air balloon) and produce a small convective current leading to the 10 to 20 % heat loss mentioned above

Evaporation

When water evaporates from the body surface, heat is lost for every unit of water that is evaporated. Evaporation can be regulated by the activity of the sweat glands but there is always a basal level of about 600 ml per day of insensible water evaporation from the skin and the lungs, leading to about 20 % of total heat loss. In extreme situations the sweat production can increase to 500 to 2000 ml an hour with a substantial rise in possible heat loss.

As evident from the above, the body has a high capacity to dissipate heat at the cost of evaporating water but conversely, a relatively poor capacity to increase body temperature by heat production. Thus, the human body is better adapted to warm environments than cold. The body temperature is governed by thermoregulatory centres in the hypothalamus in the forebrain communicating with the skin, sweat glands, piloerector muscles, vasomotor regulations, visceral organs, muscles and the frontal brain cortex. In a situation where heat must leave the body, the blood vessels will direct blood flow to the periphery, sweat production will increase and the brain will receive signals to limit muscle activity and seek colder environments. In situations of hypothermia and the need for increased heat production the blood vessels will direct blood flow from the periphery to the core, sweat glands will decrease their activity, piloerector muscles will erect body hair, visceral organs will increase heat production, muscles will become more active (shivering) and the brain will receive signals to seek warmer environment and increase body activity.

The hypothalamus has a defined temperature set point, and thermoregulatory mechanisms will continuously attempt to bring the body temperature back to this set point. There are situations when the set point is shifted to a new level, for instance when pyrogens like interleukins set the temperature point higher and the body strives for this new temperature and enters a febrile state. The chill phenomenon, associated with rising fever, comes from the anticipation that the body temperature is too low with regard to the new set point. Muscle shivering, peripheral vasoconstriction and other mechanisms will try to achieve the new, higher temperature. When the set-point is lowered again by a discontinuation of

the pyrogenic emanation or by pharmacological substances like paracetamol, steroids or non-steroidal anti inflammatory drugs, the body experiences all mechanisms to release heat (sweating, flushing, decreased shivering.) There are many pharmacological substances, as for instance sedatives and certain opioids that may offset the set point to a lower level.

The hypothalamic set point has a bearing on the difference between fever and hyperthermia. Fever is when elevation of the body temperature occurs after an upward shift of the hypothalamic set point triggered by prostaglandin E, stimulated by circulating systemic inflammatory pyrogens as for instance Tumour Necrosis Factor and interferons. Hyperthermia, on the other hand, is when the body temperature exceeds the hypothalamic set point after exogenous excessive heat when dwelling in hot environments (heat stroke) or endogenous heat production as in marathon exercise, malignant hyperthermia triggered by anaesthetics or hyperthermia provoked by for instance neuroleptics. Traditional antipyretic drugs have no effect when given for high temperatures associated with hyperthermia, and if external cooling is induced with ice bags, fans or alcohol, shivering will not occur. By contrast, antipyretics may lower the temperature in febrile states while external cooling may provoke excessive shivering.

The hypothalamic auto-regulation of body temperature is fine-tuned down to a body temperature of 34 °C, but in lower ranges it is impaired and at about 30 °C it is completely lost. Hence, humans become poikilothermic at a body temperature of around 30 °C and will cool to ambient temperature. Muscle shivering starts at just below 37 °C and ceases between 31 °C and 33 °C. Blood coagulation is impaired already at 35 °C but is becoming worse in lower ranges. Cardiac conduction is impaired at 32 °C and the risk of arrhythmia increases rapidly around 28 to 30 °C. The heart becomes more and more bradycardic and asystole will occur at a temperature of around 21 °C where the hypothermic victim also will be apnoeic.

In conclusion many of the side effects appear around 32 °C, and thus this temperature is considered the transition level from a safe zone with adequate physiological adaptations, to a danger zone with no defences (Guyton et al. 2000; Mayer 2005).

6.2 Definitions of hypothermia

There are inconsistencies in the definition of hypothermia for humans. Most definitions state that hypothermia is a body core temperature below 36 °C (Mayer 2005), but in some reports 35 °C is used (Danzl et al. 1994; Marion et al. 1996). Mild hypothermia is defined as temperatures down to 32°C, followed by moderate hypothermia to 28 °C and deep (or severe) hypothermia below 28 °C. In some definitions profound hypothermia begins at 18 °C and ultra-profound below 5 °C

(Marion et al. 1996). However these definitions and temperature ranges may have little to do with real life physiology and, as evident from the above, there is a gradual change in the activity in physiological processes over the temperature scale.

In a medical context there are two major categories of hypothermia: accidental and induced. Accidental hypothermia is an emergency situation where the patient is at risk because of the drop in body temperature, inflicted by for instance submersion into cold water, avalanche accidents, trauma, intoxications, cold environment, psychiatric disorders etc. Accidental hypothermia is uncontrolled and associated with increased energy expenditure to re-establish the normal body temperature and will subsequently lead to depleted energy stores. The risk of death is imminent for victims of accidental hypothermia and the risk increases with lower temperatures (Danzl et al. 1994).

Induced hypothermia is, on the other hand, something that is used as an intervention or therapy in medical situations; it is deliberately administered to certain patient categories, and should be controlled and monitored (Marion et al. 1996). As evident from the above, when used to treat hyperthermia, there is no need to give drugs to lower the hypothalamic set point (sedatives may have other effects than lowering the set point though, as for instance tolerating an endotracheal tube), but when hypothermia is used as a neuroprotectant to counteract ischaemia, sedatives, opioids and other medications are essential to lower the hypothalamic set point and counteract shivering. Shivering is less pronounced in the range of temperatures 32-34 °C as compared to 35-37 °C. This may be a significant problem when very mild hypothermia or attempts to reduce fever are instituted in non-sedated patients (Polderman et al. 2009).

6.3 Historical background

The first documented use of hypothermia in modern medicine is awarded to Dr Temple Fay who in the late 1930s used hypothermia, first locally and then generally to treat mainly cancer pain and also in an attempt to retard cancer growth (Fay 1959). Hypothermia as an intervention was first studied in the late 1940s and the early 1950s for the treatment of intracranial swelling, traumatic brain injury other neurosurgical procedures as well as during cardiac surgery in circulatory arrest.

Experimental findings of the use of hypothermia to reduce brain metabolism and brain swelling triggered the first use of hypothermia after cardiac arrest presented as a case series of four patients in 1958 (Williams et al. 1958). These patients were resuscitated with open heart massage and when ROSC was established, hypothermia between 30 °C and 34 °C was induced with blankets with a circulating coolant. All four patients recovered after hypothermia treatment that

was withdrawn when the patients spontaneously showed signs of regained consciousness.

In 1959 another case series was published, indicating a great benefit of hypothermia; there was one survivor of seven non-hypothermia treated while there were six survivors of twelve hypothermia treated patients (Benson et al. 1959). To reduce shivering, the opioid meperidine and the antipsychotic drug chlorpromazine were administered and titrated to effect, but without depressing cardiac function or breathing; the patients were not mechanically ventilated. Both drugs efficiently offset the hypothalamic set point downwards. The body core temperature was arbitrarily set at 30 °C to 32 °C, since the researchers knew that the risk of VF increased dramatically below these temperatures. Noteworthy is that the diagnosis of cardiac arrest was made by visual inspection of the non-beating heart. "The chest was opened and the heart was noted to be either in asystole or fibrillating."

These findings encouraged the inclusion of hypothermia in resuscitation guidelines from the University of Pittsburgh in 1961 and in the ABCs of resuscitation by Dr Safar in 1964.

Despite these anecdotal reports, the risk of adverse events and uncertainty of actual effects resulted in limitations in implementation and abandonment of the treatment. It was not until the positive results of experimental studies were presented in the 1980s that the interest again rose for the use of hypothermia after cardiac arrest.

6.4 Experimental findings

During the late 1980s and the 1990s there was a growing experimental interest for hypothermia, which at that time had become established practice in cardiac surgery. Since cardiac arrest in cardiac surgery most often is a scheduled procedure, hypothermia may be applied before the circulatory arrest to mitigate neuronal damage, so called intra-ischaemic, pre-ischaemic or intra-arrest hypothermia (Jonas 2002). Rat forebrains exposed to 20 minutes of ischaemia with intra-arrest brain temperatures ranging from 30 to 39 °C showed gradually diminishing brain damage the lower the temperature (Busto et al. 1987). One of the most vulnerable parts of the brain, the CA-1 region of the hippocampus, was markedly protected.

Confirmed in other experiments and with larger animals the protective effect of very modest reductions of brain temperature of just a couple of degrees was shown (Leonov et al. 1990; Minamisawa et al. 1990).

Post-ischaemic hypothermia was less well studied and not as impressive in efficacy as intra-ischaemic hypothermia. However, several centres worldwide discovered effects of post-ischaemic hypothermia after both global and focal

ischaemia of the brain, mainly in rats and dogs, but there were problems with enduring neuroprotection (Dietrich et al. 1993) and the effects were not as pronounced as with intra-ischaemic cooling (Boris-Moller et al. 1989). The experiments were mainly focused on mild hypothermia between 32 °C and 35 °C as deeper hypothermia produced more side effects and did not improve outcome (Weinrauch et al. 1992).

Short periods of post-ischaemic hypothermia (3 hours of hypothermia initiated 3 minutes after 10 minutes of global ischemia) indicated initial protection that declined over time, only delaying the inevitable neuron death (Dietrich et al. 1993). Longer durations of ischaemia increased the neuron damage while prolongation of the post-ischaemic hypothermic period indicated a sustained protection (Sterz et al. 1991; Colbourne et al. 1994).

In one study, delayed cooling negated the effect seen with immediate cooling (Kuboyama et al. 1993). However, in other studies delayed start of cooling up to several hours, was shown to be effective in focal ischaemia as well as in global ischaemia (Coimbra et al. 1994; Colbourne et al. 1995). When exposing the rat brain for 10 minutes of severe global ischaemia, a 48-hour period of cooling to 32-34 °C resulted in only 14 % neuronal death compared to untreated animals with 99 % neuronal death (Colbourne et al. 1999).

All together, the results of the substantial work indicate the different titration possibilities when using hypothermia as a neuroprotectant; the timing, the depth and the duration of cooling influence the final results. There is probably a gentle and still not fully elucidated balance between beneficial effects and possible harm, when altering these variables. In a study on rats, temperature management was titrated to 33 °C, 35 °C and 37 °C after eight minutes of ischaemia where the two hypothermic temperatures were equally beneficial in terms of neuroprotection and superior to temperature management at 37 °C (Logue et al. 2007).

As mentioned above, febrile temperatures are detrimental for the injured brain in the reperfusion phase after ischaemia. Bringing temperature back only to normothermia, avoiding fever, also diminishes brain damage in the experimental setting (Coimbra et al. 1996). Thus, the optimal temperature management strategy is not yet elucidated.

The brain metabolism decreases with approximately 5 % per degree Celsius reduction in brain temperature (Hagerdal et al. 1975) and physiological processes are slowed down (Nakashima et al. 1995). However, decreased metabolism cannot to the full extent explain the protective effect indicated, and therefore other mechanism are potential candidates. The ischaemia/reperfusion-induced brain damage is of multifactorial origin as mentioned above. The protective action of induced hypothermia is thus equally multifactorial, affecting multiple detrimental mechanisms (Zhao et al. 2007; Schneider et al. 2009) which may account for its efficacy as a protective treatment: lowered cell metabolism, diminished excitotoxicity, less calcium overload, less inflammation, modified gene expression

and anti-apoptosis and possibly additional, yet unknown effects. The brain damaging processes appear at different time points during the reperfusion and post resuscitation periods and hypothermia may therefore exercise its different protective actions both early and late.

6.5 Clinical findings

In the late nineties several patient series were described where hypothermia was shown to be beneficial for out of hospital cardiac arrest patients, when compared to historical case series from the same hospitals (Bernard et al. 1997; Nagao et al. 2000; Zeiner et al. 2000; Felberg et al. 2001).

Inspired by these findings two randomised clinical trials were commenced and in 2002 they were published in the same issue of New England Journal of Medicine (Bernard et al. 2002; 2002). These trials on out of hospital cardiac arrest patients with primary cardiac rhythm of VF or pulseless VT were relatively small (77 and 275 patients), but both indicated great effect of induced hypothermia for improved neurological recovery and one also showed lowered mortality.

Simultaneously one minor randomised feasibility study indicated results also in favour of hypothermia, even if the numbers were small (Hachimi-Idrissi et al. 2001) and benefit was also shown in a study presented as an abstract in 2000 (Mori et al. 2000), this study is never published. A fifth trial was prematurely aborted when the results of the Bernard and the HACA-trial were published (Laurent et al. 2005). In this trial 42 patients were randomised to either hypothermia with continuous veno-venous haemofiltration (CVVH) or normothermia with CVVH (there was also a third control arm). There was no difference in mortality or neurological function between the groups, but again the numbers were small.

Meanwhile studies on hypothermia and temperature management for stroke (Den Hertog et al. 2009) and traumatic brain injury (Hutchison et al. 2008; Saxena et al. 2008; Sydenham et al. 2009) did not show any benefit or conflicting results, but the injury mechanism differ from global ischaemia (Grande et al. 2009). However, in newborns with hypoxic ischemic encephalopathy associated with foetal asphyxia, an effect similar to what was shown in cardiac arrest patients was indicated (Gluckman et al. 2005; Shankaran et al. 2005). However there was some criticism about the solidness of these trials (Kirpalani et al. 2007), and the results from the largest trial so far, the TOBY-trial, indicated a benefit on neurological function but not on mortality (Azzopardi et al. 2008; Azzopardi et al. 2009).

6.6 Guidelines

In 2003 the International Liaison Committee on Resuscitation (ILCOR), a joint network of resuscitation councils world wide, presented an advisory statement on the use of hypothermia after cardiac arrest, based mainly on the European trial (HACA-study-group 2002) and the Australian trial (Bernard et al. 2002).

“Unconscious adult patients resuscitated after out-of-hospital cardiac arrest with initial rhythm VT or VF should be cooled to 32-34 °C for 12-24 h. Cooling may also be beneficial for in-hospital cardiac arrest patients and patients with other initial rhythms.”

In 2005 American Heart Association and European Resuscitation Council adopted this statement into their guidelines for cardiopulmonary resuscitation and advanced life support (2005; Nolan et al. 2005), and these recommendations were again repeated in an ILCOR advisory statement of treatment of the post cardiac arrest syndrome (Nolan et al. 2008).

There has been criticism about the rapid adoption of guidelines and implementation of hypothermia, since the evidence is based on rather small and selective trials (Biber et al. 2004; Moran et al. 2004; Moran et al. 2006; Fisher 2008; Pechlaner et al. 2008). The Swedish Council of Health Technology Assessment (SBU) has recommended that induced hypothermia should be subject to further randomised trials, and if used clinically, meticulously observed and registered (SBU Alert 2006).

6.7 Meta-analyses and systematic reviews

There are two meta-analyses performed pooling the effect estimates of the published trials without scrutinizing potential risk of bias (Holzer et al. 2005; Cheung et al. 2006). Recently a Cochrane review was published supporting the guidelines, but it merely considered some bias risk components and included trials with high risk of bias in the main analysis. Moreover, it did not consider possible random error (Arrich et al. 2009).

6.7 Implementation

After the randomised trials, the scientific statement by ILCOR, and the guidelines the implementation rates of induced hypothermia has gradually increased. Some regions as the Netherlands and Scandinavia have reached high implementation rates (Oksanen et al. 2007; Soreide et al. 2008; Bouwes et al.) while other regions in Europe and North America have been more reluctant (Laver et al. 2006;

Merchant et al. 2006; Sander et al. 2006; Wolfrum et al. 2007; Kennedy et al. 2008). In surveys, physicians state lack of firm evidence, lack of resources and equipment, and technical difficulties as some of the reasons for not implementing induced hypothermia (Merchant et al. 2006; Soreide et al. 2008; Bouwes et al. 2010).

AIMS OF THE THESIS

To describe the multi-professional approach of care of an out-of-hospital cardiac arrest patient treated according to modern principles.

To develop an international registry for cardiac arrest patients using the Utstein template for patients treated with induced hypothermia and to pursue long-time follow-up.

To study early predictors of outcome in out-of-hospital cardiac arrest patients with focus on factors related to induced hypothermia.

To study biochemical markers as predictors of outcome after cardiac arrest and induced hypothermia.

To study adverse events associated with cardiac arrest, induced hypothermia and intensive care for out-of-hospital cardiac arrest patients using registry data.

To evaluate current evidence for induced hypothermia after cardiac arrest through meta-analyses and trial sequential analyses in a systematic review and to GRADE the evidence.

To propose and design a randomised clinical trial of induced hypothermia after cardiac arrest by using registry data and the conclusions from the systematic review.

METHODS

1. Background data

1.1 Reporting of cardiac arrest

In 1991 resuscitation societies (later forming ILCOR) presented a guide for the uniform reporting of data from out-of-hospital cardiac arrest in order to standardise methods to allow for better comparisons between studies (Cummins et al. 1991). These guidelines were simplified and updated for resuscitation registries 2004 (Jacobs et al. 2004) and a guide for the in-hospital treatment reporting was also presented (Langhelle et al. 2005). These guidelines are called the Utstein-templates. When performing the studies in this project and when developing the protocol for the Hypothermia Network Registry (see below) we have used these templates. Recently a systematic evaluation of the Utstein-templates suggested that the recommended data elements only explained a limited proportion of the observed variability in survival (Rea et al. 2010). Thus, the optimal core elements of data registration for cardiac arrest patients are probably not yet known.

1.2 Outcome measures

The main outcome measures used in this thesis are survival and neurological function. Survival has been assessed from national registries and hospital records. Neurological function has been assessed with the five graded Cerebral Performance Category (CPC) scale: CPC 1-conscious, no or minor neurological disability, CPC 2-conscious, moderate neurological disability, can work, CPC 3-conscious, severe neurological disability, dependent, CPC 4-coma or vegetative state, CPC 5-dead; CPC 1 and 2 can live their daily lives independently and work at least part-time. The CPC scale is in paper II and III dichotomised into CPC 1 and 2 (a good neurological outcome) and CPC 3-5 (a poor neurological outcome).

1.3 Registry

After the two randomised clinical trials that constituted the base for the International Liaison Committee on Resuscitation (ILCOR) advisory statement in 2003 we thought that it was imperative that this novel intervention should be monitored during implementation. Since the cardiac arrest patients are relatively few in each centre, we realised that a registry collecting data from many hospitals would be a reasonable way to address the posed questions about outcome in clinical materials and assess the risk of adverse events outside the scope of a randomised trial. In an international steering group with the focus in Scandinavia we designed and developed the registry protocols.

In the end of 2003 we proposed a comprehensive registry for all unconscious cardiac arrest patients treated in the intensive care units of the participating hospitals. The registry started as a collaboration between centres in Denmark, the Netherlands, Iceland, Norway and Sweden and the protocol was further developed during approximately half a year during intense input from all countries. The Scandinavian Society of Anaesthesiology and Intensive Care and the Scandinavian Critical Care Trials Group supported and financed the infrastructure.

The first patients were entered October 2004 in the Hypothermia Network Registry. The first analysis was performed after the inclusion of approximately 1000 out-of-hospital cardiac arrest patients treated with induced hypothermia, where an almost 100% follow up was achieved. The registry included approximately 1400 patients before closing in December 2008.

In the fall of 2008 a new registry was proposed by the North-American Neurocritical Care Society and us as a collaborative effort, and in December 2008 the International Cardiac Arrest Registry (INTCAR) was launched with a more specific protocol and a marked neurological focus. This registry uses Expertmaker software and in March 2010 there were 700 patients included, but no analysis has yet been performed.

Participating centres were asked to thoroughly screen, consecutively include and register data on all unconscious (Glasgow Coma Scale <8) cardiac arrest patients admitted to their intensive care units. There were no formal exclusion criteria for registration and the centres treated the patients according to their own treatment protocol and all available temperature management equipments (commercial or not) were allowed. We did not monitor compliance with the registry protocols on site, but all patient data were manually checked for plausibility and site-investigators were asked for clarification and editing when needed. Also, the importance of consecutive series of intensive care patients was reinforced. Reporting centres were owners of and responsible for the data entered into the registry.

1.4 Adverse events

Bleeding was defined as an adverse event if it was intracerebral or required transfusion. Arrhythmias were categorized as VT, VF, atrial fibrillation, bradycardia <40/minute, or tachycardia >130/minute. Metabolic and electrolyte disorders included sustained hyperglycaemia (>8.0 mmol/L for >4 hours), hypoglycaemia (<3.0 mmol/L), hypokalaemia (<3.0 mmol/L), hypophosphataemia (<0.7 mmol/L), and hypomagnesaemia (<0.7 mmol/L). Seizures were diagnosed either clinically or by electroencephalogram (EEG). Sepsis was defined as severe sepsis or septic shock (Bone et al. 1992). Pneumonia was defined with four criteria: (I) new or progressive consolidation on the chest radiograph, (II) fever, (III) leukocytosis, and (IV) the presence of purulent tracheobronchial secretions. Renal replacement therapy was defined as the use of either continuous renal replacement therapy (CRRT) or intermittent haemodialysis. Centres were asked to report all adverse events during the intensive care stay.

1.5 Ethics

During the doctoral project two applications have been submitted to and approved by the ethical review board in Lund.

Regional Ethical Review Board Lund, Sweden, Protocol 2007/7 Dnr 2007/272 (Hypothermia Registry/INTCAR)

Regional Ethical Review Board Lund, Sweden, Protocol 2009/6 Dnr 2009/324 (TTM-Trial)

2. Study design, study populations, methods and objective

2.1 Paper I

Design and objective: This paper is a case report intended to describe the multi-professional approach to the care of an out-of-hospital cardiac arrest patient treated with modern therapeutic principles.

2.2 Paper II

Design and objective

This study was a prospective and observational registry report. The objective was to present the outcome in a clinical cohort of patients admitted to intensive care after resuscitation from out-of-hospital cardiac arrest, to find predictors of outcome, and to report the incidence of adverse events. The main focus was to assess the different aspects of the conduct of hypothermia (importance of time from arrest to induction of hypothermia, time from arrest to target temperature achieved, time on target temperature, target temperature and rate of rewarming) in relation to neurological outcome.

Patients

986 unconscious patients consecutively admitted to intensive care units after out-of-hospital cardiac arrest in 34 centres.

Methods

Background characteristics, cardiac arrest and intensive care data, data regarding the conduct of hypothermia (time from cardiac arrest to initiation of hypothermia and achievement of a core temperature $<34^{\circ}\text{C}$, depth and duration of hypothermia treatment and duration of rewarming) and results from the follow up were recorded. Adverse events were collected during intensive care. The main outcome was neurological function according to the CPC scale at follow-up performed 6 to 12 months after the arrest. CPC 1 and 2 were regarded as a good outcome.

2.3 Paper III

Design and objective

This was a prospective and observational study of serial serum S-100B and NSE samples. The objective was to correlate the samples to best neurological outcome during a six months follow up. The aim was to identify cut-off values with a high specificity and sensitivity for a poor neurological outcome.

Patients

Consecutively induced hypothermia treated unconscious cardiac arrest patients with ROSC from three hospitals were included with two partially overlapping groups of 107 patients for the assessment of S-100B and 102 patients for NSE.

Methods

Samples were collected at 2 ± 1 , 24 ± 4 , 48 ± 4 and 72 ± 4 hours after cardiac arrest. The samples were centrifuged and S-100 samples were analysed within 24 hours. NSE samples were either analysed within 24 hours or frozen and analysed within a week. Samples of NSE with visible haemolysis were discarded. The analyses were performed at one core laboratory with LIAISON®NSE, detection limit 0.04 µg/L, reference interval <12.5 µg/L and LIAISON®S100B, detection limit 0.02 µg/L, reference interval <15 µg/L (DiaSorinAB, Sundbyberg, Sweden).

The patients were sedated with propofol (2-4 mg/kg/h) and fentanyl (1-3 mg/kg/h) and were mechanically ventilated. Hypothermia at 33 ± 1 °C was induced and maintained for 24 hours, followed by rewarming at a rate of 0.5 °C/h during 8 hours. At normothermia sedation was stopped and neurological evaluation was performed 72 hours after rewarming or later. Follow up and outcome was assessed as described above.

A *post hoc* analysis of the serum levels for patients fulfilling the criteria for inclusion in the HACA-trial (HACA-study-group 2002) was performed to allow for comparisons with a previously reported material (Tiainen et al. 2003).

2.4 Paper IV

Design and objective

This study was a prospective and observational registry report using the same cohort of patients as in paper II. We briefly analysed adverse events in a descriptive fashion in paper II and findings of for instance aspects of bleeding (see results) indicated a rationale for a more thorough analysis. The objective in paper IV was to analyse the adverse events and their relation to mortality in the intensive care setting after resuscitation from out-of-hospital cardiac arrest. In paper II we analysed data in relation to neurological function at follow up, but for adverse events we decided to choose mortality since this seemed to be a more uniformly relevant outcome for all different adverse events.

Patients

We included the 22 hospitals reporting the full set of adverse events in the registry. We analysed 765 unconscious patients consecutively admitted to intensive care units after out-of-hospital cardiac arrest.

Methods

Background characteristics, cardiac arrest and intensive care data and results from the follow-up were recorded. Adverse events were collected during the intensive care. The main outcome was mortality at follow-up.

2.5 Paper V

Design and objective

This study was a systematic review to assess the evidence for an effect of hypothermia on mortality and neurological function after out-of-hospital cardiac arrest. The objective of the review was to systematically evaluate the benefits and harms of hypothermia for adult cardiac arrest patients taking into account the risks of systematic errors (bias) and random errors (play of chance) and to assess the quality of the evidence using GRADE-methodology (Atkins et al. 2004). Finally we wanted to establish if clinical equipoise exists in regard to further clinical trials on hypothermia after cardiac arrest (Freedman 1987).

Patients

We included 478 patients from five randomised trials.

Methods

We performed a comprehensive search of EMBASE, CENTRAL and Medline for randomised clinical trials investigating hypothermia after cardiac arrest. To evaluate the design and possible bias associated with the individual trials we used the Cochrane Collaboration methodology (Higgins 2009). To quantify the estimated effect of induced hypothermia, we conducted meta-analyses (Higgins et al. 2009) with random (DerSimonian et al. 1986) and fixed (Demets 1987) effects models and trial sequential analyses (Wetterslev et al. 2008). We also summarised the evidence using GRADE (Atkins et al. 2004).

In the first version of the systematic review we also included data from observational studies to broaden the base for judgement, but these studies were omitted in the final version. Using the same search strategy as mentioned above

we identified 882 patients from ten single centre studies using historical controls or case series.

The quality of reporting of observational studies was evaluated according to the STROBE statement (von Elm et al. 2007). The quality of the individual studies was evaluated with Thomas Quality Assessment Tool for Quantitative Studies (Thomas).

2.6 Paper VI

Design and objective

This paper is a trial proposal and a trial protocol for an international, multi-centre, randomised, parallel groups, assessor blinded clinical trial. According to paper V we are led to conclude that the accumulated evidence for induced hypothermia is of a low quality and that there is clinical equipoise whether to use hypothermia or not after cardiac arrest, albeit the evidence points in a positive direction. The optimal target temperature is not known.

Patients

850 patients will be randomised during two to three years.

Methods

Adult patients who are unconscious after resuscitation from an out-of-hospital cardiac arrest of a presumed cardiac origin will be screened for inclusion. Exclusion criteria are conscious patients obeying verbal commands, pregnancy, in-hospital cardiac arrest, OHCA of a presumed non-cardiac cause (e.g. trauma, dissection/rupture of major artery, drowning, suffocation, hanging), known bleeding diathesis (pharmacologically induced coagulopathy, as treatment with warfarin or clopidogrel, does not exclude a patient), suspected or confirmed acute intracranial bleeding, suspected or confirmed acute stroke, unwitnessed asystole, known limitations in therapy and Do Not Resuscitate-order, known disease making 180 days survival unlikely (for example disseminated end stage cancer), known pre-arrest CPC 3 or 4, >4 hours (240 minutes) from ROSC to screening, persistent cardiogenic shock with a systolic SBP <80 mm Hg in spite of volume loading/vasopressors/inotropes or mechanical assistance (if the SBP recovers within 240 minutes from ROSC the patient can be included).

Eligible patients will be randomised to target temperature management at 33 °C or 36 °C for 24 hours. The target temperature maintenance phase will be surrounded by an initiation phase of 4 hours and a rewarming phase of 8 hours, which will give a total intervention period of 36 hours.

Seventy-two hours after the intervention period is finished, a team of blinded physicians will evaluate the neurological status and assess the prognosis of the patient. Efficacy variables will be survival from national databases and/or hospital records, neurological outcome according to the CPC scale (Jennett et al. 1975) Neurological outcome and Quality of life will be tested with Mini Mental Test (Folstein et al. 1975), IQCODE (Jorm 1994) and Short Form 36 (Ware et al. 1992).

The primary outcome will be all-cause mortality at maximal follow up which will be at least 180 days. The secondary outcomes will be composite outcome of all-cause mortality and poor neurological function (CPC 3 and 4) at hospital discharge and at 180 days; all-cause mortality at hospital discharge and at 180 days; CPC at hospital discharge and at 180 days; neurological function and Quality of life at 180 days; best neurological outcome during trial period according to the CPC-scale; NSE at 48 and 72 hours. Safety and harm measures: bleeding, pneumonia, sepsis, electrolyte disorders, hyperglycaemia, hypoglycaemia, cardiac arrhythmia and the need for renal replacement therapy.

3. Statistical methods

Two tailed tests of significance were used and p-values <0.05 were considered statistically significant in all studies. Statistics were calculated using R: A Language and Environment for Statistical Computing ver. 2.8.1 2008 and 2.9.2 2009 (R Foundation for Statistical Computing, Vienna, Austria) and the mcgv 1.5-0 and 1.5-5 package (Wood 2006), SPSS software version 15.0 (SPSS Inc., IL, USA), SAS version 8.2 (SAS Institute, NC, USA) RevMan 5.0 (The Nordic Cochrane Centre 2008), TSA (Wetterslev et al. 2008) and GRADEpro version 3.2 for Windows (Brozek et al. 2008).

3.1 Descriptive statistics

Frequencies are expressed as absolute numbers and in percentages. Due to non-normal distributions, continuous data are presented as medians with interquartile range (IQR) if not specified else.

3.2 Univariate relationships

Continuous and categorical univariate relationships were tested with Wilcoxon Mann-Whitney and Fisher's exact test as appropriate giving odds ratios (OR) with 95 % confidence intervals (CI) or presented in graphs. Tests of changes over time within groups were performed with Friedman's test and if a significant difference

was detected, Wilcoxon signed ranks test was used to evaluate differences within each group. In paper III, Bonferroni-corrections were applied and sensitivity, specificity, and receiver operating (ROC) characteristics were calculated. Also the area under the curve (AUC) was calculated for the ROC curves to allow for comparisons between methods.

3.3 Multivariate analyses with Generalised Additive Models

In paper II and IV we performed multivariate analyses using logistic regression with smooth functions, i.e. a generalised additive model. Our aim was to include all potential covariates in the search for the best predictive multivariate model. A particular covariate was added to the existing model in an attempt to always include interactions with terms already present, when the largest decrease in the Akaike Information Criterion (AIC) was achieved (Akaike 1974). To avoid overfitting, the best model was defined as the model with the lowest AIC and fewer parameters than the minimum of patients with outcome (neurological function or mortality) registered, divided by 20 (Harrel 2001).

When the best model for prediction was achieved the covariates of interest (if not present in the multivariate model) were introduced in the model one at a time to give the adjusted covariates (potential predictors of the outcome). Patients with missing data in any of the selected covariates were excluded. Results are presented as OR with 95 % CI.

3.4 Trial Sequential Analysis

Meta-analyses may result in type-I errors due to an increased risk of random error when few data are collected and due to repeated significance testing when a cumulative meta-analysis is updated with new trials (Wetterslev et al. 2008; Brok et al. 2009). To assess the risk of type-I error we used trial sequential analysis (TSA).

TSA combines an estimation of the required information size (cumulated sample size of included trials) for a meta-analysis to be conclusive with an adjusted threshold for statistical significance in the cumulative meta-analyses not reaching the required information size (Wetterslev et al. 2008; Brok et al. 2009; Thorlund et al. 2009). The information size may be based on the type-I error, the type-II error and the relative risk reduction which give an information size similar to the size calculated by standard power/sample size calculations (*a priori* calculated information size (APIS)).

The calculation of the required information size may also take into account the relative risk reduction suggested by the included trials with low risk of bias

(LBIS) and the heterogeneity or diversity between the trials (heterogeneity adjusted information size (HIS) or diversity adjusted information size (DIS)).

To avoid undue increase of the type-I error risks, sequential monitoring boundaries can be applied to meta-analyses, called trial sequential monitoring boundaries (TSMB). In TSA, the addition of each trial in a cumulative meta-analysis is regarded as an interim meta-analysis and helps to clarify whether additional trials are needed or not. The idea in TSA is that if the cumulative Z-curve crosses the trial sequential monitoring boundary, a sufficient level of evidence has been reached to control the chosen type-1 error and no further trials are needed. If the Z-curve does not cross the boundary and the required information size has not been reached there is insufficient evidence to reach a conclusion (Pogue et al. 1997; Pogue et al. 1998; Wetterslev et al. 2008; Brok et al. 2009).

Further, TSA fulfil the promise you make in the beginning with a choice of a nominal type-I error risk (usually 0.05 in a two-sided test). If the Z-curve crosses the TSMB it is highly unlikely that the Z-curve will go back to insignificant values, if more trials are performed and included and the required information size eventually is reached. Also, the potential multiple updates only use so small α -increments (type-1) that the total sum of type-I error spent is within the 0.05 % nominal risk originally chosen. This strategy is used by data monitoring and safety committees for the management of interim-analyses of single trials (Lan et al. 1983). Meta-analyses should fulfil the same restrictions and demands as single trials.

TSA can be one-sided showing differences between groups only in one direction, or two-sided showing differences in both directions, with a possibility of illustrating both benefit and harm with an intervention.

We applied TSA since it avoids increase above the chosen nominal risk of type-I error in a cumulative meta-analysis and provides us with important information on how many more patients that need to be included in further trials. The required information size was calculated as a diversity-adjusted information size (DIS) (Wetterslev et al. 2009), suggested by the relative risk reduction of the included trials.

Figure 3. Example of one-sided trial sequential analysis, adapted after Brok (Brok et al. 2009).

The cumulated Z-curve was constructed with each cumulated Z-value calculated after including a new trial. Crossing the trial sequential monitoring boundary (TSMB) means that the results could be trusted as statistically significant, at a level of $p=0.05$.

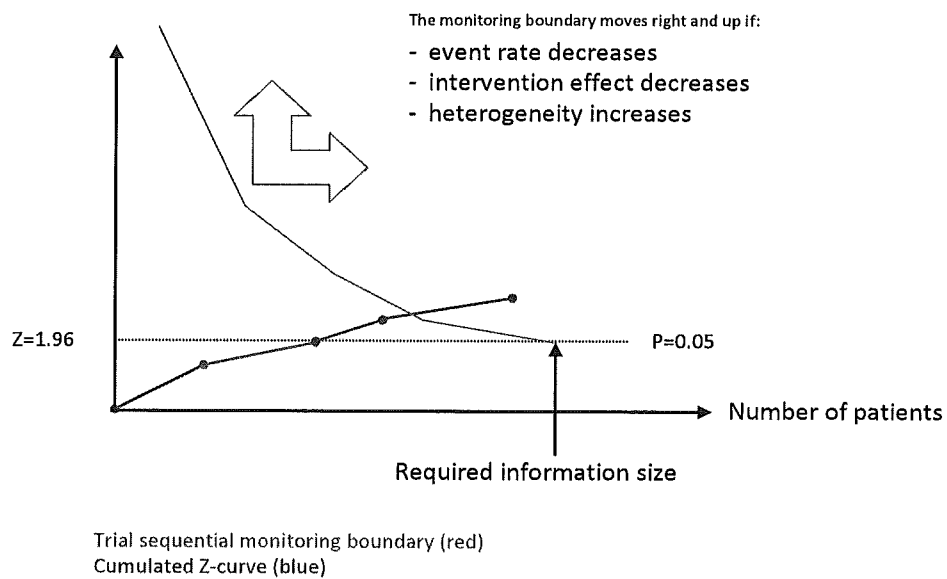
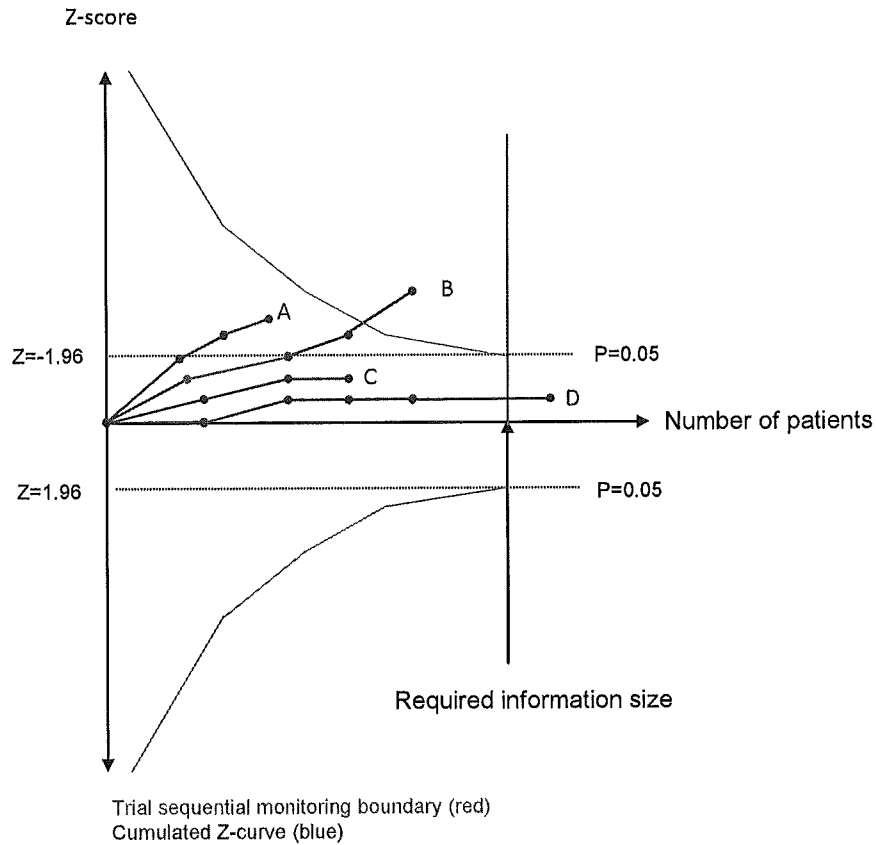


Figure 4. Examples of two-sided Trial Sequential Analyses, adapted after Brok (Brok et al. 2009).

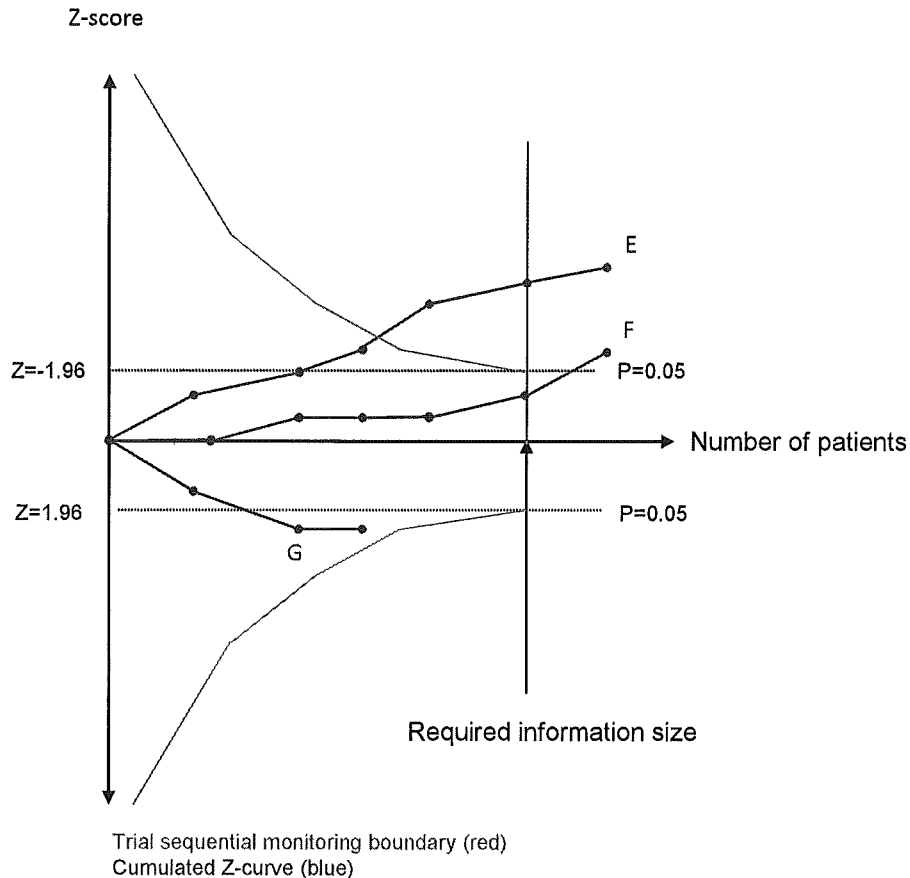


The cumulative Z-curves (A - G) were constructed with each cumulative Z-value calculated after including a new trial.

Crossing of $Z = 1.96$ provides a traditionally significant result (A). However, crossing of trial sequential monitoring boundaries (TSMB) is needed to obtain reliable evidence (B).

For curve A and B the meta-analyses do not reach the required information size. If the cumulative Z-curve does not cross the monitoring boundary the meta-analysis is inconclusive (A). If the Z-curve crosses the monitoring boundary we have evidence for at least the nominal relative risk reduction used when calculating the information size (B).

For curve C the meta-analysis does not cross the traditional 0.05 significance level, the TSMB and the information size is not reached, thus there is a clear situation of absence of evidence. For curve D-F the meta-analyses reach the required information size. If the cumulative Z-curve crosses the monitoring boundary before reaching the information size we have evidence of at least the relative risk reduction used when calculating the information size (E). If the Z-curve does not cross the monitoring boundary before the information size is accrued, the TSA rules out the relative risk reduction, but does not exclude a lower intervention effect (D and F). If a smaller intervention effect is deemed *clinically* insignificant, further trials may be regarded as futile.



Interestingly, for curve E, the last trial may be regarded as unnecessary since the intervention effect (at the chosen level) is clearly and firmly demonstrated. Curve G proceeds in a direction indicating

possible harm with the intervention. The Z-curve crosses the traditional 0.05 %-level, but as the TSMB is not passed the indication of a harmful effect may be spurious.

3.5 Assessing bias

In paper V we used the Cochrane Collaboration methodology to assess possible problems with systematic errors (bias) in the analysed trials. We evaluated the validity and design characteristics of each trial and potential sources of bias (adequate random sequence generation, adequate allocation concealment, adequate blinding, baseline differences, adequate use of interim analyses, adequate stopping rules and the possibility to perform intention to treat analysis) according to the Cochrane Handbook (Higgins et al. 2009). For complete description of the bias assessment, see Table 2.

We were aware of the inherent problems with blinding of the intervention with hypothermia and considered blinding adequate if the outcome assessors had been blinded to type of intervention (allocation group). Trials were defined as having a low risk of bias if they fulfilled the above criteria.

Table 2: Description of how risk of bias was evaluated, based on the Cochrane Handbook (Higgins et al. 2009).

Risk of bias/ Type of bias	Low risk of bias	Uncertain risk of bias	High risk of bias
Sequence generation	If the allocation sequence is generated by a computer or random number table or similar.	If the trial is described as randomised, but the method used for the allocation sequence generation was not described.	If a system involving dates, names, or admittance numbers are used for the allocation of patients (quasi-randomised).
Allocation concealment	If the allocation of patients involves a central independent unit, on-site locked computer, or consecutively numbered, sealed envelopes.	If the trial is described as randomised, but the method used to conceal the allocation is not described.	If the allocation sequence is known to the investigators who assigned participants or if the study is quasi-randomised.
Blinding	If the outcome assessors are blinded and the method of blinding is described.	If the outcome assessors are blinded and the method of blinding is not described.	If the outcome assessors are not blinded.
Incomplete data outcomes	If there are no post-randomisation dropouts or withdrawals.	If it is not clear whether there are any dropouts or withdrawals or if the reasons for these dropouts are not clear.	If the reasons for missing data are likely to be related to true outcomes, 'as-treated' analysis is performed, potential for patients with missing outcomes to induce clinically relevant bias in effect estimate or effect size.
Selective outcome reporting	If all the important outcomes are reported or if the trial's protocol is available and all of the trial's pre-specified outcomes have been reported in the pre-specified way.	If there is insufficient information to assess whether the risk of selective outcome reporting is present.	If not all the pre-specified outcomes are reported, or if the primary outcomes are changed, or if some of the important outcomes are incompletely reported.
Baseline imbalance	If there was no baseline imbalance in important characteristics.	If the baseline characteristics were not reported.	If there was a baseline imbalance due to chance or due to imbalanced exclusion after randomisation.
Early stopping	If sample size calculation is reported and the trial is not stopped or the trial is stopped early by an adequate stopping rule.	If sample size calculations are not reported and it is not clear whether the trial is not stopped early.	If the trial is stopped early without formal stopping rules.
Sponsor bias	If the trial is without specific funding, or is not funded by an instrument, equipment, or drug manufacturer.	If the source of funding is not clear.	If the trial is funded by an instrument, equipment, or drug manufacturer.
Academic bias	If the author of the trial has not conducted previous trials addressing the same interventions.	If it is not clear if the author has conducted previous trials addressing the same interventions.	If the author of the trial has conducted previous trials addressing the same interventions.

3.6 Meta-analysis

Meta-analytic estimates are presented as risk ratios (RR) with 95 % CI in forest plots.

Heterogeneity

When performing a meta-analysis, pooling effect estimates from many trials, there is almost always a certain difference between the estimates; some trials show large effects, some small effects and the effects are sometimes going in opposite directions with some trials indicating benefit and some harm with similar interventions. This almost inevitable difference can be due to chance, methodological reasons, or true differences in the intervention effect or a combination hereof.

The fraction of the difference that is not consistent with play of chance is called heterogeneity. “The between trial variance rather than sampling error” (Higgins et al. 2002). The heterogeneity could be due to methodological differences between trials and could thus be regarded as produced by different components of bias. The degree of heterogeneity could be evaluated by visual inspection of the point estimates and their confidence intervals; if there is little overlap between confidence intervals for the different trials, this would suggest heterogeneity. Also a standard statistical approach using a χ^2 test could be used, and analyses of trials yielding high χ^2 values or low p-values would suggest that the differences could not solely be regarded as due to chance and thus there is a statistically significant degree of heterogeneity.

In an attempt to convert these values to something more intuitively understandable, the concept of I^2 (inconsistency) has been proposed, where I^2 describes the percentage of variability in the effect estimates that is due to heterogeneity rather than chance (i.e. random error possibly due to sampling). 0-40% is considered to be unimportant heterogeneity, 30-60% may represent moderate heterogeneity, 50-90% may represent substantial heterogeneity and 80-100% considerable heterogeneity. As indicated by the overlap, these levels are somewhat arbitrary.

With large meta-analyses there might arise problems with statistically significant heterogeneity that is not clinically important and conversely, with small meta-analyses there might be an absence of evidence phenomenon, with non-significant, but maybe clinically important, heterogeneity due to a small sample size (Higgins et al. 2009).

When assessing these differences in effect estimates before pooling them there are two fundamentally different approaches used, based on if heterogeneity should be incorporated in the calculation or not, called fixed-effects models (Demets 1987) and random-effects models (DerSimonian et al. 1986).

A novel approach to heterogeneity is to assess the diversity between trials (D^2) where D^2 is the relative variance reduction when the meta-analysis is changed from a random effects model to a fixed effects model, taking into account the required information size for the random-effects meta-analysis to be conclusive within a predefined level of uncertainty (Wetterslev et al. 2009).

Fixed-effects meta-analysis

The basic analytic approach to a fixed-effects meta-analysis is that all trials evaluate the same intervention and there is basically a common true intervention effect. Observed differences between trials are due to random error, i.e. due to chance. The true intervention effect is fixed between trials and the observed differences are due to sampling error and the individual trials could be regarded as samples drawn from the same large population.

The fixed-effects estimate addresses the question: “What is the best weighted or pooled estimate of the intervention effect?”

Some argue that only trials with very similar design and low risk of bias should be included in meta-analyses, and with that assumption fixed-effects models may be valid.

Random-effects meta-analysis

If the observed difference cannot be explained by chance alone, i.e. there is substantial or considerable heterogeneity between the trials, a random-effects model can be used. This approach includes an assumption that the true intervention effects are not fixed across trials but rather follow a normal distribution.

The model addresses the question: “What is the average intervention effect in these trials?”

When there is no heterogeneity the fixed- and the random-effects models will give the same result, but as soon as heterogeneity is beyond zero, the point-estimates may differ and the confidence limits will become wider in the random-effects model compared to the fixed-effects model. In a heterogeneous set of trials the random-effects model will always render a higher weight to smaller trials compared to the larger ones.

Thus both models have their strengths and limitations and when the results are different a good approach is to report both models and discuss the findings. Also, a small set of trials and few patients included almost inevitably produce problems with meta-analytic estimates and pooling of trials might then best be avoided (Higgins et al. 2009).

In paper V we a priori assumed that there should be significant clinical and methodological heterogeneity and diversity between the trials, why we planned to use both a fixed- and a random-effects model.

3.7 The GRADE-assessment

GRADE is a systematic approach to assess quality of evidence and make judgements about the strength of recommendations (Atkins et al. 2004). Many systems have been proposed to rate evidence and communicate recommendations during the last decades and the GRADE working group has tried to develop a generally applicable and highly transparent system, taking into account the shortcomings of previous systems.

The quality of the evidence indicates to what extent one can be confident that an estimate of an intervention effect is correct, while the strength of a recommendation indicates to what extent one can be confident that adherence to the recommendation will do more good than harm.

In order to perform these assessments the relevant outcomes for a disease must be defined and further judge how critical this outcome is for the patient receiving the intervention (this may be illustrated by the different importance between surrogate outcomes, as for instance decrease in biomarkers, versus mortality). The GRADE levels for defining the quality of the evidence are *high*, *moderate*, *low* and *very low*. Recommendations are strong and weak either for the intervention or against the intervention or the judgement can be that the evidence is not solid enough to make a recommendation.

A systematic review of the available evidence is the base for the judgement of the quality of the evidence, but reviewers should in most cases not make recommendations; this should be left to guideline groups.

The evidence is assessed with regard to study design, study limitations and quality, consistency and directness, and if there is substantial concern with these elements the level may be rated down. Additional considerations that can lower the quality of the evidence include imprecise and sparse data and high risk of reporting bias. Very strong associations derived from observational data may raise the quality level.

Design

Randomised trials are always initially categorised as high quality, while observational trials are rated low and any other evidence is very low. When high quality randomised trials are available there is no rationale for basing recommendations on observational trials with discrepant results. There are of course situations where randomised trials are not feasible and recommendations have to rely on observational material.

Quality

If there are serious or very serious limitations in study quality the level should be rated down with one or two levels. Criteria to rate study quality are for instance the bias assessment according to the Cochrane Handbook (Higgins et al. 2009).

Directness

Directness refers to what extent the studied population, the interventions and the outcomes are generalisable to the population of interest for the intervention. For instance studies on healthy volunteers may not be generalisable to aged hospitalised patients. There is also interplay between the outcomes studied and the directness, where more stringent criteria on directness should be used if surrogate outcomes are assessed.

Consistency

Consistency refers to the similarity between effect estimates when studies are compared. Differences in effect direction or the size of the direction will guide whether important inconsistency exists.

Precision

Very wide confidence intervals and confidence intervals spanning both the possibility for harm and benefit would raise concerns of imprecision. Also sparse data based on few events may lead to the same concerns. There are arbitrary levels for when the event rate should be regarded as being low in a single study or sequential studies, but generally at least 2-300 events are recommended to be recorded before the event rate has passed the obvious risk of being low (Montori et al. 2005).

Reporting bias

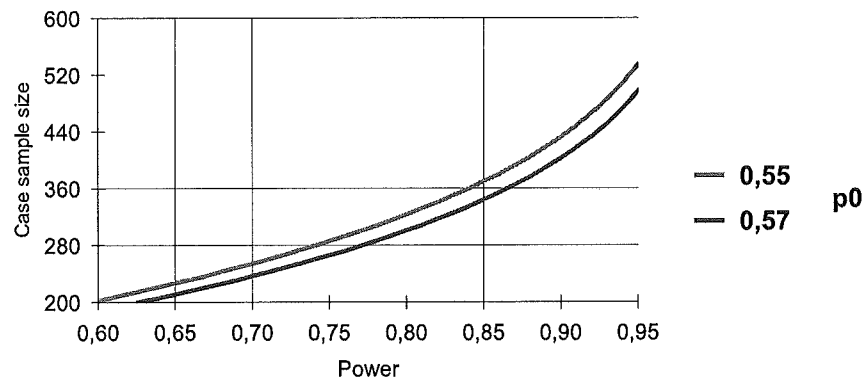
If there is an obvious risk of reporting bias, the quality may be rated down. Reporting bias is most often assessed with funnel plots (Higgins et al. 2009) visualizing the effect estimates in relation to trial size. We have not used funnel plots in this project since it is not recommended when there is a limited amount of trials (fewer than ten trials).

3.8 Power analysis

The sample size calculation was performed with a standard power (1 minus type-II error) calculation based on the type-I error, the type-II error and the estimated event rates in the control group and in the intervention group. The relation

between power, control group event proportion (55 % and 57 %) and sample size in the experimental group calculated with a relative risk reduction of 20 % are shown in Figure 5.

Figure 5. Power calculation



p_0 is the proportion of events in the control group and case sample size is the number of required patients in the intervention group. Power is 1 minus the allowed type-II error. The total sample size of a trial would be case sample size times two with an 1:1 allocation.

RESULTS

For complete details about the results, please see the enclosed original papers. Absolute numbers are here omitted in preference for proportions expressed in percent.

1. Introduction

As an introduction to the doctoral project we describe a patient treated with the different modalities of modern resuscitation. The patient in the case report was pulseless in his home and received automated mechanical CPR compression-decompression after 6 minutes. At the emergency department, 28 minutes after the arrest, he had a period of fleeting ROSC. Compression-decompression for an additional 5 minutes led to stable ROSC. The patient was unconscious with a Glasgow Coma Score of 3 but had spontaneous breathing. Hypothermia was immediately instituted and the patient was referred to the coronary angiography laboratory. The patient suffered another cardiac arrest and was coronary intervened during manual CPR. The angiogram revealed a left main stem coronary artery occlusion. After successful catheterisation and stenting of the left main stem, maximal inotropic support, and with circulatory support from an intra-aortic balloon pump the circulation stabilised and the patient could be transferred to the intensive care unit where he gradually recovered after an extended period of intensive care. The patient was neurologically recovered at 6-months follow-up with a CPC of 1.

2. The cardiac arrest population after out-of-hospital cardiac arrest

In paper II we analysed the first 994 patients with out-of-hospital cardiac arrest entered in the Hypothermia Network Registry. Because of poor data quality in eight patients, 986 patients from 34 hospitals were included in the final analysis. The cardiac arrest population had a median age of 63 years (53-73), where predominantly male (74 %) and in 83 % of the cases the cardiac arrest was

presumed to be of a cardiac cause. The initial rhythm was VT/VF in 70 %, asystole in 22 % and PEA in 7 %. For full details see Table 3.

Table 3. Patient and cardiac arrest characteristics, paper II

<i>Age and sex</i>	(n=986)	<i>Pre-arrest comorbidities</i>	n=(986)
Age	63 (53-73)	Previously healthy	226 (23)
Male sex	733 (74)	Coronary disease	351 (36)
<i>Cardiac arrest characteristics</i>		Congestive heart failure	196 (20)
		IDDM	67 (7)
		NIDDM	67 (7)
		Renal impairment	46 (5)
		Neurological disease	103 (10)
		Hepatic disease	19 (2)
		Pulmonary disease	125 (13)
		Malignancy	51 (5)
		Hypertension	307 (31)
		Alcohol/drug abuse	113 (11)
Out of hospital cardiac arrest	986 (100)		
Cardiac cause of arrest	817 (83)		
Witnessed arrest	850 (86)		
By-stander CPR	614 (62)		
VT/VF	686 (70)		
Asystole	217 (22)		
PEA	66 (7)		

Age (years) is presented as median (inter quartile range). All other data are presented as absolute numbers (percentage). CPR, cardiopulmonary resuscitation; PEA, pulseless electrical activity; VT/VF, ventricular tachycardia/ventricular fibrillation; IDDM, insulin dependent diabetes mellitus; NIDDM, non-insulin dependent diabetes mellitus

In paper IV we analysed 765 patients from the 22 hospitals that reported the full set of adverse events. The background characteristics in this subgroup were similar to the full cohort. For details when univariately comparing those alive and dead at follow-up see Table 4.

Table 4. Univariate analysis of patient characteristics among those alive or dead at 6-months follow up, categorized in background, prehospital and in-hospital factors. Paper IV.

	Alive at follow up n = 363 (48%)	Dead at follow-up n=391 (52%)	p-value
<i>Background factors</i>			
Age	60 (49-68)	67 (54-74)	<0.001
Female sex	75 (21)	128 (33)	<0.001
<i>Prehospital factors</i>			
Witnessed arrest	330 (91)	311 (80)	<0.001
Bystander CPR	252 (69)	227 (58)	0.002
Cardiac cause of arrest	334 (92)	279 (71)	<0.001
First monitored rhythm	VT/VF=304 (84), Asystole=41 (11), PEA=11 (3)	VT/VF=214 (55), Asystole=128 (33), PEA=40 (10)	<0.001
Time from emergency call to arrival of EMS team	5 (4-8)	7 (5-10)	<0.001
Time from arrest to CPR	7 (5-10)	9 (6-12)	<0.001
Time from arrest to defibrillation	10 (7-12)	11 (10-13)	<0.001
Time from arrest to ROSC	16 (11-23)	28 (19-35)	<0.001
<i>In-hospital factors</i>			
Initial temperature	36.0 (35.3-36.6)	35.7 (34.8-36.4)	<0.001
Cardiogenic shock	58 (16)	70 (18)	0.50
Time from arrest to initiation of hypothermia	90 (60-180)	90 (60-160)	0.89
Time from arrest to core temperature < 34°C	300 (200-440)	240 (145-360)	<0.001
GCS at admission	3 (3-5)	3 (3-3)	<0.001
Thrombolysis performed	21 (6)	18 (5)	0.51
Angiography performed	237 (65)	140 (36)	<0.001
PCI performed	149 (41)	76 (19)	<0.001
CABG performed	6 (2)	3 (1)	0.32
Pacemaker used	18 (4)	11 (3)	0.13
IABP	62 (17)	53 (14)	0.19
AMI	229 (63)	225 (58)	0.20
Inotropic drugs used	282 (78)	315 (81)	0.37
Length of ICU stay	120 (73-201)	96 (48-146)	<0.001

AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; ICU, critical care unit; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; GCS, Glasgow coma scale; IABP, intra aortic balloon pump; PCI, percutaneous coronary intervention; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; VF, ventricular fibrillation; VT, ventricular tachycardia. Cardiogenic shock at admission was defined as a systolic blood pressure <90 mm Hg in spite of fluid loading and/or inotropic medications and/or vasopressors, and/or the use IABP. Age in years, time points in minutes, initial temperature in °C, and length of ICU stay in hours as medians with inter quartile range (IQR). GCS as median with IQR. All other data as absolute numbers with percentages within parentheses.

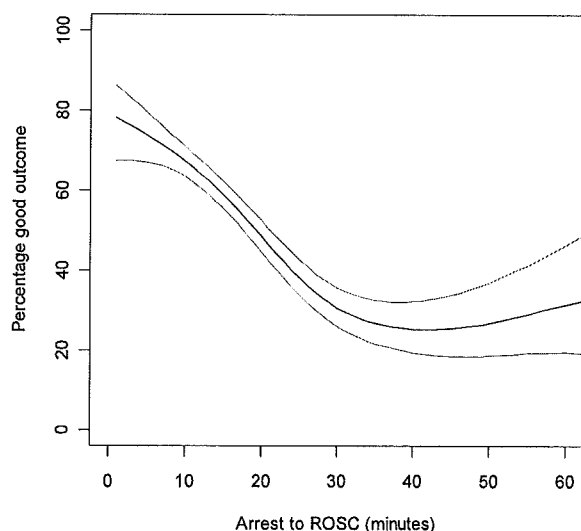
3. Outcome at ICU discharge, hospital discharge and follow-up

At ICU discharge 69 % of the patients were alive and 41 % had a good outcome with a CPC of either 1 or 2. At hospital discharge 56 % were alive, 44 % with a good outcome. Long-term follow-up was reported in 99 % of the registered patients. At follow-up 50 % of the patients were alive and 46 % had a good outcome. Thus, 91 % of the survivors had a good outcome. Only four patients of the 986 were still in coma (CPC 4) at 6-months follow up.

Patients discharged alive from the ICU who died during follow-up had a median time from cardiac arrest to death of 1 week (1-3 weeks).

In 30 % of the patients in the material, time from cardiac arrest to ROSC exceeded 25 minutes (range 25-240 min), with an overall good outcome of 23 % at long-term follow-up (Fig 6.).

Figure 6.



Percentage of a good outcome of CPC 1 or 2 correlated to increasing time to ROSC for all initial rhythms (n=986) with 95% confidence interval. There were 293 patients with a time to ROSC of 25 minutes or more (range 25-240 minutes) with an overall good outcome of 23 %.

4. Cardiac interventions

As described above the majority of the patients admitted to ICU had a cardiac arrest of presumed cardiac origin and 63 % had acute myocardial infarction. Almost 50 % of all patients were referred to coronary angiography and PCI was performed in 62 % of those patients. Patients referred to coronary angiography and PCI showed higher frequencies of a good outcome at follow-up (58 and 60 %, respectively compared to 46 % in the whole cohort). Of the 217 patients with initial rhythm asystole, 42 were referred to emergency coronary angiography and 21 had a PCI performed. Only few patients received thrombolysis or coronary artery bypass grafting.

5. General ICU care and investigations

The median ICU length-of-stay was 100 hours (IQR 65-165 hours) with longer stays for patients surviving to follow-up and with a subsequent good outcome. Inotropes and vasopressors were administered to the majority of the patients (77 %). Renal replacement therapy was used in 4 % of all patients.

Electrophysiological investigations with EEG and SSEP were performed in 41 % and 11 % of the patients, respectively while CT and MRI were performed in 50 % and 8 % of all patients. For the patients still in coma 96 hours after the cardiac arrest, these investigations were used more frequently: 72 % for EEG, 28 % for SSEP, 67 % for CT and 28 % for MRI.

6. Conduct of hypothermia

The median initial body temperature at hospital admission was 35.9 °C (IQR 35.1-36.5 °C). For patients with a cardiac cause of arrest the median initial temperature was 36.0 °C (IQR 35.2-36.5 °C). Time from cardiac arrest to initiation of hypothermia was 90 minutes (IQR 60-165 minutes) and to achievement of target temperature (≤ 34 °C) 260 minutes (IQR 178-400 minutes).

Methods for initiation and maintenance of hypothermia are presented in Table 5. Intravenous cold fluid infusion was common (80 %) as were circulating water blankets for maintenance (63 %). Combinations of methods were frequent.

All centres used 32 °C, 33 °C or 34 °C as target temperature with 85 % of the patients treated at a target temperature of 33 °C.

Hypothermia was maintained for 12, 24 and 48 hours in 5 %, 93 % and 2 %, respectively.

Duration of rewarming ranged from 4 hours (6 % of the patients) to 12 hours or more (14 %). Six hours was used in 41 %, 8 hours in 32 % and 10 hours in 7 % of the patients.

Table 5. Techniques for initiating and maintaining hypothermia, paper II

	Initiation of Hypothermia n=986	Maintenance of hypothermia n=986
Ice-packs	420 (43)	171 (17)
Cold fluid infusion	788 (80)	N/A
Air cooling	93 (9)	78 (8)
Circulating water blankets	460 (47)	625 (63)
Intravascular device	98 (10)	157 (16)
Other	61 (6)	78 (8)

Data presented as absolute numbers and percentages

7. Predictors of outcome

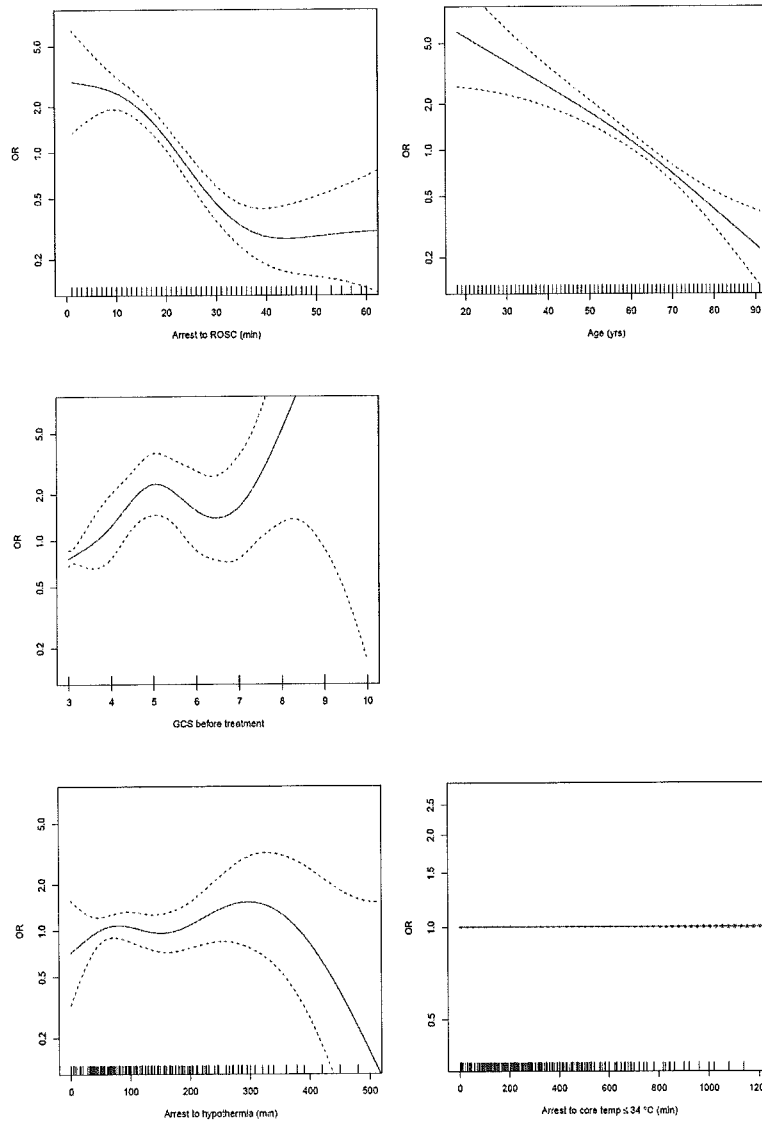
7.1 Univariate comparisons-cardiogenic shock

The 176 patients (18 %) with cardiogenic shock at ICU admittance had an overall lower chance of a good outcome compared to patients who were not in shock in a univariate comparison (39 vs. 47 %, respectively, $p<0.049$), but shock was not a predictor in the final multivariate model. Among survivors, there was no difference in good outcome whether cardiogenic shock was present or not (87 % vs. 92 %, respectively, $p=0.26$).

7.2 Multivariate comparisons with focus on induced hypothermia

The best model of prediction of a good outcome revealed shorter time to ROSC ($p<0.0001$) (Figure 7), lower age ($p<0.0001$) (Figure 8), higher GCS at admittance ($p=0.0002$) (Figure 9). An unwitnessed arrest was a predictor of a bad outcome (OR 0.30; 95 % CI 0.16-0.55; $p=0.0001$). There was an interaction between the initial rhythm and coronary angiography ($\chi^2=12.4$, $df=2$, $p=0.002$). VT/VF as initial rhythm was predictive of a favourable outcome if coronary angiography was performed (OR 1.56; 95 % CI 1.20-2.02; $p=0.0008$), whereas asystole was only predictive for a bad outcome if coronary angiography was not performed (OR 0.19; 95 % CI 0.07-0.50; $p=0.0007$). Neither time to initiation of hypothermia ($p=0.48$) (Figure 10), time to achievement of target temperature ($p=0.91$) (Figure 11), depth of hypothermia ($p=0.50$), duration of hypothermia ($p=0.19$) or rewarming time to normothermia ($p=0.73$) had an association with outcome.

Figures 7-11. Predictors of a good outcome of CPC 1 or 2 for continuous variables



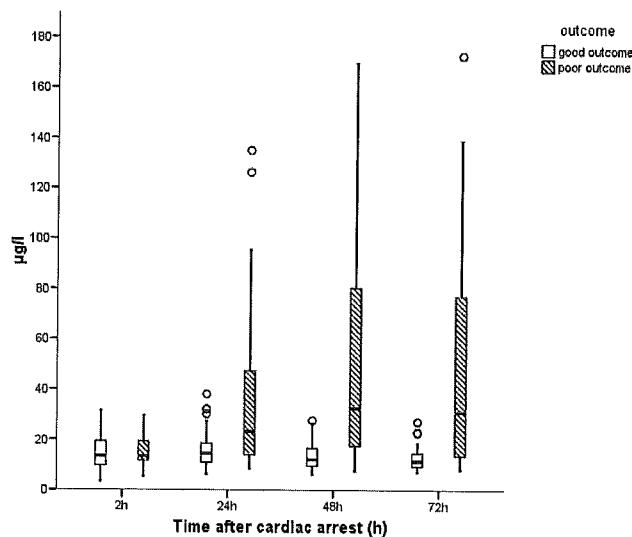
Age in years. Time from arrest to return of spontaneous circulation (ROSC), initiation of hypothermia and achievement of a core temperature below 34°C in minutes. Odds ratios (OR) with 95 % confidence intervals. Figures 7-9 are highly significant, 10 and 11 are non-significant.

8. Biomarkers of brain damage predicting outcome

8.1 Neuron specific enolase

Of the 102 patients in the NSE cohort 52 patients (51 %) had a good outcome at six months follow up. Three patients were in CPC 3 and the 47 patients were dead, thus 48% had a final bad outcome. There were statistically significant differences in serum levels for patients with a final good and a final bad outcome at all sampling times ($p<0.001$) except at 2 hours after cardiac arrest. There was a significant change over time in the group with a subsequent poor outcome ($p<0.001$) but not in the group with a good outcome ($p=0.45$) (Figure 12). NSE above 28 $\mu\text{g/l}$ at 48 hours had a specificity of 100% and a sensitivity of 67% for a poor outcome. The OR for a poor outcome was 9.8 (95% CI 3.5-27.7) when NSE increased more than 2 $\mu\text{g/l}$ between 24 and 48 hours.

Figure 12. Box plot of neuron specific enolase for good and poor outcome groups.



The horizontal lines indicate the median and the outer limits of the boxes the 25 % and 75 % quartiles. Outliers are represented with circles. There were significant differences ($p<0.001$) between the groups at 24, 48 and 72 hours and a significant change of serum levels over time in the poor outcome group.

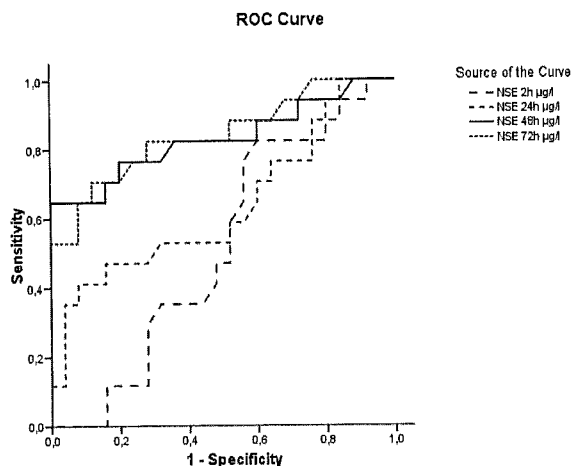
8.2 S-100B

Of the 107 patients in the S-100 cohort 52 patients (49 %) had a good outcome at six months follow up. Two patients were in CPC 3 and the 53 patients were dead, thus 51% had a final bad outcome. There were statistically significant differences in serum levels for patients with a final good and a final bad outcome at all sampling times ($p < 0.001$). There was a significant change over time in both groups over time ($p < 0.001$ and < 0.012 respectively for a good and a bad outcome). There were significant differences in serum levels between 2 and 24 hours ($p < 0.001$) and 48-72 hours ($p < 0.001$). S-100B levels above $0.51 \mu\text{g/l}$ had a specificity of 96% and a sensitivity of 62 % for a poor outcome.

8.3 Receiver operating characteristics

For NSE the AUC was 0.83 at 48 hours and 0.84 at 72 hours, both superior to the AUC at 2 hours (0.51) and 24 hours (0.64) and to all AUCs for S-100B at all sampling times (0.67-0.77).

Figure 13. Receiver Operating Characteristics (ROC) analysis of neuron specific enolase (NSE).



The largest areas under the curve (AUC) were 0.83 for 48 hours and 0.84 for 72 hours. The AUC for 2 and 24 hours are 0.51 and 0.64 respectively.

8.4 *Post-hoc* analysis of patients fulfilling HACA-criteria

There were 31 of the patients with NSE sampling that fulfilled the HACA-criteria of whom 20 (65 %) had a final good outcome and 26 of the patients with S-100B sampling of whom 20 (77 %) had a good outcome. Cut-off levels were 27 and 0.5 for NSE and S-100B respectively, with no improvement in sensitivity compared to all patients.

9. Adverse events and their relation to mortality

In paper II we presented descriptive data of adverse events and performed one univariate analysis of bleeding in relation to coronary interventions. Severe arrhythmias were present in 33 % of the patients and pneumonia was the most frequent infection (41 %). Bleeding requiring transfusion occurred in 4 % of all patients and the risk for bleeding was significantly higher if angiography/PCI was performed (2.8 % vs. 6.2 %, respectively, $p=0.02$). Hypokalaemia, hypomagnesaemia or hypophosphataemia were present in approximately 20 % of the patients. Combinations of electrolyte disturbances were common. Metabolic and electrolyte disorders were obtained from 22 centres.

After the findings in the first analysis (paper II) we wanted to investigate the relationship between adverse events and mortality and included data from the 22 centres and 765 patients where all different aspects of adverse events were fully reported. The frequencies of the adverse events are presented in Table 6 and they are in many aspects similar to the full cohort except for a larger proportion of pneumonia in the subset-cohort.

Table 6. Adverse events and their relation to mortality

Adverse event and concomitant treatment	Total n (%)	Alive n (%)	Dead n (%)	Univariate odds ratio (LCL-UCL)	p-value	Adjusted odds ratio (LCL-UCL)	p-value
	754 (100)	363 (48)	391(52)				
Bleeding requiring transfusion	43 (6)	20 (6)	23 (6)	1.1 (0.57-2.2)	0.76	1.0 (0.46-2.2)	0.91
Pneumonia	361 (48)	208 (56)	153 (39)	0.48 (0.36-0.65)	<0.001	0.52 (0.35-0.77)	<0.001
Sepsis	31 (4)	21 (6)	10 (3)	0.43 (0.18-0.97)	0.028	0.30 (0.12-0.79)	0.011
Antibiotic prophylaxis	207 (27)	94 (26)	113 (29)	1.2 (0.83-1.6)	0.37	1.6 (1.0-2.4)	0.033
Antibiotic therapy	414 (55)	242 (67)	172 (44)	0.39 (0.29-0.53)	<0.001	0.38 (0.25-0.57)	<0.001
Bradycardia <40/min	108 (14)	61 (17)	47 (12)	0.68 (0.44-1)	0.062	0.91 (0.52-1.6)	0.85
Tachycardia >130/min	50 (7)	21 (6)	29 (7)	1.3 (0.70-2.5)	0.38	1.2 (0.55-2.5)	0.67
Atrial fibrillation	70 (9)	37 (10)	33 (8)	0.81 (0.48-1.4)	0.45	0.58 (0.31-1.1)	0.082
Ventricular tachycardia	76 (10)	36 (10)	40 (10)	1 (0.63-1.7)	0.90	1.2 (0.62-2.2)	0.68
Ventricular fibrillation	58 (8)	26 (7)	32 (8)	1.2 (0.65-2.1)	0.68	2.0 (0.96-4.1)	0.057
Hypoglycaemia <3.0 mmol/l	40 (5)	12 (3)	28 (7)	2.3 (1.1-4.9)	0.022	1.9 (0.75-4.7)	0.17
Hyperglycaemia >8 mmol/l > 4 h	277 (37)	95 (26)	182 (46)	2.5 (1.8-3.4)	<0.001	2.3 (1.6-3.6)	<0.001
Hypokalaemia <3.0 mmol/l	134 (18)	54 (15)	80 (20)	1.5 (1.0-2.2)	0.046	1.4 (0.87-2.3)	0.17
Hypo-magnesaemia <0.7 mmol/l	128 (17)	61 (17)	67 (17)	1 (0.69-1.5)	0.92	1.1 (0.65-1.7)	0.80
Hypo-phosphataemia <0.7 mmol/l	141 (19)	74 (20)	67 (17)	0.81 (0.55-1.2)	0.26	0.63 (0.39-1.0)	0.050
Seizures	182 (24)	44 (12)	138 (35)	4 (2.7-5.9)	<0.001	2.2 (0.87-5.5)	0.086
Anticonvulsants	154 (20)	32 (9)	122 (31)	4.7 (3-7.4)	<0.001	4.8 (2.8-8.0)	<0.001

LCL, lower confidence limit; UCL, upper confidence limit

9.1 Univariate analyses

Bleeding

One patient had intracerebral bleeding, and bleeding requiring transfusion was reported in 6 % of the patients. There was an increased risk of bleeding associated with the use of intravascular devices for induced hypothermia (OR 2.3; 95% CI 1.1-4.9), thrombolysis (OR 3.5; 95% CI 1.1-9.1), cardiogenic shock (OR 4.1; 95% CI 2.0-8.1) and the use of intra aortic balloon pump (IABP) (OR 2.9; 95% CI 1.4-6). There was a trend towards more bleeding in patients receiving coronary angiography (OR 1.9; 95% CI 0.97-3.9). There was no statistically significant difference in the rate of bleeding for patients alive or dead at six months (5.5 vs. 5.8 %, $p=0.76$).

Infections

The use of intravascular devices was associated with a higher frequency of sepsis, with an OR of 2.6; 1.2-6.5 for intravascular cooling devices and 3.2; 1.3-7.3 for intra aortic balloon pumps (IABP). Coronary angiography was also associated with sepsis (OR 4.4; 95% CI 1.7-13). Pneumonia and sepsis were associated with a decreased mortality in the univariate analyses (OR 0.48; 95% CI 0.36-0.65 and 0.43; 95% CI 0.18-0.97, respectively), as was use of antibiotics for therapy of infection (OR 0.39; 95% CI 0.29-0.53). Antibiotics given as prophylaxis were not associated with mortality in the univariate analysis (OR 1.2; 95% CI 0.83-1.6).

Metabolic and electrolyte disorders

Hypoglycaemia (OR 2.3; 95% CI 1.1-4.9), hyperglycaemia (OR 2.5; 95% CI 1.8-3.4) and hypokalaemia (OR 1.5; 95% CI 1-2.2) were all associated with increased mortality while there was no apparent relationship between mortality and hypophosphataemia (OR 0.81; 95% CI 0.55-1.2) or hypomagnesaemia (OR 1.0; 95% CI 0.69-1.5).

Arrhythmias

Occurrence of VT, VF, tachycardia or atrial fibrillation during the critical care period was not statistically significantly associated with mortality. There was a strong trend towards lower mortality for patients experiencing at least one episode of bradycardia (OR 0.68; 95% CI 0.44-1, $p=0.06$).

Seizures

Seizures (OR 4; 95% CI 2.7-5.9) and the use of anticonvulsant medications (OR 4.7; 95% CI 3-7.4) were strongly associated with increased mortality. Patients developing seizures had longer ischaemia times, with longer times from arrest to initiation of CPR and achievement of ROSC ($p<0.001$). Patients with seizures also more frequently had a non-cardiac cause of their arrest ($p=0.001$) and an initial rhythm of asystole or PEA ($p=0.002$). Related to hypothermia, patients with seizures had a shorter time to achievement of target temperature ($p=0.006$)

9.2 Multivariate analyses

The best model for predicting six-month mortality given the constraints of available degrees of freedom included longer time from arrest to ROSC, older age and lower level of consciousness at hospital admission, with similar patterns as for the predictors in the multivariate model for neurological function in the full cohort. Additionally referral to coronary angiography was associated with lower mortality (OR 0.34; 95 % CI 0.23 to 0.52) and the administration of anticonvulsants were associated with increased mortality (OR 4.8; 95 % CI 2.9-8.1)

When the adverse events occurring during the critical care period and their specific treatments were introduced one at a time in the final model, i.e. adjusted for strong predictors of mortality, sustained hyperglycaemia (OR 2.3; 95% CI 1.6-3.6, $p<0.001$) was highly associated with increased mortality, whereas pneumonia (OR 0.52; 95% CI 0.35-0.77, $p<0.001$) and the use of antibiotic therapy (OR 0.39; 95% CI 0.29-0.53, $p<0.001$) were associated with decreased mortality.

A less evident, but still significant relationship was found with a decreased mortality for patients developing sepsis (OR 0.30; 95% CI 0.12-0.79, $p=0.01$). Antibiotic prophylaxis was associated with a higher mortality (OR 1.6; 95% CI 1.0-2.4, $p=0.03$). Bleeding was not associated with mortality (OR 1.0; 95% CI 0.46-2.2, $p=0.91$) (Table 3).

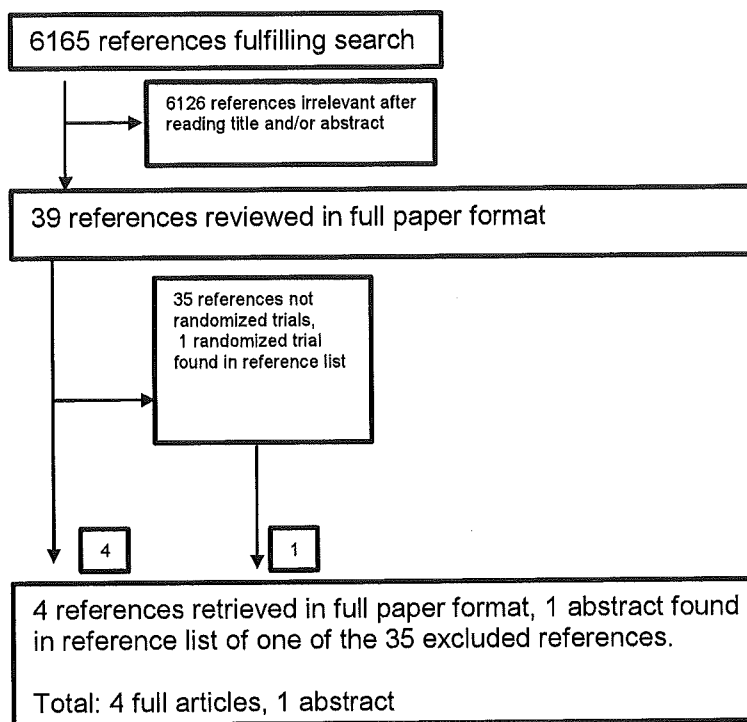
10. Systematic review of the evidence for induced hypothermia after cardiac arrest.

10.1 Search results

We identified 6165 references and excluded 6126 after screening titles and abstracts for hypothermia, cardiac arrest, and randomised trial. We retrieved 39 articles in full paper format of which four fulfilled our search criteria: a European multicentre trial, Hypothermia after Cardiac Arrest (HACA-study-group 2002), an Australian trial (Bernard et al. 2002), a Belgian feasibility trial (Hachimi-Idrissi et

al. 2001), a French trial (Laurent et al. 2005). One additional trial (Mori et al. 2000), only presented as an abstract, was found in the reference list of one of the retrieved trials (Figure 14).

Figure 14. PRISMA-flow chart



10.2 Characteristics of included randomised trials

The five trials included 478 patients. The patients were with few exceptions adult patients with out-of-hospital cardiac arrest randomised to induced hypothermia of 32-34 °C versus control intervention.

Three trials used external cooling with either forced cool airflow over the patient (HACA-trial), ice-packs (Bernard-trial) or a cooling helmet (Hachimi-Idrissi). The Mori-trial did not report the method of cooling. The Laurent trial was three-armed with no intervention (control), continuous veno-venous haemofiltration (CVVH) to a target temperature of 37 °C and CVVH to a target temperature of 33 °C.

Four trials were designed as outcome trials with neurological function as primary outcome. The Hachimi-Idrissi-trial aimed at evaluating feasibility with a cooling strategy. The Mori-trial did not report mortality. Length of follow-up ranged from hospital discharge to six months.

10.3 Systematic errors

None of the trials had low risk of bias according to Cochrane definitions. The HACA and Laurent-trials reported adequate generation of allocation sequence, allocation concealment, blinding of outcome assessors (however the procedure was not specified), intention-to-treat analyses and provided 180-day follow-up. On the contrary, these trials did not report the level of coma prior to randomisation, and reported baseline imbalance for bystander CPR and diabetes. Also, both trials were terminated early without reporting *a priori* defined power calculations, the HACA-trial because of lack of funding and low enrolment and the Laurent-trial because of publication of the results from the HACA and Bernard-trials and the publication of the ILCOR advisory statement. We characterised the HACA and Laurent-trials as having the least risk of bias among the trials included.

None of the included trials reported the full details on how the decision to withdraw intensive care treatment was determined and if the assessor of the prognosis was blinded to allocation of intervention.

The time for outcome evaluation was hospital discharge for the Bernard and Hachimi-Idrissi-trials and 30 days for the Mori-trial.

The Bernard trial used quasi-randomization with odd and even dates. This trial also had major baseline differences and conducted a non-scheduled interim analysis after inclusion of 80 % of the patients with no adjustment of the P-value (Table 1).

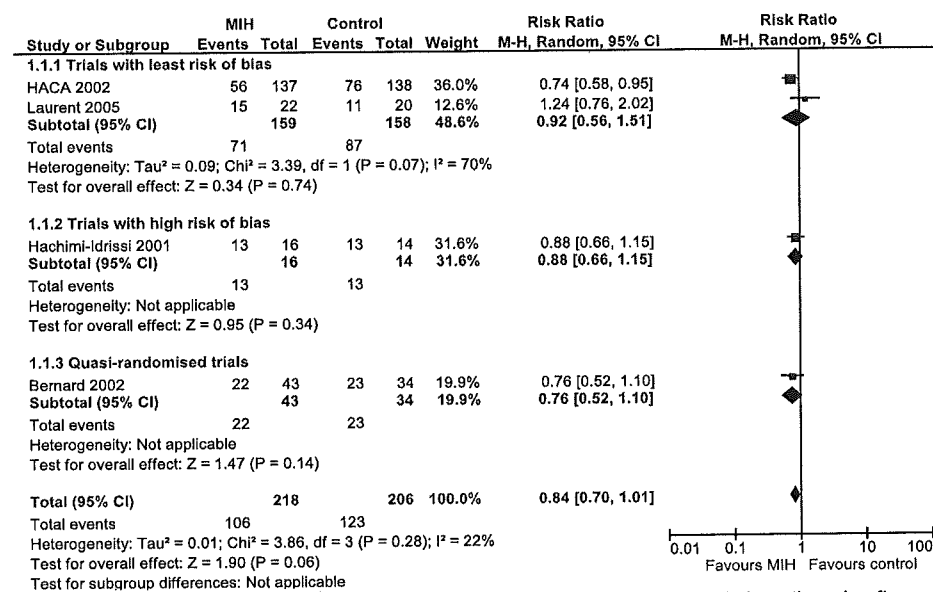
10.4 Meta-analysis

Because of differences in risk of bias, we present the effect estimates of induced hypothermia in the trials with least risk of bias (HACA and Laurent), high risk of bias (Mori and Hachimi-Idrissi) and the quasi-randomised trial (Bernard) separately, but also a meta-analysis of all trials using fixed- and random-effects models.

10.5 All-cause mortality

In the trials with least risk of bias the RR for induced hypothermia versus control intervention was 0.92; 95 % confidence interval 0.56 to 1.51. In the trial with high risk of bias the RR was 0.88; 95% CI 0.66 to 1.15. In the quasi-randomised trial the RR was 0.76; 95% CI 0.52 to 1.10. A meta-analysis of all trials showed RR 0.84; 95% CI 0.70 to 1.01). These analyses were performed using a random-effects model and none were statistically significant (Table 7). In a fixed-effects model of all trials, the RR did not change substantially but the results became statistically significant (RR 0.80; 95% CI 0.68 to 0.96).

Table 7. Forest plot of the effect of mild induced hypothermia on mortality suggested by the randomised and quasi-randomised clinical trials in the review.

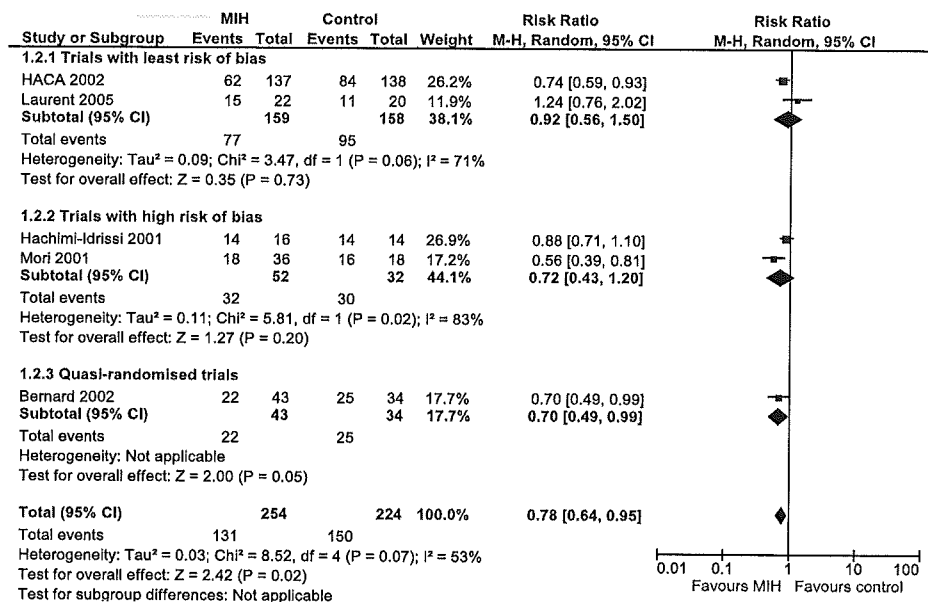


Risk Ratio with 95% confidence interval. MIH=mild induced hypothermia. HACA=hypothermia after cardiac arrest. Df =degrees of freedom. I^2 =heterogeneity.

10.6 Neurological function

In the trials with least risk of bias the RR for a poor neurological outcome was 0.92; 95% CI 0.56 to 1.50. In the trials with high risk of bias the RR was 0.72; 95% CI 0.43 to 1.20. In the quasi-randomised trial the RR was 0.70; 95% CI 0.49 to 0.99. All the trials showed RR 0.78; 95% CI 0.64 to 0.95. These analyses were performed using a random-effects model (Table 8). In a fixed-effects model, the RR of all trials did not change substantially (RR 0.76; 95% CI 0.66 to 0.88).

Table 8. Forest plot of the effect of mild induced hypothermia on neurological function suggested by the randomised and quasi-randomised clinical trials in the review.



Risk Ratio with 95% confidence interval. MIH=mild induced hypothermia. HACA=hypothermia after cardiac arrest. df =degrees of freedom. I^2 =heterogeneity.

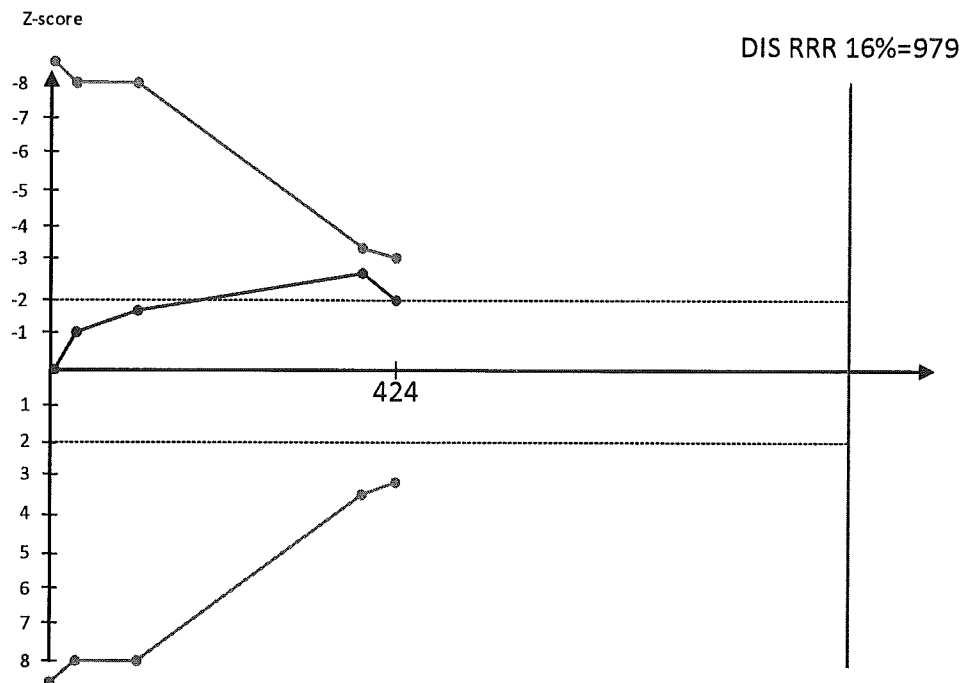
10.7 Adverse events

There were only two trials reporting on adverse events, but since these two trials did not report the same set of adverse events, a meta-analytical estimate could not be calculated. However, there was a trend towards more complications in the induced hypothermia group in the HACA-trial.

10.8 Random errors – trial sequential analysis

TSA were calculated with $\alpha=0.05$ and $\beta=0.20$ (power 80 %) and a required diversity-adjusted information size based on the intervention effect suggested by the included trials using a random-effects model (RRR of 16 % regarding mortality and 979 patients; RRR of 22 % regarding poor neurological function and 729 patients). TSA indicated lack of firm evidence for a beneficial effect of induced hypothermia for both mortality (Figure 1) and poor neurological outcome, since the monitoring boundaries were not finally surpassed and the required information sizes not reached. None of the estimated required information sizes were accrued, and an intervention effect of 16 %, for a reduction of mortality, or of 22 %, for a reduction of poor neurological function, could not be excluded.

Figure 15. Trial sequential analysis of the 4 trials reporting mortality



Random effects trial sequential analysis based on a relative risk reduction (RRR) of 16% suggested by the four trials (HACA, Bernard, Hachimi-Idrissi and Laurent). A required diversity adjusted information size (DIS) with diversity (D^2) 23 % ($I^2=20$ %) and a relative risk reduction of 16 % suggested by the trials. $\alpha=0.05$ and $\beta=0.20$ (power=80 %). The cumulative z-curve (blue) crosses the traditional level of significance (0.05) but not the trial sequential monitoring boundary indicating lack of firm evidence for a beneficial effect of 16 % RRR of the intervention when the analysis is adjusted for repetitive testing on accumulating data. There is insufficient information to reject or detect an intervention effect of 16 % RRR of all-cause mortality as the required information size is not yet reached.

10.9 Summary of evidence according to GRADE

Randomised trials *per se* are rated high on the GRADE scale. As indicated above there were variable but serious risks of bias of the trials, leading us to rate down the quality of the evidence.

Apart from the Laurent-trial there was no serious inconsistency between trials.

The HACA-trial, representing 59 % of the randomised participants, included only 8 % of the screened cardiac arrest population presenting at the emergency department with ROSC. The HACA and Bernard-trials only included patients with ventricular fibrillation or pulseless ventricular tachycardia without circulatory instability. The Hachimi-Idrissi trial included exclusively patients with asystole or pulseless electrical activity. Hence there was a questionable directness in the trials.

The accumulated sample size and event rates were low and the two trials with least risk of bias had a combined wide confidence interval spanning both the potential for benefit and harm. However according to our judgement and in context with the other measures, this may not implicate serious imprecision.

Our application of GRADE-methodology led us to conclude that the accumulated evidence is of low quality. For a GRADE-profile see Table 9.

Table 9. GRADE profile for assessing quality of evidence for mild induced hypothermia after out-of-hospital cardiac arrest

Author(s): Nielsen, Friberg, Glud, Herlitz, Wetterslev
Date: 2010-02-15
Question: Should mild induced hypothermia be used for out of hospital cardiac arrest?
Settings: Critical care unit
Bibliography:

Quality assessment							Summary of findings				Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			
							mild induced hypothermia	control	Relative (95% CI)	Absolute		
Mortality (follow-up 180 days ¹)												
4	randomised trials	serious ²	no serious inconsistency	serious ³	no serious imprecision ⁴	none	106/218 (48.6%)	123/206 (59.7%)	RR 0.84 (0.7 to 1.01)	96 fewer per 1000 (from 179 fewer to 6 more)	⊕⊕⊕⊕ LOW	CRITICAL
Neurological function (follow-up 180 days ¹ ; Cerebral performance category ⁵)												
5	randomised trials	serious ²	no serious inconsistency	serious ³	no serious imprecision	none	131/254 (51.6%)	150/224 (67%)	RR 0.78 (0.64 to 0.95)	147 fewer per 1000 (from 33 fewer to 241 fewer)	⊕⊕⊕⊕ LOW	CRITICAL

¹ The two trials with least risk of bias had 180 days follow up. The two trial with high risk of bias had follow up until 14 days. The quasi-randomized trial had follow up until hospital discharge.

² All trials had substantial risk of bias.

³ The targets trial included only 8 % of the screened patients with ROSC in the emergency department. The second largest trial included only a subset of the cardiac arrest population.

⁴ The total sample size is limited and event rates are low. The two trials with least risk of bias have a wide confidence interval spanning both the potential for benefit and harm. We address this problem with Trial Sequential Analysis. In context with the other measures of evidence quality we choose not to downgrade on imprecision.

⁵ The second largest trial judged neurological outcome based on whether patients were discharged.

ROSC, return of spontaneous circulation; RR, relative risk.

10.10 Observational data

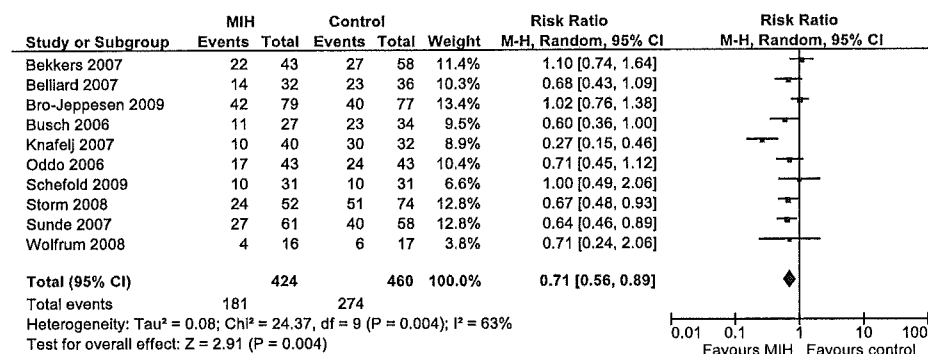
We identified ten observational single centre studies with a total of 884 patients (range 33 to 156 patients) comparing patients receiving induced hypothermia with patients not receiving induced hypothermia (Busch et al. 2006; Oddo et al. 2006; Bekkers et al. 2007; Belliard et al. 2007; Knafelj et al. 2007; Sunde et al. 2007;

Storm et al. 2008; Wolfrum et al. 2008; Bro-Jeppesen et al. 2009; Schefold et al. 2009). One was a case-control study with matched historical controls and the rest compared two different time periods, where patients from the period before implementation of induced hypothermia were used as historical controls. Nine were retrospective and one was prospective. The majority were designed primarily to address feasibility and not efficacy.

When evaluating the studies with the STROBE-checklist, we found a mean agreement of 58% (range 30% to 81%), with major deviations in reporting of sample size and power calculations, selection of study population, and interpretation and generalisability of results. When evaluating the studies with Thomas Quality Assessment Tool, we found three with moderate rating of quality and seven with weak rating.

There were also large differences when outcome was evaluated (intensive care unit discharge to follow up at one year after cardiac arrest). Mortality and poor neurological function between intervention and control periods were compared in forest plots yielding an RR of 0.71; 95% CI 0.56 to 0.89, $I^2=63\%$ (Figure 5) and 0.64; 95% CI 0.55 to 0.75, $I^2=29\%$, respectively, in random effects models, both in favour of induced hypothermia periods (Table 10).

Table 10: Forest plot of the effect of mild induced hypothermia on mortality suggested by the observational studies in the review. Risk Ratio with 95% confidence interval.



MIH=mild induced hypothermia. HACA=hypothermia after cardiac arrest. df=degrees of freedom.
 I^2 =heterogeneity.

Three registry-based studies (where our registry is one) pooling data from several hospitals were identified, but none of these compared patients treated with induced hypothermia with a relevant control group (Arrich 2007; Oksanen et al. 2007; Nielsen et al. 2009).

DISCUSSION

In this doctoral dissertation project we have investigated cardiac arrest patients treated with induced hypothermia after its implementation into clinical practice in 2002. In an attempt to describe and evaluate the clinical aspects of hypothermia treated patients, we have developed a registry and analysed registry data as well as collected data at three regional hospitals in Southern Sweden in the search for a useful biomarker of outcome after cardiac arrest. Further we wanted to assess the current evidence for hypothermia and, in the context of our findings from the registry, propose a new trial investigating induced hypothermia.

The main findings are that about half of the patients admitted to intensive care units after out-of-hospital cardiac arrest and who receive hypothermia treatment survive, and more than 90 % of the survivors have a good neurological function at long term follow up, when measured with the cerebral performance category scale.

Factors related to the conduct of induced hypothermia, such as time to initiation of hypothermia and achievement of target temperature had no apparent relation to the subsequent outcome. Strong predictors of a poor neurological outcome and mortality were: increased time from arrest to ROSC, higher age, lower GCS at admission, unwitnessed cardiac arrest, initial rhythm asystole, no angiography, anticonvulsant medication and sustained hyperglycaemia.

The incidence of adverse events was in many aspects similar to historical materials, but the risk of bleeding and infection was increased when invasive procedures were performed. However, neither infection nor bleeding were associated with increased mortality.

Of the biomarkers tested, neuron specific enolase was superior to S-100B.

A systematic review of the trials of induced hypothermia indicated a low quality of the evidence to support the intervention. Moreover, the required information size, i.e. the amount of patients that need to be investigated to provide firm evidence, is not yet achieved, and thus reliable conclusions could not be drawn.

There is a need for a large randomised trial, which we propose based on the findings from this project.

The first large descriptive materials of cardiac arrest patients were presented in the 1950s where the authors reported a hospital survival of 50 % for patients with

sustained ROSC (Stephenson et al. 1953). These figures have been more or less static during the following decades with in hospital mortality after out-of-hospital cardiac arrest between 34 % and 56 % (Böttiger et al. 1999; Herlitz et al. 2003; Langhelle et al. 2003; Herlitz et al. 2006; Carr et al. 2009). Many therapies have been proposed and tested during previous decades without proven beneficial effects.

The margins between success and failure for resuscitation from cardiac arrest are small and every minute counts. The concept of the chain of survival has been proposed indicating the importance of every aspect of resuscitation. There has been a distinct focus on the initial part of resuscitation, with layperson education and improvements in the performance of cardiopulmonary resuscitation. However, the post cardiac arrest phase in the intensive care units has been a missing link in the chain of survival (Herlitz et al. 2006).

When two trials (Bernard et al. 2002; 2002), investigating induced hypothermia after cardiac arrest, were published there was an awakening interest in cardiac arrest patients, who in many aspects previously had been neglected in the intensive care setting. This interest was evident among different specialities as emergency physicians, cardiologists and neurologists as well as for anaesthesiologists and intensivists.

Introductory work

The introductory paper I illustrates the relay between pre-hospital and in-hospital caregivers and also describes a possible outcome in a very critically ill patient if active and standardised treatments are commenced in sequence. This patient was transported to hospital with mechanical compression-decompression CPR, hypothermia was induced immediately in the emergency department, after which the patient was referred to the coronary intervention laboratory. The no-flow and low-flow periods lasted 66 minutes in total.

Animal studies have shown significant improvement in coronary perfusion pressure, cardiac output and carotid artery blood flow with mechanical CPR (Steen et al. 2003). These studies also show that the blood volume eventually will pool on the venous side during the cardiac arrest before CPR is started, with an empty left heart and a congested right heart decreasing the chance for a successful ROSC. Mechanical CPR before defibrillation increased the chance of ROSC.

This is also shown in humans, where chest compressions, before attempts to defibrillate the heart, seem to benefit survival for patients when CPR is delayed more than 5 minutes after the cardiac arrests.

In the emergency department the ECG for this particular patient showed minimal anterolateral ST-elevations, prompting the cardiologist to refer the patient to coronary intervention, which resolved the underlying culprit lesion: the occluded left coronary main stem. In many regions coronary angiographies and

interventions were not performed on cardiac arrest patients a decade ago but this routine has changed. Without a cardiological focus this patient had never survived, and therefore this case illustrates the importance of immediate referral for possible coronary intervention when indications are fulfilled.

The patient was hypothermic when arriving in the emergency department and after standard induction of induced hypothermia with 4 °C intravenous crystalloid solution (Bernard et al. 2003) he was in the range that has been proposed as neuroprotective (32 °C to 34 °C). The subsequent cardiac arrest in the intervention laboratory thus occurred when the neuroprotective temperature had been established. Hence this case illustrates both possible intra-ischaemic as well as post-ischaemic hypothermia.

The case was referred to in the European Resuscitation Council guidelines 2005 (in spite of its low quality of evidence) (Nolan et al. 2005).

Rationale for developing the registry

When induced hypothermia was implemented, mainly based on the two trials published in New England Journal of Medicine (Bernard et al. 2002; 2002) and the advisory statement from ILCOR (Nolan et al. 2003), we thought it imperative to monitor its use in clinical practice, to follow outcome for a period longer than merely hospital stay, to find predictors of survival and a good neurological outcome and to collect adverse events and analyse safety aspects. The foremost aims were to assess if this novel therapy would increase the group of vegetative and severely brain injured patients at long-term follow-up the association between the conduct of hypothermia treatment and outcome.

Descriptive outcome

About half of the patients survived with the absolute majority with a CPC of 1 or 2 at six-months follow up. Only very few patients survived but remained in coma. These vegetative patients were all from one country (data not shown), which might indicate a different attitude to prolongation of life support in that specific country. This is important information. When induced hypothermia was introduced, there was concern that this strategy, albeit increasing the net good outcome, would also increase the proportion of alive but brain-injured patients. The conclusion is that in the majority of the cases the patient will either die or survive with a good outcome sustaining the ability of independent life. This almost dichotomous outcome is similar to the pattern seen prior to the introduction of hypothermia.

The reported proportion of survivors (Busch et al. 2006; Oddo et al. 2006; Arrich 2007; Bekkers et al. 2007; Belliard et al. 2007; Oksanen et al. 2007; Storm et al. 2008; Wolfrum et al. 2008; Bro-Jeppesen et al. 2009; Schefold et al. 2009) is today better or equal to historic intensive care materials (Bottiger et al. 1999; Herlitz et al. 2003; Langhelle et al. 2003) and our registry data compare well to the

clinical trials on hypothermia, indicating that the results may be generalisable from the controlled setting into clinical practice. There are also larger patient materials indicating a better outcome for patients with VT/VF today (Becker et al. 2008; Hollenberg et al. 2008).

However, it is evident that the general care of cardiac arrest patients has changed for the better in recent years and that an outcome comparison with historical controls may be of limited value. Parallel to the introduction of hypothermia as a neuroprotective therapy there have been improvements in pre-hospital care and in several aspects of post cardiac arrest intensive care where the most important probably is the more liberal indication for emergency angiography and revascularisation in comatose patients. This has been shown to be an important predictor of a good outcome and survival in various observational reports (Knafelj et al. 2007; Sunde et al. 2007; Werling et al. 2007; Reynolds et al. 2009) as well as in our material. It must be highlighted that some of these studies include both emergency and delayed coronary angiography/intervention, which might select patients with a favourable outcome during the first days. Also, coronary angiography and coronary intervention are not evaluated in large randomised trials for cardiac arrest patients and therefore its final role is not known.

Another factor that might influence our long-term survival rate is that many patients discharged alive from hospital receive an implantable cardioverter-defibrillator (ICD), but we have no data of the frequency.

The introduction of bundle care (performing a group of interventions simultaneously) is associated with increased survival in intensive care patients (Ferrer et al. 2008) as well as protocolised care per se (Kern et al. 1999; Holcomb et al. 2001). The bundle of improved chest compressions, active and goal-directed intensive care, coronary intervention and temperature management seems to be a promising approach (Sanders et al. 2002; Sunde et al. 2007; Bobrow et al. 2008; Rittenberger et al. 2008). Hopefully, the contribution to the cardiac arrest population by the individual strands of this bundle will become more clear in the future, as we collect more information.

Another factor important for the outcome is a possible Hawthorne effect (Roethlisberger et al. 1939) associated with the novel focus and interest.

As indicated above there have been several single centre studies and two additional registry reports describing outcome after the introduction of hypothermia (Busch et al. 2006; Oddo et al. 2006; Arrich 2007; Bekkers et al. 2007; Belliard et al. 2007; Oksanen et al. 2007; Storm et al. 2008; Wolfrum et al. 2008; Bro-Jeppesen et al. 2009; Schefold et al. 2009). They quite consistently report a mortality rate of approximately 50 % for out-of-hospital cardiac arrest patients admitted to intensive care for induced hypothermia treatment, but these studies are all relatively small and many have discharge from intensive care or hospital discharge as outcome measures, which might be troublesome since the

evolution of neurological status reaches baseline after approximately six months (Arrich et al. 2009). This is highlighted by a comparison of two of the available registry reports. The publication from ERC-HACA-R (Arrich 2007) shows 36 % patients in CPC 3 and 4 (severely impaired neurological function and dependent daily life or vegetative) as an outcome evaluated at hospital discharge, compared to our data with 4 % at six months.

Additionally, none of the observational studies, including our own registry report, could be regarded as being of highest quality and, on average, they do not fulfil essential demands for the reporting of observational data (Thomas).

Observational studies and registries can answer questions of a descriptive nature, elucidate rare serious adverse events and generate hypotheses and may thus be used in the design of clinical trials. However, they can never prove efficacy of an intervention since they inherently have high risk of bias caused by confounding by indication, possible selective reporting, and the inclusion of non-comparable groups (Deeks et al. 2003; Friberg et al. 2009).

The conclusion in a general perspective, mainly based on studies with relatively high risk of bias, is that hypothermia does not appear to be associated with making a large group of patients vegetative and outcome results for out-of-hospital cardiac arrest patients today are comparable to or better than reports from previous time periods, also suggested by others (Tiainen et al. 2007).

Subsets of cardiac arrest patients

Most centres in our registry, in the ERC-HACA-registry and in other reports induce hypothermia today for cardiac arrest patients, irrespective of initial rhythm if active treatment is decided (Oddo et al. 2006; Arrich 2007; Sunde et al. 2007; Bouwes et al. 2010). The distinct divisors in the cardiac arrest population except from in-hospital and out-of-hospital arrests are the aetiology of the arrest and if the initial rhythm is shockable or not. The observational reports cited above report survival with a good neurological outcome in around 60 % of hypothermia treated patients with initial shockable rhythms, which is almost identical to our results.

We also report 22 % good outcome in patients with initial rhythm asystole, and for witnessed asystole the rates increase to 28 %. Even better outcome is reported for witnessed asystole of cardiac aetiology, with a six months good outcome rate of 39 % (data not shown). On the contrary, in our material unwitnessed asystole had a good outcome of only 10 % with all survivors being young patients with drug and alcohol associated arrests. Therefore for patients with initial rhythm asystole and where the arrest was unwitnessed the prognosis is very pessimistic which is also supported by other reports (Vayrynen et al. 2008).

The outcome for patients with time to ROSC >30 minutes is dismal (Herlitz et al. 2006). In our material of patients admitted to intensive care treatment survival with a good outcome remained at 23 % when time to ROSC exceeded 25

minutes contrary to results in a study where no patients with time to ROSC > 25 minutes survived with a good neurological function (Oddo et al. 2008). Thus, increased time to ROSC is a predictor of a poor outcome, but there is no cut-off that can be used clinically.

The randomised trials on hypothermia included VF and non-perfusing VT of a cardiac aetiology only. The exclusion of 92 % of the screened cardiac arrest patients with ROSC in the HACA-trial was, at the time when the study was designed, motivated by the wish for a substantial amount of survivors, regardless of allocation group to give the analysis increased power. The investigators chose a population with a demographic pattern and an ischemic insult that theoretically might have a high chance of getting a beneficial effect of induced hypothermia (survival approximately 50%). In this context, the study was designed as a possible proof-of-concept trial but it limits the generalisability and directness of the results.

Thus, hypothermia has not been tested on non-VF/VT arrests, but ILCOR and the guidelines state, "for any other rhythm, or cardiac arrest in hospital, cooling may also be beneficial". Since resuscitated patients who remain in coma suffer from an ischaemia-reperfusion injury regardless of the initial rhythm, this might be a defensible rationale. The injury ought to be dependent on the cause of the arrest, anoxia/ischaemia time and also on the quality of CPR performed, rather than on the nature of the rhythm causing the arrest. However, as indicated in the introduction, the duration of cardiac arrest will affect the cardiac rhythm as VF may proceed to asystole. Therefore, there is an interaction between rhythm and cardiac arrest duration.

Accordingly, based on the findings that other witnessed rhythms of a cardiac cause except from VT/VF have a fairly good chance of survival and that a more pragmatic approach when choosing study population is warranted, future trials of induced hypothermia ought to include a broader selection of the cardiac arrest population than the HACA-trial. In fact, from our registry data we conclude that the selection of all initial rhythms of a cardiac cause including patients irrespective of time to ROSC and patients in cardiogenic shock, but limiting age to over 18 years, we comprise 80 % of the out-of-hospital cardiac arrest patients admitted to intensive care for induced hypothermia. The survival for this group is 56 % with a good neurological outcome of 52 % (data not shown), which ought to be optimal with respect to power calculations and sample size for intervention event rates in future trials. This strategy would include a large majority of patients that are eligible for active intensive care today, improving the directness and generalisability of the trial results.

Predictors of outcome – clinical data

As mentioned above, there is a small difference between the two different outcomes poor neurological outcome and mortality, when assessed at six months. Only few individuals are in CPC 3 and 4 creating an almost as dichotomous outcome for neurological function as for mortality/survival, which means that overall survival principally is the same as survival with good neurological outcome. Therefore, the predictors found in our multivariate models using first neurological outcome and then mortality are similar.

The strongest predictors of a poor neurological outcome and mortality were increased age, longer time from arrest to ROSC and lower GCS at admission, all three confirming earlier findings (Herlitz et al. 2003; Langhelle et al. 2003; Skrifvars et al. 2003; Herlitz et al. 2005; Nolan et al. 2007; Carr et al. 2009). In paper II, where we assessed neurological function, we also found strong predictors in whether the arrest was witnessed or not, and whether the patient was found in VT/VF and was referred to emergency coronary angiography or the patient was found in asystole and was not referred to emergency coronary angiography. Hence, there was an interaction between initial rhythm and the performance of angiography. The importance of angiography as a marker of outcome (*nota bene* confounded by indication-patients might have been selected to angiography on other grounds than strict criteria) was confirmed in paper IV, where angiography *per se* was a predictor of survival.

In the latter study the administration of anticonvulsants was also a strong predictor of mortality, which is plausible with its close link and strong correlation to having seizures. In paper II, covariates associated with intensive care after the induction and maintenance phases for hypothermia were not introduced in the multivariate model. Only covariates accessible up to the point of interest (in this case hypothermia related variables) should be introduced (Harrel 2001). Therefore, adverse events, such as for instance seizures, were for methodological reasons unable to present as predictors.

Also, in paper IV only three quarters of the amount of patients in paper II were analysed, limiting the number of possible predictors in the results of the multivariate model (Harrel 2001). Gender and the presence of cardiogenic shock, which could be plausible predictors, at least when assessing univariate relationships, were not obvious in our material, possibly due to insufficient sample size.

Summarizing this, we found predictors similar to what have been presented before in non-hypothermia treated patients. All these factors have been considered in the design of our proposed novel trial and also used when stratification and design variables have been chosen.

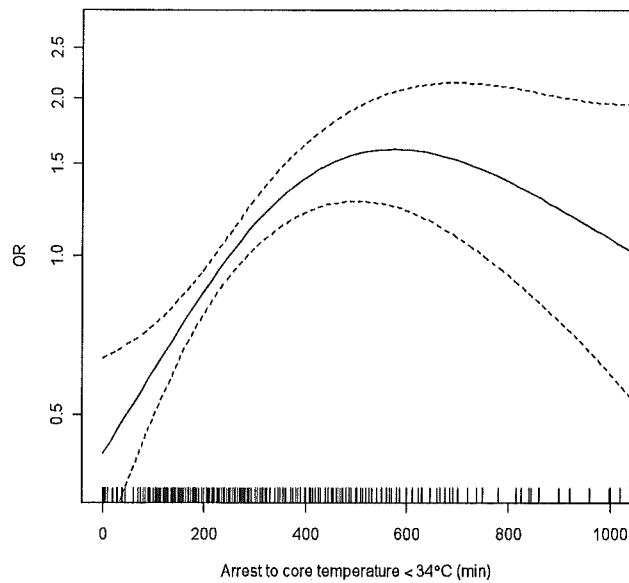
Predictors of outcome – hypothermia data

When designing the registry we wanted to focus on details in the conduct of induced hypothermia and we collected data on different techniques to induce and maintain temperature management, the time to induction of hypothermia and achievement of target temperature, the depth (chosen target temperature), duration of hypothermia as well as the rate of rewarming.

None of the factors related to hypothermia were significantly associated with neurological outcome in our material. The target temperature and duration of hypothermia had a very concentrated distribution with the vast majority of the patients being treated at 32-34 °C for 24 hours, and thus these variables were difficult to interpret.

There are animal data indicating benefit of early cooling (Kuboyama et al. 1993) and guidelines stress that hypothermia should be induced as early as possible (Nolan et al. 2005). However, we could not confirm this in our registry data. There was no difference in neurological outcome in our multivariate models, whether hypothermia was introduced early or in relation to when target temperature was achieved. The univariate relationship indicated a negative association with a worse outcome for early achievement of target temperature (Figure 16). There was also a trend towards a worse outcome in the multivariate model for time to induction of hypothermia, while time to achievement of target temperature was neutral over the entire time span (see Results).

Figure 16. Univariate relationship between good neurological outcome (odds ratio) and time to achievement of a core temperature below 34 °C (minutes)



These findings should be interpreted with caution since they are purely observational and may be substantially biased. One possible explanation may be that we have too little data to elucidate the full relationship.

Another explanation is that there is a major confounder that we do not have access to. The univariate association between early cooling and a poor outcome might be related to the severity of the brain injury caused by the cardiac arrest, not explained solely by surrogate predictors as time from arrest to ROSC, age, GCS and initial rhythm. A severely injured brain may have lost its defence to counteract imposed hypothermia and therefore it is easier to cool such a patient. Instability in temperature regulation has been linked to a worse outcome in in-hospital cardiac arrest patients (Suffoletto et al. 2009).

We have tried to adjust for the severity of the insult in the model using these predictors, as a proxy for the ischaemic insult, but this might not have been sufficient. Also, delay in the start of hypothermia caused by angiography and other interventions may confound the results, even if measures were taken to adjust for this in our multivariate models.

A third explanation is that hypothermia does not have the great effect that the randomised trials suggest, especially not in a much broader patient material than studied in the randomised trials, or hypothermia may even be detrimental in an unselected pragmatic population as the one studied in the registry.

A more conservative explanation is that other factors are more important than the timing of hypothermia. Previous animal experiments have shown sustained effect of hypothermia when introduced with a delay (Coimbra et al. 1994) and the HACA-trial had a median time from arrest until target temperature was reached of eight hours, with a suggested benefit on both mortality and neurological function when the intervention started late and cooling was slow. This might indicate that the window of opportunity is indeed wider than anticipated and that the maintenance period is the crucial time. Another possible explanation for a favourable effect is that the total time of target temperature management is prolonged if the cooling rate is lower and the time to achieve target temperature is longer. Hence this scenario will provide a longer time of controlled temperature below normal temperatures of 37 °C, thus avoiding fever, and this might be enough to induce neuroprotection.

There is only one observational study indicating benefit of early cooling (Wolff et al. 2008) but this study is seriously flawed on many levels, hence strong inferences are inadvisable (Nilsson et al. 2009), while other centres report equally non-significant effect of timing of hypothermia in large materials (F. Sterz, oral presentation, 3rd International Hypothermia Symposium, Lund, 2009).

As a conclusion we have chosen to include and randomise patients and start intervention in the planned trial (paper VI) until 240 minutes from ROSC, which will cover more than 90 % of a population similar to the patients in the HN registry. As there are no obvious differences in outcome between early and late induction of temperature management, there should be no disadvantage of a wide time limit to the start of the intervention.

Predictors of outcome – biomarkers

In our study we found that NSE as a predictor of a poor neurological outcome was superior to S100-B at all sampling times. S100-B in other materials has shown similar patterns over time with an early peak and subsequent low values in the good outcome group and sustained high levels in the bad outcome group (Bottiger et al. 2001; Rosen et al. 2001; Pfeifer et al. 2005; Prohl et al. 2007). However the two groups are difficult to separate with a useful cut-off level when using S-100B as indicated by the ROC-curves.

NSE above 28 µg/L at 48 hours and an increase in the NSE serum levels between 24 and 48 hours were the best predictors of a poor neurological outcome in our material. In other materials of non-sedated cardiac arrest patients the best cut-off value for NSE is reported to vary between 24 and 33 µg/L, 24 to 72 hours after the arrest (Meynaar et al. 2003; Zandbergen et al. 2006) and in two reports on sedated hypothermia treated patients one reported 25 µg/L and the other 33 µg/L (Tiainen et al. 2003; Oksanen et al. 2009). The variation may be caused by

different study populations, but may in a greater degree be due to methodological variations using different assays.

Many patients are still sedated and mechanically ventilated at these time points, limiting the possibility for neurological evaluation. Therefore a laboratory marker may be of great prognostic value. However, the use of a single laboratory value is not recommended and repeated sampling and time trends may be equally important.

Also, the combination of a laboratory test and other methods to assess prognosis is advocated. One of the reports used a clinical score combined with NSE (Oksanen et al. 2009). The best combination is probably with neurophysiological tests as for instance SSEP, and of course a neurological evaluation including GCS-motor score.

In the American Academy of Neurology guidelines for neurological prognostication after cardiac arrest the use of a NSE of >33 µg/L is recommended to be used in clinical practice as a marker of a poor prognosis (Wijdicks et al. 2006). With the varying results in the few trials presented this may be a too bold approach, especially after the introduction of hypothermia where slower metabolism, altered injury progress, increased sedation and attenuated drug clearance may influence the interpretation of biomarkers. The cautious use of biomarkers is discussed in a recent article by one of the authors behind the American Academy of Neurology guidelines (Young 2009).

Based on these findings, we have in the planned randomised trial decided to include NSE as a mandatory test to be evaluated in a blinded fashion. The samples will be collected, shipped and batch analysed to rule out differences attributed to type of assay or analysis method. We will thus have the opportunity to evaluate NSE in over 800 patients in the two allocation groups, which will be a great advantage.

Predictors of mortality – adverse events

After the initial findings about the frequencies of adverse events when analysing hypothermia treated out-of-hospital cardiac arrest patients in the HN-registry we decided to investigate the data and the association between mortality and adverse events more thoroughly. However, only 22 centres reported the full set of adverse events (including metabolic and electrolyte disturbances) while all centres reported a selected set (infections, arrhythmias, bleedings and seizures). In the analysis, we included 765 patients from those centres reporting all adverse events.

The frequencies of adverse events reported by all centres and by the selected group of 22 hospitals compared well, except for more pneumonia in the selected group. However, these findings suggest that there was no systematic underreporting of the selected adverse events in the full cohort.

Arrhythmias, pneumonia, metabolic and electrolyte disorders were common in the intensive care period, which is well known from investigations in the pre-hypothermic era as well in recent years. The unconscious cardiac arrest patients with need for intensive care and mechanical ventilation is a severely ill group with high risk of complications and adverse events related to the period precipitating the cardiac arrest, the severity of the global ischaemic insult, myocardial dysfunction, or the critical care treatment itself.

Hypothermia may induce arrhythmias, induce electrolyte disorders, impair defences against infections and increase the risk of bleeding. Therefore this area is interesting to pursue in a cardiac arrest population treated with hypothermia. Moreover, clinical trials and observational studies have in general reported poorly on these issues.

In paper II we report a doubled risk of bleeding for patients undergoing angiography and PCI. This was also found in the selected cohort. We could also show associations between bleeding and thrombolysis, other intravascular procedures (as intravascular cooling devices and the use of IABP) as well as the presence of cardiogenic shock. However, bleeding was not associated with increased mortality either in the adjusted or the unadjusted models. Invasive procedures should increase the risk of bleeding, but this increased risk may not offset the beneficial effects of performing these procedures.

Pneumonia was common, affecting almost half of the patients in our registry data, however not associated with increased mortality. The diagnosis was based on the criteria: purulent secretions, new infiltration on chest radiograph, white blood cell count elevation and the presence of fever. We did not demand microbiological investigations. It is more than plausible that these findings overrate the incidence of pneumonia since these criteria are frequent in mechanically ventilated patients. However, underreporting is probably more common than overreporting in clinical registries, hence the numbers may be valid.

Pneumonia is common in unconscious cardiac arrest patients with or without the use of induced hypothermia and is also common in other unconscious intensive care patients (HACA-study-group 2002; Alp et al. 2004; Gajic et al. 2004; Tsai et al. 2005; Knafelj et al. 2007; Sunde et al. 2007).

Sepsis was rather uncommon. However, similar to the risk of bleeding, sepsis was associated with patients having intravascular devices for cooling but also coronary angiography.

Neither pneumonia nor sepsis were associated to increased mortality, rather the contrary. This might be due to confounding or a time induced bias favouring patients surviving the initial phases of intensive care. Thus, our conservative interpretation is that *infections are not associated with mortality*, rather than *infections are associated with better survival*. A very important implication of this is that infections should not be used as a marker of a poor prognosis when assessing the patients in the intensive care for possible extended care.

Hyperglycaemia was strongly associated with increased mortality but hypoglycaemia, which was a much more rare event, only revealed a trend towards increased mortality. It is plausible that mortality would increase in both ends of the scale (Losert et al. 2008; Beiser et al. 2009). Hypoglycaemia is in most cases an effect of insulin administration, while hyperglycaemia may appear due to the insult of the arrest as well as of induction of hypothermia. The magnitude of hyperglycaemia may in part reflect the severity of the ischaemic insult, since hyperglycaemia is related to endogenous and exogenous catecholamines released during the cardiac arrest. Hypothermia decreases the endogenous insulin secretion and induces a state of insulin resistance (Schubert 1995; Polderman 2004), and thus the hyperglycaemia seen after cardiac arrest may be even more pronounced in patients receiving hypothermia treatment. Accordingly, the effect of exogenously administered insulin is reduced when lower temperatures are achieved. Since only observational data were available, we could not isolate the effect of hypothermia on the presence of hyperglycaemia, and this should be highlighted as a potentially interesting field in future trials having a valid control group.

None of the electrolyte disorders were associated with increased mortality in our material, except for a trend towards increased mortality for events with hypokalaemia. Possibly the material was too small to address these questions.

Arrhythmias are commonly registered and some of them, as for instance bradycardia, are even expected when induced by hypothermia. Most probably arrhythmias are related to the underlying cardiac cause of the arrest and associated myocardial dysfunction.

There are no randomised trials evaluating treatment of post cardiac arrest seizures and seizures are associated with a poor prognosis (Rossetti et al. 2009). There are however case reports and case series where patients with seizures have had a final good outcome (Bone et al. 1992; Hovland et al. 2006; Sunde et al. 2006; Rossetti et al. 2009). In our material 17 % of all patients with reported seizures had a favourable outcome, but we do not have data on the duration, type or timing of the seizures and therefore this area must be further investigated. Nevertheless, seizures should probably not be regarded as an irrevocable sign of a poor outcome. In our multivariate model seizures were not a predictor of a bad outcome, but medication with anticonvulsants was, and therefore this is probably a proxy for seizures as they correlate. The interpretation might also be that only the severe seizures, in need of anticonvulsants, had a poor outcome.

Overall the occurrence of adverse events in our registry data is similar to earlier reports on cardiac arrest patients, but since there is a lack of large-scale investigations firm conclusion are difficult to draw. Also, we could not isolate the effect of hypothermia on any of the adverse events since all patients were hypothermia treated. We could only present descriptive data and associations to mortality in a cohort treated with hypothermia, which is a limitation outside randomised trials.

It is tempting to argue that the similarity of the frequencies of adverse events today and in the past would be in favour of the use of hypothermia; it does not seem to increase the risk of adverse events and hence it should be safe. However, the evidence is of low quality and the conclusions are far from firm. One might as well argue that the safety profile would be in favour of yet another trial on induced hypothermia; if hypothermia does not prove to be as efficient as suggested by previous trials, we will not impose extra risks with regard to adverse events while performing the trial. In the HACA-trial there was a trend towards more adverse events in the hypothermia treated group. However it did not offset the net efficacy of hypothermia. The studied patient group was on the other hand very selected, and thus we do not know if this trend would be obvious and significant in a larger and unselected material. If the possible effect of hypothermia in an unselected material is attenuated and the risk of complications increased, the net effect may be negative when broad indications are implemented. This underlines one of the arguments for performing a broad pragmatic trial on hypothermia after cardiac arrest.

The evidence for induced hypothermia

The main objectives with the HN Registry were to assess safety and outcome in an unselected cardiac arrest population admitted to intensive care. However, we thought that we could possibly gain information on aspects of the conduct of hypothermia and on basis of this generate hypotheses to test in randomised trials. There were no such indications obvious in the material.

We then decided to thoroughly assess the available evidence for induced hypothermia to see whether the entire concept should be challenged. There are two meta-analyses of the data published but they are not formal systematic reviews limiting their quality (Holzer et al. 2005; Cheung et al. 2006) and in addition there is one Cochrane review, but that analysis only considered some bias risk components and also included a trial with very high risk of bias in the main analysis, leaving another trial with less risk of bias outside the analysis (Arrich et al. 2009).

In summary, we found five randomised trials with a total of 478 patients. All of the trials were in a varying degree associated with substantial risk of bias. The most obvious problems were lack of proper randomisation, baseline differences and no reporting of important predictors of outcome, as for instance GCS at admission, hence baseline differences were in that aspect impossible to assess.

Moreover there was no standardisation of the withdrawal of intensive care. This fact in conjunction with an unblinded intervention may raise suspicion if withdrawal was informative or dependent of allocation group (Moran et al. 2006).

Also, in one of the trials the outcome was evaluated at hospital discharge instead of at six months, which is recommended (Arrich et al. 2009). Also, one of the two trials that constitute the fundament to the guidelines included an unadjusted interim-analysis and the other was terminated early without a predetermined power analysis reported and no adjustment of p-values, intervention effect estimates or confidence limits for early stopping (Haybittle 1971; Lan et al. 1983; Montori et al. 2005).

When pooling data from the two trials with the least risk of bias the point estimate was mildly in favour of hypothermia but the confidence intervals spanned both the potential for benefit and harm, thus the results being non-significant. When introducing all trials in the analysis, regardless of bias risk, the results for a benefit in mortality were significant in the fixed-effects model but not in the random-effects model. Due to the clinical heterogeneity between trials the fixed-effects model is problematic and a conservative approach with a random-effects model may be advisable.

When assessing the evidence according to GRADE we down-rated the evidence because of substantial risk of bias. We also judged the directness and generalisability of the evidence to be limited and mandating down-rating, since only 8 % of the screened patients were included and randomised in the largest trial and the rest of the trials also investigated various subsets of patients. Apart from the small and prematurely stopped trial by Laurent, the trials had a fair consistency, and therefore we did not rate down the evidence according to that aspect. However, the accrued data in the field could be regarded as scarce with not enough events to draw firm conclusions. Moreover, for the trials with least risk of bias the pooled results may be classified as imprecise, since the confidence intervals of the point estimates are wide and spanning no difference in risk or harm. However, judging the overall quality of the evidence we decided to keep a GRADE level of *low* instead of *very low*, which may have been the suggestion from a more conservative standpoint.

If there is overwhelming evidence (relative risk >2 or <0.5) from well performed observational trials with no obvious confounders, or very strong evidence of association (relative risk >5 or <0.2), as for instance with the effect of antibiotics, the GRADE level might be rated up with one or two levels, also in the absence of randomised trials. This might also be the case if there are obvious dose-response phenomena (Atkins et al. 2004). However this is not the case with the observational trials of hypothermia, which are small, single centre trials with many plausible confounders.

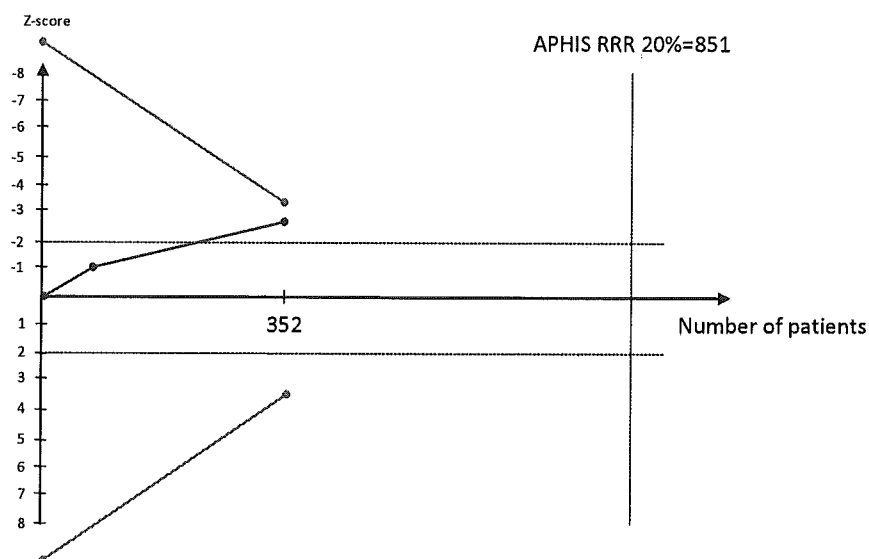
In the observational studies comparing induced hypothermia to standard intensive care, the pooled RR in the random effects model was 0.71; 95 % CI 0.56 to 0.89 indicating a somewhat larger effect on mortality than the estimated RR of 0.84; 95 % CI 0.70 to 1.01 from the randomised trials. Hence one could argue that the results of the observational studies support the conclusion that induced

hypothermia reduces mortality. However, this conclusion is only statistically significant when supported by the fixed effects meta-analysis of randomised trials and only if we include the quasi-randomised trial and the trials with high risk of bias. Therefore, one could just as well argue that the presently published trials of induced hypothermia possess nearly as high risk of bias as the inherent risk of bias present in the observational studies (Deeks et al. 2003). Instead of concluding that randomised trials and observational studies suggest equally beneficial intervention effects, the comparable intervention effects more logically suggest that they may be biased in the same direction.

The trial sequential analyses performed indicate that the accumulated trials do not convey a firm confidence in the evidence, as the trial sequential monitoring boundaries are not passed and the information size is not accrued. Only trials with low risk of bias should be included in meta-analyses and trial sequential analyses to ensure reliable data. Even if the trials on hypothermia had been free of bias and other problems, which they are not, the evidence would not have been enough. On the other hand, since the required information size is not yet reached, there is insufficient information to reject the risk reduction suggested by the trials. So, in a context evaluating the possibility of random error we still do not know if hypothermia is beneficial, harmful or neutral.

The two trials that have been the foundation of clinical guidelines reveal the same pattern as all the trials pooled, as is shown in figure 17. Here an a priori calculated relative risk reduction of 20 % is used.

Figure 17. Trial sequential analysis of HACA and Bernard-trials



Trial sequential analysis of mortality of two of the trials for hypothermia after cardiac arrest, which are the fundament for the guidelines. A priori required information size (APHIS) of 851 patients is based on a relative risk reduction of 20 %, a two-sided type-1 error of 5 %, a power of 90 % and a heterogeneity (I^2) of 20 %. The blue line is the cumulative Z-score and it has crossed the traditional level of significance of 5 % but it has not crossed the trial sequential monitoring boundary (TSMB) hence there is no firm evidence for a risk reduction. The APHIS is not yet reached and therefore we cannot rule out a relative risk reduction of 20 %.

Summarizing the evidence, the trials suggest a possible beneficial effect of hypothermia since the point-estimates are positive. However, this is not the case when pooling the two trials with least risk of bias and since they accordingly are of better quality, this estimate should have a higher weight when performing the overall judgement. Using GRADE methodology and trial sequential analysis the evidence is associated with substantial risk of systematic as well as random errors and we are led to conclude that the appropriate GRADE-level is *low*. Thus, the risk of spurious findings is non-negligible. The definition of GRADE level *low* is when further research is very likely to have an important impact on our confidence in the estimate of the effect and is also likely to change the estimate. In this sense clinical equipoise exists and new trials could and *should* be commenced (Freedman 1987).

Rationale for a randomised trial

As evident from above there is a need for new trials of induced hypothermia after cardiac arrest. The optimal delivery of temperature management is not known with respect to timing, duration, depth and rewarming rate. However, before commencing those trials, the obvious and fundamental question has not yet been answered: Is hypothermia at all an efficient intervention and, more specifically, is it efficient for all cardiac arrest patients admitted to intensive care for active treatment? This basic question must be pursued from the existing experimental studies, via the preliminary trials and the possible proof-of-concept trials all the way to a broad and pragmatic well-controlled trial with a low risk of bias, performed on a sufficiently large sample of cardiac arrest patients.

Rationale for comparing 33°C with 36°C: One aspect of the existing trials is that the patients in the control groups were allowed to follow their natural temperature course and had median temperatures between 37 °C and 38 °C with ranges of temperatures being definitely febrile. This has been highlighted as a possible obstacle when interpreting the results of the trials (Arrich et al. 2009). Was the reported risk reduction an effect of fever in the control group and the avoidance of fever in the intervention group, an effect of hypothermia in the intervention group or a combination thereof? It is not tested if strict normothermia is effective in reducing mortality and neurological impairment in humans, and if this strategy was equally beneficial as hypothermia, or even more beneficial, the patient group might be spared the additional risks associated with hypothermia.

Meanwhile, induced hypothermia has been introduced into clinical practice with a novel focus on temperature management, and there are indeed experimental and observational findings suggesting that hyperthermia may be detrimental after brain damage (Busto et al. 1987; Zeiner et al. 2001; Langhelle et al. 2003).

Accordingly, a reasonable way to proceed would be a trial of induced hypothermia with the comparator temperature close to normothermia. In case of a beneficial effect of hypothermia in such a trial, the implementation of hypothermia will be founded on more solid evidence, and in a utilitarian perspective more patients will receive hypothermia. In the case where a target temperature management of 36 °C is superior, the question whether normothermia is superior to standard care should also be considered. In case of a neutral finding we believe that this would probably stimulate further trials trying to elucidate the optimal target temperature after cardiac arrest rather than suggest succumbing to previous treatment traditions.

We therefore propose to compare temperature management at 33 °C with 36 °C. The admission temperature of cardiac arrest patients is between 35 °C and 36 °C (Zeiner et al. 2001) which is also confirmed in our registry data (paper II), but for patients with a cardiac cause of arrest it is 36.0 °C according to the HN registry. Thus, a comparator temperature of 36 °C would ensure that patients (at least as a median) were not imposed any temperature different to their admission

temperature and it would also see to it that patients will not encounter the possible risk of entering febrile temperature ranges.

Rationale for including patients with non-shockable rhythms: It is reasonable to assume that the potentially neuroprotective effect of hypothermia would be equal, regardless of initial rhythm inflicting the cardiac arrest. However, patients with cardiac arrest of non-cardiac cause with non-shockable rhythms have a very poor prognosis and thus we abstain from including this patient group. The baseline risk would have increased substantially and the sample size would have multiplied accordingly. In contrast, cardiac arrest patients with a cardiac cause of arrest and non-shockable rhythms have a fair prognosis, and when combining patients with cardiac cause of arrest with and without shockable rhythms we find a mortality of 44 % and a poor neurological outcome of 48 % in hypothermia treated patients in the HN Registry. These numbers combined with an *a priori* stipulated relative risk reduction of 20 % would be optimal regarding sample size.

Rationale for not including patients with in-hospital cardiac arrest: There are numerous reports indicating that in-hospital cardiac arrest is an entity very different from out-of-hospital cardiac arrest with different time aspects of the arrest, different chances to achieve ROSC and different long-term survival (Herlitz et al. 2000). There is for in-hospital cardiac arrest an underlying reason for the hospitalisation that will affect the natural course of the disease. Also, there are reports indicating a great difference in the reason for the observed mortality, with a neurological cause in the majority of out-of-hospital cardiac arrests (70 % for out-of-hospital vs. 30 % for in-hospital) (Laver et al. 2004; Olasveengen et al. 2009).

Rationale for duration of intervention: There are no conclusive studies indicating which duration of temperature control that has the highest yield after cardiac arrest. The previous randomised studies used 12 and 24 h respectively. Data from preliminary studies on stroke and traumatic brain injury indicate that the risk of adverse effects increases when induced hypothermia is applied for more than 24 h. Thus we have chosen a target temperature management maintenance duration of 24 hours (Polderman et al. 2009).

Rationale for mode of delivering the interventions: Reports indicate that both external and intravascular cooling methods are feasible and that they maintain temperature with high accuracy (Holzer 2008). There are no randomised studies so far indicating that any of the treatments is superior. To minimise economic burden we will allow trial sites to use temperature management system at their discretion. Each trial site will need to describe the temperature management before randomisation and will also need to report any amendments during the trial period.

Rationale for having a standardised withdrawal strategy: Prolongation of active intensive care will inevitably affect the chance of survival for a patient. This is especially true for cardiac arrest patients in a comatose state where the first days may look very pessimistic, while the subsequent outcome may be fair when

extending the observation period for a few days. A non-standardised approach to withdrawal of intensive care will thus create a great risk of bias in respect to physicians acting differently (deliberately or not) on prognostic data for patients in different allocation groups, since the intervention of inherent reasons could not be properly blinded. We have therefore chosen conservative criteria based mainly on motor response and SSEP. The biomarker NSE will be evaluated in a blinded fashion.

Rationale for mortality being the primary outcome: Based on previous trials the relative risk reduction was smaller for mortality compared to neurological function. When powering the analysis for detecting a plausible intervention effect on mortality, the primary secondary outcome (neurological function) will automatically benefit, increasing the chance of detecting a difference. Also, mortality is an outcome measure minimising evaluation bias and, compared to neurological function, it is not prone to competing risks (Moran et al. 2006).

Rationale for evaluating neurological outcome not only with CPC: Earlier trials have had neurological function assessed with the CPC scale as primary outcome. However, the CPC scale is crude, has a modest precision and may poorly discriminate between subtle neurological defects (Raina et al. 2008). Also, the CPC scale has often been presented in a dichotomous fashion, further hampering the modest precision. We therefore propose an evaluation of all patients with more specific tools as the Mini Mental Test and the IQCODE, but we will also present the CPC scale in its ordinal scale. Dedicated centres will also use more in-depth tests of memory and frontal lobe dysfunctions increasing the precision in how the groups may differ in neurological outcome. Here it is also imperative that a six-months perspective is exercised.

Limitations and strengths

Registry: There are numerous possible limitations with registries based on voluntary contribution of data. The sample populations registered may not be representative and thus may not provide reliable estimates of true implementation and outcome rates. There is a substantial risk of selection bias. However, we have stressed the importance of reporting all patients consecutively, but the registry will nevertheless encompass all the inherent problems with possible bias because of selection and confounding by indication. Also a great limitation is that the study material does not contain a comparator group, precluding the evaluation of direct effects of induced hypothermia. Furthermore, we do not know the background material from the pre-hospital setting or the emergency department and thus we are unable to integrate the studied sample into a full epidemiological context. On the other hand, the strategy with voluntary reporting has produced a unique material with a size allowing for relatively robust analyses. Moreover, we have a

high number of patients followed for at least six months and we believe that to be a great strength.

The inclusion of many centres and countries may increase the external validity of the findings, but a variation in treatment traditions and performance between registry sites may also have influenced the results. There is always a risk that Simpson's paradox obfuscate the results (Abramson et al. 1992). Moreover, it is always a problem to discriminate between causation and association in observational studies and non-apparent associations may be valid, even if we have failed to show statistically significant relationships, because of a too limited sample size (Altman et al. 1995). However, the findings could suggest possible associations, indicate in what areas a cautious approach should be recommended and illustrate where future controlled studies could be important. The data set is also of indisputable help when constructing new trials and choosing inclusion and exclusion criteria, stratification variables and deciding on end-points and outcome measures.

From a statistical point of view, a survival analysis might have been beneficial. An extended observation in the intensive care unit would yield a longer time to develop and register events. On the other hand the studied time at risk comprised only the intensive care stay, and for instance short durations in the unit could be attributed to both early death and early awakening and transfer to a ward, and therefore a strict time perspective might be difficult to interpret. Also, our data did not allow for strict survival analysis because of lack of exact time points for some of the covariates.

We have instead chosen to use logistic regression models. However we have used generalised additive models to allow for true continuous patterns rather than rigidly assuming linearity of continuous data, which we believe is a great strength. We have also introduced all available covariates giving all data elements a possibility to unveil their effect on or association with the chosen outcome.

Biomarkers of brain damage: This study comprises many of the limitations stated above. One of the main issues is that the care giving physicians were not blinded to the biomarkers of brain damage, as it was an open and unblinded study. Thus, the physicians may have acted on the serum levels creating bias of self-fulfilling prophecies (Nolan et al. 2008). A very important step in the validation of prognostic markers to assess the generalisability of the findings is to test the cut-off levels on a material different from the material where the cut-off levels were obtained. Ideally this should be done for all prognostic markers.

Systematic review: It might be that we did not find all trials in the field, but we believe that it is unlikely that there should exist trials that could possibly refute our results. We have contacts in all major centres investigating temperature control and after discussions with several experts we have not heard of any unpublished trials. There is one trial of in-hospital cardiac arrest but it is not yet finished. A great strength with our systematic review compared to previous ones, is that we

assessed all available subsets of bias risk and used the validated and comprehensive GRADE-methodology to set the findings in context and perspective. Also, trial sequential analysis may possibly be of value to the assessment of the available evidence as spurious findings from sparse data and cumulative meta-analyses may be a major problem (Borm et al. 2009; Brok et al. 2009)

Trial: We have tried to design a trial addressing the problems with bias in earlier trials. The main objection is the sample size that may be criticised for being too limited. This is always a risk, but we argue that the inclusion of 850 patients would increase the available information size with almost 200 %. We are also aware of the problem of a neutral trial. If we encounter this scenario we will conclude that we were unable to prove a relative risk difference of 20 %, in either direction. We will not claim that the interventions are equally efficient. If a smaller risk reduction is considered clinically significant a larger trial must be designed and performed. Finally, an individual trial is rarely the last piece in the puzzle but will convey a little bit of information, hopefully contributing to the available knowledge.

CONCLUSION

Approximately 50 % of out-of-hospital cardiac arrest patients admitted to intensive care for induced hypothermia survive to 6-months follow-up.

More than 90 % of surviving patients have a good neurological function when assessed with the cerebral performance category scale.

Only few patients remain in a comatose state at 6-months follow-up.

Time from arrest to initiation of induced hypothermia and arrest to achievement of a core temperature below 34 °C were not apparently associated to outcome.

Lower age, shorter time from arrest to return of spontaneous circulation, higher Glasgow Coma Scale score at admission, initial rhythm ventricular fibrillation, if the arrest was witnessed or not and angiography were all predictors of a favourable outcome. Asystole with no referral to angiography, the use of anticonvulsants and sustained hyperglycaemia were all predictors of an unfavourable outcome.

Neuron specific enolase predicted outcome better than S-100B

The overall rate of adverse events was high as expected in a severely critically ill population, but numbers were comparable with historical materials. Bleeding and infection were more common after invasive procedures, but these adverse events were not related to increased mortality.

In a systematic review we found that the accumulated evidence for the clinical use of induced hypothermia is of an overall low quality. The evidence is associated with substantial risks of systematic errors. The required information size allowing firm conclusions is not yet reached.

Clinical equipoise exists with regard to induced hypothermia and sufficiently large, broad and pragmatic randomised trials are needed.

We propose such a concept when evaluating two sub-febrile temperatures in the target temperature management trial (TTM-trial).

FUTURE ASPECTS

Paper VI in the thesis already lines out what we believe is the most important next step in temperature management after out-of-hospital cardiac arrest. There are different possible scenarios depending on what the findings will be from this trial.

If the intervention with a target temperature of 33 °C is superior to 36 °C, the use of induced hypothermia will rely on more solid evidence than what is currently present. However, in a true methodological sense the information gap will probably just be a little narrower. The two published trials with least risk of bias suggest a relative risk reduction of only 8 %, and thus the required sample size will increase accordingly. In a very conservative perspective the estimated diversity adjusted required information size could then be calculated to between 5000 and 7000 patients as the intervention effect then is smaller than earlier individual trials and *a priori* defined plausible effects suggest. A new trial sequential analysis incorporating information already present with the data from the TTM-trial would answer the question of how robust the present conclusions are to support the current guidelines.

If the results suggest a benefit of 36 °C the obvious next question would be if temperature management is at all superior to no temperature management.

With a neutral effect we will not be able to ignore the possibility that there could be clinically significant effects still not unveiled, since absence of evidence is not equal to evidence of absence (of an intervention effect) (Altman et al. 1995). However, we believe that such a finding would probably stimulate further trials designed to elucidate the optimal target temperature after cardiac arrest. The indicated relationship between febrile temperatures and a poor outcome may however be a relationship of mere association and not causation. The high temperatures associated with a bad outcome could be just a marker of a severely damaged brain.

The next step in the in-hospital management of OHCA patients, if the TTM-trial suggests benefit of 33 °C, will probably be to evaluate the time aspect of temperature management. A trial of 24 vs. for instance 72 hours would be a possible continuation. There are of course ethical aspects on this since many patients will spontaneously awake from unconsciousness long before 72 hours post arrest, if unsedated. Many patients will thus be forced to unnecessary sedation and mechanical ventilation. Also, prolonged hypothermia is associated with a higher incidence of adverse events.

Another interesting aspect of the optimal delivery of temperature management in case of positive findings is the speed of the rewarming process, where observational reports indicate a benefit of slow rewarming (Suehiro et al. 2003; Lavinio et al. 2007). Data from experimental studies, studies on traumatic brain injury and also data from cardiac surgery with extra corporeal circulation show somewhat conflicting results but there are indications of rebound fever, rebound increase in intracranial pressure and the début of seizures if the rewarming phase is too short (Suehiro et al. 2003; Lavinio et al. 2007). The proposed rate of 0.5 °C/h could be challenged with a much slower rate of for instance 0.1 °C/h. Again, this would imply prolonged temperature management with possibly increased risks for adverse events.

Our registry data did not show any association between a rapid cooling process and a subsequent good outcome. This was also confirmed by Austrian registry data (Sterz et al, oral presentation, 3rd International Hypothermia Symposium, Lund, 2009) A small German study reported an association between a rapid cooling and a good outcome, but this study was flawed on many levels hence strong inferences should be discouraged (Nilsson et al. 2009).

There will always be inherent differences in cooling speed due to body size, level of consciousness, severity of the insult, age and muscle mass why in-hospital slow or rapid cooling will be difficult to compare. However early versus late onset of hypothermia treatment may be studied, for instance comparing hypothermia started pre-hospitally versus in-hospitally in a randomised fashion. There is one trial demonstrating feasibility with pre-hospital cooling with cold saline (Kim et al. 2007). There is also a preliminary trial using nasal cooling pre-hospitally (PRINCE-trial, presented at the American Heart Association, Resuscitation Science Symposium, 2009).

Since 2009 the Hypothermia Network Registry has merged with the American Neurocritical Care Society and formed the International Cardiac Arrest Registry (INTCAR-www.intcar.org), where the concept from the HN Registry will be continued with a more detailed and comprehensive focus on prognostic factors and the possibility to predict outcome on different time points during the care of a cardiac arrest patient. In the work with predictive models we will use traditional statistical multivariate methodology, but hopefully we will also introduce new aspects of data analysis and prediction models. The ideal model would allow prediction of survival and survival with a good neurological outcome at all time points of care, using the information provided at the time being (from the acute emergency room admission through the first days of intensive care to the prolonged care for those not regaining immediate consciousness). As always with predictive models, they must be evaluated thoroughly before taken into practice, since they may establish self-fulfilling prophecies.

SWEDISH SUMMARY

Swedish abstract

Bakgrund: Nio av tio patienter som läggs in på sjukhus efter hjärtstillestånd utanför sjukhus är medvetslösa och behöver intensivvård. Dödligheten och risken för varaktiga hjärnskador är stor. Förhöjd kroppstemperatur under intensivvården är förenat med sämre överlevnad och hjärnfunktion. Nedkylning har i djurexperimentella och preliminära kliniska studier visat sig vara gynnsamt.

Metod: Information om hjärtstoppspatienter som behandlats med nedkylning har samlats in systematisk. Vi har bedömt överlevnad, neurologisk funktion, utförande av nedkylning, risk för komplikationer samt bakgrundsfaktorer och blodprover som kan förutsäga patienternas prognos. Vi har bedömt tidigare studier av nedkylning i en systematisk översikt och lagt samman data från dessa studier.

Resultat: Ungefär hälften av de som läggs in på intensivvårdsavdelning efter hjärtstopp utanför sjukhus är vid liv efter ett halvår och få har bestående allvarliga hjärnskador. Tid till start av nedkylning och tid att nå måltemperaturen var inte relaterat till patienternas prognos. Hjärnskademarkören neuronspecifikt enolas var bättre än S-100 på att förutsäga prognos. Lunginflammation och andra infektioner, kramper, hjärtrytmrubbningar och störningar i salt- och blodsockerbalans är vanliga efter hjärtstillestånd men endast långvarigt förhöjt blodsocker och behandlingskrävande kramper var förenat med ökad dödlighet. Risken för komplikationer efter införandet av nedkylning ter sig vara jämförbart med riskerna innan nedkylning infördes, men direkta jämförelser är osäkra. I den systematiska översikten ser vi att tidigare studier ej håller tillräckligt hög kvalitet för att vi skall kunna vara förvissade om nedkylningens effekter.

Slutsats: Ungefär hälften av hjärtstoppspatienterna som behandlas på intensivvårdsavdelning med nedkylning överlever och få har bestående hjärnskador. Kortare tid till start av nedkylning och måltemperatur är inte förenat med ökad överlevnad med god funktion. Bevisläget för nedkylning är relativt svagt och förnyade studier behövs. Vi föreslår och har fått etiskt godkännande för en stor studie av nedkylning med 850 patienter som drabbats av hjärtstopp utanför sjukhus. Vår förhoppning är att resultaten skall medföra att fler patienter får optimal vård.

Summary

Ett hjärtstopp är i de flesta fall en naturlig avslutning på livet. Ibland inträffar dock ett hjärtstopp oväntat och kanske alldeles för tidigt. De personer som förhoppningsvis befinner sig i närheten, räddningstjänst och ambulanspersonal samt vårdpersonal bör då försöka återupprätta hjärtaktiviteten med hjärt-lungräddning.

Under tiden då hjärtat står stilla kommer det inget syre eller några näringsämnen till hjärnan och efter några minuter börjar skador att uppstå. Hjärt-lungräddning med bröstkompressioner och lunginblåsningar ger en viss cirkulation med syresatt blod vilket kan förlänga den tid som hjärnan klarar sig utan skador, men det är avgörande att hjärtat kommer igång med egenaktivitet inom en inte alltför lång tidsrymd.

Ungefär en av tio personer som får hjärtstillestånd utanför sjukhus och där man påbörjar hjärt-lungräddning skrivs ut från sjukhuset vid liv. I det stora flertalet fall kommer hjärtat aldrig igång igen och många av de som får tillbaka hjärtaktiviteten under hjärt-lungräddning avlider under de första timmarna på sjukhus. Dödsorsaken är då ofta relaterad till sjukdomen i hjärtat.

Av de patienter som återupplivas och läggs in på sjukhus är ungefär en av tio vid medvetande medan den stora majoriteten är medvetslös på grund av syre- och näringsbristen i hjärnan. De som är medvetlösa behöver intensivvård med mekanisk ventilation med respirator och även annan understödjande behandling fram till dess att man kan bedöma ett eventuellt uppvaknande. Sjukdomen i hjärtat kan behöva åtgärdas akut med kranskärlsröntgen, ballongvidgning eller med operation, men då detta är genomfört är det ofta medvetlösheten som utgör det största medicinska problemet. Skador på hjärnan är ofta dödsorsaken för de som avlider dagar eller veckor efter hjärtstilleståndet.

I tidigare studier ser vi att ungefär en tredjedel till hälften av de som läggs in på intensivvårdsavdelning efter hjärtstillestånd utanför sjukhus lämnar sjukhuset vid liv. Ungefär två tredjedelar av dessa patienter som skrivs ut uppvisar helt normaliserad hjärnfunktion vid uppföljningsbesök efter ett halvår, men många har bestående skador som spänner mellan vegetativt koma och endast smärre minnesproblem.

Från så kallade observationella studier (studier där man inte tillför något eller ändrar på något i behandlingsstrategin utan bara observerar och beskriver skeenden) vet vi att höga kroppstemperaturer är förenat med ökad risk för bestående hjärnskador, och i djurexperimentella studier är det visat att undvikande av feber och även nedkylning till temperaturer under kroppens normaltemperatur kan vara skyddande för hjärnan.

I två kliniska försök, där man slumpmässigt (randomiserat) delade in patienter i en grupp som behandlades med nedkylning och en som fick gängse

normalbehandling, visade resultaten att nedkylning minskade risken för hjärnskada och också minskade risken för att avlida. Nedkylning är dock i sig behäftat med risker så som ökad infektionskänslighet, ökad blödningsbenägenhet, rubbningar i saltbalans och metabola störningar. Nedkylning kan också öka risken för hjärtrytmrubbningar och medför att patienterna behöver högre dos sömnmedel och längre respiratorbehandling. Nedkylningen kan på så sätt leda till förlängd intensivvårds- och sjukhusvistelse.

När de kliniska försöken hade publicerats 2002 var sjukhus i södra Sverige tidiga med att införa behandlingen i klinisk praxis och den första svenska patienten behandlades i Helsingborg i maj 2002. I samband med detta insåg vi värdet av att kontrollera och övervaka införandet i kliniken genom att följa alla patienter med hjärtstillestånd, registrera händelser under deras intensivvårdstid och följa upp dem i minst ett halvår efter insjuknandet. Då relativt få hjärtstoppspatienter behandlas på varje sjukhus valde vi att skapa ett större register för sjukhus i Skandinavien och Europa. Med många registrerade patienter fick vi ett material som möjliggjorde relativt robusta statistiska analyser. I en rapport från statens beredning för medicinsk utvärdering (SBU) förordades behovet av ytterligare kliniska prövningar, men om nedkylning användes kliniskt, utanför en kontrollerad prövning, rekommenderade de medverkan i registret. Våra två viktigaste mål var att utvärdera överlevnad och framförallt överlevnad med god neurologisk funktion samt att försöka finna samband mellan hur nedkylningsbehandlingen genomfördes och hur resultatet blev av behandlingen. Djurexperimentella studier har nämligen visat att tidig, snabb och förlängd nedkylning skulle kunna vara fördelaktig.

I arbete I beskriver vi ett patientfall där moderna behandlingsprinciper illustreras. Patienten fick mekanisk hjärt-lungräddning, blev nedkyld på akuten och fördes omgående till kranskärlsröntgen för ballongsprängning av ett igensatt kranskärl. Trots att hjärtstilleståndet var långt och att patienten fick upprepade hjärtstillestånd under röntgen kunde vi se ett gott slutresultat.

I arbete II beskriver vi en analys av de första knappt 1000 patienterna i registret som behandlades med nedkylning. Vi kunde påvisa att ungefär hälften av dessa patienter överlevde och att de i hög grad var neurologiskt återställda vid sex månader. Mycket få patienter befann sig i ett tillstånd av koma vid halvårsuppföljningen, vilket är viktig information. En farhåga tidigare var att behandling med nedkylning eventuellt skulle rädda en del patienter, men samtidigt skapa en större grupp patienter med permanent medvetslöshet; patienter som tidigare skulle ha dött. Vår slutsats blev att utfallet antingen är död eller levande med relativt god neurologisk funktion.

Vi fann också att faktorer runt behandlingen med nedkylning inte påverkade chansen för att överleva med god neurologisk funktion. Varken tid till det att nedkylningen påbörjades eller tid till att uppnå måltemperaturen påverkade utfallet. Det bör poängteras att detta är observationella resultat och därför kan man inte utesluta att det ändå finns skillnader.

I arbete III använde vi data från de patienter som registrerades från tre sjukhus i södra Sverige för att utvärdera om det fanns blodprover som kunde ge en prognos för om patienten skulle avlida eller få en permanent hjärnskada eller överleva med god funktion. Vi fann i det arbetet att ett ämne kallat neuronspecifikt enolas (NSE) ger mer information än ett ämne kallat S-100B. Slutsatsen här är också att ett blodprov i sig inte ger tillräcklig information för att säkerställa hur det skall gå för patienten. Provresultatet måste sättas in i ett större sammanhang och värderas tillsammans med information från andra undersökningar.

I arbete IV använde vi registerdata för att visa hur mycket komplikationer man kan räkna med i en grupp patienter som drabbas av hjärtstillestånd och behandlas med nedkylning. Komplikationer uppstår ofta hos hjärtstoppspatienter eftersom de är en mycket kritiskt sjuk patientgrupp. Komplikationerna kan vara relaterade till hjärtstilleståndet i sig, till bakomliggande sjukdomar, till intensivvården eller relaterade till specifika behandlingsstrategier, så som till exempel nedkylning. Vi kunde påvisa att komplikationer var vanliga, vilket man sett tidigare, men att endast höga blodsockernivåer och förekomst av behandlingskrävande kramper var relaterat till ökad risk för död. Blödning och infektion var relaterat till användningen av åtgärder som innebär att man behöver punktera blodkärl, men detta var inte associerat med ökad risk för död.

Efter att ha genomfört den första analysen av registerdata var vår förhoppning att vi skulle kunna få en indikation på vilken fördjupad studie som skulle vara ett logiskt nästa steg. Det var, som vi beskriver ovan, emellertid ingen skillnad i hur behandlingen med nedkylning förändrade sannolikheten för död eller hjärnskada. Vi valde därför att från grunden gå igenom bevisläget för nedkylning.

I arbete V gör vi en systematisk genomgång med sammanläggning av resultat från samtliga randomiserade studier av nedkylning. Vår slutsats är att bevisläget är relativt svagt och att det vilar på studier med för få patienter och där de studerade grupperna ej har varit representativa. Det föreligger därför en stor risk för att de resultat vi idag ser är behäftade med systematiska samt slumpmässiga fel och att vi riskerar att övervärdera behandlingseffekten. De patienter som ej fick nedkylningsbehandling i de tidigare presenterade studierna behandlades inte heller med temperaturreglering och uppvisade därför feber i hög grad. Då feber efter hjärtstillestånd är förenat med sämre överlevnad och sämre neurologisk funktion, kan man heller inte dra slutsatser om den påvisade effekten var en effekt av nedkylning eller helt enkelt en effekt av att patienterna inte hade feber.

Studierna om nedkylning har ökat intresset för hjärtstoppspatienter inom flera olika medicinska specialiteter vilket sannolikt lett till förbättrad vård. De behandlingsresultat vi ser i registerstudier och andra presenterade studier kan därför vara en effekt av detta förändrade intresse, med förbättrad hjärtvård i det akuta skedet, standardiserad och noggrann intensivvård och förbättrad prognostisering och uppföljning.

Trots att behandlingen i den djurexperimentella miljön, i inledande kliniska studier samt i observationella studier (från bland annat register) verkar gynnsam och lovande, kan vi idag inte med förvisning sluta oss till om behandlingen med nedkylning är gynnsam, neutral eller rentav skadlig. Vi föreslår därför att en förnyad större studie genomförs.

I arbete VI beskriver vi bakgrunden och designen av en sådan studie. Vi föreslår en studie där nedkylning till 33 °C jämförs med temperaturbehandling vid 36 °C under drygt ett dygn efter hjärtstilleståndet. Vi undviker med denna strategi feber i kontrollgruppen och kan utvärdera effekten av två reglerade temperaturbehandlingar. Studien beräknas innefatta 850 patienter i ett flertal länder i Skandinavien och Europa. Studien har etiskt godkännande och har fått projektbidrag från Hjärt-lungfonden.

Om slutresultaten visar sig vara gynnsammast för de som behandlas vid 33 °C så kommer behandling med nedkylning att vara betydligt bättre bevisad och fler patienter i världen kommer förmodligen då att erhålla behandlingen. Om behandling vid 36 °C visar sig vara bättre kan man framöver undvika många av de biverkningar som behandling vid 33 °C innebär, men dessutom bör man göra förnyade studier för att visa om behandling vid 36 °C är mer gynnsam än normal intensivvårdsbehandling. Om vi inte kan påvisa någon skillnad mellan behandlingsgrupperna bör nya större studier för att hitta den optimala behandlingstemperaturen genomföras.

Förhoppningen är att vi skall kunna klargöra flera av de frågetecken som finns avseende behandling och temperaturkontroll med nedkylning efter hjärtstopp vilket därmed på sikt förhoppningsvis kommer att medföra att fler patienter får en optimal vård.

ACKNOWLEDGEMENTS

This doctoral dissertation project has been made possible by generous grants from the Stig and Ragna Gorthon Foundation, Helsingborg; The Torsten Birger Segerfalk Foundation, Helsingborg; the Vera and Carl J. Michaelsen Foundation, Helsingborg; Gyllenstierna Krapperup's foundation, Nyhamnsläge and the Skåne county council's research and development foundation.

The Scandinavian Society of Anaesthesiology and Intensive Care and the SCCTG supported the development and funding of the Hypothermia Network.

The project outlined in Paper VI will be based on grants from the Swedish Heart and Lung Foundation, Stockholm, Sweden.

And now to something completely different. I would like to sincerely express my gratitude to everyone, in one way or the other involved in this dissertation project:

Hans Friberg, my friend and tutor (not the reversed order) who initiated it all in Helsingborg nine years ago. For all discussions and good laughs, at home and abroad. For you and the Friberg family: Salute!

Johan Herlitz, for being the foundation for my knowledge of cardiac arrest. It is a great honour to have you as my co-tutor. Thank you for providing an important link back to Gothenburg and for your first question: "What soccer team do you support?"

Jørn Wetterslev, after the mind opening lecture on trial sequential analysis in Copenhagen 2008 nothing has been the same! With a stringent academic aura, a generous and warm hearted mind and a response time measured in milliseconds you are an endless source of inspiration.

Malin Rundgren, you have been my supporting sparring-partner, always one step ahead and always prepared with some valuable advice. For this day!

Fredrik Nilsson, I have really appreciated our discussions on statistics and life in general. Even in absence of firm evidence I believe we have a significant friendship.

Kjetil Sunde, my foremost reviewer. We still have the best left. See you at Rockefeller din stabukk!

Michael Wanscher, for friendship and gentlemanship!

To my friends, co-authors and steering group fellows Sven-Erik Olsson, Fredrik Scherstén, Lennart Sandhall, Sten Rubertsson, Felix Valsson, Jan Hovdenes, Pascal Stammel, Richard Riker, David Seder, Kees Polderman, Tobias Cronberg, Janneke Horn, David Erlinge, Christian Gluud, Jesper Kjaergaard, Christian Hassager, Anders Aneman, Arthur van Zanten, Anders Perner and the 6S-team

Per-Olof Grände, the academic anchor and sail.

All my coworkers in Helsingborg and especially Frida Stafilidou, Heléne Petersson och Eva-Lott Nilsson.

Ulla-Britt, Anders and everyone at the outstanding hospital library of Helsingborg.

Elisabet Blank for always covering up when my administration lagged behind.

Christer Malmros, Annika Beskow and Per-Anders Larsson, for the important signatures, the scheduled time, and all cheers.

To Bert Gustavsson, Johan Malm and Lars Hård and all brainiacs at Expertmaker.

Göran Karlström and Bengt Mattsson for invaluable assistance in the beginning.

Everyone på Voss!

Helsingborg Chamber Choir for moments of ultimate resonance. Singet!

Henrik Béen and the wizard program from QlikTech.

Erik Lindeman. Friends.

My mother, Kari and Helena for reading the text.

And to my family: Mina älsklingar Carl, Gustav, Olof och Kari. Till mamma och pappa, Ulrika och Ninna, Zacke. Momma och moffa et al. Alla ni andra. Och en gång till: Kari!

Appendix

Members of the Hypothermia Network contributing to this project

Hospital, City (local investigator, patients enrolled)

DENMARK: Rigshospitalet, Copenhagen (M Wanscher); Aarhus University Hospital; Aarhus (HM Betsch); GERMANY: Charite Campus Virchow, Berlin (D Hasper); Evangelisches Krankenhaus, Bonn (M Födisch); ICELAND: Landspítali University Hospital (F Valsson); LUXEMBOURG: Centre Hospitalier de Luxembourg, Luxembourg (P Stammet); NORWAY: Buskerud Hospital, Drammen (S Balsliemke); Rikshospitalet, Oslo (J Hovdenes); Ullevål University Hospital (T Draegni); SWEDEN: Academic Hospital, Uppsala (S Rubertsson); Danderyd Hospital, Stockholm (E Oddby, J Lindahl); Falu Hospital, Falun (P Guldbrand, M Sellert-Ryding); Halmstad Hospital, Halmstad (J Undén); Helsingborg Hospital, Helsingborg (H Petersson, F Stafilidou); Jönköping Hospital, Jönköping (K Johansson); Centralsjukhuset, Karlstad (K Edqvist); Karlskrona Hospital, Karlskrona (S Juhl-Andersen); Karolinska Hospital, Solna, Sweden (Å Bengtsson); Kungälv Hospital, Kungälv, Sweden (R Zätterman); Lidköping Hospital, Lidköping (I Lindström); Lund University Hospital, Lund (M Rundgren); Malmö University Hospital, Malmö (T Karlsson); Mälarsjukhuset, Eskilstuna (A Lifbom); Vrinnevi Hospital, Norra Älvsborgs Läns sjukhus, Trollhättan-Vänersborg, Sweden (A G Larsson); Norrköping (R Svensson); Örebro University Hospital, Örebro (S Persson); Östersund Hospital, Östersund (M Schindele); Piteå Älvdal Hospital, Piteå (K Lindgren); Kärnsjukhuset, Skövde (B Gardell, A Paulsson); Södersjukhuset, Stockholm (S Forsberg); Sahlgrenska University Hospital, Östra, Göteborg (R Sarbinowski); Värnamo Hospital, Värnamo (A Dynebrink); Ystad Hospital, Ystad (U Hyddmark); UNITED STATES OF AMERICA: Maine Medical Center, Maine (R Riker, D Seder)

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