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Targeted temperature management and coronary care

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DOCTORAL DISSERTATION
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Out-of-hospital cardiac arrest is a devastating manifestation of coronary artery disease. For patients who are initially resuscitated and are admitted to an intensive care unit, mortality is high. Roughly half of all patients die, primarily due to neurological injury. In recent years, some improvement in outcomes has been seen, perhaps in some part due to interventions performed in hospital.

This thesis consists of four papers that examine different aspects of post-cardiac arrest care.

**Paper I** – A retrospective study of 84 patients with both in-hospital and out-of-hospital cardiac arrest examines the potential utility of Heparin-binding protein as a prognostic biomarker. HBP, an early marker of circulatory failure in sepsis was generally elevated after cardiac arrest, primarily very early after ROSC. Levels of HBP were associated with critical illness as assessed by the SOFA-score. HBP had a modest ability to predict neurological outcome.

**Paper II** – A post-hoc analysis of the TTM-trial studied the use of early coronary angiography for patients without ST-elevation on their initial ECG. Out of 939 patients included in the TTM-trial, 544 did not have initial ST-elevation. Among these patients 46% received a coronary angiography within 6 hours of arrest, obstructive coronary artery disease was common, as evidenced by 101 patients who received a percutaneous coronary intervention. In an adjusted analysis neither survival nor a good neurological outcome were associated with the use of an early coronary angiography. Results were similar in a propensity score analysis.

**Paper III** – Based on the hypothesis that targeted temperature management is primarily efficacious for patients with severe brain damage, paper III examined the relationship between the effect of targeted temperature management at 33°C and 36°C in relation to no flow-time. There was no significant interaction between no-flow time and temperature. Using adjusted predictions there was no evidence that a target temperature of 33°C was more effective for patients with long no-flow times.

**Paper IV** – There is conflicting evidence regarding if target temperature management to 33°C is associated with an increased risk of infections. Whether infections after cardiac arrest are associated with mortality is also debated. In paper IV, a post-hoc analysis of the TTM-trial, the incidence of infections was not significantly higher among patients treated at 33°C as compared to 36°C. However, there was a trend towards more infections in the 33°C group. In a multivariate analysis, infections...
Post-cardiac arrest care

Targeted temperature management and coronary care

Josef Dankiewicz
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Medical Faculty | Department of Clinical Sciences Lund | Lund University Anaesthesiology and Intensive Care

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“The natural cause of the human mind in certainly from credulity to scepticism” - Thomas Jefferson
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Original papers

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


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### Abbreviations

<table>
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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AUC</td>
<td>Area under the curve</td>
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<tr>
<td>CAG</td>
<td>Coronary angiography</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CPC</td>
<td>Cerebral performance categories</td>
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<td>CPR</td>
<td>Cardiopulmonary resuscitation</td>
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<tr>
<td>CRP</td>
<td>C-reactive protein</td>
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<tr>
<td>IABP</td>
<td>Intra-aortic balloon pump</td>
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<tr>
<td>ICD</td>
<td>Implantable cardioverter-defibrillator</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>IHCA</td>
<td>In-hospital cardiac arrest</td>
</tr>
<tr>
<td>ILCOR</td>
<td>International liaison committee of resuscitation</td>
</tr>
<tr>
<td>NSE</td>
<td>Neuron specific enolase</td>
</tr>
<tr>
<td>OHCA</td>
<td>Out-of-hospital cardiac arrest</td>
</tr>
<tr>
<td>PCAS</td>
<td>Post cardiac arrest syndrome</td>
</tr>
<tr>
<td>PCI</td>
<td>Percutaneous coronary interventions</td>
</tr>
<tr>
<td>PCT</td>
<td>Procalcitonin</td>
</tr>
<tr>
<td>PEA</td>
<td>Pulseless electrical activity</td>
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<tr>
<td>ROC</td>
<td>Receiver operating characteristic</td>
</tr>
<tr>
<td>ROSC</td>
<td>Return of spontaneous circulation</td>
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<tr>
<td>SOFA</td>
<td>Sequential organ failure assessment</td>
</tr>
<tr>
<td>SSEP</td>
<td>Somatosensory evoked potentials</td>
</tr>
<tr>
<td>VF</td>
<td>Ventricular fibrillation</td>
</tr>
<tr>
<td>VT</td>
<td>Ventricular tachycardia</td>
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</table>
Introduction

Historical background

In 1929, Dr. Hooker reported that he had successfully terminated ventricular fibrillation in the heart of dog by injecting potassium chloride followed by a calcium chloride solution. The dog survived, and was kept by Dr. Hooker as a pet. He called him “Knowsy”. Knowsy seemed a fitting name because the animal had been dead and knew what the other side looked like.¹

The description of cardiac arrest as death is not surprising considering that the concept of brain death has not been around for a century yet. And a century is a short time to redefine such a fundamental concept as death. With this in mind, one can understand that the cessation of cardiac function is still often considered a moment of death, if not always the moment of death.

The potential for reversal of a cardiac arrest is an exception, and in the vast majority of cases cardiac arrest constitutes a natural ending to life. Though CPR is often portrayed as a panacea in popular culture, its effectiveness is primarily seen in patients who suffer a cardiac arrest due to an ischemic event – a heart attack. It was for these patients; the golfer who suddenly collapsed, or the office worker who became unresponsive that Dr. Becker created a vision for how to perform resuscitation outside the hospital to save “hearts to good to die”. His claim that “any intelligent man or woman can be taught to do resuscitation” received considerable attention, primarily as it entailed that lay persons would surgically open the chest to perform internal defibrillation. He was vindicated within a decade with the advent of closed chest cardiac massage and external defibrillation developed by Kouwenhoven et al.² at Johns Hopkins hospital in Baltimore and, Zoll and colleagues in Boston.³

Twenty years earlier, the team of scientists working at Johns Hopkins had received a grant from The Consolidated Edison Group (ConEd) of New York to study the effects of electricity on humans. The grant was prompted by the occurrence of electrical accidents among line workers within the company who were unexplainably dying due to ventricular fibrillation. After studying rats and dogs, Kouwenhoven and colleagues noted that a second electrical shock - a counter-
shock, could restore the heart to a normal rhythm. This terminology is often still used, although the “original shock” from an electrical device is seldom present.

With the publication of a second paper in JAMA 1961 the group at Johns Hopkins presented a report of 161 patients treated with external cardiac massage. In this publication the authors, to a large extent foretold cardiac arrest research still being pursued today. For example, they described the need for 72 hours to pass before prognostication could be undertaken and the potential need for hypothermia, one of the subjects of this thesis, 55 years later.

Types of cardiac arrest

Definition

Cardiac arrest is the cessation of cardiac mechanical activity, confirmed by the absence of a detectable pulse, unresponsiveness, and apnoea (or agonal, gasping respirations). A cardiac arrest may be reversible by a prompt intervention but will lead to death in its absence. Whether the cardiac arrest is reversible or not is of course unknown when resuscitation is begun and thus the Swedish Cardiac Arrest Registry (SCAR) use a somewhat simpler definition. They define a cardiac arrest as any case where CPR has been attempted by medical personnel, other emergency services, or a witness to the event.

Location

There are several major differences between cardiac arrests that occur inside the hospital walls and those that occur outside. An in-hospital cardiac arrest (IHCA) usually means that there is access to medical practitioners with experience in advanced resuscitation techniques, whereas an out-of-hospital cardiac arrest (OHCA) usually entails a significant response time for emergency services. Beyond the time to an initial response, the biggest difference between these two types of arrest are the physiological processes that lead to them. Whilst OHCA is usually caused by an ischemic event, IHCA can be associated with other conditions such as respiratory failure or sepsis. As the causes and response differ, so do the outcomes and the mode of death. In OHCA some arrests take place at home and others in public places. Due to faster response times, the availability of more people to perform bystander CPR, and potential access to an automated external defibrillator (AED), cardiac arrests in public locations have a better prognosis. In fact, rapid
Defibrillation by nonmedical personnel can achieve survival rates of more than 50% in some public places, such as casinos.  

**Initial rhythm and symptoms**

Cardiac arrests are usually separated by the different arrhythmias recorded on an initial ECG (electrocardiogram), most commonly this is recorded on a defibrillator. Thus the initial rhythm is the first recorded rhythm, as it is impossible to acquire information about the true initial rhythm (patients with ICDs being the exception). The possible categories are ventricular fibrillation (VF), ventricular tachycardia (VT), pulseless electrical activity (PEA) or asystole. VF and VT are grouped together as shockable rhythms, PEA and asystole are unshockable rhythms.

Though the initial rhythm has strong prognostic implications, both with regards to possible return of spontaneous circulation (ROSC) and long-term survival, the rhythm is not constant. Studies show that most cardiac arrests start off as VF and then devolve into asystole. A heart with VF that is shocked might result in PEA and PEA might convert to VF after chest compressions. Further, PEA may itself be difficult to differentiate from a severely shocked state with cardiac activity but without palpable pulses (pseudo-PEA).

If a non-shockable rhythm is converted to a shockable one this is associated with an improved probability of survival. Conversely a patient who is in a non-shockable rhythm after twenty minutes of resuscitation has a very poor prognosis.

Though cardiac arrest is often used with the qualifier “sudden”, i.e. sudden cardiac arrest (SCA), studies have shown that about half of all patients experience some type of warning symptoms during the weeks before cardiac arrest. The most common symptoms resemble those of a myocardial infarction and include chest pain, dyspnoea and syncope or palpitations.

**Aetiology**

The majority of all cardiac arrests are of cardiac origin, with the most common subtype being ischemia related. Malignant arrhythmias (VF/VT) can develop either during the acute phase of myocardial ischemia, after plaque rupture and thrombus formation in a coronary artery, or after reperfusion. Another common cardiac cause of arrest is an arrhythmia caused by chronic myocardial scarring after infarction. The scar tissue, especially in combination with heart failure and decreased left ventricular ejection fraction forms a substrate for an electrical disturbance (Figure 1). In addition to these more common causes, cardiac arrest can occur due to genetic ion-channel abnormalities and cardiomyopathies.
In the initial version of the “Utstein style” guidelines for uniform reporting of data from out-of-hospital cardiac arrest, an arrest was presumed to be of cardiac aetiology if there was no other obvious explanation (drug overdose, suicide, drowning, asphyxia, exsanguination, cerebrovascular accident, subarachnoid haemorrhage, and trauma). In the most recent version however this category has been changed to a “medical cause of arrest”, which encompasses a presumed cardiac aetiology and other medical causes such as pulmonary embolism and anaphylaxis. A cardiac cause is now considered a sub-category of “medical-cause”. Other obvious causes (drug overdose, suicide, etc.) are categorised as non-medical.

Figure 1. Pathophysiology of life threatening tachyarrhythmias in coronary artery disease. Reproduced with permission from: Implantable cardioverter-defibrillators after myocardial infarction. Copyright Massachusetts Medical Society
Epidemiology of Cardiac Arrest

Globally, cardiovascular disease is the most common cause of death and cardiac arrest accounts for approximately half of all cardiovascular deaths.\textsuperscript{21,22} Every year approximately 300 000 Europeans suffer an out-of-hospital cardiac arrest. In 2014, 5127 cardiac arrests were reported in the Swedish cardiac arrest registry, this translates to an incidence of 54 per 100 000 persons.\textsuperscript{23} Internationally rates of cardiac arrest vary between 50 and 100 per 100 000 in the general population.\textsuperscript{24-26} Reported incidence rates of IHCA vary considerably between hospitals but usually range between 3-5/1000 admissions.\textsuperscript{27}

OHCA occurs predominantly in men. Other risk factors include age, previous coronary events, a low left ventricular ejection fraction and a prior cardiac arrest. Though these risk factors are well studied, cardiac arrest is still difficult to predict. The reason for this being that the vast majority of cases occur in the general population rather than any of the known at-risk categories (Figure 2).\textsuperscript{28}

![Figure 2. Estimates of incidences and absolute numbers of sudden cardiac deaths. Adapted from Myerburg et al.\textsuperscript{28}](image-url)
Resuscitation of cardiac arrest

In 1991, the concept of “Chain of survival” was proposed by Cummins et al. and is now a well established part of CPR-instruction and resuscitation science. Using a chain as an analogy for the concept of resuscitation stresses the fact the the resuscitation is only as strong as its weakest link. The original four parts of chain of survival were:

- Early access: Which implicitly includes early recognition as well as prompt access to emergency services.
- Early CPR: Preferably immediate bystander CPR by trained citizens, as reliance on CPR by a medical provider is often too late.
- Early defibrillation: By a bystander, using a public access automatic external defibrillator or as soon as possible by emergency services.
- Early advanced care: by providers trained in advanced cardiac life support (ACLS), access to adrenalin and antiarrhythmic drugs, and knowledge of advanced airway management.

With increased focus being placed on interventions and care performed in hospitals the updated chain is now presented with “post resuscitation care” as the final link. Additionally, to place more importance on the early recognition of critical illness and angina for prevention of cardiac arrest, the first link was modified in 2005.

Figure 3. Chain of survival
Though the chain of survival is at the core of resuscitation guidelines the quality of evidence of the different components differ. That early recognition leads to increased survival is well established, as is the increased survival associated with bystander CPR and early defibrillation. However, neither the concept of advanced cardiac life support (ACLS) as a whole, nor the individual components that comprise the bundle of care that is recommended have any strong evidence to support them.

Interestingly, though time to defibrillation has remained relatively unchanged over the last decades, one-month survival in the Swedish cardiac arrest registry has increased from 4.8% in 1992 to 11% in 2014. Although the main driver behind this improvement is probably increased rates of bystander CPR, this does not explain all of the increase. Rates of survival to hospital admission have for example not increased to the same degree as the rate of one-month survival, this points to the fact that modern intensive care, acute coronary interventions and management of the post-cardiac arrest syndrome have some effect on outcomes.
The post cardiac arrest syndrome

After the development of treatments to ‘reanimate’ patients suffering cardiac arrest came the realisation that survivors suffered a new type of disease process that was independent of the factors causing the cardiac arrest, but associated with global ischemia and reperfusion caused by resuscitation in itself. This new nosological concept was described by Negovsky and colleagues in a series of experiments during the 1970s and was dubbed the post-resuscitation disease, though it is also commonly known as the post-resuscitation syndrome or post-cardiac arrest syndrome (PCAS). PCAS is characterized by multi-organ failure and neurological damage. Though the pathophysiological processes associated with ischemia and reperfusion can be seen as separate from the factors that contribute to a cardiac arrest, in clinical reality they overlap and are difficult to distinguish from one another. The current definition of PCAS by ILCOR, therefore includes the following factors:

- Post-cardiac arrest brain injury
- Post cardiac arrest myocardial dysfunction
- Systemic ischemia/reperfusion response
- Persistent precipitating physiology.

The Brain

Ischemia

The awake brain accounts for about 15% of total metabolism in the body, though it only constitutes 2% of body weight. Most other tissues in the body can survive without oxygen for prolonged periods of time by utilizing an anaerobic metabolism. The brain however is almost entirely dependent on glucose and oxygen to produce high-energy phosphates due to the high metabolic demand of the neurons. Supporting glial cells have a much lower metabolic demand. As the demand for membrane transport of sodium and calcium out of the cell, and potassium to the cell interior increases each time a neuron fires, brain metabolism can double during high activity. Cessation of blood flow leads to almost completely depleted stores of ATP within 2 to 3 minutes of the onset of complete ischemia. However loss of consciousness occurs within 10 seconds and electroencephalographic (EEG) activity becomes isoelectric within 20 seconds. Within 2 minutes of cardiac arrest, interstitial potassium begins to increase as membrane transport can no longer be upheld. This leads to cell depolarisation and a large influx of calcium, chloride and sodium. A large release of neurotransmitters (especially glutamate), coupled with the anoxic
depolarisation of the neurons may cause excitotoxicity. If these mechanisms are not halted by restored perfusion, the process devolves into cell death.

After return of spontaneous circulation

If perfusion of the brain is restored within 3 to 12 minutes of cardiac arrest, the ion-gradients can be largely restored within some minutes. In this early reperfusion phase there is a surge of oxygen radical production and release of iron from storage proteins. Neurons respond through increasing transcription of antioxidant mRNA and mRNA associated with membrane repair, a process that preferentially occurs in neurons with selective vulnerability, for example in the hippocampus. However, in the post resuscitation phase, translation is depressed and thus the increased transcription does not result in the necessary proteins. Therefore, cell death might continue after circulation has been restored, both through necrosis and apoptosis. One factor that can mitigate depressed translation is growth factors such as neuronal growth factor and IGF-1, but these cell pathways have yet to result in any specific treatment of post ischemic neuronal damage.49

The cellular processes described above result in brain injury that accounts for 50-70% of all in-hospital mortality after out-of hospital cardiac arrest. All neuronal death after cardiac arrest is not instantaneous, instead delayed neuronal death plays a significant part in the final extent of neuronal damage. This prolonged period of time suggests that the brain might be amenable to neuroprotective therapies; a therapeutic window.

Beyond the cellular response to ischemia and reperfusion the cerebral circulation is also affected after cardiac arrest, which can result in secondary ischemia and injury. The cerebral microcirculation can be impaired as evidenced by the ‘no-reflow’ phenomenon, in which parts of brain are not perfused despite adequate cerebral perfusion pressure. ‘No-reflow’ has been attributed to microvascular thrombosis and experimental studies have suggested an improved cerebral circulation after treatment with tissue plasminogen activator (tPA). However this did not translate into a survival benefit, or improved neurological function in a clinical trial on tPA in humans.53

Normal autoregulation of cerebral blood flow keeps flow constant within a wide range of arterial pressures, but in the post-cardiac arrest phase perfusion is first hyperaemic and in the sub-acute phase cerebral vascular resistance is increased resulting in decreased cerebral blood flow. Another mechanism which can cause further cerebral damage is oedema, though this occurs to a lesser extent, and in clinical practice doesn’t warrant invasive monitoring of intracranial pressure.55

These pathways to cerebral injury can be exasperated by hypotension, hypoxemia, seizures, pyrexia, hyperglycaemia and electrolyte abnormalities, all of which are
common after cardiac arrest. A common factor for all these potentially deleterious elements is that data on optimal treatment and target values are lacking.

What is known however, is that hyperglycaemia, seizures and fever are associated with a poor neurological outcome, whether it follows that treatment of these conditions is beneficial is nevertheless unproven. With glucose control for example there are numerous studies showing a relationship between hyperglycaemia and poor outcomes,\textsuperscript{56,57} one small randomized trial that showed no benefit of strict glucose control,\textsuperscript{58} and mixed results from other intensive care settings.\textsuperscript{59,60} Seizures occur in 18-25\% of patients after cardiac arrest, increase cerebral metabolism\textsuperscript{61,62} and are associated with a very poor prognosis. Treatment of seizures with antiepileptic drugs is currently recommended in guidelines although randomized trials have not shown improved neurological outcomes.\textsuperscript{63,64}

An elevated body temperature is common after cardiac arrest and multiple studies have shown an association between an increased body temperature and poor neurological outcome.\textsuperscript{55,66} The mechanism that precipitates an increased body temperature after cardiac arrest is not entirely clear, but probably multifactorial. Initially pro-inflammatory cytokines released after reperfusion might affect the hypothalamus and induce an increased temperature. Elevated temperature might also be due to direct ischaemic damage to the thermoregulatory centre in the preoptic nucleus of the hypothalamus.\textsuperscript{67} Infection might also cause an increased body temperature as both aspirations and translocation of gut bacteria can occur.

Animal studies have shown that an elevated body temperature can worsen outcome by exasperating inflammatory cascades,\textsuperscript{68} increasing neuronal excitotoxicity\textsuperscript{69} but also directly induce neuronal injury if temperatures are above 40°C for a prolonged period of time. In humans however it remains to be proven conclusively if an elevated body temperature is merely a marker of brain damage, or an additional cause of neuronal damage.\textsuperscript{67}
The Heart – post cardiac arrest myocardial dysfunction

Ischemia
Immediately after cardiac arrest antegrade flow through the aorta and pulmonary circulation continues for 30-60 seconds due to the pressure gradient between the aorta and the right side of the heart, and the gradient between the pulmonary artery and the left atrium, respectively. As arterial pressure falls, sympathetic tone increases because of baroreflex withdrawal and release of endogenous catecholamines, thus increasing the duration of antegrade flow. When antegrade flow ceases and coronary blood flow stops however, levels of creatine phosphate and ATP decrease, and lactate increases. This process leads to myocardial dysfunction though progressive thickening of the left ventricular wall and a resistance to defibrillation.

After return of spontaneous circulation
A depressed cardiac function is common after cardiac arrest and contributes to the high mortality for initial survivors. Studies have shown that a significant portion of patients die due to cardiac causes, however estimates vary considerably. The lack of a clear definition of a cardiac death and a clear distinction against multi-organ failure makes exact figures difficult to ascertain.

Cardiac function and blood pressure can vary between cardiogenic shock and states with relatively normal function. The degree of post-cardiac arrest myocardial dysfunction tends to increase with longer durations of ventricular fibrillation, but both endogenous and iatrogenic catecholamines contribute the hemodynamic state after arrest.

If an acute coronary syndrome is not present, coronary blood flow remains essentially unaffected. Despite this, post-arrest myocardial dysfunction is associated with a reduced ejection fraction and global myocardial dysfunction, rather than regional hypokinesis. This pattern, taken together with reversibility indicates that post-global ischemia myocardial depression is primarily a stunning phenomenon. Kern and colleagues demonstrated this in an experimental swine model which showed both systolic and diastolic dysfunction after 15 minutes of untreated cardiac arrest, full recovery was seen after 48h. In clinical practice this pattern is often less obvious due to concomitant disease states such as coronary occlusions, infections and treatment with inotropic agents.
Systemic ischemia/reperfusion syndrome

CPR is not an adequate substitute for a normal beating heart. During cardiac arrest the systemic oxygen delivery is halted and a metabolites are not removed at the required rate. An oxygen debt is created which leads to endothelial activation and a systemic inflammatory response. As in sepsis an activation of immunological and coagulation pathways lead to a physiological state with vasodilation, increased vascular permeability and increased risk of multi-organ system failure. The similarities between the systemic ischemia/reperfusion syndrome and a septic state were studied in the seminal paper in 2002 by Adrie and colleagues in which they showed that the dysregulated production of cytokines after cardiac arrest (IL-6, IL-8 and IL-10 among others) was similar to the immunological state in septic patients.

The stress caused by ischemia and reperfusion is associated with a relative adrenal insufficiency and levels of cortisol have been shown to be lower among patients who die from an early shocked state. As in sepsis this has been deemed a potential target for treatment. Two randomized controlled trials have shown a beneficial effect of a treatment protocol that includes cortisone, but result have yet to be corroborated by international trials. In the mean time clinical practice remains to treat hemodynamic instability and counteract any associated pathologies as soon as possible.
Intensive Care after cardiac arrest

Patients who suffer very short cardiac arrests, i.e. those who are defibrillated within a few minutes, by a bystander in a shopping mall or in the coronary care unit may not require intensive care. But when the period of global cerebral ischemia is too long, as is the case for most patients who suffer an out-of-hospital cardiac arrest, unconsciousness ensues. With unconsciousness and coma comes an inability to protect the airway and impaired breathing, thus necessitating mechanical ventilation, sedation and intensive care.

The general management of cardiac arrest patients does not differ significantly from other severely ill patients. There is a need for close attention to oxygenation, blood pressure and basic body functions. However, there are some areas that warrant special consideration after cardiac arrest.

Targeted Temperature Management (TTM)

The deep tissues in the human body, maintain a more or less constant temperature. In contrast, skin temperature can vary and plays an important part in thermoregulation. Therefore, reliable assessment of temperature is made by measuring the "core" temperature - in the deep tissues. In clinical practice this is accomplished by using temperature probes in the bladder or in the oesophagus.

During normal homeostasis the core temperature remains constant within ±0.6°C, when an individual is not febrile. On the other hand the average normal temperature is difficult to define as humans have a range of normal temperatures, between 36.0°C and 37.5°C. 42

Hypothermia

Early work on hypothermia and studies on “refrigeration of the human brain” were performed by Tempel Fay in the 1940s, the primary goal being treatment of cancer. 81 Later, in the early 1950s Bigelow performed animal experiments on the effects of hypothermia during cardiac surgery, which showed that thoracotomy at 20°C was a “safe procedure”. 82 During this period, reliable models of cardiac arrest were lacking but Rosomoff and Holaday showed that cerebral oxygen consumption and blood flow decreased with the use of hypothermia. 83 Williams and Spencer published the first description of the use of hypothermia for cardiac arrest that occurred outside the operating room. 84 In their case series of four patients, two of which were children, all patients survived without significant impairment.

Due to a concern that hypothermia at 30°C led to a high risk of arrhythmias (most significantly ventricular fibrillation), human research on hypothermia was largely
abandoned during the 1960s and 1970s. Although in the 1980-1990’s interest was rekindled and number of important papers studied different variations of pre-arrest, intra-arrest, and post-arrest cooling. Notably, Busto et al. showed that the amount of neuronal damage in the rat brain decreased for every degree the body temperature was lowered intra-arrest. Other work also showed that post-arrest cooling was beneficial. The mechanism by which hypothermia blunts neurological damage is not completely understood, but a lower temperature probably effects multiple pathways: decreasing neuronal metabolism and inflammation, modifying gene expression and, lessening calcium overload and excitotoxicity.

Clinical evidence
Beyond experimental evidence for a beneficial effect for hypothermia, retrospective clinical studies showed an association between hyperthermia and a poor outcome. Also adding support to the beneficial effects of hypothermia were numerous case reports of successful prolonged resuscitations of cardiac arrest victims with accidental hypothermia. With this framework of ideas backing the use of hypothermia in humans, two randomized trials were performed in 2002. Bernard et al. included 77 patients resuscitated from ventricular fibrillation or pulseless ventricular tachycardia who were allocated to 33°C or standard care based on odd or even days. The hypothermia group showed improved neurological outcome, but there was no difference in mortality between groups. The HACA-trial randomized 275 patients to 33°C or normothermia and showed both improved neurological outcomes and improved survival in the hypothermia group.

Following the two original randomized trials on hypothermia for cardiac arrest, temperature management was widely adopted. However, a review, using the GRADE-methodology found that both trials were at a high risk of both systematic and random error. After the review, a randomized trial was conducted by Nielsen et al. – the TTM-trial. The trial randomized 939 patients to 33°C or 36°C, and notably included patients with both shockable and non-shockable rhythms. The primary outcome, death at the end of the trial, did not differ between temperature groups.
Complications

Hypothermia is associated with a myriad of physiological changes including shivering, bradycardia, an increased risk of infection, electrolyte disorders, coagulopathy, and a decreased drug metabolism. As targeted temperature management after cardiac arrest does not aim for a temperature below 32°C physiological changes are not as pronounced as in experimental conditions or accidental hypothermia. Moreover, in the randomized trials on hypothermia for cardiac arrest the “classical” side-effects of hypothermia such as bleeding and infections have not been significantly more common in the hypothermia group. In fact, early rewarming due to adverse events is relatively uncommon, with arrhythmias being the most common reason.

Acute Coronary Syndromes

Patients who suffer an acute coronary syndrome, but not a cardiac arrest, benefit from coronary angiography and PCI. There is a survival benefit both for patients with non-STEMI acute coronary syndromes (NSTEMI) and for patients with ST-elevation myocardial infarction (STEMI). Both NSTEMI and STEMI are common causes of cardiac arrest. When the initial post-resuscitation ECG shows STEMI, immediate coronary angiography and primary PCI is recommended.

Cardiac arrest patients were not included in the randomized controlled trials that compared thrombolysis to primary PCI. Despite this fact, it seems reasonable to assume that primary PCI is the treatment most likely to improve electrical stability.
and haemodynamics. Especially taking into account the SHOCK-trial, which showed primary PCI to be effective in patients with cardiogenic shock.\textsuperscript{103}

In patients who present after cardiac arrest without ST-elevation on the ECG the decision to perform immediate coronary angiography and primary PCI is not as well established, despite the fact that about a quarter of these patients will have acute occlusions.\textsuperscript{104,105} Coronary angiography, a relatively safe procedure, still carries the risk of acute kidney injury and bleeding. Additionally, culprit lesions are not always obvious, raising the possibility of an “unnecessary” acute revascularisation and possible complications associated with PCI.

However, it stands to reason that if one were able to predict which patients without ST-elevation had acute occlusions, they would benefit from acute revascularization. Unfortunately, cardiac troponins provide little guidance in this context, but the presence of a ventricular fibrillation and antecedent chest pain is associated with an acute occlusion.\textsuperscript{106,107} In lieu of a randomized trial, current guidelines recommend considering emergent cardiac laboratory evaluation in patients with the highest risk of a coronary cause.\textsuperscript{61,108} Patients who do not receive an emergent evaluation should receive a coronary angiography later during the hospital stay.
Prognostication

Patients who are treated in an intensive care unit after cardiac arrest are initially comatose. Either due hypoxic brain damage, sedative drugs, or a combination of both. Most patients wake up within 4.5 days\textsuperscript{109,110} but awakening has been described much later.\textsuperscript{111}

To predict which patients will wake up is important to avoid expensive and traumatising futile care. Although early prognostication can provide valuable information to the the treating physician, prognostication is predominantly used to assess those patients who remain comatose after several days. In these patients a decision whether to continue intensive care or to deescalate needs to be made. The implications of a false prediction of a poor outcome are immense, which emphasizes the need for rigorous standards.

To avoid false predictions of a poor outcome therefore necessitates a multimodal strategy based on demographic and cardiac arrest parameters, a clinical neurological exam, biomarkers, neuroimaging and neurophysiological tests. This approach is also recommended by current guidelines. The guidelines also recommend waiting for at least 72h after ROSC, or rewarming, to perform prognostication.\textsuperscript{61,112}

\textit{Pre- and peri-arrest factors}

Though many demographic and peri-arrest factors are well established predictors of outcome at the population level, they are generally not sensitive enough to be used for individual outcome prediction. Apart from age and presenting rhythm, the most commonly used parameters in clinical practice are; time to start of CPR (no flow-time) and the time from CPR until return of spontaneous circulation (low flow-time).

\textit{Clinical Neurological Exam}

A requirement for a reliable clinical examination in a patient who remains comatose, is that adequate time has passed to allow for clearance of any sedative drugs. The exam includes evaluation of brain stem functions and corneal reflexes, these “basic” functions are typically the ones that are regained first.

Coma depth is assessed by gauging the patients’ response to pain. An extensor response or a lack of response to pain on day 3 after cardiac arrest was previously considered a satisfactory criterion for prognosticating a poor neurological outcome\textsuperscript{113,114}, although a study by Rosetti et. al of patients managed with TTM showed a false positive rate of 4%.\textsuperscript{114}
Another grave prognostic clinical sign is a generalised myoehloconic state early after cardiac arrest. If myoclonic jerks are present in both the face and limbs during the first day, recovery is extremely uncommon.115

Neurophysiological tests and neuroimaging

The two neurophysiological tests that are most commonly used in clinical practice are somatosensory evoked potentials (SSEP) and electroencephalography (EEG). EEG can be performed as a full study at one time-point or continuously (cEEG), either a full montage or a simplified form with fewer channels, can be used.

SSEPs test the afferent sensory pathways and are studied by stimulating the median nerve and registering the responses in the contralateral sensory cerebral cortex (N20). The absence of a response bilaterally is a strong predictor of a poor neurological outcome.116 Though the number of false positive cases are few, the utility of SSEP is limited primarily by its poor sensitivity.

In the setting of cardiac arrest EEG is routinely used to identify patterns associated with a poor outcome such as very low-voltage EEG or a suppression-burst pattern after 24h.117 If electroencephalographic status epilepticus is present during TTM or early after rewarming, this is usually indicative of poor outcome.118 However, if the status epilepticus evolves from a continuous EEG the prognosis is somewhat better.119 The main limitations of EEG as a prognostic tool are that it is influenced by sedation, and that there is significant inter-rater variability. Another limitation is that the EEG is in effect a “snapshot” of the brain. To some extent this can be counteracted by the application of a cEEG.120 Despite its drawbacks, EEG is the most commonly used prognostic tool.121

The use of a brain computed tomography (CT) after cardiac arrest has several benefits. Firstly, it rules out other causes of cardiac arrest and coma such as a subarachnoid- or intracerebral haemorrhage. A brain CT can also be used as a prognostic tool in its own right, but there is no consensus on when to perform it. If there is effacement of the cortical sulci and generalized swelling, prognosis is poor.122 Another sign of a poor prognosis is a loss of differentiation between the grey and white matter.123 Magnetic resonance imaging of the brain is yet another possible adjunct in the assessment of prognosis, ideally performed at 3-5 days after arrest and clearly superior to CT with regard to visualisation of hypoxic damage. Diffusion weighted imaging (DWI) is the modality of choice when gauging hypoxic damage and has been shown to improve the sensitivity of a clinical examination.124

Biomarkers

A general definition of a biomarker is "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".125 In the context of
prognostication after cardiac arrest biomarkers are typically biological substances measured in blood. Neuron specific enolase (NSE) and S100b are the two biomarkers most commonly used to assess the grade of anoxic brain injury and are released following injury to neurons and glial cells, respectively. Of these two NSE is the most established, and also the single biomarker recommended in current guidelines.\textsuperscript{61} As levels are influenced by storage and the choice of assay,\textsuperscript{126} no specific cut-off level is mentioned, but levels over 60 mcg\textsuperscript{-1} at 48-72h after arrest are rarely associated with a good outcome.\textsuperscript{127}

NSE, which is a 78 kDa dimeric glycolytic enzyme is also found in neuroendocrine cells and in red blood cells. It is thus also released when haemolysis occurs. Despite these drawbacks a recent large study showed that NSE values at 48h and 72h after arrest had a high predictive value for a poor outcome. In this study where all samples were batch-analysed and samples with haemolysis were omitted, no values higher than 50 mcg\textsuperscript{-1} were compatible with a good outcome.\textsuperscript{128}

Perhaps the most important limitation of brain-derived biomarkers is that patients that die from other causes are not identified. Therefore, efforts have been made to use other biomarkers associated with an inflammatory response, such as procalcitonin,\textsuperscript{129,130} or combinations of biomarkers to yield increased discrimination between good and poor outcomes.\textsuperscript{131}

![ROC curve for NSE at 48h](image)

\textbf{Figure 5.} - Adapted from Stammet et.al. JACC 2015
Outcome

In contrast to other areas of cardiovascular research mortality is usually not the outcome of choice after cardiac arrest. Increased survival can be achieved both by means of improved treatment and by avoiding withdrawal of live sustaining therapies. Current guidelines therefore suggest reporting survival at 30 days after cardiac arrest and neurological outcome assessed at six months. Neurological assessment can be performed according to the cerebral performance category (CPC)-scale or modified Rankin scale (Table 1).

Table 1
Description of what is considered a good outcome according to the CPC and mRS scale. The scales are not comparable and specific levels can therefore not be equated.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cerebral Performance Category</th>
<th>Modified Rankin Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>CPC 1. Good cerebral performance: conscious, alert, able to work, might have mild neurologic or psychological deficit</td>
<td>0 - No symptoms at all</td>
</tr>
<tr>
<td></td>
<td>CPC 2. Moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life. Able to work in sheltered environment.</td>
<td>1 - No significant disability despite symptoms; able to carry out all usual duties and activities</td>
</tr>
<tr>
<td></td>
<td>CPC 3. Severe cerebral disability: conscious, dependent on others for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis</td>
<td>2 - Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance</td>
</tr>
<tr>
<td></td>
<td>CPC 4. Coma or vegetative state: any degree of coma without the presence of all brain death criteria. Unawareness, even if appears awake (vegetative state) without interaction with environment; may have spontaneous eye opening and sleep/awake cycles. Cerebral unresponsiveness</td>
<td>3 - Moderate disability; requiring some help, but able to walk without assistance</td>
</tr>
<tr>
<td></td>
<td>CPC 5. Brain death: apnea, areflexia, EEG silence, etc.</td>
<td>4 - Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 - Severe disability; bedridden, incontinent and requiring constant nursing care and attention</td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td>6 - Dead</td>
</tr>
</tbody>
</table>

Most survivors of cardiac arrest in Sweden have a good outcome according to the scales above. However recent studies have shown that cognitive impairment is common, which suggests that more subtle instruments to assess cognition and quality of life may need to be included in future trials on cardiac arrest.
Heparin-binding protein (HBP)

Paper I in this thesis is a study of Heparin-binding protein (HBP). HBP, also called azurocidin is a 37kD, neutrophil-derived protein with antimicrobial properties. It was identified in 1984 by Shafer et al. and is stored in two different types of granule subsets. Partly in azurophilic granules which are largely inert and partly in secretory vesicles, which are readily mobilized and can be excreted rapidly.

Once released from the neutrophil, HBP binds to endothelial glycocalyx and has several different effects.

- **Chemoattraction** - and activation of monocytes.
- **Antibacterial** - by enhancing the antibacterial effect of monocytes, or opsonization of bacteria.
- **Increased vascular permeability** - by cytoskeletal rearrangement.

Considering especially HBPs role in increasing vascular permeability it appears that the protein is involved in the pathogenesis of sepsis and the systemic inflammatory syndrome. In clinical practice, it seems that HBP is a reliable predictor of organ failure among patients with infections.
Aims of the thesis

This thesis focuses on the utility and complications associated with the two most common interventions performed in-hospital after cardiac arrest: coronary angiography and targeted temperature management.

I. To investigate levels of heparin-binding protein after cardiac arrest and to assess any association with the incidence of infectious complications, and with neurological outcome.

II. To investigate whether early coronary angiography after out-of-hospital cardiac arrest of a presumed cardiac cause is associated with improved outcomes in patients without ST-elevation.

III. To explore any potential interaction between temperature and no-flow time to investigate whether patients with longer periods of cerebral ischemia had a better response to the lower target temperature of 33°C in the TTM-trial.

IV. To describe the incidence of infections after out-of-hospital cardiac arrest and to investigate if infections are associated with an increased mortality. Additionally, to study any differences in the incidence of infections between patients who received a target temperature of 33°C compared to 36°C.
The present thesis includes four papers, the first of which is based on data from a single center study from Skåne University Hospital Lund, Sweden. The remaining three studies are analyses of patients included in the TTM-trial. Detailed descriptions of the methods and statistics used in each paper are available separately in each attached paper.

Table 2
Overview of study participants and study design.

<table>
<thead>
<tr>
<th>Paper</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Single-center, retrospective</td>
<td>post hoc analysis of a multicenter, randomized trial</td>
<td>post hoc analysis of a multicenter, randomized trial</td>
<td>post hoc analysis of a multicenter, randomized trial</td>
</tr>
<tr>
<td>Participants</td>
<td>n=84</td>
<td>n=544</td>
<td>n=939</td>
<td>n=939</td>
</tr>
</tbody>
</table>
Targeted Temperature Management (TTM) – Trial

Papers II, III and IV in this thesis are secondary analyses of the TTM-trial, which was performed between November 2010 and January 2013. The trial posed the clinical question: “In adults who are comatose after out-of-hospital cardiac arrest of presumed cardiac cause, does targeting a temperature of 33°C improve survival compared to a target temperature of 36°C?”

The TTM-trial was a multicentre, international, outcome assessor-blinded, parallel group, randomized clinical trial. The major difference between the TTM-trial and the first two randomized trials on hypothermia were:

- **Size:** The TTM-trial randomized more than twice as many patients as the first two RCTs together. A total of 950 patients at 36 intensive care units in Europe and Australia.

- **Inclusion criteria:** Patients with all initial rhythms were randomized, whilst only patients with shockable rhythms were included in the earlier trials.

- **Control group:** In contrast to the HACA and Bernard trials, temperature was actively managed at 36°C in the control group using a device. In the earlier trials patients were allowed to develop fever.

- **Withdrawal of life sustaining therapies:** In the TTM-trial prognostication and WLST was protocolized. As prognostication influences WLST\textsuperscript{146} this might have affected the results of earlier trials.

![TTM-trial Intervention period](image)

*Figure 6. Mean temperature in TTM33 and TTM36, error bars are 1-SD. Adapted from Nielsen et.al. NEJM 2013.*
Results
The TTM-trial showed no benefit of TTM at 33°C compared to 36°C with regards to the primary outcome of death at the end of the trial, neurological outcome or quality of life. The interpretation of the trial results has differed, but guidelines have adjusted the recommended target temperature after cardiac arrest to 32-36°C and downgraded the quality of evidence supporting the intervention to low. Some of the main criticisms of the trial include a high proportion of bystander CPR - not representative for many parts of the world, high doses of sedatives in the TTM 33 group, and a fast rewarming protocol.

Paper I

Patients
Eighty-four adult (≥18 years) patients resuscitated from in-hospital cardiac arrest or out-of-hospital cardiac arrest with sustained unconsciousness (GCS≤7) were included in the study. Both patients with cardiac and non-cardiac causes of arrest were included. All patients were treated at Skåne University Hospital, Lund, between 2003 and 2007 and included in a prospective trial. Major exclusion criteria were terminal disease, intracerebral hemorrhage, aortic dissection or major trauma.

Ethics
Study I was approved by the Regional Ethical Review Board at Lund University (decisions 411/2004 and 223/2008). Informed consent was obtained from the patients who survived. For patients who died, informed consent was obtained from the next of kin.

Treatment protocol
Patients were cooled to 33°C with cold saline (30ml/kg). The target temperature was maintained with an external (CritCool, MTRE Advanced Technologies Ltd., Israel or Arctic Sun, Bard Medical Inc, Louisville, USA) or intravenous device (Icy Cath, Zoll Medical Corp., Chelmsford, USA) for 24 hours. Rewarming was controlled at 0.5°C/hour.
Sedation was achieved by means of propofol or midazolam and fentanyl. Rocoronium was used to treat shivering at the discretion of the attending ICU-physician.

**HBP-analysis**

Plasma samples were obtained on admission, at 2h, 6h, 12h, 24h, 36h, 48h and 72h after CA. Samples were centrifuged and frozen immediately. The concentration of HBP was determined by ELISA in 2012.

**Statistics**

The distribution of HBP-levels was compared between groups with the Mann-Whitney U-test. Bonferroni corrections were made for multiple comparisons. The discriminatory ability of HBP was calculated by receiver operating characteristic (ROC) analysis and corresponding area under curve-values were calculated.

**Outcome**

Infection was diagnosed prospectively by the treating physician. Additionally, infection was assessed retrospectively using two different definitions. The first, or *restricted* definition, included all patients with positive microbial cultures. The second, or *extended* definition, included all patients treated with antibiotics. Neurological outcome was assessed at six months, a CPC-score of 1 or 2 was considered a good outcome, a CPC-score of 3-5, was considered a poor outcome. (Table 1).
Paper II, III and IV

Patients

The patients included in papers II, III and IV were part of the TTM-trial. Inclusion criteria were age $\geq$ 18 years, out-of-hospital cardiac arrest of presumed cardiac cause, unconsciousness (GCS<8) and sustained ROSC, defined as no requirement for chest compressions for at least 20 minutes.

Exclusion criteria were: Pregnancy, a known bleeding diathesis, suspected or confirmed intracranial bleeding, suspected or confirmed acute stroke, unwitnessed asystole, known limitations in care, a known disease making 180 day survival unlikely, a pre-arrest status of CPC 3 or 4, more than 240 minutes between ROSC and screening, a temperature <30°C on admission or a systolic blood pressure <80mm hg despite fluid loading, vasopressors, inotropes and/or an aortic balloon pump.

The patients included in all three studies were part of the intention-to-treat population (n=939). Eleven patients were excluded after randomization.

Ethics

Ethical approval was obtained in each participating country according to local laws and regulations. Informed consent was obtained or waived according to national regulations. The trial was monitored by national Good Clinical Practice (GCP)/monitoring offices.

Protocol

Patients were randomized to a target temperature of 33°C or 36°C. Patients in both groups were sedated, endotracheally intubated, and mechanically ventilated. Core body temperature was measured via a urinary catheter. Temperature was managed with an external or internal device.

For patients randomized to 36°C who initially had a lower body temperature, the body temperature was allowed to rise passively. For patients randomized to 33°C the goal was to achieve the temperature as rapidly as possible using ice-cold fluids, ice packs and a device.
The intervention period lasted for 36 hours and commenced after randomization. After 28 hours of temperature management, warming, no faster than 0.5°C / hour, commenced in both groups. At 36 hours, mandatory sedation was tapered. Following the intervention, a body temperature ≤37.5°C was maintained in patients who remained unconscious.

**Outcome**

*Paper II*

The primary outcome was death at the end of the study. This allowed for a minimum of 180 days of follow-up for the last included patient. The median follow-up time was 427 days. Secondary outcome was neurological function at six months, dichotomized into good and poor outcome (Table 1). Bleeding, a possible complication of coronary angiography was included as a safety outcome.

*Paper III*

The primary outcome was neurological function, assessed at six months. As an additional outcome mortality at six months was also studied.

*Paper IV*

The primary outcome was death at the end of the study.

Infectious events were pneumonia, severe sepsis and septic shock. Diagnosis of pneumonia was based on the presence of a new or progressive consolidation on chest x-ray, leukocytosis, fever and purulent tracheobronchial secretions. Severe sepsis was defined as a suspected infection with two or more SIRS criteria (temperature >38°C or <36°C, a heart rate >90 beats/min, a respiratory rate >20 breaths/min or PaCO2 <4.3 kPa, a white blood cell count >12000 cells/µL or <4000 cells/µL, or >10% immature (band) forms) and hypoperfusion, hypotension or organ dysfunction. Septic shock was defined as severe sepsis with hypotension or the requirement for vasoactive drugs, despite adequate fluid resuscitation.
Results

Detailed descriptions of the results are available in the separate papers (see attachments)

**Paper I**

*HBP release pattern*

Levels of HBP were elevated after cardiac arrest, both among patients with a poor and a good neurological outcome. HBP exhibited a pattern of very early release. The highest values were seen on admission. HBP-levels then plateaued out at a slightly elevated level between 12 and 72 hours. (Figure 7)

![Figure 7](image_url) – HBP levels grouped by outcome. The line in the box is the median value. Boxes represent inter-quartile range. Whiskers represent the lowest/highest value within 1.5 IQR of the lower/upper quartile. Dots are outliers.
Accuracy for predicting infections and neurological outcome

HBP was not significantly higher among patients with infection. This was true for all the definitions of infection used. Using the restricted definition of infection, the AUC value was not higher than 0.6 at any time point.

Accuracy for predicting neurological outcome

HBP values were higher (after correction for multiple testing) at 6h and 12h among patients who had a poor outcome. The corresponding AUC-values were 0.68 and 0.70 respectively.

Correlation with severity of illness and time to ROSC

There was a modest correlation between HBP-values at 6h after arrest with APACHE II score and SOFA score on day 1 (rho= 0.36 and 0.32). A stronger correlation (rho=0.61) was seen between time to ROSC (minutes) and HBP levels at admission (Figure 8).

![Figure 8. Correlation between HBP levels at admission and time to ROSC, Spearman correlation coefficient of 0.61](image)

Summary of Paper I

As expected by its storage in secretory granules, HBP was rapidly released after cardiac arrest. Probably due to leukocyte activation triggered by ischemia/reperfusion and a systemic inflammatory response. Earlier studies have shown HBP to be very sensitive for predicting organ dysfunction in patients with infection144,155, but this study shows that (as is the case for all known biomarkers of infection) HBP is also released in response to non-infectious stimuli. Release of
HBP has also been documented in other instances of systemic inflammation, such as burns. Interestingly, there was no correlation between HBP-levels and infection in this study. With regard to prognostication, HBP was an early predictor of both outcome and critical illness, however diagnostic accuracy was considerably worse than for example NSE, which makes any use of HBP in this capacity unlikely.
Paper II

Mortality and Neurologic function

In the TTM-study 544 patients did not have ST-elevation on their initial ECG. A total of 252 patients underwent a coronary angiography within six hours of arrest. These patients had a lower mortality in an unadjusted analysis (HR 0.82, 95%CI 0.64-1.03, p=0.09) (Figure 9). In an adjusted analysis the hazard ratio for death at the end of study was 1.03 (95%CI 0.80 - 1.32, p=0.82). Similar results were found in a propensity matched analysis.

Neurological function at six months was similar between patients who received an early coronary angiography and those who did not. (Adjusted relative risk (RR) for a poor neurological outcome in the early coronary angiography group was 0.87, 95%CI 0.75-1.02, p=0.08)

Bleeding

Bleeding was more common among patients who received an early coronary angiography (RR 1.62, 95%Ci 1.12-2.34). However, the comparison group consisted both of patients who received a late CAG, and those who did not receive one at all. There was no difference between groups with regard to uncontrolled bleeding and bleeding in a critical organ. The difference in bleeding rates was therefore due to minor bleeds, primarily from insertion sites.
Summary of Paper II

Paper II confirms the finding from other studies that acute coronary syndromes, as evidenced by a high percentage of PCIs, is common after cardiac arrest. Despite this, no obvious benefit, with regards to survival and neurological function, could be found. This also held true in the propensity score analysis which aimed to adjust for the underlying imbalance between groups.

Paper III

Bystander CPR

Patients who received bystander CPR were on average younger (p<0.01) and more often had an initial shockable rhythm (p<0.01). Although survival and a good neurological outcome were more common with bystander CPR, it was not independently associated with mortality or neurological function (odds ratio (OR) 1.09, 95% CI 0.66 – 1.82, p=0.73) or mortality (OR 0.89, 95% CI 0.54 – 1.47, p=0.64. On average patients with bystander CPR had shorter no-flow times and longer low-flow times.

No-flow time

The median no-flow time was low – 1 minute (Inter-quartile range (IQR 0-5min). For each increase of one minute of no-flow time, survival dropped. (OR 1.13/minute, 95% CI 1.06-1.20, p<0.001). Using marginal effects, this translated to a 1.6% increase in mortality per minute without CPR (p<0.001).
**Temperature effect**

A multivariate analysis was performed to assess the potential interaction between target temperature and no-flow time with regard to neurological outcome. In this analysis the main effect of temperature was not significant. The interaction term was not statistically significant (p=0.11). When adjusted predictions were computed from the model the predicted probability of a poor outcome did not differ between temperature groups (Figure 11).

![Figure 11. Predicted probability of a poor neurological outcome, derived from multivariate logistic regression](image)

**Summary Paper III**

One of the main criticisms of the TTM-trial has been that bystander CPR was "too common" to ensure generalizability. This argument is based on the idea that patients who receive bystander CPR do not have enough brain damage to be responsive to a neuroprotective intervention such as targeted temperature management at 33°C.

In this post hoc analysis we show that the effect of a target temperature of 33°C or 36°C does not appear to be influenced by the time to initiation of CPR and that TTM at 33°C was not associated with an improved neurological function for patients who had long no-flow times. The hypothesis that the efficacy of target temperature management at 33°C vs. 36°C degrees is influenced by no-flow time could not be supported.
Infections were common in the TTM-trial. Five-hundred patients (53%) developed an infection whilst in the ICU, pneumonia being the most common (Figure 12). In univariate analysis, these patients were more likely to have a pulmonary comorbidity and to have a witnessed cardiac arrest. Patients with infections on average also had a higher extended cardiovascular SOFA-score.

![Infections in the ICU](image)

**Mortality**
Mortality was 240/500 (48%) in patients who developed pneumonia or sepsis, compared to 220/439 (50%) in patients who did not (p=0.52). In a time-dependent univariate Cox model, patients with pneumonia or sepsis had a significantly higher hazard of death (HR 1.38, 95%CI 1.14 – 1.67, p=0.001). In multivariate analysis, the hazard ratio was 1.39 (95%CI 1.13 – 1.70, p=0.001).

**Effect of temperature**
The cumulative incidence of an infectious complication before death was 56% in the 33°C-group and 51% in 36°C-group at the end of the trial. A comparison was made by means of competing risk which showed that there was no significant difference between groups (sub-hazard ratio (SHR) for an infectious event 0.88,
Median time to an infectious event was 3 days (IQR 2-4 days) in both temperature groups.

**Biomarkers**

C-reactive Protein (CRP) and (Procalcitonin) PCT levels at 24h, 48h an 72h were batch-analysed. Patients with infections had significantly higher levels of both biomarkers at all times (all p<0.001). There were no significant differences between temperature groups for PCT-levels (mixed model, p=0.39). In the mixed model analysis of CRP there was no overall difference between temperature groups (p=0.18). However, there was a significant interaction between temperature group and time (p<0.001). When levels of CRP were compared at each separate time point, they only differed at 24h. On average levels of CRP were 17.3 mg/dl higher in the 33°C group at 24h (Figure 13).

![Figure 13. Levels of CRP and PCT in the two temperature groups. The line in the box is the median value. Boxes represent inter-quartile range. Whiskers represent the lowest/highest value within 1.5 IQR of the lower/upper quartile. Dots are outliers.](image-url)
Survival after cardiac arrest in Sweden has increased dramatically over the last two decades. According to data from the Swedish Cardiac Arrest Registry survival was 4.8% for out-of-hospital cardiac arrest in 1992, and increased to 11% in 2014. The rise has been most pronounced for patients with shockable rhythms, from 12% to 34%. However, there has also been an increase, although from a low level, among patients with PEA and asystole – from 1% to 4%. The main reason for these improvements is probably higher rates of bystander CPR, and improvements in pre-hospital CPR in general.23

Interestingly the average time to defibrillation has not changed significantly during the last twenty years, this begs the question if there are other improvements in the care of cardiac arrest victims which have contributed to improved survival. One factor likely to have contributed is the in-hospital care.

This thesis is largely a study of two of the interventions used as part of modern in-hospital care: coronary angiography and targeted temperature management. Though not as easily quantifiable in clinical studies as specific interventions, the general quality of intensive care has probably also improved substantially, leading to better results. One can also hypothesize that the increased interest in cardiac arrest patients caused by the resurge of hypothermia in the early noughties has contributed to improved care and consequently, improved survival.

Coronary Angiography

In paper II, there was no benefit of an early coronary angiography for patients with out-of-hospital cardiac arrest of a presumed cardiac cause, without ST-elevation on their initial ECG. In a propensity score score analysis, the results were the same. There have been a number of studies that have found a benefit of either PCI or angiography after cardiac arrest. This study differs in several ways. First, patients with all rhythms were included, and patients with STEMI were excluded. In some studies, only patients with ventricular fibrillation were included,157 and in other both patients with, and without STEMI.158 Second, a propensity score analysis was performed, which to some extent can adjust for the selection bias associated with
early CAG. This is important as treating physicians might be prone to a more invasive strategy in patients with a presumed better prognosis.

One study evaluated the association between PCI and survival after cardiac arrest and found that survival improves when PCI is performed. The authors therefore concluded that this finding supports the use of immediate coronary angiography in patients without an obvious non-cardiac cause.\(^{159}\) The findings of paper II, although by no means conclusive, do not support that conclusion. Also, the inference that coronary angiography would improve survival because PCI is associated with reduced mortality can be questioned.

Another potential source of bias in studies on coronary angiography after cardiac arrest is time-dependent bias. In a study by Reynolds et al, coronary angiography was associated with a good prognosis, however patients who received the procedure after targeted temperature management were included. This might lead to time-dependent bias as there is a non-negligible risk of death during the first days after arrest (although patients who died within six hours were excluded).\(^{158}\) This type of bias may also exist in paper II, as patients who died within six hours of arrest might have received an early angiography, had they survived.

In conclusion, all retrospective studies on the topic of coronary angiography are at a high risk of bias, be it selection bias or time-dependent bias. Future studies should try to address the clinical question if all patients without ST-elevation after cardiac arrest should receive an immediate coronary angiography, or if a selective approach is equally good. This might be the case as large randomized trials in patients with acute coronary syndromes without ST-elevation and no cardiac arrest have failed to show that an immediate invasive strategy is superior to a selective approach.\(^{160}\)

**TTM and no-flow time**

In 2002, Weisfeldt and Becker proposed a three phased model of out-of-hospital cardiac arrest. The first, or *electrical* phase is characterized by ventricular fibrillation with defibrillation being the most important intervention. The second phase, lasting approximately from four to ten minutes of ventricular fibrillation is the *circulatory* phase, and chest compressions are the most crucial intervention. The third phase is the *metabolic* phase, which starts at approximately ten minutes of cardiac arrest.\(^{161}\)

The metabolic phase of arrest is characterised by injury from ischemia and reperfusion as well as gut mucosal translocation.\(^{162}\) It is in this phase that hypothermia is hypothesized to have its greatest effect as a neuroprotective treatment of ongoing damage after reperfusion.
According to this hypothesis, targeted temperature management should have a larger (and potentially its only) effect in patients with cardiac arrests of long duration, and specifically those cases where bystander CPR is not provided. Some support of this theory can be found in a study by Testori et. al, which showed an adjusted OR for a good neurological outcome of 6.15 for patients with more than >8 minutes of no-flow time.\textsuperscript{163}

Based on the abovementioned ideas, one of the explanations of the the overall negative result of the TTM-trial has been that the average ischemic result was too small, as evidenced by a short median no-flow time (1 minute) and a high percentage of bystander CPR (73%).

In contrast to the study by Testori et al. we found no statistically significant interaction between no-flow times and temperature group in paper III. In fact, the point estimate of the adjusted predictions indicated a somewhat better effect of 36°C for patients with no-flow times >10 minutes. One reason for the divergent results might be that the Testori study was not randomized, making selection bias likely. Another explanation might be that there was no active temperature management in the control group.

Paper III neither definitely confirms or rejects a relationship between no-flow time and temperature. However, if one were to design a study and have a power of 80% to detect a relative risk reduction of 20%, that study would need to include more than 20000 patients, based on the results of the TTM-trial. It therefore seems unlikely that such a trial will be performed.

### Infections

Experimental studies have shown that hypothermia is associated with an impaired immune response.\textsuperscript{164,165} It also been shown that perioperative hypothermia is associated with an increased risk of infection.\textsuperscript{96} The association between temperature management at 33°C and infections is less clear, although two meta-analyses strongly suggest a moderately increased risk.\textsuperscript{166,167} It is also unclear whether this tendency towards an increased risk of infections translates to any meaningful harm.

In paper IV, we found no difference in the hazard of developing an infection between patients treated at 33°C and 36°C in contrast to an earlier study on early pneumonia after cardiac arrest by Perbet et. al.\textsuperscript{168} Despite the lack of significance in paper IV, there was a trend towards more infections among patients managed at 33°C, taken together with prior results, this may suggest a lack of power. Interestingly, the lower bounds of the 95% confidence interval of the SHR for
infection in the 33°C group was 0.75, indicating that any difference is probably small.

In the analysis of mortality in paper IV cox-analysis pointed towards an increased mortality associated with infections. Other studies have either shown no difference in mortality or a survival benefit. It is likely that the results of paper IV differ due to the use of a time-dependent variable, as this decreases the risk of “survival-bias”.

**Biomarkers**

Evidence regarding the response of inflammatory biomarkers and cytokines to mild hypothermia is conflicting. In paper IV, PCT and CRP, two inflammatory biomarkers, commonly used in clinical practice were assessed. No difference was found in biomarker levels between the 33° and 36°C groups. In contrast to earlier studies, the control group in paper IV also received targeted temperature management, which might have concealed any possible difference. However, with samples batch analysed from more than 600 patients, any alterations in serum levels caused my hypothermia are likely to be clinically insignificant.

Levels of PCT and CRP were higher among patients with infections at all time points but there was a large amount of overlap, as evidenced by comparatively poor AUC-values. These results are broadly in line with previous work, which leads us to consider the diagnostic value of both CRP and PCT as low.

Even though PCT and CRP cannot be considered clinically useful biomarkers, levels were higher among patients with infections. In contrast, levels of HBP in paper I were not. This could be explained by the heterogeneous patient population or the lower sample size in paper I. Considering that HBP has performed better than both CRP and PCT in the diagnosis of infection, another possible explanation is that most infections were not associated with circulatory failure and thus did not elicit a rise in HBP-levels.

**Prognostication**

In paper I, HBP showed only a modest ability to predict long-term outcome but was associated with the severity of critical illness. Later work has confirmed these findings suggesting that HBP might be used as an indicator of a high 24h SOFA score and early death in the ICU. In this regard the clinical use of HBP might be similar to that of lactate. However, in a study by Ristango et al. HBP was not superior to lactate with regards to predicting early death. Thus, at the present moment there is no obvious clinical use of measuring HBP for prognostic purposes.
in patients resuscitated from cardiac arrest. If HBP has any use as a predictor of infections with circulatory compromise, i.e. septic shock in this population, remains to be investigated.

Limitations

A general limitation of paper I is that the study population consisted of both IHCA and OHCA-patients. Additionally, both cardiac and non-cardiac causes of arrest were included. This case-mix could perceivingly mask findings in particular subgroups. Another limitation in the long storage time, which could have impacted the results. Paper I was a retrospective study and it is difficult to exclude any bias in the classification of infection.

The TTM-trial had an active control group with temperature managed to 36°C. This makes comparisons with earlier studies somewhat difficult as most prior studies have compared hypothermia to a control group without temperature management.

In paper II patients were randomized to 33°C or 36°C, but allocation of early coronary angiography was not randomized. Despite adjustments for demographic information, cardiac comorbidities and arrest-related factors, there is still a non-negligible risk of bias. Although the sample size was relatively large, the study was not powered to draw any definitive conclusions. Other limitation in paper II include lack of data on troponins, angiographic findings and echocardiographic assessment.

The data on no-flow time and low-flow time, which is central to paper III was based on reports by emergency services and relatives. Considering the stressful situation of a cardiac arrest there may be errors in reporting despite data being monitored (time to ROSC and time to advanced live support).

A major difficulty in studying infection after cardiac arrest, and perhaps the biggest limitation of paper IV is the difficulty of establishing a reliable diagnosis of infection. There is considerable overlap between the post-cardiac arrest syndrome and symptoms of infections making a definitive diagnosis difficult. Hypothermia also hampers the diagnosis of infection by definition, as fever is avoided. A reliable diagnosis of pneumonia in particular can be difficult as resuscitated cardiac arrest patients often have infiltrates on chest x-ray caused by various non-infectious causes, such as aspiration pneumonitis and lung contusions after CPR.

In paper IV the diagnosis of infection relied on the judgement of the treating physician and events were not adjudicated. This could conceivably have led to an over-diagnosis of infection in the 33°C group. As hypothermia is generally considered to be associated with infection, this might have increased the perceived
pre-test probability of an infection, which could lead to bias in the interpretation of vital signs, biomarkers and cultures.

One important limitation in paper IV is the lack of patient level data on the use of prophylactic antibiotics. The effect of different treatment strategies should however be marginal as randomization was stratified by site.
Conclusions

• An early elevation of Heparin-binding protein was seen in a majority of patients after cardiac arrest.
• Levels of Heparin-binding protein were not associated with infection after cardiac arrest.
• Levels of Heparin-binding protein correlated with severity of illness and were moderately associated with a long-term outcome.
• Early coronary angiography after out-of-hospital cardiac arrest of a presumed cardiac cause was not associated with improved survival or neurological outcome for patients without ST-elevation on their initial ECG.
• The effect of a target temperature at 33°C compared to 36°C does not appear to be influenced by the time to initiation of CPR.
• A target temperature of 33°C compared to 36°C did not confer a survival benefit for patients who had longer durations of no-flow time.
• Pneumonia, severe sepsis and septic shock after out-of-hospital cardiac arrest may be associated with an increased mortality.
• The hazard of developing pneumonia, severe sepsis or septic shock after out-of-hospital cardiac arrest did not differ between two target temperatures (33°C and 36°C).
Future Aspects

Coronary Angiography

Though the effect of immediate coronary angiography for patients with cardiac arrest and STEMI has not been examined in a randomized trial, the benefit of this procedure is considered established and is unlikely to be studied in a trial. However, the potential benefit of an acute coronary angiography compared to a sub-acute procedure after targeted temperature management is being examined in a randomized trial: Direct or sub-acute coronary angiography for out-of-hospital cardiac arrest (DISCO, NCT02309151). Results from this trial, currently in a pilot phase, will hopefully be able to guide future treatment.

Other future developments include combining early reperfusion with extracorporeal membrane oxygenation (ECMO) assisted CPR (E-CPR). E-CPR has been used as a treatment primarily for refractory cardiac arrest due to an acute coronary occlusion, pulmonary embolism or severe metabolic acidosis both in IHCA and OHCA. Guidelines currently suggest that E-CPR is a reasonable rescue therapy when conventional CPR is failing (weak recommendation, very-low-quality evidence).

When coronary angiography was used in combination with peri-arrest hypothermia and E-CPR in a pilot trial (CHEER) with a highly selected population, a PCI was performed in 42% of patients and survival with full neurological recovery (CPC 1) occurred in 14/26 (54%) patients. The results of the CHEER-trial indicate that ECPR is feasible at an ECMO center, but many knowledge gaps remain, especially regarding patient selection.
Targeted Temperature Management

There are a number of knowledge gaps regarding the optimal utilization of TTM, such as how long to control body temperature, which subgroups are most prone to benefit, and how fast to cool and rewarm. Considering the results of the TTM-trial and the low quality of evidence for TTM in general, perhaps the most important path for future research is to investigate if TTM at 32-33°C has any benefit for patients resuscitated from OHCA. At the same time, it is important to clarify if standard care and avoiding fever, is sufficient to achieve a good functional outcome.

In this context we propose a new clinical trial: TTM2. (NCT02908308)

We propose to compare rapid cooling to 32-33°C and standard care avoiding pyrexia (≤37.5°C) after OHCA in a randomized trial with the following PICO:

**Population:** Unconscious, adult, patients resuscitated from out-of-hospital cardiac arrest of a medical cause.

**Intervention:** Rapid cooling with cold fluids and feedback cooling device (intravascular or body surface) aiming for 32°C, followed by maintenance phase at 33°C for 24 hours.

**Control:** Standard intensive care, avoiding pyrexia (≤37.5°C) by using antipyretic medication or a cooling device, as needed.

**Outcome:** Survival at 180 days after cardiac arrest.

**Initial rhythm**

There are three main reasons for including both patients with shockable and non-shockable rhythms. The first is that any neuroprotective effect of a lower target temperature reasonably would apply to both patient groups as the mechanism of cerebral injury is the same. Second, it is reasonable to presume that any evidence for or against an intervention for patients with shockable rhythms will also be used for patients with non-shockable rhythm, as evidenced by the widespread use of hypothermia in both groups during the last decade. Third, including patients with non-shockable rhythms would increase the proportion of patients with a poor outcome, leading to an increased power to detect an *a priori* set relative risk reduction of 20%.

**Sedation**

To isolate the neuroprotective effect of hypothermia in a clinical trial is difficult. Any trial investigating hypothermia versus standard care is almost per default pragmatic in that there is a host of interventions and physiological changes that are a direct effect of hypothermia, other than its effect on the central nervous system. For example, it is possible that hypothermia has a neuroprotective effect but that a
low temperature simultaneously causes excess mortality due to hemodynamic instability. Likewise, isolating the effect of hypothermia is challenging in the context of different lengths of sedation.

In TTM2 we propose an equal length of sedation in both groups to, in as large an extent possible, limit the difference between groups. If this is accomplished one of the potential difficulties in interpreting the trial results can be eliminated.

**Outcome**

Positive results of a neuroprotective intervention might not be evident by studying mortality alone, instead they might only be evident when assessing neurologic function or cognitive disability. Additionally, prior trials have shown a smaller reduction in the relative risk of mortality than a poor neurological function. On the other hand, mortality has the smallest risk of a biased assessment and if there is adequate power to detect a difference in mortality this should ensure a high likelihood of finding any differences in neurological function or cognitive disability.
Summary in Swedish

Populärvetenskaplig sammanfattning

Varje år räddas livet på cirka 500 människor som fått ett hjärtstillestånd. Dock är dessa 500 bara ca 10% av de 5000 människor där någon har påbörjat HLR.

De senaste 20 åren har överlevnaden förbättrats avsevärt, sannolikt beror detta på en större medvetenhet bland allmänheten och att fler påbörjar HLR. I stora delar av Sverige så rycker även räddningstjänsten ut om någon har drabbats av ett hjärtstillestånd och i vissa län larmas även lekmän – så kallade ”SMS-livräddare” via en mobilapp, eller SMS. Även detta kan ha påverkat överlevnaden.

Under ett hjärtstillestånd upphör den normala cirkulationen vilket främst påverkar kroppens känsligaste organ, hjärnan. De människor som återupplivas efter HLR har därför i de allra flesta fall fått en större eller mindre hjärnskada till följd av syrebrist. På grund av hjärnskadan är därför patienten oftast medvetslös vid ankomst till sjukhus. På grund av medvetslösheten och en ofta sviktande funktion i flera av kroppens organ vårdas dessa patienter på en intensivvårdsavdelning där man kan understödja andningen och cirkulationen. Av de patienter som hamnar på en intensivvårdsavdelning så överlever ungefär hälften, den andra hälften dör antingen i en multiorgansvikt eller på grund av sin hjärnskada. I de fall någon dör av hjärnskada beror detta i allmänhet på att man stänger av den livsunderstödjande behandlingen när man vet att det inte finns några möjligheter för patienten att vakna.

För att kunna ta beslut om att avsluta livsuppehållande behandling utförs ett antal undersökningar för att bedöma vilken prognos patienten har. I första hand utförs en klinisk neurologisk undersökning för att bedöma basala reflexer och andning. I tillägg till detta använder man röntgenologiska metoder (CT och MR-undersökning av hjärnan), neurofysiologiska test och biomarkörer.

eller fick svåra hjärnskador. Vi visade att nivåerna av HBP var högre hos patienter som hade sviktande vitala funktioner och hos de som dog, men tillförlitligheten var inte tillräckligt bra för att vara del av en klinisk bedömning.

Bortsett från att understödja kroppens funktioner utför man på sjukhus även andra behandlingar som kan ha en del i den förbättrade överlevnad som setts sedan 1990-talet. Det är om dessa interventioner som övriga arbeten i avhandlingar handlar.

En del av vården på sjukhus fokuserar på att hitta orsaken till hjärtstilleståndet och behandla den. Den vanligaste, men inte enda anledningen är att patienten drabbats av en hjärtinfarkt som i sin tur har lett till ventrikelflimmer - ett elektriskt kaos i hjärtat. Vid en hjärtinfarkt blockeras ett av kärlen som försörjer hjärtat. Om blockeringen är total syns detta på EKG och man är då överens om att en snabb röntgen av hjärtats kransärt och efterföljande behandling med ballongsprängning är det bästa alternativet. Om blockeringen inte är total är man dock inte lika säker på nyttan av en akut kransröntgen. I en studie på 544 patienter där vissa fick en akut kärlsröntgen och andra inte, kunde vi inte visa att den akuta undersökningen var associerad med högre överlevnad.


Vid låga kroppstemperaturer är det lättare att få infektioner. Detta är särskilt uttalat vid mycket låga temperaturer men vissa studier tyder på att det även kan stämma vid temperaturkontroll på 33°C. Vi undersökte därför hur vanligt det var med infektioner i de två temperaturgrupperna i TTM-studien och hittade en trend, men inga övertygande bevis, för fler infektioner bland de patienter som kyldes till 33°C. Det framkom också att det kan finnas ett samband mellan infektioner och en ökad dödlighet vilket man inte visat i tidigare studier.

För att fortsätta undersöka nyttan av temperaturkontroll planerar vi för en ny studie där vi jämför överlevnaden hos patienter som får temperaturkontroll till 33°C med patienter där man enbart undviker feber.
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