Aspects of post-resuscitation care after out-of-hospital cardiac arrest

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”Skäms inte för att du är människa, var stolt!
Inne i dig öppnar sig valv bakom valv oändligt.
Du blir aldrig färdig, och det är som det skall.”

Tomas Tranströmer

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ABSTRACT

Background: Cardiac disease is the most common cause of death in the western world and the majority of these deaths are due to out-of-hospital cardiac arrest (OHCA). In Sweden, approximately 10,000 persons suffer an OHCA annually and in 5000 cardiopulmonary resuscitation (CPR) is initiated. The successful return of spontaneous circulation (ROSC) and admission to hospital are just the first steps towards the goal of complete recovery from cardiac arrest.

Aims: The aims of Papers I, II and IV were to evaluate different aspects of post-resuscitation care and their importance for survival after OHCA. These aspects included the use of implantable cardioverter defibrillators (ICD) and mild induced hypothermia (MIH). The aim of Paper III was to use variables and information available at intensive care unit admission to develop a risk score for poor outcome useful for comparing populations and defining patient risk when assessing effects and creating power calculations in interventional studies.

Methods: Papers I, II and IV were retrospective observational studies of OHCA patients admitted to hospital in Gothenburg during different periods of time from 1980-2015 (n=1,609, n=390 and n=871). Paper III is a post-hoc analysis of the randomized multicenter Target Temperature Management trial (n=933).

Results: In Paper I, we did not find any significant change in one-year survival between the two time periods (1980-2002 and 2003-2006) when all the patients were studied (27% vs. 32%; P = 0.14). Among patients found in ventricular fibrillation, an increase in one-year survival was found (37% vs. 57%; P=0.0001). The proportion of survivors to hospital discharge with low cerebral function (cerebral performance category score 3) decreased from 28% to 6% (P = 0.0006) among all patients.

The use of ICDs increased (Paper II), but, in overall terms, only 58 of 390 survivors (15%) received an ICD. Among patients who received an ICD, the two-year mortality was 2%, versus 25% among those who did not ($p < 0.0001$). The long-term follow-up showed that the use of an ICD had a borderline association with lower risk of death (adjusted hazard ratio 0.49; 95% confidence interval (CI), 024-1.01; $p = 0.052$).

In Paper III, we identified ten independent predictors of a poor outcome among patients who had ROSC on admission to hospital and created a risk score based on the impact of each of these variables. This score yielded a median area under the curve of 0.842 (range; 0.840-0.845) and good calibration.

In Paper IV, we used a stratified propensity score analysis to adjust for factors potentially influencing choice of treatment with MIH. The odds ratio (OR) for 30-day survival was not significantly higher in patients treated with MIH compared with non-MIH-treated patients; OR 1.33 (95% CI 0.83-2.15; $p=0.24$). A good neurological outcome at hospital discharge was seen in 82% of patients who were discharged alive from hospital.

Conclusions: We did not find any overall improvement in survival over time among patients who had ROSC on admission to hospital after OHCA, but we found signs of improved cerebral function among survivors to hospital discharge, following the introduction of more intensified post-resuscitation care. The use of ICDs was low but increased over time. Among survivors of OHCA caused by ventricular fibrillation or tachycardia who received an ICD during hospitalization, only 2% died during the following two years. Patients running a high risk of a poor outcome after OHCA could be identified at an early stage by using a simple, easy-to-use risk score, based on ten independent predictors of a poor outcome at six months. Treatment with mild induced hypothermia was not significantly associated with an increased chance of 30-day survival among patients who were still unconscious on admission to hospital after OHCA.

Keywords: Out-of-hospital cardiac arrest, survival, Implantable Cardioverter Defibrillator, prediction of prognosis, mild induced hypothermia

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SAMMANFATTNING PÅ SVENSKA

Ischemisk hjärtsjukdom (kranskärlssjuka) är en av de vanligaste dödsorsakerna i världen och majoriteten av dessa dödsfall sker till följd av hjärtstopp utanför sjukhus. I Sverige drabbas varje år cirka 10 000 personer av plötsligt oväntat hjärtstopp och i cirka 5000 fall påbörjas hjärt-lungräddning.

Då hjärtat står stilla kommer det inget syre eller näringsämnen till hjärnan och inom några få minuter börjar skador att uppstå. Hjärt- lungräddning kan ge en viss cirkulation med syresatt blod vilket kan förlänga den tid som hjärnan klarar sig utan skador.

Av de patienter som läggs in på sjukhus efter framgångsrik hjärt-lungräddning är den stora majoriteten medvetslösa, då de kommer till sjukhus, och behöver intensivvård med understödjande behandling såsom respirator. Efter framgångsrik hjärt-lungräddning får dessa patienter avancerad vård på sjukhus med akuta åtgärder mot bakomliggande orsaker såsom t.ex. kranskärlsröntgen med ballongvidgning. För de som avlider dagar eller veckor efter att hjärtat har stannat är skador på hjärnan ofta dödsorsaken.

Dödligheten och risken för varaktiga hjärnskador är stor. Ungefär en av tio personer som får hjärtstillestånd utanför sjukhus, och där man påbörjar hjärt-lungräddning, skrivs ut från sjukhuset vid liv. Den här avhandlingen handlar om olika faktorer av vården på sjukhus och deras betydelse för patienternas överlevnad och neurologiska funktion.

I delarbete I, II och IV i avhandlingen studerades patienter som lagts in på sjukhus i Göteborg efter hjärtstopp utanför sjukhus. I delarbete III gjordes en analys av de patienter som deltagit i en internationell studie från 36 olika intensivvårdsavdelningar i olika världsdelar.

I delarbete I fann vi inga statistiskt signifikanta skillnader i ett-års överlevnad mellan patienter som behandlats före och efter införandet av moderna behandlingsmetoder såsom kylbehandling och behandling för att förbättra hjärtats genomblödning. Men andelen patienter som skrevs ut levande med svåra neurologiska handikapp minskade. Användande av implanterbara defibrillatorer (ICD) som kan ge en elchock vid återkommande rytmrubbningar i hjärtat ökade men endast 15 % av de studerade patienterna fick en sådan inopererad (delarbete II). Vid långtidsuppföljning sågs en antydan till att de som behandlats hade en lägre risk att dö och denna risk var

bland patienter som fått en ICD enbart två procent under två års uppföljning.

I delarbete III studerades oberoende faktorer av betydelse för risken att dö eller att få en nedsatt funktion efter hjärtstopp hos patienter som lades in på intensivvårdsavdelning. Med hjälp av dessa skapade vi ett risk bedömningsinstrument med poängsystem för att tidigt kunna värdera patientens risk för ett misslyckat resultat redan vid ankomst till sjukhus. Denna risk värderades med hjälp av 10 faktorer som kan mätas vid patientens ankomst till sjukhus.

I arbete IV studerades effekten av kylbehandling hos patienter som lagts in på sjukhus medvetslösa efter hjärtstopp. Något statistiskt signifikant samband mellan kylbehandling och 30 dagars överlevnad sågs inte hos dessa patienter. Det stora flertalet av de som överlevde (82 %) skrevs ut med god funktion efter hjärtstoppet.

Sammanfattningsvis har vi inte funnit någon ökad överlevnad bland patienter som drabbats av hjärtstopp utanför sjukhus och lagts in levande på sjukhus sedan 1980, när vi studerat patienter som vårdats efter införande av mer moderna behandlingsmetoder. Ett bedömningsinstrument för att tidigt kunna förutsäga prognos för patienter som kommer in till sjukhus efter hjärtstopp utanför sjukhus har tagits fram inom ramen för avhandlingsarbetet.

LIST OF PAPERS

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

I. Martinell L, Larsson M, Bång A, Karlsson T, Lindqvist J, Thorén AB, Herlitz J.
Survival in out-of-hospital cardiac arrest before and after use of advanced post-resuscitation care: a survey focusing on incidence, patient characteristics, survival and estimated cerebral function after post-resuscitation care.
Am J Emerg Med. 2010;28(5):543-51.

II. Martinell L, Herlitz J, Lindqvist J, Gottfridsson C.
Factors influencing the decision to implant an ICD in survivors of OHCA and its influence on long-term survival. Resuscitation. 2013;84 (2):213-7.

III. Martinell L, Nielsen N, Herlitz J, Karlsson T, Horn J, Wise MP, Undén J, Rylander C.
Early predictors of poor outcome after out-of-hospital cardiac arrest. Accepted for publication in Critical Care.

IV. Martinell L, Herlitz J, Karlsson T, Nielsen N, Rylander C.
Mild induced hypothermia and survival after out-of-hospital cardiac arrest in a Swedish urban area.
Submitted manuscript.

CONTENT

ABBREVIATIONS

AED	Automatic External Defibrillators
AHA	American Heart Association
AMI	Acute Myocardial Infarction
AUC	Area Under the Curve
CI	Confidence Intervals
CPC	Cerebral Performance Category
CPR	Cardio-Pulmonary Resuscitation
ECG	Electrocardiography
EEG	Electroencephalography
EMS	Emergency Medical Services
ERC	European Resuscitation Council
FOUR	Full Outline of UnResponsiveness
GCS	Glasgow Coma Score
ICD	Implantable Cardioverter Defibrillator
ICU	Intensive Care Unit
ILCOR	International Liaison Committee on Resuscitation
MAR	Missing At Random
MCAR	Missing Completely At Random
MIH	Mild Induced Hypothermia
MNAR	Missing Not At Random

mRS	modified Rankin Scale
OHCA	Out-of-Hospital Cardiac Arrest
OR	Odds Ratios
PEA	Pulseless Electrical Activity
PCI	Percutaneous Coronary Intervention
PPV	Positive Predictive Value
ROC	Receiver-Operating Characteristic
ROSC	Return Of Spontaneous Circulation
SOFA	Sequential Organ Failure Assessment
SRCR	Swedish Registry of Cardiopulmonary Resuscitation
SSEP	Somatoensory Evoked Potentials
STEMI	ST-segment-Elevation Myocardial Infarction
TTM-trial	Target Temperature Management trial
VT/VF	Ventricular tachycardia or Ventricular fibrillation

1 INTRODUCTION

1.1 Cardiac arrest

In most cases, a cardiac arrest is the natural ending of life. When the cardiac arrest is premature, unexpected and sudden, we strive to prevent death.

Working in intensive care, guiding patients through death when survival is futile, has taught me a great deal and helped me to understand, as described by others, that the end of life is more of a process and not as depicted in movies, when someone takes their last breath. On many occasions, a deterioration in organ function leads to effects on other organs and a cascade of events occurs. Sudden cardiac arrest usually results from an electrical disturbance in the heart that disrupts its pumping action, stopping blood flow to the rest of the body. It is triggered by an electrical malfunction in the heart that causes an arrhythmia. When the function of the heart as the engine of our circulation stops, the cells of the body require the restoration of blood flow within minutes for the delivery of oxygen and energy and the removal of waste products. Without blood flow, the cells and tissues lose their capacities and this eventually leads to death. Within seconds after the heart stops pumping blood, a person loses consciousness and has no pulse. Death occurs within minutes if the victim does not receive treatment.

According to Swedish law, death has occurred when the brain has irreversibly lost all its functions. In most cases, indirect criteria, such as the cessation of breathing and pulse for a sufficient time, are enough to assume that no brain activity remains.

1.1.1 The history of cardio-pulmonary resuscitation

Cardio-pulmonary resuscitation (CPR) buys us time and reduces the damage to the cells. The time to defibrillation and the restoration of blood flow is crucial. Cardio-pulmonary resuscitation can keep oxygenated blood flowing to the brain and other vital organs until more definitive medical treatment is able to restore a normal heart rhythm. The lack of oxygenated blood can cause brain damage after only a few minutes. A person may die within eight to ten minutes after a cardiac arrest.

When mouth-to-mouth ventilation was combined with closed chest compressions in the 1960s, modern CPR was born. Clinicians translated observations relating to external chest compressions from the laboratory to patients. Closed chest compressions were described for the first time as a method for emergency circulation by Boehm in 1878, as cited by Kouwenhoven et al. (1). It was rediscovered in the 1950s and, in 1960, Koeuwenhoven demonstrated the effectiveness of closed chest compressions on humans. “The cardiac pump theory” states that circulation is the result of blood being forced out of the heart by compressions of the heart between the sternum and vertebrae (1, 2). Later studies showed that circulation is a result of variations in intrathoracic pressure, “the thoracic pump theory” (3). It appears that both mechanisms work at the same time and the relative importance of the two is uncertain and is yet to be discovered (4).

In the 1960s, CPR increased survival for patients who had cardiopulmonary collapse outside the operating room from none to a few. Incremental improvements in survival from CPR occurred as more people were trained in CPR and as defibrillators became portable and were deployed in more locations.

The International Liaison Committee on Resuscitation (ILCOR) was set up in 1992 to provide a forum for liaison between principal resuscitation organizations worldwide. The European Resuscitation Council (ERC) and American Heart Association (AHA) are two of the main members of the ILCOR. The publication of guidelines drawn up in co-operation has taken place on four occasions, in 2000, 2005, 2010 and 2015. The most recent guidelines put the emphasis on high-quality chest compressions and at a somewhat higher pace of 100-120 per minute. As before, chest compressions with a 30:2 ratio to ventilation and early defibrillation form the cornerstones of the new guidelines.

1.1.2 Causes of cardiac arrest

The etiologies of cardiac arrests are mainly cardiac, which explains about 80% of the cases. A Scottish study of 21,175 OHCAs showed that presumed cardiac disease accounted for 82%, other internal etiologies (lung disease, cerebrovascular disease, pulmonary embolism and so on) for nine percent and external etiologies (trauma, asphyxia, near drowning and so on) for nine percent (5). In one Finnish study of survivors of non-cardiac etiology OHCA: trauma, non-traumatic bleeding, intoxication, near drowning and pulmonary

embolism were the most common etiologies, comprising 61.2% of all cases (6).

There is a high probability of identifying an acute coronary syndrome in a patient who is resuscitated from cardiac arrest. In OHCA studies, acute myocardial infarction (AMI) has been documented in more than 50% of adult patients (7-9). There are several mechanisms behind ventricular tachyarrhythmias. The most common etiologies are either an acute coronary ischemic thrombosis in an otherwise normal heart that can cause ventricular fibrillation, or chronic myocardial tissue scars that can cause tachyarrhythmias. Metabolic and ionic changes lead to differences in refractoriness within the ischemic zone. This can cause re-entry tachycardia leading to ventricular fibrillation (VF) evolving from an ischemic zone close to dead tissue caused by myocardial infarction (10).

Another thromboembolic disease to consider as etiology after cardiac arrest is pulmonary embolism. Pulmonary emboli have been reported to occur in 2-10% of sudden deaths (6, 11). Primary pulmonary disease such as chronic obstructive pulmonary disease, asthma, or pneumonia can lead to respiratory failure and hypoxic cardiac arrest or circulatory collapse because of increased intrathoracic pressure and seizure of venous return.

1.1.3 Epidemiology

Ischemic heart disease is the leading cause of death in the world (12). Sudden cardiac arrest is responsible for more than 60% of adult deaths from coronary heart disease (13). Between 40 and 54 patients per 100,000 inhabitants per year suffer from OHCA in which CPR is attempted (14, 15). In Sweden, the annual occurrence of OHCA when CPR is attempted is 5,000, i.e. about 50 patients per 100,000 inhabitants per year. Slightly more than 20% of these patients arrive at hospital with the return of spontaneous circulation (ROSC) (16). The incidence of OHCA increases with age and is higher for men than for women.

Approximately 80-90% of patients hospitalized after OHCA are unconscious and require intensive care. Of the comatose patients admitted to intensive care units (ICU) after cardiac arrest, as many as 35-50% survive to be discharged from hospital depending on the cause of the arrest, the system and the quality of care (7, 17, 18). Of the patients who survive to hospital discharge, the vast majority have a good neurological outcome, although many suffer from subtle cognitive impairment (19, 20).

It is impossible to register the real initial arrhythmia, except for patients with an ICD. As the closest substitute, the arrhythmia first recorded, by either the emergency medical services (EMS) crews or a first responder using an automated external defibrillator (AED), is registered. Ventricular tachycardia or fibrillation (VT/VF), asystole and pulseless electrical activity (PEA) are the main electrical pathophysiological mechanisms that lead to cardiac arrest.

Although difficult to assess, a few studies have attempted to estimate the proportion of patients with VF at the time of collapse. In one study, the results of the VF versus the time from cardiac arrest relationship were extrapolated to an incidence of VF at the time of cardiac arrest of 60-70% in all patients and 80-85% in cases with a probable heart disease (21). When the rhythm is recorded soon after collapse, in particular by an on-site AED, the proportion of patients found in VF can be as high as 70% (22). According to the initial heart rhythm analysis made by the EMS, about 25-30% of OHCA victims are found in VF, a percentage that has declined over the last 20 years (16, 23, 24).

Even if some patients present with asystole at the time of collapse, most or many patients found in asystole have initially, at the time of collapse, had VF. The theory is that, with time, VF slowly deteriorates into fine VF and then finally converts to asystole (25, 26).

1.1.4 Changes in survival over time

The incidence and survival to hospital discharge among patients with OHCA vary considerably, with total survival reports ranging between 1-31%, but, in overall terms, the mortality and risk of neurological impairment is high (24). Most of the reported 30-day survival figures are around 10% among patients in whom the EMS has attempted CPR.

Survival figures vary greatly depending on both regional differences and methods of the study. Examples where differences are found are inclusion criteria, way of reporting and type of presentation of the data. This makes comparing survival after OHCA over time even more complicated. One interesting question linked to this is whether modern methods of treating patients after OHCA result in increasing survival or better neurological function among survivors. Most evidence comes from retrospective studies that compare outcome in different regions over time. The majority of studies compare total survival, from OHCA to a follow-up time point. Most of them indicate a positive trend in terms of an increase in survival over time. A large retrospective cohort study from Osaka reported an increase in total survival

after OHCA between 1998 and 2006 from five to 16% (27). The authors drew the conclusions that improvements in the chain of survival and, first and foremost, prehospital factors explained the increase in survival.

The in-hospital survival of all patients regardless of rhythm who were admitted to an ICU after OHCA also tends to show higher numbers over time in several studies. Patients who took part in a survey of different centers in Europe and one in the US between 2004 and 2008 had a survival rate of 56% to hospital discharge (18). A long-term follow-up from discharge from hospital to six to 12 months later showed a survival rate of 50%, where 46% survived with a good outcome (18). In-hospital survival after OHCA (from arrival at hospital until discharge from hospital) in four different hospitals in Norway, in 2001-2002, varied between 34% and 56% (28).

Among patients studied between 2001 and 2009 in Washington, 17% of all patients survived from the start of CPR until discharge from hospital. Reports of follow-up among these patients from discharge from hospital to one year and five years showed a survival rate of 82% and 64% respectively (29).

There are more positive reports from Denmark and Sweden, for example. In a Danish study, the percentage of patients that were successfully resuscitated to hospital admission increased from 37% in 2007 to 43% in 2011 (30). This indicates improvements in prehospital care in Denmark. Data from the Swedish Registry of Cardiopulmonary Resuscitation (SRCR) showed that 30-day survival doubled from 4.8% in 1992 to 10.7% in 2011 among patients with OHCA in whom CPR was attempted (16).

1.2 Secondary prevention

The innovation of the ICD represents a modern medical achievement with substantial life-saving potential for patients at risk of potentially life-threatening arrhythmias. The first ICD implantation was performed in 1980 and changed cardiac care. The introduction was met by skepticism and rejection by some. However, large, well-performed clinical trials clearly demonstrated the survival benefit of the ICD, as compared with anti-arrhythmic drugs (31-33). The results of these studies led to the initiation of implantation and an increase in the number of patients undergoing ICD implantation after OHCA. In spite of this, the ICD implantation rate varies between countries and within different regions in the same country. The majority of survivors of OHCA are found with an initial rhythm of VT/VF. If no reversible cause such as a myocardial infarction is found, these patients

are candidates for ICD as secondary prevention. Because of skepticism and since it is a costly intervention, there is a risk that the implementation of ICD treatment is an underutilized intervention in the OHCA population.

1.3 Possible in-hospital treatments

Spontaneous circulation can be achieved in 20-40% of patients suffering from OHCA (16, 30). The majority of these patients still die in hospital. Mortality is largely due to brain injury after global cerebral ischemia (34).

The observed development of brain injury evolves over days and this gives us time potentially to minimize the cerebral damage and thereby affect the outcome. Not only the initial reperfusion phase, but also several other factors can potentially compromise cerebral oxygen delivery and possibly produce a secondary injury. Several physiological disturbances, such as body temperature, blood pressure, serum electrolytes and blood glucose, are possible to control. We do not know the optimal targets for either of these factors or whether they can affect the outcome of patients.

The underlying pathology causing the OHCA needs to be further evaluated and addressed. Examples include coronary angiography when coronary ischemia is suspected and a CT scan in order to investigate other causes of OHCA, such as pulmonary embolism or intracranial bleeding.

Arterial hypotension is an important predictor of mortality in critically ill populations, as well as in patients who have experienced cardiac arrest. In a study of the autoregulation of cerebral blood flow, the majority of cardiac arrest patients in the acute phase displayed dysfunctional cerebral autoregulation. This indicates that the mean arterial pressure should perhaps be kept at a higher level than commonly accepted to secure cerebral perfusion (35).

Despite an unstable hemodynamic situation, it is important to maintain good perfusion to minimize hypoperfusion and hypoxic injury to the brain. The maintenance of normoxia and normocarbia also improves cerebral perfusion. Secondary brain injury can be mediated by excitotoxicity which means the process where nerve cells are damaged or killed by excessive stimulation by neurotransmitters such as glutamate. It is thought that the inflammatory cascade and excitotoxicity may be reduced by mild induced hypothermia (MIH).

Seizures are common in the post-cardiac arrest phase and they are probably both a consequence and a cause of further brain damage. Little is known about how aggressive the antiepileptic treatment should be. The EEG of cardiac arrest patients often shows a post-anoxic status epilepticus (36). Whether these findings are signs of anoxic brain damage or whether they are signs of ongoing cerebral damage from seizures in need of treatment has been the subject of discussion. Antiepileptics and sedatives are themselves associated with side-effects and perhaps impact the making of prognoses, which makes the question crucial.

In the general intensive care unit population, the NICE-SUGAR trial (Normoglycemia in Intensive Care Evaluation and Surviving Using Glucose Algorithm Regulation) demonstrated that patients randomized to moderate glucose control (< 10.0 mmol/l) had a lower 90-day mortality than those randomized to tight glucose control (4.5-6.0 mmol/l) (37). In cardiac arrest patients, the evidence indicates that moderate glucose control is advantageous (38, 39). With tight glucose control in critically ill patients, there is a high risk of more frequent episodes of severe hypoglycemia, which is associated with an increased risk of worsening the brain damage. Current recommendations suggest that moderate glycemic control (8.0-10.0 mmol/l) should be considered (40).

Glucocorticoids have been evaluated from a database study and showed no improvement in terms of survival or neurological recovery (41).

Thiopental as neuroprotection has also been studied (42). Comatose survivors of cardiac arrest (n=262) were randomly assigned to receive standard brain-oriented intensive care or the same standard therapy plus a single intravenous loading dose of thiopental (30 mg per kilogram of body weight). At the end of one year of follow-up, there was no statistically significant difference between treatment groups regarding the proportion of patients who died or regarding their neurological outcome.

Other neuroprotective drugs, such as coenzyme Q10 (43), nimodipine (44), magnesium or diazepam (45), have not been shown to increase neurologically intact survival when included in the treatment of cardiac arrest after resuscitation.

There are theories that reperfusion fails completely in some areas of the brain, a so- called no-reflow phenomenon, partly caused by capillary congestion because of disseminated intravascular coagulation among other pathologies. Thrombolytic therapy has been studied with the goal of

modifying this complication. So far, there is no evidence that thrombolytic therapy is more beneficial than placebo (46).

1.4 Coronary angiography and percutaneous coronary intervention

Recommendations for the emergency treatment of acute coronary syndrome have varied over the years. In the1980s, treatment started with intravenous streptokinase and tissue plasminogen activators were subsequently introduced. In the late 1990s, facilitated angiography and percutaneous coronary intervention (PCI) were introduced. This is now the recommended first-line therapy for ST-segment-elevation myocardial infarction (STEMI).

Urgent coronary angiography after OHCA has demonstrated evidence of coronary artery disease in 80% of patients and the presence of an acute thrombotic lesion in 38% to 48% (47, 48). There is increasing support for the hypothesis that early PCI, even for patients without ST elevation, might improve survival (47, 49, 50).

Many OHCA patients will have an acute coronary occlusion with signs of STEMI on their electrocardiogram (ECG), but cardiac arrest due to ischemic heart disease can also occur in the absence of these findings. In patients with STEMI or new left bundle branch block following ROSC after OHCA, immediate angiography and PCI or fibrinolysis should be considered. It is reasonable to perform immediate angiography and PCI in selected patients, despite the lack of ST elevation on the ECG, if the collapse was preceded by acute chest pain. However, information about symptoms before the OHCA can be difficult to obtain and a liberal indication might benefit the patients. Reperfusion treatment should not prevent other therapeutic strategies including MIH. There is still a need for more evidence in this area. Randomized trials to clarify whether there are benefits in survival as a result of coronary interventions in the early phase are warranted.

1.5 Post-cardiac arrest syndrome

The consequences of complete whole-body ischemia and reperfusion were first described in the 1970s and named “post-resuscitation disease”. In 2008, the terminology changed and this condition is now more frequently referred to as “post–cardiac arrest syndrome”. The return of spontaneous circulation

after cardiac arrest is an unnatural pathophysiological state created by successful CPR and involves all the body's organs.

Post–cardiac arrest syndrome is a complex combination of three main pathophysiological processes, which are post-cardiac arrest brain injury, post–cardiac arrest myocardial dysfunction and systemic ischemia/reperfusion response. It is important to take all these processes into consideration, as therapies that focus on individual organs may compromise other injured organ systems. The underlying pathological process that caused cardiac arrest also needs to be addressed and, if possible, treated.

1.5.1 Systemic ischemic-reperfusion response

Whole-body ischemia and the following reperfusion leads to a general reaction of inflammation called the systemic ischemic-reperfusion response. It manifests clinically as intravascular volume depletion, impaired vasoregulation, impaired oxygen delivery and utilization and increased susceptibility to infection. In most cases, it is both responsive to therapy and reversible.

Myocardial dysfunction in combination with hemodynamic instability in need of vasopressors after ROSC can lead to inadequate tissue oxygen delivery. Accumulated oxygen debt leads to endothelial activation and causes the generalized activation of immunologic and coagulation pathways, which increase the risk of multiple organ failure and infection. This condition has many features in common with sepsis (51).

1.5.2 Post–cardiac arrest brain injury

Post-cardiac arrest brain injury is the most common cause of morbidity and mortality after cardiac arrest and it accounts for at least two thirds of in-hospital mortality. Many of the patients who die from other causes would eventually have succumbed to their brain injury if they had not died for other reasons (52, 53). The brain is particularly vulnerable when exposed to ischemia and it has a unique response to reperfusion that makes it vulnerable to the development of a permanent injury. The mechanisms of post-cardiac arrest brain injury include immediate cellular energy substrate depletion and a switch to anaerobic metabolism, intracellular acidosis and hypercalcemia, mitochondrial dysfunction, glutamate release and neuronal hyper-excitability. The inflammatory cascade reaction is activated within hours, with the accumulation of inflammatory cells in the brain, complement activation and

an increase in the production of free radicals. The ischemic injury disrupts the blood-brain barrier, which can cause increased vascular permeability and lead to edema. These mechanisms are shown in experimental models (54, 55). Many of these mechanisms take place over a period of hours to days after ROSC and therefore create a window of opportunity for neuro-protection.

Clinical signs of post-cardiac arrest brain injury are coma, seizures, myoclonus, varying degrees of neurocognitive dysfunction and brain death.

Physiological disturbances such as hyperglycemia and increases in body temperature may aggravate the brain injury. The activation of coagulation and intravascular thrombosis may cause ischemia and the failure of cerebral microcirculation. Impaired cerebral auto-regulation and elevated cerebral perfusion pressure can lead to global cerebral hyperemia, which can worsen the reperfusion injury (54). In a small proportion of patients, especially younger ones, this may lead to brain edema and finally to total brain infarction.

1.5.3 Post-cardiac arrest myocardial dysfunction

Post-cardiac arrest myocardial dysfunction also contributes to the low survival rate after OHCA (56). Within minutes of ROSC, post–cardiac arrest myocardial dysfunction can occur. In animal studies, the ejection fraction decreases from 55% to 20% and left ventricular end-diastolic pressure increases as early as 30 minutes after ROSC (57). Results from studies indicate that the post–cardiac arrest myocardial dysfunction is both responsive to therapy and reversible (56, 58). Studies indicate that the dysfunction is more like a stunning phenomenon than a permanent injury or infarction. The dysfunction is global and transient and full recovery can occur. The lowest cardiac output is often seen around eight hours after the arrest and it has usually improved by 24 hours and returned to normal by 72 hours in patients who survived OHCA (56, 58). Patients who die from cardiovascular failure mostly succumb during the first three days after collapse, while brain injury accounts for most of the later deaths (34).

1.6 Target temperature management – mild induced hypothermia

The search for a treatment to affect brain injury after OHCA has led to the development of MIH. Mild induced hypothermia is the only therapy applied in the post-cardiac arrest setting that has indicated increased survival rates.

Cooling below body temperature has shown promising effects in animal models (59, 60). Results have indicated that, the deeper the hypothermia, the better the results, while simultaneously increasing the risk of side-effects, however.

For each degree of Celsius drop in body temperature, brain metabolism slows by approximately five percent (61). This is one of the protective actions that have been shown, but hypothermia influences the pathophysiology in a number of ways, including reduced cell metabolism, diminished excitotoxicity, lower calcium overload, less inflammation, modified gene expression and anti-apoptosis (62, 63). The specific protective effects of MIH are, however, not fully understood.

The post-ischemic period is complicated by hyperthermia induced by the generation of pyrogens in the brain. Fever occurring during the first 48 hours after global brain ischemia may contribute significantly to neuronal damage (64). Elevated body temperature is common during the first 48 hours after cardiac arrest and is associated with a poorer outcome. In one study, patients with body temperatures of 39°C in the first 72 hours after OHCA ran a significantly increased risk of brain death (65). It has not been clarified whether elevated body temperature is simply a marker of severe brain injury or a factor that itself affects survival.

In the 1950s, hypothermia underwent its first medical application as an intervention for intracranial swelling, traumatic brain injury and the prevention of post-cardiac surgery brain injury. Most of the early research focused on the applications of deep hypothermia, defined as a body temperature between 20-25°C. Case series of patients treated with hypothermia after cardiac arrest were described in 1958 (66). The risk of adverse events and uncertainty about the actual beneficial effects of this treatment precluded further implementation of hypothermia.

Hypothermia became established practice in cardiac surgery and inspired experimental studies in cardiac arrest patients in the late 1980s and the 1990s. In the planned event of cardiac surgery using circulatory arrest, the focus was

hypothermia before and during the ischemic event. In an experimental study, variations in brain temperature between 30°C and 39°C in rats during brain ischemia showed gradually decreasing brain damage, the lower the temperature (59). This has also been shown in other studies and in larger animals with more modest reductions in temperature (60, 67).

Studies of hypothermia after the ischemic event (post-ischemic hypothermia) are fewer and have not shown such promising results. Most of the experiments have been performed on mild hypothermia between 32°C and 35°C as nadir temperatures and these interventions have been associated with more side-effects and did not improve the outcome (68). Intra-ischemic hypothermia had a sustained beneficial effect, whereas post-ischemic hypothermia did not have any effect on hippocampal cell survival in rat experiments (69). In the 1990s, several patient series were described in which hypothermia was shown to be beneficial to OHCA patients, when compared with historical case series from the same hospitals (70, 71). Two randomized clinical trials in 2002 suggested improved outcome after MIH in adults who remained comatose after initial resuscitation from OHCA when they were found in VF (72, 73). Based on these two studies, the recommendations were that unconscious adult patients with spontaneous circulation after OHCA and VF should be cooled to 32°C to 34°C for at least 12 to 24 hours after collapse (74). The theoretical extrapolation of the results and data from observational studies led to the recommendation also to use MIH in unconscious adult patients after OHCA if they were found in a non-shockable rhythm (75-77). However, patients with OHCA found in a non-shockable rhythm have not been studied in any randomized study and it is therefore not evident whether these patients would also benefit from this intervention. Some observational studies support an effect of MIH in a general OHCA population (7, 78).

Target temperature, duration and rewarming rate have yet to be established. The therapeutic window, or time after ROSC at which mild induced hypothermia is no longer beneficial, is yet to be defined. Slow rewarming is recommended (0.25°C to 0.5°C per hour), although the optimum rate for rewarming has not been defined clinically.

In 2013, a randomized multicenter trial, the Target Temperature Management (TTM) trial, was published. It showed no difference in survival or neurological outcome between patients treated with 33°C compared with 36°C after OHCA (79). Substudies from this trial have not shown any substantial benefits or differences between the two target temperatures (20, 80, 81). After the TTM trial, the 2015 guidelines changed to recommend 32-36°C for 24 hours (82). The results from existing evidence still leave some

doubt about the effect of MIH and it is possible to argue that there is a lack of evidence of its beneficial effects.

Mild induced hypothermia is associated with several complications. Systemic vascular resistance is increased at lower body temperatures, which reduces cardiac output. Bradycardia is the most common arrhythmia, but other arrhythmias may be induced by hypothermia. Hypothermia induces a diuresis and diuresis may produce electrolyte abnormalities, which may, in turn, cause dysrhythmias. Insulin sensitivity and insulin secretion decrease and this results in hyperglycemia (72). Effects on platelet and clotting function result in impaired coagulation and increased bleeding. Hypothermia can impair the immune system and increase infection rates (83). On the other hand, the TTM trial did not reveal any significant difference in complication frequencies between treatment with 33°C compared with 36°C, with the exception of hypokalemia, which was the only complication that was more common in the 33°C group (84).

Evidence for MIH in children is not convincing and one large randomized study exist that did not show a significant benefit in survival with a good functional outcome at one year (85) when MIH was compared to normothermia. A study of in-hospital cardiac arrests in children showed the same disappointing results (86).

1.7 Factors of importance for prognosis

The majority of prognostic factors are found in the prehospital phase of OHCA and are well documented at group level.

In many studies, a first recorded rhythm of VT or VF has been associated with a more favorable prognosis as compared with a non-shockable rhythm. It has even been referred to as the most important factor for both an increased chance of survival and neurological outcome (87). It is instinctively easy to imagine that shockable rhythms are easier to treat and have a better prognosis. A meta-analysis showed that the pooled odds ratios for survival to hospital discharge among patients found in VF/VT compared with those found in all other rhythms ranged from 2.91 to 20.62 (88).

Asystole is regarded as a lethal sign or even as a sign of an irreversibly damaged heart. The reasons for this perception are also based on the fact that survival is extremely low in patients found with asystole. Studies have

demonstrated zero or only up to at most five percent of patients surviving an asystolic OHCA (89-91).

The magnitude of the ischemic insult is important and the time from arrest to the start of CPR and the time from arrest to ROSC are important predictors of the outcome (87). Time to ROSC has been shown to be an important and independent predictor of the risk of death or of an adverse neurological outcome in several case series, even in the era of advanced post-resuscitation care (18, 92). Adverse neurological outcomes have been shown to occur from five minutes of global cerebral ischemia (93).

Other important factors that indirectly indicate early and effective CPR and hence are important for the prognosis are whether or not the cardiac arrest was witnessed, whether bystander CPR was performed before the arrival of the EMS, the response time for the EMS, the age of the patient (94) and the level of consciousness on admission to hospital (18).

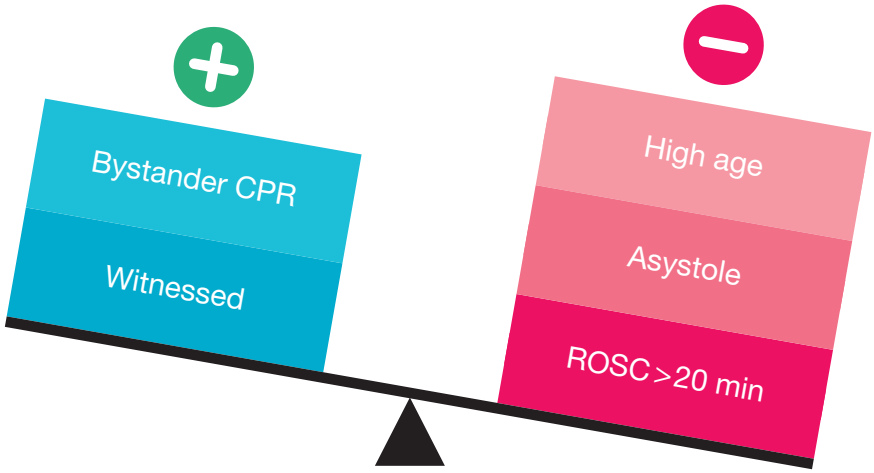

Figure 1. Factors of importance for prognosis

1.7.1 Settling a prognosis

When patients arrive at hospital unconscious after a cardiac arrest, we have limited knowledge of their prognosis. Mortality remains close to 50% for comatose patients admitted to ICUs following OHCA (84). For patients

whose cardiac function is re-established and who do not die due to multi-organ failure, the long-term prognosis depends on the neurological outcome (34). However, the neurological outcome cannot be assessed with any certainty during the initial days of intensive care. Uncertainty about the prognosis is a challenge for patients, relatives and caregivers. Extended care might also be painful for relatives and take resources from other patients if survival is not possible. Post-cardiac arrest brain damage ranges from very subtle defects in memory to persistent coma and vegetative states. It is therefore important to try to find prognostic tools to identify the patients who will benefit from prolonged intensive care treatment; both because of the cost of care but also in order to avoid more stress for the patient and relatives. We need a reliable tool with no or a very low margin for a false prediction of a poor prognosis, since this can lead to the premature withdrawal of life support. The risk of a self-fulfilling prophecy is substantial if we make incorrect decisions. At the same time, we need to take account of the risk of extending futile care with pointless suffering for the patient and the relatives.

Within minutes of circulatory arrest, all brain functions cease. After ROSC, there is a gradual recovery of neurological functions. The first to recover are brainstem reflexes, followed by a stereotypical reaction to painful stimuli and subsequent cortical activity and consciousness (95). Prolonged circulatory arrest is associated with a more delayed or incomplete recovery. However, even in the group of patients where more than 25 minutes from collapse to ROSC have passed, meaningful survival rates are reported (96).

There is no test that predicts outcome during the first 24 hours after collapse. Previous guidelines recommended predictions of prognosis 72 hours after the cardiac arrest (97). Mild induced hypothermia, as well as additional factors such as the use of sedatives and organ dysfunction, can further affect brain function. This might delay the recovery of cerebral function for up to six days (98).

The more recent recommendations are to wait four to five days before making a final prognosis, after which the withdrawal of life support can take place unless a few rare negative predictors are present. There are specific guidelines for prognosis in these patients (99). A multimodal approach is important in order to evaluate whether further care of the unconscious patient is meaningful. This includes both a clinical examination of brainstem reflexes and electroencephalography (EEG), somatosensory evoked potentials (SSEP), biochemical markers (NSE) and brain imaging with computed tomography and magnetic resonance techniques (99). It is unfortunately not

possible to perform an SSEP test in many hospitals and the routine for biochemical testing varies.

If, at an examination performed 72 hours after the cardiac arrest, the pupillary light and corneal reflexes are abscent and the patient has bilaterally absent response in the SSEP, this combination gives a sufficient predictive value of close to 100% for a poor neurological outcome.

The withdrawal of life-sustaining therapy is the most frequent cause of death (approximately 50%) in patients with the prognosis of a poor outcome (34), proving the importance of the prognosis plan.

A questionnaire study revealed that the Nordic countries do not treat OHCA patients in a uniform way. There are large differences with regard to the patients that are admitted to an intensive care unit, the patients who are treated with MIH, revascularization routines and prognosis after OHCA. The most alarming fact described in this study was that, in many cases, making a prognosis after OHCA appears premature (<72h) and only based on clinical findings (100).

1.7.2 Early assessment of the risk of a poor outcome

Non-disease-specific prediction methods have been investigated in terms of capacity to predict the outcome after OHCA. The Acute Physiology and Chronic Health Evaluation II (APACHE) score (101) has repeatedly been shown to be a poor predictor of outcome in OHCA (102). Efforts to construct specific scores to assess the individual risk of a poor outcome based on the set of data available at hospital admission have yielded the out-of-hospital cardiac arrest (OHCA) score (103) and the cardiac arrest hospital prognosis (CAHP) score (104).

The OHCA score presented in 2006 was based on a small cohort (n=130) and the patients were relatively young compared with other OHCA cohorts, including patients with a median age of 55 years and no patients older than 69 (103). The CAHP score, published in 2015, based on a large number of patients, has performed best so far, with an area under the curve (AUC) of 0.93. None of these scores has been validated for clinical use.

A robust prediction score could be helpful in estimating the possible effects of potential interventions in clinical trials, guiding critical care and informing relatives.

Another illness severity score presented in a study from Pittsburg in 2011 was created by combining the Full Outline of UnResponsiveness (FOUR) score and the Sequential Organ Failure Assessment (SOFA) score. Four distinct categories of post-cardiac arrest illness severity could be measured during the first few hours after ROSC. Survival and good outcome varied greatly between the categories. However, no category excluded survival with good neurological outcome (105). This score was validated in a later study where it was concluded that the Pittsburg Cardiac Arrest Category illness severity score could be used to make early estimations of prognosis but not with good individual precision (106).

1.7.3 Assessment of cerebral function in survivors

Most survivors in previous studies made a good recovery, as defined by the Cerebral Performance Category Scale (CPC) (Figure 2), even after the implementation of MIH. The fear expressed by some people that MIH would result in improved survival but with more patients with severe neurological deficits has not been confirmed. The best time point to evaluate neurological outcome has not been established, but most facts indicate a time point of six months after collapse. There is a change over time where patients who are still in a comatose state, CPC 4, at hospital discharge have a high probability of dying and patients in a CPC category of 2 and 3 may improve during the first six months or die (107).

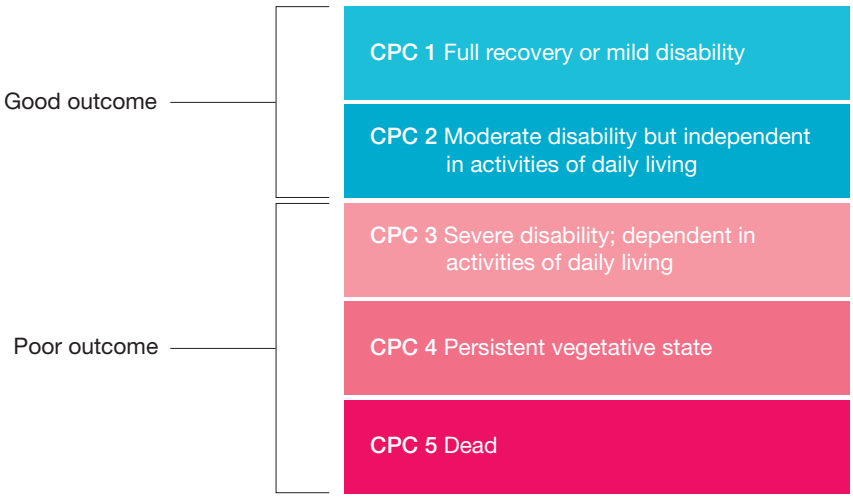

Figure 2. Cerebral Performance Category (CPC) Scale

A study of MIH-treated patients showed that a mild cognitive impairment was common, but this impairment had only minor effects on activities of daily living or quality of life. The mild impairments were not discovered in CPC, as the patients were classified as CPC 1 or 2, which represent a high functional level. Memory deficits and frontal lobe dysfunction were the most common neurological impairments (108). Results from other MIH-treated cardiac arrest patient groups showed results similar to those presented in a review (109).

To detect more subtle neurological deficits and cognitive defects, we need to use other tests, which are more sensitive to detect the degree of neurological recovery. The modified Rankin Scale (mRS) has shown that many patients with CPC 1 or 2 (good cerebral performance) still have degrees of disability and dependence on others, according to their mRS score (84). The precision can be further improved by neuropsychological testing and a meta-analysis of studies using these tests reports that as many as half the survivors of OHCA have measurable cognitive deficits (110). At the moment, no neuropsychological tests are recommended for survivors of OHCA because of their complexity and the lack of trained neuropsychologists who are able to perform them.

1.8 Gender differences

Epidemiological studies have shown gender differences within the population of OHCA patients, where women are generally older (111, 112), are less likely to have either a witnessed arrest (113, 114) or an arrest in public places (111, 115), to receive bystander CPR (111, 113, 114), or to have a shockable rhythm (112, 115).

While the pursuit of equality in treatment, with respect to gender, is an important objective for many societies, there is evidence that invasive cardiac procedures are performed less frequently in female than in male patients with an AMI (116, 117). In one study, female gender predicted both the lower use of MIH and poorer survival among patients hospitalized alive after OHCA. This might indicate the underutilization of medical resources among women who have suffered from OHCA (118).

Women more often had non-cardiac etiologies behind their arrests (5). However, in one study, female gender was shown to be an independent predictor of an overall increase in 30-day survival when including all patients with OHCA and not only focusing on those who were brought alive to a

hospital ward (119). The question of whether gender plays an independent role in variations in health-care delivery and whether this affects prognosis remains controversial and uncertain (119).

2 AIM

Many efforts are made to improve the care of patients who have suffered from OHCA. New treatment strategies have been introduced and it is important to evaluate and strive to obtain data for evidence-based medicine among these patients as well. The main goal is always to give the patients the best possible care. The present thesis had five major aims.

1) To study changes in survival and neurological outcome in relation to the introduction of modern post-resuscitation care.

2) To describe long-term outcome after VF in relation to the use of ICD and factors related to the implantation decision.

3) To develop a risk score for the prediction of outcome early after admission to hospital after OHCA. It is intended for population comparisons and to define patient risks when assessing effects and creating power calculations in interventional studies.

4). To evaluate the association between the use of MIH and 30-day survival.

5) To describe, in a 35-year perspective, the change in the number of patients who were brought alive to hospital after OHCA, the proportion and the number of patients who survived to 30 days after collapse.

3 PATIENTS AND METHODS

3.1 Background data

3.1.1 Reporting of cardiac arrest

All the studies in this thesis have an observational design and data are registered according to the Utstein guidelines (120).

The Utstein guidelines were created as a collaboration project to create uniform reporting to enable the comparability of data from cardiac arrest studies. In 1990, there was an international resuscitation meeting at the historic Utstein Abbey in Norway (121). The problems of nomenclature and the lack of standardized language in reports were discussed. The discussions resulted in recommendations as a starting point for the more effective exchange of information and for improvements in international audits.

3.1.2 Outcome measurements

The main outcome measurements used in this thesis are survival and neurological function. We measure survival at 30 days (Paper IV), six months (Paper III), one year (Paper I), two years (Paper II) and also up to 10 years (Paper II). Survival has been assessed from national registers and hospital records.

The ultimate goal of resuscitation is survival with a good outcome. There is no recommended scale to measure outcome after cardiac arrest, but the standard for a long time has been to measure, as we did, a neurological outcome scale called the Cerebral Performance Category Scale (CPC) (122). The CPC was adapted from the Glasgow Outcome Scale for traumatic head injury (123). The strengths of the CPC score are its extensive use, simplicity and the fact that it can be dichotomized into a good (CPC score 1 or 2) and a poor (CPC score 3-5) neurological outcome.

Despite the historical importance and widespread use of the CPC, no validity or reliability studies have ever been conducted at any post-resuscitation time points at which it has been used (122). With regard to our retrospective data analyses, more advanced outcome scales than the CPC could not be used in the setting of our studies.

3.1.3 Registers

The Swedish Register of Cardiopulmonary Resuscitation (SRCR) started in 1990, after which its coverage has increased so that it now includes all the emergency medical services that report prospectively to this register. In Papers I, II and IV, some of the prehospital data were extracted from this source.

In the city of Gothenburg, a specific database for patients who were brought to a hospital ward with ROSC after OHCA was created. This register is an on-going project and now includes data from 1980 to the end of 2015.

Patients were prospectively included in the SRCR and prehospital data in the Gothenburg register come from the SRCR. Further medical data on patients admitted to hospital were obtained from hospital records. The data were collected retrospectively and include age, gender, previous medical history, the etiology behind OHCA, status on admission to hospital and, finally, investigations, treatments and complications during hospital stay. Cerebral function was estimated by a careful evaluation of the hospital records according to the CPC scale among survivors at discharge from hospital. The evaluation of the OHCA etiology was based on investigations after hospital admission. Information on hypothermia was also registered in more detail.

Information relating to factors at resuscitation was collected prospectively, whereas information relating to history and post-resuscitation care was collected retrospectively a couple of months after hospital discharge.

3.2 Ethics

Participation in the SRCR is voluntary. The research ethics guidelines including information, informed consent and confidentiality are taken into account and adapted to the documentation of data in the registry.

The majority of the patients who are reported to the SRCR are deceased. With respect to information and informed consent, there has been no contact with their relatives or acquaintances after they were reported to the register. All survivors after an OHCA are supposed to receive information about their participation in the SRCR. All data in the SRCR and the Gothenburg register were handled without the personal identity of patients and analyzed at group level.

Ethical approvals for the Gothenburg Register of Cardiac Arrest were applied for and were authorized by the regional ethics committee in Gothenburg, on 23 October 2000 (S394-00).

Following a subsequent application, the ethics committee gave its opinion that analyses from the register were uncontroversial and ethical approval was deemed unnecessary by the Gothenburg ethics committee on 7 January 2008 (465-07).

The Regional Ethical Review Board in Gothenburg, Sweden (S937-16), granted ethical approval for Paper IV on 5 December 2016.

The ethics committees in each participating country and institution approved the TTM protocol.

3.3 Study design, study populations, methods and objective

3.3.1 Paper I

Design and objective: This study was an observational register study. The objective was to present the outcome in a clinical cohort of all patients admitted to hospital after resuscitation from OHCA and to evaluate changes in survival and neurological outcome after the implementation of modern post-cardiac arrest care.

Patients: The study included all patients who were brought alive to a hospital ward after an OHCA in the Municipality of Gothenburg (n=1,603). They were found among patients in whom CPR was attempted between 1 October 1980 and 17 June 2006 (excluding the latter part of 2002 and the first part of 2003). No patients were excluded because of the cause of the arrest, age or other circumstantial factors.

Methods: Patients were divided into two time periods. The two periods included the following times: period 1 = 1 October 1980 to 30 June (n=1,415) 2002 and period 2 = 22 May 2003 to 17 June (n=188). The division of time periods was chosen because of the change in post-resuscitation care, with the introduction of MIH from 2003.

Data on the entire cardiac arrest cohort were obtained from the Gothenburg EMS system. Information from both the SRCR and the Gothenburg register constituted the source of data for the study.

3.3.2 Paper II

Design and objective: This study was an observational register study. The objective was to describe long-term survival among OHCA patients who were discharged from hospital in a 21-year perspective with particular emphasis on the implementation of ICDs among patients found in VF who survived to hospital discharge. A secondary aim was to study the characteristics of patients who were treated with ICDs compared with those who were not and factors of importance for mortality during long-term follow-up.

Patients: Patients who suffered an OHCA in the Municipality of Gothenburg who had VT/VF as the initial rhythm and survived to hospital discharge were included (n=390). They were selected from all the patients in whom CPR was started from 1 January 1988 to 31 December 2008. All patients were included regardless of age or the cause of the cardiac arrest. The time point of 1988 was chosen because that was the time when the first ICD implantation took place in our OHCA cohort.

Methods: Data on the entire cardiac arrest cohort were obtained from the Gothenburg EMS system. Information from both the SRCR and the Gothenburg register constituted the source of data for the study.

3.3.3 Paper III

Design and objective: This was a post-hoc analysis of the TTM trial (84) which recruited patients in 36 ICUs in Europe and Australia. The objective was to find predictors of poor outcome (CPC 3-5) at six months after collapse and to construct a score for prediction of outcome.

Patients: We performed a post-hoc analysis of data obtained in the TTM trial. The trial comprised adult patients (≥18 years) resuscitated from OHCA with a presumed cardiac cause, who remained unconscious (Glasgow Coma Score; GCS < 8) for more than 20 minutes after ROSC. The main exclusion criteria were 1) unwitnessed asystole as the primary rhythm and 2) refractory shock at the time of admission to hospital defined as sustained systolic blood pressure less than 80 mmHg despite the administration of fluids,

vasopressors, inotropes and/or treatment with an intra-aortic balloon pump or left ventricular assist device.

A total of 939 patients were included in the original study. Neurological outcome data six months after cardiac arrest were available for 933 (99%) patients and were thus included in the present analysis.

Methods: Prehospital data and data from admission to hospital from the TTM trial were analyzed. Patients were included in the present post-hoc analysis if their CPC was recorded at six months after cardiac arrest.

3.3.4 Paper IV

Design and objective: This study was an observational register study. The objective was to present the outcome in a clinical cohort of unconscious patients admitted to intensive care after resuscitation from OHCA in relation to treatment with MIH. Neurological outcome was described.

Patients: Consecutive patients who were admitted unconscious to hospital were included among all adult patients with an OHCA in Gothenburg. The time period studied was 1 January 2003 to 31 December 2015 and all patients in whom resuscitation was started were monitored (n=871).

Methods: Data on the entire cardiac arrest cohort were obtained from the Gothenburg EMS system. Information from both the SRCR and the Gothenburg register constituted source of data for the study.

3.4 Statistical methods

Two-tailed tests of significance were used. P-values of <0.05 were considered statistically significant in Papers II and IV. In Papers I and III, the significance level was set at 0.01, because of the large number of comparisons.

All analyses were performed using SAS 9.3 for Windows or SPSS v23.

3.4.1 Descriptive statistics

Categorical variables are presented as numbers and percentages, while continuous variables are presented as medians with 25th and 75th percentiles or 10th and 90th percentiles, or as means with standard deviation.

3.4.2 Univariate relationships

Fisher's permutation test or the Mann-Whitney U test were used for group comparisons regarding continuous/ordered variables, whereas Fisher's exact test was used for dichotomous/categorical variables.

Logistic regression was used to calculate odds ratios (OR) with corresponding confidence intervals. Continuous variables not fulfilling linearity assumptions were transformed using either natural logarithm or square root transformation.

3.4.3 Multivariate analyses

Cox's proportional hazard model was used for the multivariate analysis in Paper II. In Papers III and IV, multiple logistic regression was used for the multivariate analysis, in a backward stepwise mode to select relevant variables.

3.4.4 Multiple imputation

Multiple imputation is a statistical technique for analyzing incomplete data sets. It aims to allow for the uncertainty associated with missing data by creating several different plausible imputed data sets and appropriately combining the results obtained from each of them. This technique was used in Papers III and IV. Missing data were assumed to be missing at random (MAR), $p<0.05$ for Little's test of missing completely at random (MCAR) and 50 imputed data sets were generated with the Markov Chain Monte Carlo method and using the expectation-maximization algorithm. Rubin's rules were used when pooling the results from the imputed data sets.

3.4.5 Score system

In Paper III, we developed a risk score for poor outcome (CPC 3-5) at six months. The model quantifies the impact of measurable risk factors. We strived to reach a model that is both easy to use and can be statistically

derived using known techniques. The model was based on a method described in an article from the Framingham material (124).

Because of the number of missing values, multiple imputation was performed. Multiple logistic regression was performed in each of the 50 imputed data sets and the variable with the highest p-value in the pooled result was excluded from the model. A new regression analysis was then performed in each imputed data set and, of the remaining variables, the one with the highest p-value in the pooled result was excluded. This procedure was repeated until all the remaining variables yielded a p-value of below 0.01 in the pooled result and these variables were identified as predictors.

These variables were then used to develop our prognostic risk score (TTM risk score). Briefly, the increase in risk associated with a five-year increase in age was set to correspond to one point in the score. Using the beta coefficients from the final multiple regression model, each risk factor category was allocated points based on its relationship with the model's beta coefficient for age (times five).

The area under the receiver-operating-characteristic (ROC) curve was used to evaluate discrimination, while the Hosmer-Lemeshow goodness-of-fit test and the concordance percentage was used to evaluate calibration.

3.4.6 Propensity score

Propensity may be defined as an individual's probability of receiving the intervention given the complete set of all the individual's covariate values. Matching, stratification, or regression adjustment with the propensity score can be used to produce unbiased estimates of the treatment effects and create covariate balance between groups. In Paper IV, we used stratification on the propensity score, by grouping subjects into quintiles of the propensity score. Treatments were then compared by pooling the results from the different quintiles, using Zelen's test to test for homogeneity across strata. The propensity score was constructed using multiple logistic regression on complete data, with backward stepwise selection and $p < 0.30$ as the condition for staying in the model.

3.4.7 Long-term follow-up

In the long-term follow-up in Paper II, percentage cumulative mortality was assessed by 100*(1- Kaplan–Meier survival estimate).

3.4.8 Patient selection and risk of bias

Selection bias is most likely an issue in our studies in the form of decision-making for interventions and non-measured confounders for this choice.

The effect of a treatment strategy in heterogeneic patient groups is very difficult to evaluate. The possibility that the difference in outcome is simply due to differences in baseline characteristics within the study population cannot be eliminated. The problem of the heterogeneity of study participants is especially pronounced in observational studies. This problem is given different names: selection bias, bias by indication or poor internal validity. Even though adjustments can be made for known confounding factors, unknown confounding factors are more difficult to tackle.

4 RESULTS

4.1 The cardiac arrest population after out-of-hospital cardiac arrest

In Paper I, we analyzed all the patients with OHCA, between 1980 to 2006, in the Gothenburg register (n=1,603). They were analyzed in two time periods in which the cardiac arrest population in the two cohorts had a median age of 67 and 66 years respectively and were predominantly male (70%). The percentage of patients admitted alive with a shockable rhythm decreased and, in the latter time period, the initial rhythm was shockable in 50% of the cases compared with 62% in the first period. There was no significant difference in terms of a previous history of myocardial infarction or heart failure between the two time periods and, in the first time period, a history of myocardial infarction was found in 37% of the patients and heart failure in 30%.

In Paper II, we analyzed data from a subset of patients in the Gothenburg register with an initial shockable rhythm, who were discharged from hospital between 1988 and 2008 (n=390). The patients receiving an ICD were younger (57 years) and often had a previous history of myocardial infarction (53%) or heart failure (37%).

In Paper IV, we analyzed data from a subset of patients from the Gothenburg register, who were unconscious at admission to hospital between 2003 and 2015 (n=871). This patient cohort was somewhat older, mean age 69, and 67% were male. The percentage of patients with a shockable rhythm was 41% among those who were unconscious (47% in all patients; both awake and unconscious). Fewer patients had a previous history of myocardial infarction or heart failure compared with the percentages in Paper I. The majority of patients had a cardiac arrest of presumed cardiac cause (59%) and 41% had an AMI.

The population in Paper III came from the multicenter TTM trial, recruited from November 2010 until January 2013 (n=933). They were unconscious OHCA patients who required intensive care. All types of rhythm, with the exception of unwitnessed asystole, were included. The patients had a mean age of 64 years and were predominantly male (81%). The initial rhythm was shockable in 80% of the patients.

4.2 Cardiac interventions

As shown in Paper I, an increasing number of patients (11% increasing to 33%) were referred to coronary angiography and PCI was performed in 3% in the first period. This increased to 20% in the latter period. Only a few patients received thrombolysis or coronary artery bypass grafting.

4.3 Implantable cardioverter defibrillator

More investigations were conducted on the patients in the ICD group (Paper II). Eighty-six percent underwent coronary angiography, 67% electrophysiological testing and 98% ultrasound cardiography. In the ICD group, however, only 10% underwent PCI and 10% underwent coronary artery bypass surgery. Significantly more patients in the ICD group had been treated with MIH.

Patients who received an ICD had a better CPC score at hospital discharge compared with those who did not.

4.4 Outcome at hospital discharge, 30 days, six months and two years

Survival to 30 days in Paper I was 33% and 35% in the two time periods respectively, while a good outcome (CPC of 1 or 2) among survivors had increased between the studied time periods from 71% to 94% at hospital discharge. No patient was in a coma (CPC4) in the second time period compared with 3% in the first time period. The long-term follow-up showed no difference in one-year survival between the two time periods and was just slightly lower compared with 30-day survival.

In Paper II, there was no difference in survival to 30 days between patients receiving an ICD or not. However, there was a significant difference in survival to one and two years in favor of the patients receiving an ICD, where 98% of the patients with an ICD were alive two years after the cardiac arrest, compared with 75% in the group without ICDs.

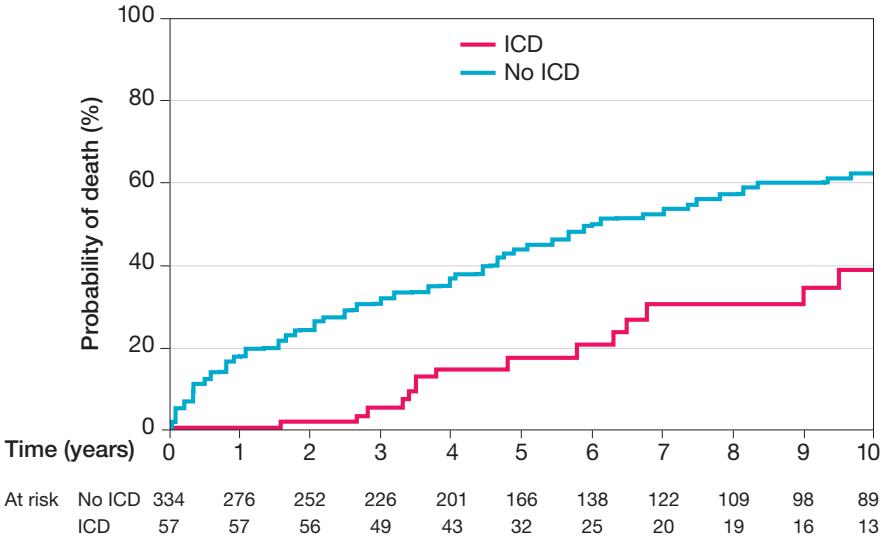

Figure 3. The probability of death over time in the group who received ICDs and the group that did not (Figure adapted from Paper II, with permission from the publisher).

As shown in figure 3, the Kaplan-Meier curves indicate an increased risk of death in patients without ICDs during the first two years, but the curves appear to run more parallel thereafter. The mean follow-up period was 5.5 years (Paper II).

In Paper III, survival with good outcome (CPC 1 or 2) at six months was 47% (440/933 patients).

In Paper IV, including patients who were unconscious on hospital admission, the total survival to 30 days was 23.5%. Survival among patients found in a shockable rhythm was 43.8% compared to 9.6% among patients found in a non-shockable first rhythm. Survival to 30 days in patients not treated with MIH was 13.2% versus 36.5% in patients treated with MIH. The unadjusted odds ratio (OR) for 30-day survival in patients treated with MIH compared with non-MIH treated patients was 3.79 (95% CI 2.71-5.29; $p<0.0001$). After adjusting for factors potentially influencing outcome, using stratified propensity score analysis, the OR for 30-day survival was not statistically significantly higher in patients treated with MIH compared with non-MIH treated patients; OR 1.33 (95% CI 0.83-2.15; $p=0.24$). Using multiple imputations to handle missing data yielded a similar OR of 1.40 (95% CI 0.88-2.22; $p=0.15$).

Eighty-two percent of the patients had a good neurological outcome at discharge from hospital.

4.5 Predictors of outcome

We identified ten independent predictors of a poor outcome (Paper III): higher age, cardiac arrest occurring at home, initial rhythm other than VF/VT, longer duration of no flow, longer duration of low flow, administration of adrenaline, bilateral absence of corneal and pupillary reflexes, Glasgow Coma Score – Motor 1, lower pH and a $PaCO_2$ value lower than 4.5 kPa at hospital admission. No-flow and low-flow times were defined as the time from the cardiac arrest to the start of CPR (basic or advanced life support) and the time from the start of CPR to ROSC respectively.

4.6 Score

Independent predictors of outcome were used (Paper III) to create a score for the early prediction of survival with poor outcome (CPC 3 to 5) at six months. The score was based on the impact of each of the ten independent variables and it yielded a median AUC of 0.842 (range:0.840-0.845) and good calibration. Internal validation of the score, using bootstrapping, yielded an AUC corrected for optimism of a median of 0.818 (range; 0.816-0.821). Using our score, a high value (>16 points, applying to 23-24% of the patients) represented a satisfactory positive predictive value (PPV) of 91% and a specificity of 95-96% and therefore a satisfactory margin not to predict a poor outcome in a patient with a good prognosis. However, the corresponding sensitivity was only 40-41%. Optimizing both sensitivity and specificity (only 69-70% and 83-84% respectively) would render a cut-off score >13 points, which was no more useful, as the PPV was reduced to 71% (table 1).

Table 1. Discrimination performance of the TTM risk score – min-max of the first 5 imputations

	>10	>13	>16
n (%)	612–615 (66–66)	410–417 (44–45)	217–221 (23–24)
Sensitivity (%)	86–87	69–70	40–41
Specificity (%)	57–58	83–84	95–96
PPV (%)	69–70	82–83	91–91
NPV (%)	79–80	71–71	59–59

Table 1. Discrimination performance of the TTM risk score in our cohort. The TTM risk score is divided in quartiles where the Youden's J statistic cut-off (>13 points) coincides with second quartile upper limit (i.e. the median). n-number, PPV-Positive Predictive Value, NPV -Negative Predictive Value.

Table 2. Independent predictors of long-term risk of death

	Hazard ratio	95% confidence	p interval
Cerebral function at discharge CPC score	1.71	1.43–2.04	< 0.0001
Previous history of			
Myocardial infarction	1.90	1.38–2.61	< 0.0001
Congestive heart failure	1.49	1.07–2.07	< 0.0001
Age (continuous variable)	1.06	1.04–1.08	< 0.0001
Investigation			
Coronary angiography	0.63	0.42–0.95	0.03

Table 2. In Paper II we found these factors which were associated with the long-term risk of death in the group of patients discharged from hospital who were found with an initial rhythm of VF. The increase in hazard ratio for CPC represents each increment in the CPC scale.

5 DISCUSSION

In order for studies to be comparable, they need to use the same definitions of the cardiac arrest and population at risk. The definition of an OHCA could be either all patients who suddenly collapse outside a hospital or only those attended by EMS personnel or only those in whom resuscitation was attempted or only those with a presumed cardiac cause and so on. The population may include all the people in a region, only adults or only children and patients may also be included by cause of the arrest. The main definition of an OHCA is a cardiac arrest outside a hospital. CPR is not started in all these cases, but, of those in which CPR is started and that are reported, approximately 20% to 25% regain circulation and are admitted to a hospital ward. This thesis focuses on the patients admitted to hospital after a reported OHCA where CPR was attempted and therefore comprises an uncertain fraction of all patients with an actual OHCA. On the other hand, the fraction of patients in whom resuscitation is started represents all the patients with the potential to survive.

In this doctoral dissertation project, we have investigated cardiac arrest patients from various aspects of post-cardiac arrest care. In an attempt to describe and evaluate the clinical aspects of ICD, MIH and other hospital interventions, we have evaluated data from the Gothenburg register in the search for factors associated with positive effects on survival and neurological outcome. We have also strived to create a tool for predicting a poor outcome to be used as an assessment of risk after cardiac arrest. This would be of great value for comparing populations and defining patient risk when estimating possible treatment effects in future interventional studies.

5.1 Epidemiological changes in out-of-hospital cardiac arrest over time

The majority of studies that compare total survival from OHCA indicate a positive trend in terms of an increase in survival over time (16, 125). The sometimes pessimistically described static survival rate in OHCA over the past few decades (88) is not the result of an unchanged pattern of prehospital and in-hospital characteristics but appears to represent a change in the balance of prognostic factors.

The incidence of patients found in an initial rhythm of VF has decreased in recent decades (23, 24, 126, 127). Among the different initial arrhythmias, VF is the most common among patients with a cardiac etiology. The majority of survivors are patients found with an initial rhythm of VT/VF. The trend towards increasing survival in VF (15) was also found in our analyses (Paper I), although it does not correspond to any increase in total survival. The improvement in survival in VF OHCAs suggests that modern post-resuscitation cardiac care has changed for the better.

Time intervals from cardiac arrest to the start of CPR and defibrillation have increased in Sweden (128). The proportion of patients who receive bystander CPR has also increased and, in some countries such as in Sweden, the change has been dramatic, from 46% to 73% between 1992 and 2009 (111). More frequent bystander CPR probably increases the number of cases in which EMS personnel initiate resuscitation efforts and it is believed that bystander CPR slows down VF deterioration into asystole. To improve the time to defibrillation, there have been large-scale efforts involving the placement of AEDs in public areas in the western world.

Patient characteristics such as age, gender distribution and the location of the arrest have mainly remained unchanged. Out-of-hospital cardiac arrests most frequently occur in the patient's home (two thirds), but the prognosis is shown to be better when they occur in a public place.

Changes in hospital care include the introduction of MIH and the more detailed monitoring and manipulation of physiological parameters and earlier revascularization.

5.2 Prediction of prognosis on arrival to hospital

Many studies have identified factors associated with poor functional outcome after resuscitation, but none of these is useful alone in predicting survival. For all patients who suffer from OHCA, the most important predictors of survival are whether the arrest was witnessed or not (89, 129); whether the patient was found in ventricular fibrillation or not (89, 129); whether bystander CPR was performed or not (21, 89, 129, 130); and the time to ROSC (18, 92).

Most of the currently available scores for evaluating general severity in ICU patients (101) require a 24-hour wait for data collection and history taking. A score that predicts outcomes based on variables available at ICU admission

could be used both in randomized studies and in interpreting the results of epidemiological studies. The OHCA score (103) and CAHP score (104) both used variables readily available at admission to the ICU. The OHCA score studied a small sample size and a selected cohort and deserves to be replicated. The CAHP score was based on the larger database from the Paris Sudden Death Expertise Center (104).

In Paper III, we identified ten early predictors of a poor outcome (CPC 3-5) at six months and used these to create a prognostic score. These independent predictors of a poor outcome were higher age, cardiac arrest occurring at home, initial rhythm other than VF/VT, longer duration of no flow, longer duration of low flow, administration of adrenaline, bilateral absence of corneal and pupillary reflexes, Glasgow Coma Score – Motor 1, lower pH and a $PaCO_2$ value lower than 4.5 kPa at hospital admission. A risk score based on the impact of each of these variables in the model yielded a median AUC of 0.842 (0.840-0.845) and good calibration. Internal validation of the score, using bootstrapping, yielded an AUC corrected for optimism of a median of 0.818 (0.816-0.821).

The results of our study show that, by using a simple, easy-to-use risk score system based on these variables, patients running a high risk of a poor outcome after OHCA could be identified early. As our score shows a somewhat linear association with outcome, there was no optimal cut-off at which both sensitivity and specificity were high.

All the scores described above require external validation before extensive use and they all appear to have the same problem of losing sensitivity when reaching an acceptable specificity. I believe the most important aspect of a good score to predict prognosis is to have good specificity in order not incorrectly to predict a poor prognosis that might prevent treatment and survival.

When using the OHCA and CAHP scores in our patient material, they both lost power in terms of sensitivity and specificity in the same fashion as our score most likely also would have done when used in a patient population other than the one on which it was modeled. Does this mean that these score systems are useless? None of these scores is optimal and they need to be used with a knowledge of their weaknesses. So far, they are not suitable for clinical use and definitely not for predicting individual patient prognoses.

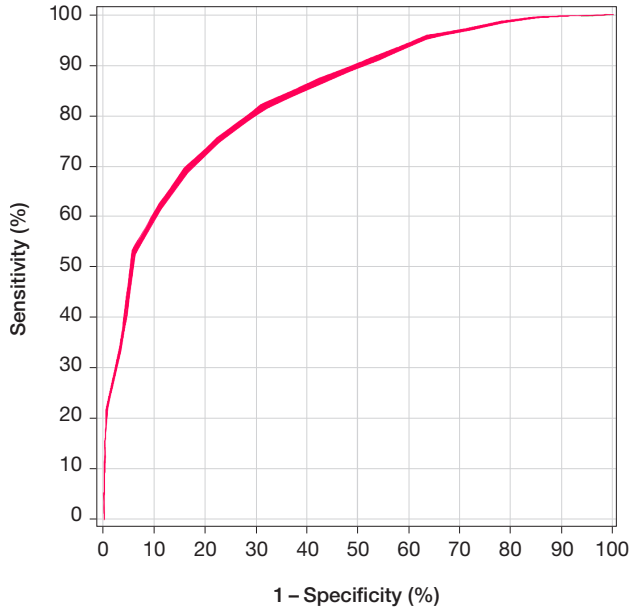

Figure 4. Area under the receiver operator curve for the TTM risk score

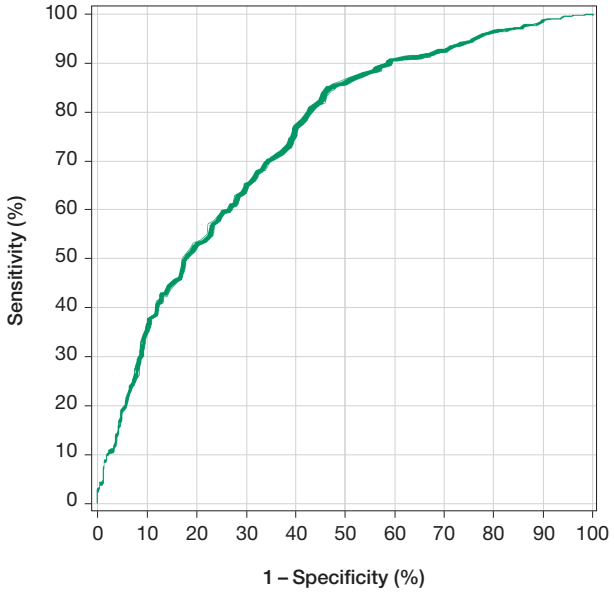

Figure 5. Area under the receiver operator curve for the OHCA risk score

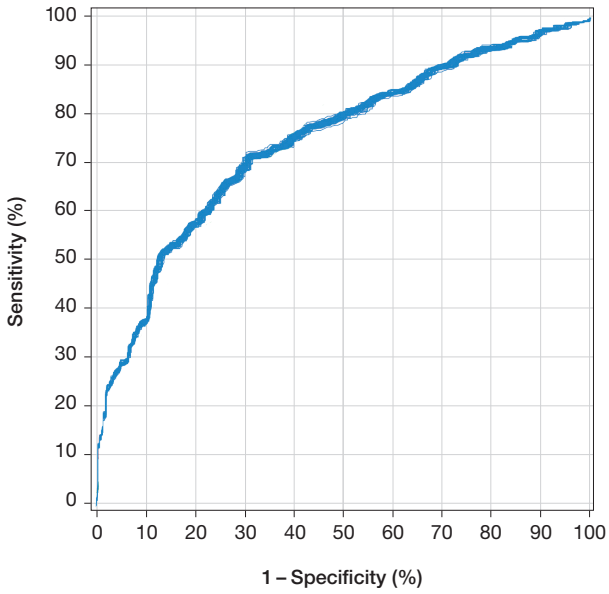

Figure 6. Area under the receiver operator curve for the CAHP risk score

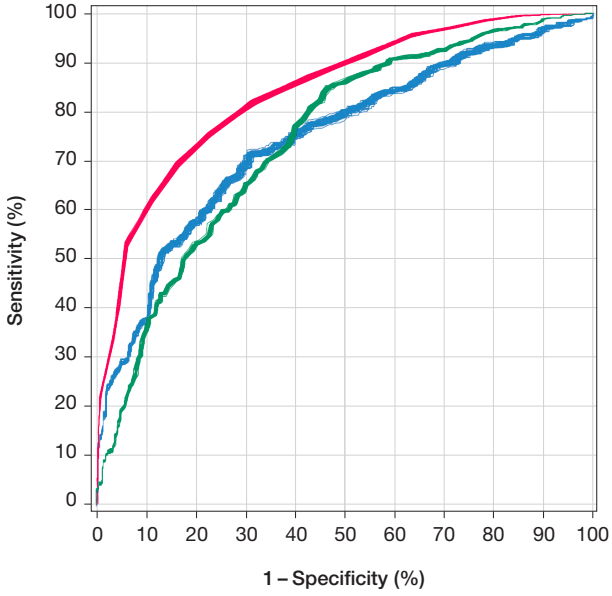

Figure 7. Area under the receiver operator curve for the three risk scores; red lines TTM score, green lines OHCA score and blue lines CAHP score.

5.3 Changes in survival over time among patients hospitalized after an out-of-hospital cardiac arrest

The proportion of patients who survive the hospital phase of an OHCA varies considerably. Studies of large patient series have shown that between 30% and 60% of hospitalized patients can be discharged from hospital (28, 52, 131).

In-hospital survival also varies between hospitals and regions within the same country with similar medical systems and populations (28, 132). In Sweden, it was shown that the figures could vary from 14% to 42% (132).

One of our main findings is that mortality for patients admitted to hospital after OHCA in Gothenburg has not increased since the database was created in 1980 (Papers I and IV), as shown in Figure 8.

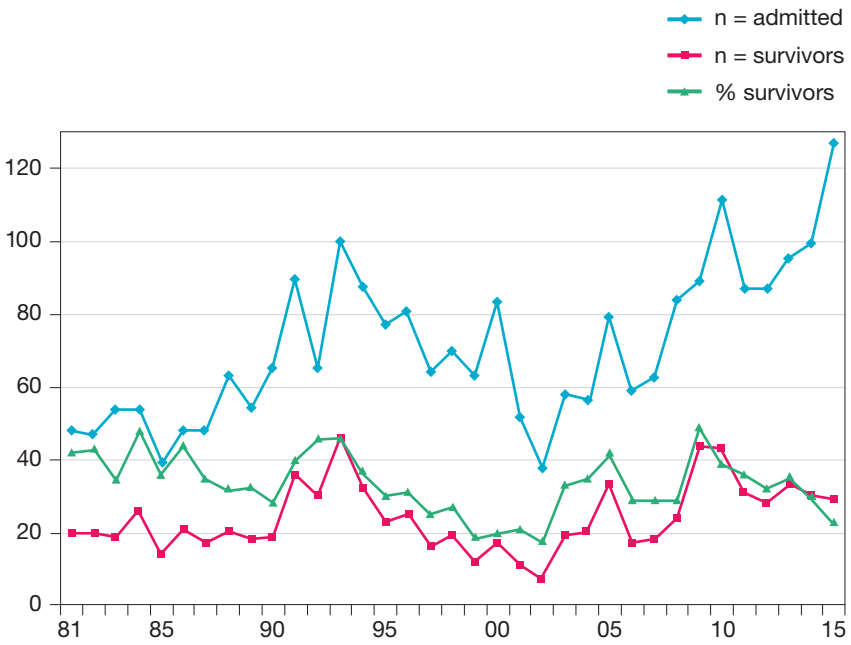

Figure 8. Survival per year 1981-2015 described as number of patients admitted to hospital after ROSC, number of survivors and percentage of patients who survive to 30-days.

We did not find any sign of an increase in 30-day survival after the implementation of modern post-resuscitation care with MIH and more standardized care (Paper I). Instead, we found a trend indicating that survival, if anything, might be decreasing in terms of percentage values (Paper IV), Figure 8. There are no good explanations of this trend. To speculate, there might be a change in the group of patients admitted to intensive care where boundaries are pushed and we treat patients with more advanced diseases. However, this was not reflected in the patients' previous history, which did not become more severe over the years. It is encouraging that most patients survive with a good neurological outcome and that this fraction has increased over the years. What this means is that 82% (Paper IV) to 94% (Paper I) of the survivors have good neurological function, when measured with the CPC score at discharge from hospital. There is evidence that these numbers increase with a longer follow-up, even if the optimal timing of measurement is not clear (107).

With the exception of a decrease in the occurrence of VF/VT as the initial arrhythmia, there is no good explanation for the fact that survival following OHCA in Gothenburg had not increased from 1980 (Papers I and IV). Clearly, cardiac treatment such as anti-arrhythmic drugs, medical treatment for ischemic heart disease, ICDs and PCI has improved over the years. This has led to increased survival in patients with AMI (without OHCA) since the mid-1990s (133), mainly believed to be an effect of the above-mentioned treatments. However, as previously stated, the number of survivors appears to increase (although not the proportion of survivors, figure 7), as well as the proportion of survivors with good cerebral function.

As previously stated, an additional possible explanation of the lack of increase in survival rates includes the decline in the proportion of patients with OHCA found in VF. This finding has also been reported by others (126, 134).

About 35% of the patients survived and the absolute majority had a CPC of one or two at discharge from hospital (Paper I and Paper IV). Only a few patients survived but remained in a coma. When MIH was introduced, there was concern that this would also increase the proportion of patients who were alive but were severely brain injured. The conclusion from our results is that, in the majority of cases, the patient will either die or survive with a good or relatively good cerebral outcome.

Most studies report overall survival and not hospital survival specifically. A meta-analysis of 79 cohort studies, published between 1984 and 2008,

showed that survival from OHCA had not improved significantly in almost 30 years. They presented aggregate survival rates, recorded across various populations, of between 6.7% and 8.4% (88). Another large meta-analysis comprising 67 studies also showed average survival following adult OHCA of 7% (24). Differences between continents were found in this analysis. Asia had the lowest percentage of VF and also the lowest survival rates. Asia also had the highest percentage of EMS-treated OHCA, which was negatively associated with survival. It was reported that the EMS crews in Asian countries initiate CPR in patients even when the patient appears to have been without circulation for a long time. In these cases, it is likely that they would have encountered less VF and had lower survival rates.

It is important to stress that the studies referred to (24,44) were published seven years ago. More recent studies based on nationwide data suggest an improvement in 30-day survival after OHCA both in Denmark and in Sweden (16, 125).

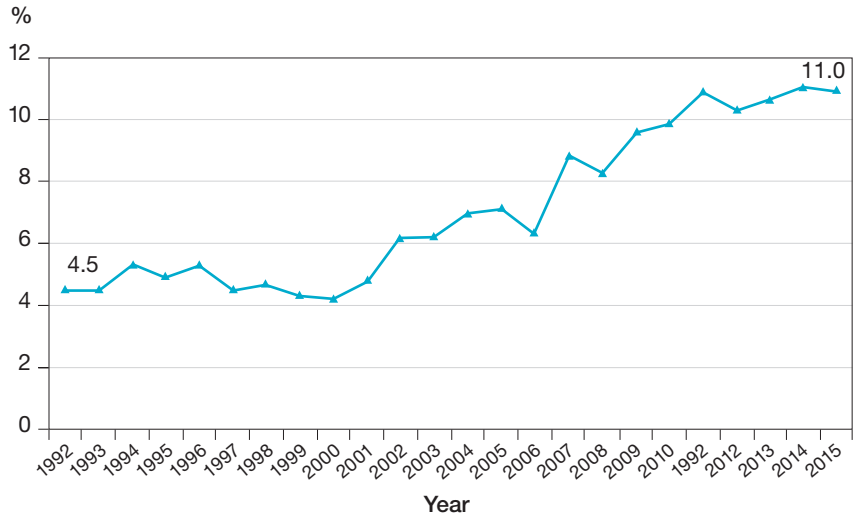

Figure 9. The total 30-day survival from the 2016 report from the Swedish Register of Cardiopulmonary Resuscitation between 1992 and 2015. Source SRCR 2016.

Survival over time presented in the annual report of the SRCR shows increasing survival that more than doubled between 1992 and 2015 (Figure 9).

A reflection from my clinical experience is that most professionals have an exaggeratedly pessimistic opinion of the prognosis for OHCA patients. The in-hospital survival of OHCA patients is between approximately 30% and 55%. The appearance of an unconscious patient without any recurrence of brainstem reflexes naturally fails to generate optimistic feelings about prognosis, but it is important to remember that the brain needs time to recover.

5.4 Changes in survival over time among patients found in ventricular tachycardia or fibrillation admitted to hospital

Ventricular fibrillation as the first registered rhythm is one of the absolutely strongest predictors of survival in OHCA (24, 135). In the present investigations, the proportion of patients found in VF decreased in Gothenburg from 62% to 52% (Paper I).

Analyses of survival from specific groups of patients such as OHCAs found in VF are more positive. A cohort study of OHCAs found in VF in Sweden showed an increase in overall 30 day-survival from 12% to 23% between 1990 and 2009.

The true distribution of arrhythmias at the time of collapse is not known, since several minutes most often elapse between collapse and rhythm assessment. Since there are theories and evidence that VF deteriorates into asystole over time, shortening the time from collapse to defibrillation could increase survival. The application of AEDs by bystanders enables defibrillation attempts prior to EMS arrival. Bystander CPR slows down VF deterioration and thereby makes VF persist for a longer time period.

Several groups have pointed to a decreasing proportion of patients found in VF. A study from Minnesota, from 1989-2002, showed a clearly decreasing incidence of OHCA where patients were found in VF (126) and this was also shown in another part of the US, in Seattle, in 1971-2001 (127). Kuisma and co-workers in Finland in 1994-1999 (134) also reported a decline in the proportion of patients with VF as the presenting rhythm, all in accordance with the results of Paper I. In parallel with a decrease in the proportion of patients with OHCA presenting with VF as the initially registered rhythm, survival among VF patients was observed to increase in our investigations. The results from Paper I indicate that the increase in survival was mainly

encountered in patients who had been found with a shockable rhythm. In this group, survival increased from 45% to 59%.

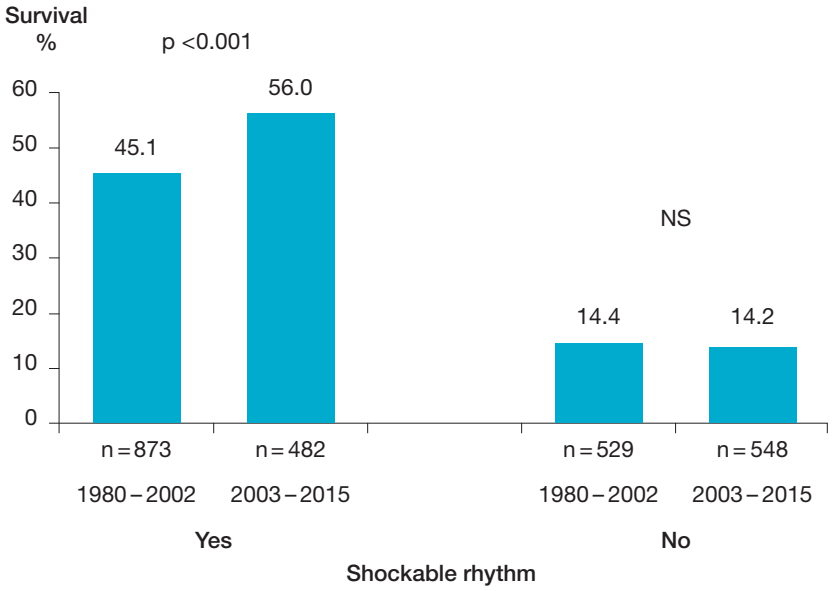

Figure 10. The 30-day survival in relation to initial rhythm in Gothenburg between 1980-2015. Source Gothenburg registry.

When analyzing survival in patients found with an initial shockable rhythm over time 1980 to 2015 there is a significant increase in from 45.1% to 56.0%. This was already shown in Paper I but in a smaller group of patients (Figure 10).

The reasons for a decline in the proportion of patients found in VF, in combination with the increased survival in this group, are not fully understood. Suggested causes of a decline in patients with OHCA who were found in VF include the decreasing incidence of coronary heart disease (134), as well as the presumption that more patients today (with updated therapeutic regimens including new medications, such as beta-blockers and ACE inhibitors, earlier revascularization and ICD implantation) reach an "end-stage" heart disease prior to OHCA (23). It is thus possible to speculate that OHCA patients nowadays present to a larger extent with non-shockable rhythms as part of heart failure. Possible contributory explanations for the improvement in survival in OHCA patients with VF could be the higher

proportion of patients receiving bystander CPR, working as a bridge to defibrillation by maintaining VF amplitude (136).

Increasing EMS response times have been reported in Sweden and also in Gothenburg over the years, as described in Figure 11. This might also influence the decreasing proportion of patients with VF as the presenting rhythm.

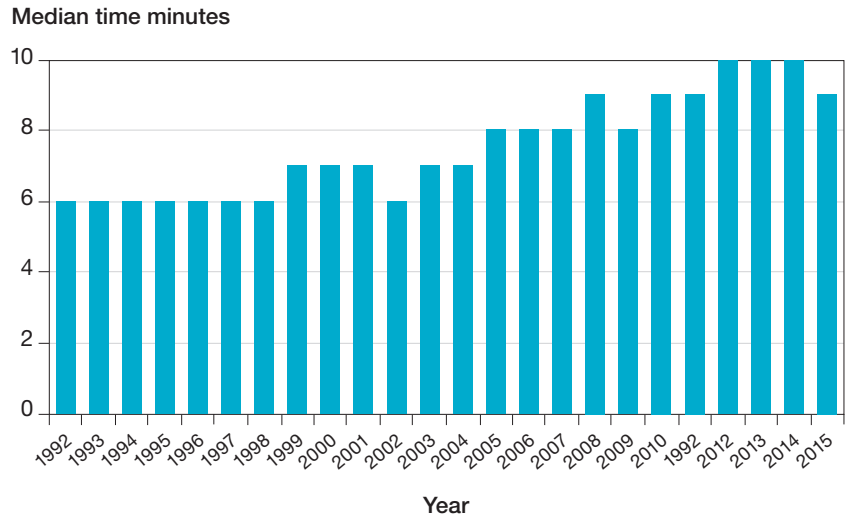

Figure 11. Time from emergency call to arrival of EMS 1992-2015. Source SRCR 2016.

Most of the VF OHCAs have a cardiac etiology and many in-hospital factors have changed mainly for this patient group. A more liberal indication for emergency coronary angiography has evolved. It was initially only this group which was treated with MIH, although this has changed over the years.

5.5 Changes in neurological function over time in survivors after out-of-hospital cardiac arrest

The improved survival that is being found in some studies has not been accompanied by an increase in survivors with severe neurological deficits. Survival rates after OHCA have increased between early neuroprotective trials of thiopentone (42) and subsequent studies using hypothermia (72, 73)

and most survivors in these trials consistently made a good recovery, as defined by the CPC. Mild cognitive impairment is common in hypothermia-treated OHCA survivors. Despite mild impairment, survivors have a high level of function, as reflected in the CPC categories, and their quality of life appears to be generally good. Overt neurological findings are uncommon in a clinical examination. The outcome categorized by CPC is dichotomized into survival with a good or poor neurological outcome or in fact a good outcome and death.

Cognitive impairments are common after OHCA and all cognitive domains can be affected, with memory being the most commonly and severely affected domain, followed by attention and executive functioning. An improvement in cognitive function over time was seen in some of the studies. A review article stated that, in the best three prospective studies that were found, cognitive problems were reported in 42%, 48% and 50% of the participants respectively (110). However, similar problems with memory and executive functioning have also been reported among survivors of myocardial infarction (19).

5.6 Long-term prognosis among patients who survived an out-of-hospital cardiac arrest

Studies from the 1980s, 1990s and 2000s all show four- to five-year survival after discharge from hospital of between 49% and 68% (137-139).

A previous study from Gothenburg showed that, in those patients who were discharged from hospital after an OHCA, one in five died during the first year and one in five survived 10 years after discharge. The prognosis was associated with a history of myocardial infarction, the prescription of beta-blockers at discharge, age and CPC at discharge (140). In a more recent study from Washington, a favorable CPC score at hospital discharge predicted a better long-term prognosis (29).

Many studies report a better long-term outcome if the cardiac arrest took place in connection with an AMI. Other frequently reported independent predictors of death after hospital discharge include increased age (140), low ejection fraction or other signs of heart failure (141) and a history of myocardial infarction (140). Although long-term survival in patients found with a non-shockable rhythm or non-cardiac etiology is lower than in patients

found with a shockable rhythm or a cardiac etiology, almost half have been shown to be alive five years following hospital discharge (138).

5.7 The role of implantable cardioverter defibrillator implantation after an out-of-hospital cardiac arrest

One factor that might influence the long-term survival rate after OHCA is the proportion of patients discharged from hospital who received an ICD. The implementation of an ICD in the OHCA population might be underused, since we found the number of patients who received an ICD was lower than expected, even if the implantation rate was increasing (Paper II). It is possible to speculate that a common reason for not implanting an ICD may have been that the cause of the OHCA was considered to be reversible. The most common reversible or transient cause of OHCA is AMI, but the diagnosis may be uncertain in some cases, particularly among cardiac arrest patients. The presence of chest pain before cardiac arrest is often unknown and the ECG may show signs of myocardial ischemia as a result of the cardiac arrest. Furthermore, CPR in combination with defibrillation may cause a transient leakage of biochemical markers, thus mimicking an AMI. The implantation of an ICD is also a costly procedure and recent studies have shown that physicians had a poor knowledge of the indications for ICD (Kinch et al. dissertation Karolinska Institute, Stockholm, non-published work). In earlier studies, there was evidence of a lack of diagnostic procedures among patients who survived the initial phase of OHCA and some of the patients who could benefit from an ICD may therefore have been missed.

It goes without saying that the chance of selection bias is obvious when comparing patients who received an ICD with those who did not. To some extent, we were able to compensate for this in the multivariable analysis with the known factors that differed such as age, previous history of myocardial infarction and heart failure, frequency of bystander CPR, neurological function when discharged from hospital and if discharged to previous residence and so on. In spite of this, we did not find that an ICD was an independent predictor of increased survival, but the benefit of an ICD after an OHCA has already been demonstrated with good quality evidence (31, 32).

Many patients who suffer from cardiac arrest and are treated with an ICD suffer from the combination of coronary artery disease and depressed

myocardial function. Even so, there was excellent two-year survival (98%) among these patients.

5.8 Evidence-based medicine in post-resuscitation care

Several treatment strategies are applicable during the post-resuscitation care phase, but the level of evidence is weak for most of them. Evidence-based therapeutic options can be divided into three groups.

1) The optimization of systemic physiological variables (body temperature, blood pressure, blood glucose, acid-base balance and electrolytes)

When it comes to the optimal physiological targets and general intensive care, the evidence indicates that severe hypo- and hypertension should be avoided, as well as hypo- and hyperglycemia. The treatment must focus on reversing the manifestations of the post-cardiac arrest syndrome with aspects of timing taken into account. Guidelines and the structured treatment optimization of post-cardiac arrest care may prevent the premature withdrawal of care before a long-term prognosis can be established. Improved outcome was shown at two different centers after the implementation of protocol-based therapy (7, 142).

2) Coronary interventions (thrombolysis, PCI and coronary artery bypass grafting)

Percutaneous coronary intervention is indicated when the probable etiology behind the cardiac arrest is myocardial infarction and a culprit lesion is found at coronary angiography. In recent years, there has been a more liberal indication for emergency angiography in comatose patients.

3) Anti-arrhythmic therapy (ICD, beta-blocking agents and amiodarone)

The evidence favors ICD therapy over anti-arrhythmic medical therapy (31, 32).

The patient's cerebral function might influence the implementation of treatment with an ICD and, to some extent, also the chance of angiography/PCI. Further randomized clinical trials of other post-resuscitation therapies are essential. The general care of cardiac arrest

patients has changed over the past few decades with the implementation of MIH and changes in prehospital care and in several aspects of post-cardiac arrest intensive care. Treatment at specialized institutions for a variety of medical diseases has been associated with a reduction in both mortality and morbidity. This might also be the case for post-resuscitation care. The standardization of prognosis is important for outcome and might avoid the premature withdrawal of care. Another factor that is important for the outcome is a possible Hawthorne effect (143) associated with the focus on and interest in this patient group.

5.9 Mild induced hypothermia and its role after an out-of-hospital cardiac arrest

Many therapies have been proposed and tested in previous decades without any proven beneficial effects. The concept of the chain of survival has been established, indicating the importance of each link in the treatment chain. There has been a distinct focus on the initial part of resuscitation, with layperson education and improvements in the performance of CPR. However, the post-cardiac arrest phase at ICUs has been a missing link in the chain of survival for decades (144, 145).

When two trials (72, 73), investigating the use of MIH after cardiac arrest, were published, there was an awakening in the interest in cardiac arrest patients, who in many respects had previously been neglected in the intensive care setting. The randomized trials of MIH included patients with VF and non-perfusing VT of cardiac etiology only and one of the studies excluded 92% of the screened cardiac arrest patients with ROSC (73). This limits the generalizability of the results. Mild induced hypothermia has been recommended in international resuscitation guidelines since 2005 and, despite a lack of proof beyond OHCA with an initial shockable rhythm, its use has been extended beyond the studied population also to include patients with cardiac arrest of other causes and with other initial rhythms, as well as to the in-hospital setting (76, 82, 146, 147). Numerous observational studies have indicated that MIH is beneficial in patients in the general OHCA population, including patients found in a non-shockable rhythm (7, 75-78). However, doubts still exist about the beneficial effect of MIH, especially in patients found in non-shockable rhythms (148, 149).

In 2013, a randomized multicenter trial showed no difference in survival or neurological outcome between patients with an OHCA with a presumed

cardiac cause, excluding unwitnessed asystole, managed at 33°C compared to 36°C (79). Studies of numerous subgroups in this trial have not yet shown any substantial benefits or differences between the two target temperatures (20, 80, 81).

We did not find any association between MIH and survival to 30 days (Paper IV). This could be due to either a) too small a number of patients in our analysis, indicating that the study was underpowered, or b) the fact that survival is not related to treatment with MIH. There was no indication that the survival rate has increased over the last 35 years in the Gothenburg area.

Two recent larger registry studies, conducted in Paris and parts of the United States showed no association of MIH with survival after adjusting for other prognostic factors (150, 151) and in one study MIH was even associated with worse outcome in patients found in non-shockable rhythms (150). Our results are in line with these two studies and do not provide further support for MIH but at the same time does not contradict the effect.

Many retrospective cohort studies have investigated the relationship between MIH and survival finding a positive association. That might be expected since negative results tend to be less published and because before/after studies seem to overestimate suggested treatment effects. This was the case in early goal directed therapy (EDGT) which was introduced as standard sepsis shock care after positive results in one RCT in 2001 (152). Later observational studies supported the results but when evaluated in two RCTs in 2014 the positive effect of EDGT could not be proven (153, 154).

During the studied time period (2003-2015), the MIH regimen changed. Both indications from only VT/VF to all initial rhythms and, furthermore, a target temperature of first 32°C to 34°C and, after the TTM trial, a change in practice to 36°C took place in Gothenburg. The question of whether these changes have affected the outcome has not been evaluated. The TTM trial did not reveal any difference in outcome between the two temperature regimens (84) and we therefore felt it was possible to compare different targets of MIH with non-MIH. Perhaps the future will reveal differences between the different temperatures and we look forward to the results of an upcoming study on normothermia as compared with MIH.

Evidence has shown that there is a relationship between febrile temperatures and a poor outcome in OHCA patients who were brought to hospital with ROSC, but this may be explained by a relationship of mere association rather than causation. The high temperatures associated with a poor outcome could

thus be a marker of a severely damaged brain.

There are still strong recommendations for using temperature control in OHCA patients with all initial rhythms in post-resuscitation care, but the overall quality of the evidence ranges from low to very low (82).

5.10 Gender perspective of post-resuscitation care

Women differ from men in terms of characteristics and outcome after OHCA. The incidence of OHCA is lower among women in every age group (155). In a report on sudden cardiac death in the United States, the age-adjusted decline in mortality rates was greater in men than in woman (13). Women have myocardial ischemia as the underlying etiology less frequently than men (141). Furthermore, when suffering from OHCA, they are less frequently found in VF (114) (156) and they less frequently receive bystander CPR (114).

The mean age of women, at the time of OHCA, is significantly higher than that of men. When suffering from OHCA, women had a higher likelihood of a cardiac arrest while they were at home or when they were admitted to a nursing home, while men more frequently had cardiac arrests in public places and workplaces.

Some investigators have attributed differences between women and men to the protective effects of endogenous estrogen described as the “estrogen effect”. Endogenous estrogen has both positive and negative effects on the cardiovascular system. It has also been suggested that estrogen is a potent neuroprotectant (157).

A number of investigators have identified gender differences in survival outcome after OHCA. Although no gender differences have been found in the delivery of resuscitation care (111, 113, 115, 141), multivariate analyses have revealed that female gender is associated with an increase in immediate survival (patients being hospitalized alive). With regard to survival to discharge from hospital, the results have been conflicting (111, 113, 114, 156).

5.11 Age and post-resuscitation care

Aging is not a state related to chronological age alone. It can be regarded as a

multifactorial issue combining chronic diseases and poorer function in multiple organs. A universal therapeutic approach is unlikely to be successful in the total cohort of elderly patients with OHCA. It is more reasonable to individualize the treatments while considering life expectancy, risk, potential benefit and information from relatives about preferences. In a recent study, advanced age turned out to be an independent predictor of the risk of death in OHCA patients over 70 years of age, but, even in patients above 90 years of age, there were subsets of patients with a 30-day survival rate of more than 10%. The neurological outcome remained similar, regardless of the age of survivors (158). Previous studies of hospitalized elderly victims of cardiac arrest have shown a poor prognosis (159). These data were unfortunately extrapolated to all elderly patients and led to the incorrect assumption that efforts to resuscitate elderly people were futile and should be withheld. More recent studies have shown that the prognosis for the elderly with OHCA is improving over time, although overall survival was still lower as compared with younger patients (160).

5.12 Methodological aspects

5.12.1 Patient selection, hospital, sample size

Before making comparisons with the results of other studies, it is important to consider the question of whether the patients who were included in this thesis are representative and whether they were recruited in the same way as OHCA patients in other studies. The cohorts in this thesis only included patients who were resuscitated by the EMS and were admitted to hospital with ROSC. Comparisons with other studies should, however, be regarded as valid, since the vast majority of these comparative studies also included EMS-resuscitated patients. The register (Papers I, II and IV) covers all etiologies among patients with OHCA where CPR was attempted. In Papers II and IV, we selected subgroups according to treatment, i.e. ICD and MIH (survivors with a shockable initial rhythm for ICD and unconscious patients admitted to hospital for MIH). Paper III included unconscious patients with all rhythms, except for unwitnessed asystole, who were admitted to an ICU.

The studies that are performed can never be better than the data they rely on. The register data in Papers I, II and IV are based on the SRCR and also the registration of hospital variables specifically for the Gothenburg register. The SRCR was validated by Strömsoe et al. (161) and they showed that some information on reported OHCAs was missing. This detection has led to

marked improvements in terms of reporting to the register.

The patient data in Paper III are based on the randomized multicenter TTM trial (84). These patients represent most of the unconscious patients with a cardiac cause of the arrest admitted to an ICU, except for patients found with an initial rhythm of unwitnessed asystole. Patients who were in severe shock were excluded. There is, however, a selection of patients with a higher incidence of individuals found with a shockable rhythm, 80% compared with the unconscious patients in Paper IV, where the corresponding number was 41%. The data in this randomized study were monitored and of high quality and the long-term neurological outcome was assessed using personal interviews.

The comparability of results presented in studies is still problematic, even after the large-scale efforts made by the Utstein consortium. Survival after OHCA varies between communities, due in part to variations in the measurement methods. The Utstein template was disseminated to standardize comparisons of risk factors, quality of care and outcomes among patients with OHCA.

Data presented on survival still represent different groups, based on etiology (all cardiac arrest or cardiac cause), initial rhythm, global survival or in-hospital survival to different time points and so on. Comparing study results may not be possible (comparing the same patients), since there are variations in the inclusion criteria. For example, some studies include patients with OHCAs assessed or treated by EMS personnel or defibrillated by laypersons, whereas others only include patients with OHCAs treated by EMS personnel. Survival rates from OHCAs vary greatly among studies and regions.

The definition of a small sample size depends on the study objective, but, the larger the study, the more reliable the results. The width of the 95% confidence intervals depends directly on the sample size, where large studies produce more precise results and more narrow confidence intervals. The sample size depends on the magnitude of the expected effect size, which is often quantified by a relative risk or odds ratio. The smaller the true effect size, the larger the required sample size. This is because it is more difficult to distinguish between a real effect and random variation when the expected effect size is small.

Studies with a small number of subjects can be conducted rapidly and can be performed at a small number of centers. We encountered the issue of difficulty in interpreting the results in Paper II and IV, depending on a

relatively small sample size. The overall conclusion from Paper IV must be that the lack of statistical significance does not exclude the possibility of a true effect of MIH.

5.12.2 Missing data

Missing data occur in most clinical studies and can create biased results, if data are not missing completely at random (162).

Missing data can belong to three main categories; missing completely at random (MCAR), missing at random (MAR), or missing not at random (MNAR).

When data are MCAR, the complete cases are a random subset of all cases. Little's test is the most common test for confirming that missing cases are MCAR. If the p value for Little's MCAR test is not significant, the data can be assumed to be MCAR.

When data are MCAR, the listwise deletion of observations with missing values is appropriate, provided the number of missing values is not very large (<5%). The cases with missing data are simply dropped from the analysis.

When data are MAR, missingness may be predicted by other observed variables and does not depend on any unobserved variables. If missingness can be effectively predicted from observed variables, then multiple imputation is appropriate.

MNAR is the most problematic form. This happens when missingness depends at least in part on unobserved variables, which is why observed variables fail to predict missingness.

In Paper III, the proportion of cases that had one or more pieces of missing data was 25%. Of the total data, there was naturally a much lower proportion of missingness. In Paper III, Little's test was significant ($p<0.05$). MCAR could be rejected and we assumed MAR on the basis of excluding MNAR on the pattern of missingness in our dataset and performed multiple imputations.

In Paper IV, we compared the odds ratio for survival for MIH using propensity scores based on complete data and, in addition, due to the amount of missing data for several of the variables, multiple imputation was used in combination with a full-model multivariable logistic regression analysis. Missing data were assumed to be MAR ($p<0.05$ for Little's test of MCAR)

and 50 imputed datasets were generated. The results based on this generation were very similar.

5.12.3 Assessment of neurological function

An extensive number of cognitive tests are available and selecting the most accurate test to evaluate patients surviving an OHCA is challenging, because no gold standard method currently exists. We chose the CPC scale because of its established role in the cardiac arrest patient cohort and its simplicity and feasibility.

Cerebral function at discharge (Papers I, II and IV) was estimated from the hospital records of survivors. In Paper III, the evaluator who interviewed the patient assessed the CPC score at six months. It was categorized according to the CPC scale as described in the introduction (123, 163).

Only a few individuals are in CPC 3 and 4 at discharge from hospital, creating an outcome for neurological function that is relatively similar to that for mortality/survival, which means that overall survival is principally the same as survival with good neurological outcome.

As shown in other studies of cognitive function, survivors have a high level of functioning, as reflected in the CPC categories, despite mild cognitive impairment, and their quality of life is good (19, 108). Mild cognitive impairment is common and it is characterized by memory and executive, frontal lobe disturbance (108).

Cognitive impairment at levels similar to those of the OHCA population has been reported for other patient groups treated at the intensive care unit without primary brain injury (164). The cognitive impairment might not only be a result of the ischemic brain injury resulting from the cardiac arrest, but it might also have a relationship to age, previous cardiovascular disease, suffering a critical illness and prolonged care at the intensive care unit.

The method for measuring cognitive status is of course important and there is a difference in quality between face-to-face interviews, as in Paper III, compared with retrospective judgment based on data from medical records (Papers I, II and IV).

5.13 LIMITATIONS

The use of retrospective register-based data in observational studies has several limitations. The quality and reliability of data must be controlled.

Much of the data rely on documentation in medical charts and there might be factors that are not reported in medical charts.

The CPC score was used as an outcome measurement. As discussed earlier, this score is a rough estimate of outcome and many minor deficits will be missed. Moreover, the timing of measurements of CPC at hospital discharge might not be optimal, since many patients improve their CPC if assessed at a later time point.

There is almost always an issue of missing data and knowledge of handling this issue is increasing. It is important to take this into consideration and to consider its potential risk of bias.

6 CONCLUSIONS

- We did not find any overall improvement in survival over time from a 35-year perspective, after introduction of modern post resuscitation care, among patients who had ROSC on admission to hospital after OHCA.
- A good neurological outcome is seen in 80-90% of the patients at discharge and this appears to have increased since the start of our investigations in the 1980s.
- The use of ICDs was low but increased over time and long-term survival among patients in whom it is used is excellent. Only two percent died during the following two years.
- Patients running a high risk of a poor outcome after OHCA could be identified at an early stage by using a simple, easy-to-use risk score system based on ten independent predictors of a poor outcome six months after the event.
- Treatment with MIH was not significantly associated with an increased chance of 30-day survival among patients remaining unconscious on admission to hospital after OHCA.

7 FUTURE PERSPECTIVES

In the future, post-resuscitation care should be standardized and perhaps even centralized to improve outcome still further. In-hospital standardized treatment protocols are important, especially to reduce the risk of premature prognoses or the inadequate withdrawal of care.

In my opinion, maximum survival has not been achieved. There is still room for improvement, as almost 90% of the patients who suffer an OHCA in whom resuscitation is attempted will die. Important prehospital areas for improving survival might be to identify high-risk patients prior to their arrest and to increase the use of bystander CPR through training, increased access to AEDs and simplified CPR techniques.

Intensive care management and a better knowledge of the optimal targets for physiological variables are needed. We need to improve our understanding of the use of MIH and we need to determine which patients should undergo immediate coronary angiography on hospital admission. The early prediction of the severity of disease might help caregivers more effectively to modify and customize the treatment.

The quest for clear evidence of the clinical effect of MIH must proceed. Further trials are needed and should be designed to clarify the optimal target temperature after cardiac arrest.

In future studies, predictive models could be used to evaluate whether MIH has a differential effect on various particular groups of survivors of OHCA. There has been speculation about whether there are three main categories of patients: 1) those who will survive with a good outcome with or without MIH, 2) those who benefit from MIH and 3) those who will not survive, no matter which treatment they receive. The ideal model would allow the prediction of survival and survival with a good neurological outcome at all time points of care, using the information provided at the time in question (from acute emergency room admission through the first days of intensive care to prolonged care for those not regaining immediate consciousness). As always with predictive models, they must be evaluated thoroughly before they are put into practice, since they may become self-fulfilling prophecies.

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10 APPENDIX I-IV