Cardiac Arrest in a Community:

Epidemiology, Treatment, and Outcome

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Scientific environment

The dissertation originates from the Department of Anaesthesia and Intensive Care at Haukeland University Hospital, and the University of Bergen. The first article in the dissertation is a result from collaboration with the Section for Emergency Medicine within our Department.[1] Research in the Section for Emergency Medicine focuses on cardiac arrest, education, quality improvement and safety culture. The section has produced two PhD degrees over the past five years, and seven publications during 2016. The second article in the dissertation stems from collaboration with the Research group on Quality, Safety and Outcome after Surgery and Critical illness at the University of Bergen, with financial support from the Laerdal Foundation.[2] The article covers a field of research at the border between several clinical specialities, and includes collaboration with researchers at the Department of Neurology, the Department of Heart Diseases and the Centre for Clinical Research at Haukeland University Hospital. The Research group on Quality, Safety and Outcome after Surgery and Critical illness has produced one PhD degree over the past five years, and eight publications during 2016. The third article in the dissertation is a result of continued collaboration with existing partners, and makes use of methodological skills obtained in the PhD program coursework.[3]

Acknowledgements

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Bergen, May 2017

Abstract

Background: Incidence and mortality from sudden cardiac arrest is high, making it a prevalent cause of death. Both incidence and survival rates show great variability between populations. In order to improve survival from sudden cardiac arrest, it is necessary to view aetiology, treatment effects, and outcome as a whole.

Aim: To investigate cardiac arrest incidence, treatment, and outcome in one geographic area during a limited period of time.

Method: Paper I and Paper II prospectively included consecutive patients suffering cardiac arrest in one of our local hospitals, or in the geographical area delivering patients to these hospitals, between 1 December 2008 and 30 November 2009. Paper I compared out-of-hospital cardiac arrest with in-hospital cardiac arrest in terms of Utstein characteristics and survival. Paper II compared cognitive function in cardiac arrest survivors with good neurologic outcome at hospital discharge with an age- and gender-matched reference population. Paper III retrospectively examined consecutive out-of-hospital cardiac arrest survivors from December 2003 to December 2008 admitted to the emergency department in a comatose state. Propensity score matching was used to compare intensive care treatment including targeted temperature management with intensive care treatment not including targeted temperature management in regard to survival.

Results: The incidence was 60.6 per 100.000 person-years for out-of-hospital cardiac arrest and 41.3 per 100.000 person-years for in-hospital cardiac arrest. Survival to hospital discharge was 16.2% for in-hospital cardiac arrest and 16.8% for out-of-hospital cardiac arrest. Pooled mortality from cardiac arrest in our community was 85.0 per 100.000 person-years. Four years after cardiac arrest, 29% of patients had mild cognitive impairment. Restricted mean survival time increased by 57 days as a result of targeted temperature management. Standardised mortality ratio was 2.8 for cardiac arrest survivors over the first four years following hospital discharge, compared with an age- and gender-matched normal population.

Conclusion: Survival to hospital discharge was similar between in-hospital and out-of-hospital cardiac arrest. The majority of cardiac arrests occurred out-of-hospital. Nearly one-third of patients with good cerebral outcome on hospital discharge had mild cognitive impairment four years after cardiac arrest. Targeted temperature management increased survival after cardiac arrest.

List of publications

Paper I

Buanes EA, Heltne JK.

Comparison of in-hospital and out-of-hospital cardiac arrest outcomes in a Scandinavian community.

Acta Anaesthesiol Scand. 2014; Mar; 58(3):316

Paper II

Buanes EA, Gramstad A, Sovig KK, Hufthammer KO, Flaatten H, Husby T, Langørgen J, Heltne JK.

Cognitive function and health-related quality of life four years after cardiac arrest.

Resuscitation. 2015; Apr; 89:13

Paper III

Buanes EA, Hufthammer KO, Langørgen J, Guttormsen AB, Heltne JK.

Targeted Temperature Management in Cardiac Arrest: survival Evaluated by Propensity Score Matching.

Scand J Trauma Resusc Emerg Med. 2017; Mar; 25(1):31

Contents

Abbreviations

AED	Automated external defibrillator
BLS	Basic life support
CA	Cardiac arrest
CANTAB	Cambridge Neuropsychological Test Automated Battery
CAT	Cardiac arrest team
CPC	Cerebral Performance Category
CPR	Cardiopulmonary resuscitation
DC	Direct current
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
EMS	Emergency Medical Service
GCS	Glasgow coma score
HADS	Hospital anxiety and depression rating scale
ICU	Intensive care unit
IHCA	In-hospital cardiac arrest
MCI	Mild cognitive impairment
OHCA	Out-of-hospital cardiac arrest
PCI	Percutaneous coronary intervention
PEA	Pulseless electric activity
TTM	Targeted temperature management
VF	Ventricular fibrillation
VT	Ventricular tachycardia
UK	United Kingdom
US	United States of America

1. Introduction

The title of this dissertation is broad because my research in cardiac arrest (CA) is not concerned with one single topic which I focus upon very closely and discuss in minute detail. Rather, I attempt to pan out in order to get an understanding of the big picture. Research in CA deals with unexpected death, cases where there is no medical history which would lead anyone to believe that death is imminent. The dissertation discusses some of the challenges with research in this population.

1.1 Classification and aetiology of cardiac arrest

The Utstein template for uniform reporting of data from out-of-hospital cardiac arrest was published in 1991 as a result of panel discussions between experts in the field.[4] The publication clearly defined the terminology used in CA research, highlighted important structural parameters which should be reported, and defined a set of standardised outcome measures so that future reports would be comparable. (Figure 1, Appendix 8.1) According to the revised Utstein template published in 2004, CA is *the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation*. These signs of circulation include breathing (more than the occasional gasp), coughing, or movement. For healthcare personnel, signs of circulation may also include evidence of a palpable pulse or a measurable blood pressure.[5, 6]

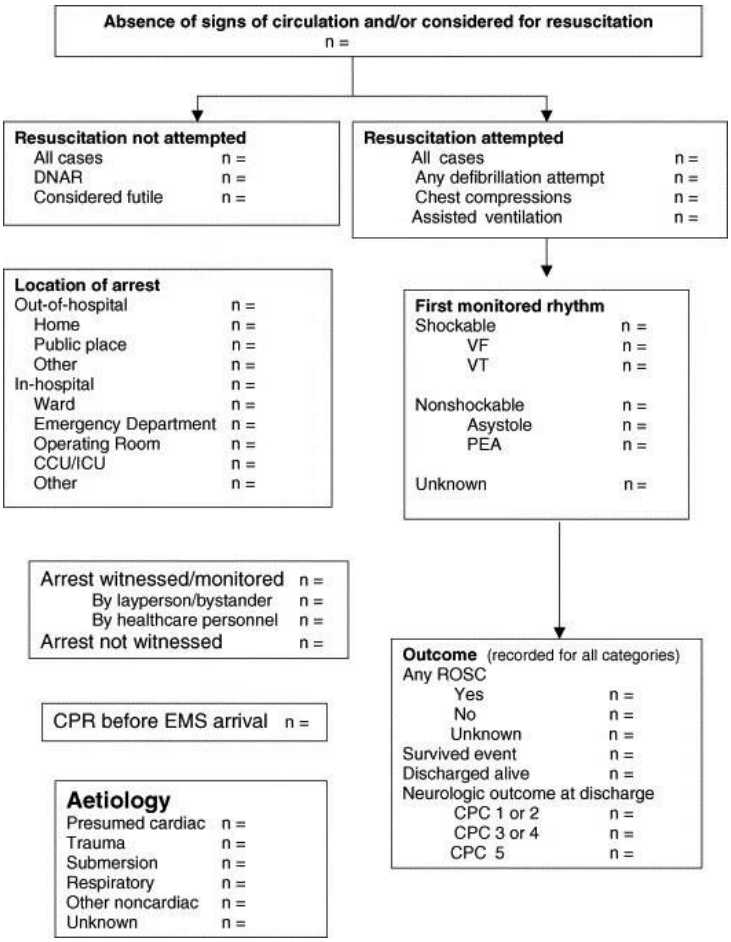

Fig. 1. Utstein reporting template for core data elements

Although the definition is clearly stated, a clinical definition like this one poses problems. Firstly, the clinical condition of CA may arise from different causes. Secondly, it may be difficult to determine the exact duration of symptoms before CA, especially if the event was not observed.[7] As a consequence, several approaches to define the population of interest have emerged in CA research.

One approach is to include sudden and unexpected causes of CA in which the emergency medical team judges that cardiopulmonary resuscitation (CPR) is

warranted. The term “sudden cardiac arrest” has been used to describe this population. It has been in use sporadically since the 1960’s and more regularly following the landmark publication *“Improving survival from sudden cardiac arrest: the "chain-of-survival" concept”* by the American Heart Association in 1991.[8] Although the term excludes events that are not medical emergencies, it includes patients with vastly differing aetiology. Apart from cardiac causes, CA from respiratory, traumatic, metabolic and toxic causes fall within the definition. There is also no clear definition of how abrupt an event needs to be for it to fall within the definition of sudden cardiac arrest.

Another approach is to include CA of cardiac causes only. The term “sudden cardiac death”, coined by cardiologists in the late 1970’s, has been used in conjunction with this population. Sudden cardiac death describes the unexpected death from a cardiac cause within a short time period, generally less than one hour from the onset of symptoms, in a person without any prior condition that would appear fatal.[9] This definition is more precise, defining a more homogenous population than sudden cardiac arrest. Further exploration, however, reveals again the problems of a clinical definition. Essentially different conditions like arrhythmia, cardiomyopathy, valvular disease and coronary disease contribute to the population. [9] (Figure 2) Some researchers therefore choose to include patients with sudden cardiac death and primary ventricular fibrillation (VF) only. A consequence of this approach is a population dominated by patients with coronary disease.

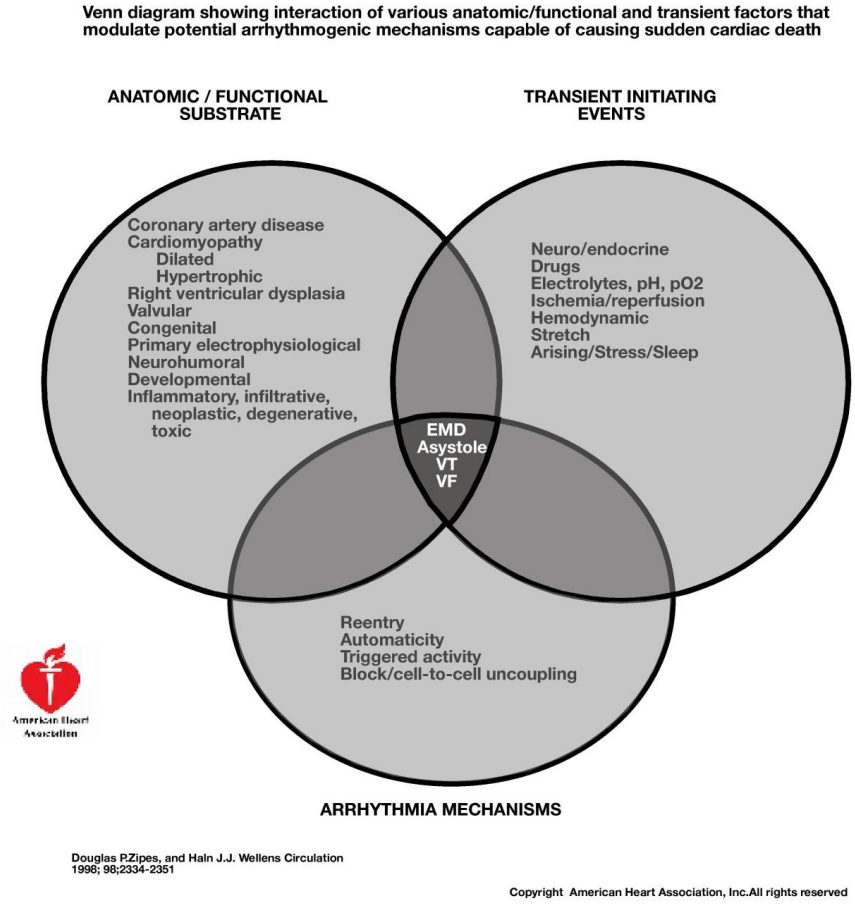

Fig. 2

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A third approach is to separate out-of-hospital cardiac arrest (OHCA) from in-hospital cardiac arrest (IHCA). Traditionally, CPR was performed by direct open-chest heart compressions and ventilation via an endotracheal tube in a hospital setting.[10] Modern CPR techniques comprising closed-chest compressions, external defibrillation, mouth-to-mouth ventilation and bag-mask ventilation emerged in the 1950s and 1960s.[10-14] As community emergency medical teams emerged, several educational programs were launched in order to teach these skills to emergency

medical technicians and bring CPR out to the public.[15] Outcome reports from OHCA were published, and it has since remained common to distinguish OHCA from IHCA.[16] The Utstein templates for reporting on cardiac arrest outcomes maintain the separation, perhaps because the two populations are intuitively different.[4, 5, 17] Direct comparisons between the two populations, however, are sparse.[18, 19]

It is common in epidemiological studies to include all CA patients assessed by emergency medical services (EMS), whether they are treated or not.[20] This approach avoids selection bias when comparing EMS. Still, incidence will be affected by local routines for involvement of EMS.[21] Patients with unwitnessed CA discovered when they are obviously dead are often missed. These patients may be found using death certificates. The best solution for identifying the vast majority of CA patients for epidemiological purposes is to combine information from several sources, including EMS, death certificates, and results from post-mortem investigations.[22]

1.2 Incidence rates

Bearing in mind the various definitions of CA, reports of varying incidence are to be expected. Around the globe, CA incidence varies from 28.3 per 100.000 person-years in Asia to 54.6 per 100.000 person-years in North America.[23] Within Europe, incidence rates vary from 28 to 244 per 100.000 person-years, averaging at 84 per 100.000 person-years.[24] A similar variation is reported for IHCA, where rates vary from 1.3 to 4.0 per 1000 admissions.[25-29]

Many publications report incidence rates unadjusted for the age and gender composition of the study population. This is problematic because population characteristics vary, even within the same country.[30] When adding differences in how EMS are organized, it becomes evident that incidence rates will vary, and comparison is difficult.

While heterogeneous study populations may account for some of the differences, an argument can be made that CA incidence is variable. This is supported in a registry-based study which demonstrates varying OHCA incidence rates across North

America.[31] A study using geographic information systems revealed varying incidence rates even within communities.[32] A reason for some of the variation may be socioeconomic status, which is commonly omitted from studies, but has been found to have impact on CA incidence rates.[27, 32-34]

The difference in incidence for IHCA between the United Kingdom (UK) and the United States of America (US) may serve as an example.[27, 35] Both being developed countries, one would expect similar incidence rates. Yet the UK incidence rate is 1.6 per 1000 hospital admissions while the US incidence rate is 2.85 per 1000 hospital admissions. The UK report includes all IHCA attended to by a hospital-based resuscitation team in response to an emergency call. The US report includes all patients ≥18 years of age who underwent CPR for IHCA according to diagnose codes in the Nationwide Independent Sample, the largest publicly available all-payer inpatient care database in the US. Since CA in children has a lower incidence than CA in adults, the inclusion of children to the study population will lower the overall incidence. This illustrates a difference in methodology. While the UK report is based on collection of data specifically for the UK National Cardiac Arrest Audit, the US report is based on data extracted from a general inpatient database. As a result, it is difficult to conclude whether incidence rates are different or not between the UK and the US.

1.3 Resuscitation effort

Cardiac arrest patients are resuscitated according to a standard procedure described in guidelines for resuscitation.[36] The guidelines are more or less uniform worldwide due to collaboration via the International Liaison Committee on Resuscitation (ILCOR), although some modifications exist.[37] The recent guidelines issued by the European Resuscitation Council have a broad scope. They focus on technical, educational, community, and ethical aspects.[38-40] This is a consequence of the chain-of-survival concept, which states that good outcome from CA depends on good performance in each link in the chain of events from CA to full recovery.[8, 41] In order to maximise the potential for good outcome there has to be a rapid activation of EMS. Emergency

medical dispatchers must rapidly recognize CA, initiate a timely response and emergency teams must arrive swiftly on scene. Bystanders need to start CPR immediately after alerting the EMS, preferably using an automated external defibrillator (AED) which has been made publicly available. Emergency medical teams need to have good technical skills in order to achieve return of spontaneous circulation (ROSC). Post ROSC care must meet high standards so that patients survive to discharge. Finally, there has to be good follow-up after discharge to ensure the best physical and cognitive recovery for each individual patient.

The 2015 guidelines identify areas of improvement based on available evidence. These include recommendations to increase bystander CPR and to improve performance of the EMS. There is a continued focus on good quality chest compressions and reduction of hands-off time as well as early defibrillation. There is also a trend towards using novel technologies such as ultrasound and capnography to identify precipitating causes of cardiac arrest and to guide prognostic decisions during CPR.[36]

Although these recommendations are clearly stated and based on the best evidence available, they do not necessarily reflect the need for improvement in local or national organizations. A weak link in the chain of treatment in one system may be strong in another. Both systems may have potential for improvement, but the way to achieve improvement differs. The complexity is illustrated in a study from Texas in the US where neighbourhood-level race and income characteristics within the same EMS system are shown to influence rates of bystander CPR.[42] In order to improve one must start with a good knowledge of the shortcomings in the local treatment chain. Given that prerequisite, community programs aimed at improving links in the treatment chain may increase survival from CA.[43]

1.4 Post ROSC treatment

The evolution of catheter technology during the past two decades has made percutaneous coronary intervention (PCI) increasingly available. As a result many

CA patients may be transported directly to a PCI centre for intervention. Prevalence of coronary disease in OHCA survivors without obvious non-cardiac aetiology is approximately 65% with PCI being performed in approximately 40%.[44] Although the predictive value of electrocardiogram (ECG) changes in CA survivors is low, current practise is to offer emergent coronary angiograms with immediate PCI if necessary in CA survivors with novel ST segment elevations or left bundle branch block in their ECG.[45, 46] Coronary angiograms in patients without ECG changes are controversial due to conflicting evidence.[47, 48] Factors like primary heart rhythm, witnessed arrest, time to ROSC, circulatory stability and cerebral function are taken into consideration in order to decide which of these patients are likely to benefit from PCI.[45]

The introduction of targeted temperature management (TTM) occurred in parallel with the evolution in catheter-based coronary interventions and was introduced to clinical practice following the publication of two controlled studies in 2001, one randomised and one pseudorandomised.[49, 50] Despite early reports of benefit, systematic reviews revealed a low quality of evidence and risk of bias at some level in all randomised studies.[51-53] This led to the publication of a randomised controlled trial comparing TTM at 33 and 36 °C in which no differences in mortality or cognitive functions were found.[54, 55] As a result, guidelines now recommend TTM at 32 to 36 °C for comatose CA survivors instead of the previous suggestion of TTM at 32 to 34 °C.[45, 56] Evidence is limited regarding when to initiate TTM, which temperature to target, and duration of TTM.

A thorough review of which aspects of intensive care therapy might influence outcome in CA patients is beyond the scope of this dissertation. However, it should be mentioned that CA survivors are complex patients. Patients with post CA syndrome have similarities with septic patients, patients with heart failure, and patients with cerebral injury.[57] Consequently, many aspects of intensive care treatment potentially influence outcome.

1.5 Outcome measures

Cardiovascular disease is the most common cause of death in Europe today, with ischaemic heart disease accounting for approximately 125 age- and population adjusted deaths per 100.000 person-years.[58] The figure includes both patients dying from unexpected CA and patients with chronic disease following its natural course.

Survival is the traditional outcome measure from CA. It is often reported as survival of the event, survival to hospital discharge, or survival to a defined point in time after CA.[27, 35] These data are readily available, but as reliable outcome measures they fall short. Survival to hospital discharge does not take into account that the time to discharge following CA may vary between subjects and between health care systems. As a consequence, direct comparisons of survival to hospital discharge are not necessarily valid. Survival to a defined point in time after CA, typically 30 days, takes accounts for variable discharge routines, but does not differentiate between deaths at different times between CA and follow up. With a 30 day follow-up, for instance, the analysis does not differentiate between a patient dead on the day of CA and a patient dead on day 29 after CA. A better solution would be to use more sophisticated survival analyses, which would give a better approximation of survival.[59]

Brain function is another important outcome measure from CA. The brain is particularly vulnerable to hypoxia. Within minutes, untreated CA leads to global brain ischemia with a rapid progress towards brain death. Introduction of new CPR techniques such as defibrillation, mouth-to-mouth ventilation and closed-chest compression in the 1950s and 1960s gave CA victims a chance of surviving the initial event and be admitted to hospital.[60] [10, 61] Hospital wards providing intensive monitoring and specialised care emerged. Even though patients started surviving to hospital discharge, good neurological outcome was not always the case.[62] This spurred an interest in brain resuscitation among critical care investigators.[63] In order to standardize assessment of outcome after severe brain damage, the Glasgow outcome scale (GOS) was introduced.[64] A Pittsburgh modification, the Cerebral

Performance Category scale (CPC) was included in the Utstein guidelines as a meaningful outcome measure describing brain function in resuscitation research.[4, 65] The CPC has five categories, ranging from normal brain function (1) to brain death (5). This crudeness does not allow a detailed description of brain function, and research on cognitive outcome in CA survivors has relied on neuropsychological testing to provide more thorough assessments.[66] While neuropsychological tests provide detailed assessments of brain function, they are not suited to larger trials or clinical practice because they are time consuming and depend on specially trained personnel. This has led to an interest in cognitive tests which are more easily administered. Recently, there has been an interest in computerized neuropsychological assessment devices.[67, 68]

The increasing number of CA survivors with good brain function has prompted research into patient-reported outcome measures. This is a broad field of research, as the World Health Organization defines health as "*a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity*".[69] Consequently, a large number of instruments are available to assess patient-reported outcome measures. Each individual instrument focuses on different aspects of health. The aspects include physical function and symptoms, self-rating of health, satisfaction with care, psychological and social well-being, role activities, personal constructs, and cognitive function.

Based on their focus, instruments are generally divided into generic and specific tools. Generic instruments assess aspects of health which have broad relevance, such as physical and social function and psychological well-being. Generic tools have the potential to assess side effects of treatment on health, but may lack relevance and responsiveness to issues concerning a specific condition. Specific instruments assess aspects of health of special importance to a specific patient group, a specific disease or a specific health domain.[70] Specific instruments are targeted, relevant, and responsive, but have limited potential to capture unexpected side effects of treatment.

Generic and specific instruments are complementary. A complete picture of health state is acquired only if both types of instruments are used. Some of the generic instruments include population norms with which the study population may be compared.[71, 72] In general, instruments which allow comparison to a norm may be of preference to those who do not. The drawback is that some of these tools are commercial and impose a cost to research and clinical practice.

1.6 Temporal trends

Even when comparing results from the same healthcare system, temporal trends introduce complexity.

Improved prevention increases life expectancy and changes the burden of disease. This means that the population at risk changes with time, which has a direct effect on incidence and outcome from CA.[73-75] New treatment strategies also improve survival with time.[47] Patients who survive from illness or disease due to new treatment become part of the population at risk after discharge, causing a further change in the population at risk.[76]

The health care system itself also changes with time. Many EMS have implemented improvements in their local treatment protocols inspired by the chain-of-survival concept.[8] Some EMS report substantial increases in survival after implementation.[70, 77]

1.7 Comparison between health systems

From the previous sections it should be evident that comparison between health systems is difficult due to the number of factors which influence incidence and outcome. As a minimum, the composition of the study population and a description of the health care system in which the study was undertaken should be reported. For better comparison, estimates of incidence and outcome should be standardised.[78] The process of standardisation adjusts estimates according to a population with different

characteristics than the study population. The European Standard Population, for instance, standardises according to age.[79] Estimates from research populations with differing age compositions are better compared if both have been standardised to the same reference population.

2. Aims

The overall aim of the dissertation was to investigate CA incidence and outcome in a limited geographic area during a restricted period of time. This allowed us to reduce the effects of time and population characteristics on outcome measures.

Aims of each paper were as follows:

Paper I

The objective was to investigate whether survival for IHCA was higher than survival from OHCA.

Paper II

The primary objective was to test the hypothesis that cognitive impairment persists in CA survivors with good outcome according to the CPC scale. Secondary objectives were to investigate health-related quality of life and whether cognitive function after CA could be predicted.

Paper III

The primary objective was to test the hypothesis that TTM improves survival after CA in clinical practice. The secondary objective was to investigate treatment effect of TTM on cognitive function in CA survivors.

3. Methods

3.1 Design

Paper I

Prospective population-based cohort study.

Paper II

Prospective population-based cohort study.

Paper III

Retrospective population-based cohort study.

3.2 Populations

The Bergen region comprises 15 counties with 372.651 inhabitants as of 1 January 2009 populating an area of 3294 km^2 of which 3125 km^2 is dry land (Statistics Norway, 2009). The population density is sparse, with a mere 119 persons per km^2 of dry land. Western Norway has a challenging geography with mountains, islands and fjords, generating a coastline of 5064 km in our catchment area. There are two hospitals in the Bergen region. Haukeland University Hospital is a tertiary teaching hospital with approximately 62.000 admissions a year. Haraldsplass Deaconess Hospital is a local area hospital with around 11.000 admissions a year. Both hospitals recruited patients for papers I and II, while patients for paper III were recruited from Haukeland University Hospital.

Paper I

We included unconscious patients with abnormal breathing where basic life support (BLS) was initiated either by lay or trained personnel in the Bergen area from 1 December 2008 to 30 November 2009. Patients with suspected CA of all aetiologies, both in-hospital and out-of-hospital, were included. Resuscitation of newborns was not included. Employment of an AED only was not defined as BLS. Patients who were most likely dead before the start of BLS as judged by the EMS or the cardiac arrest team (CAT) and patients judged by the study group to have suffered only respiratory arrest were excluded. Patients suffering CA of duration less than three minutes during invasive cardiologic procedures were excluded due to methodological concerns.

Paper II

Patients discharged alive after cardiac arrest in Bergen between 1 December 2008 and 30 November 2009, above the age of 18, and alive in October 2012 were considered for inclusion. Patients with cerebral performance category (CPC) above 2 on hospital discharge, patients who could not be reached, and patients with an unknown identity, were excluded.

Paper III

Survivors from OHCA available for targeted temperature management (TTM) in the emergency department of Haukeland University Hospital between December 2003 and December 2008 were considered for inclusion. Patients with Glasgow Coma Score (GCS) > 8 and patients with coagulopathy or terminal illness were excluded.

3.3 Interventions and control groups

Paper I

The paper compared IHCA with OHCA in the geographical area served by Helse Bergen Hospital Trust.

Paper II

Cognitive function in survivors from CA was compared with an age- and gender-matched normative sample consisting of British controls. Health-related quality of life in CA survivors was compared with an age- and gender-matched Danish normative population. Patients were tested on a single occasion a median of 3.6 years after CA.

Paper III

Patients receiving intensive care treatment including TTM were compared with patients receiving intensive care treatment not including TTM in the same hospital during the same time period. TTM was induced using axillary and femoral ice bags before hospital admission and cold saline after admission until invasive TTM was established. The CoolGard Temperature Management System with ICY Catheters (Zoll Medical Corporation, MA, USA) was used for invasive TTM. Patients were cooled to 33 °C at a rate of 0.5 °C per hour and maintained at 33 °C for 24 hours before rewarming at a rate of 0.5 °C per hour to 37 °C. Seven patients included in the intervention group received surface cooling because invasive cooling was unavailable. In these seven patients, TTM was established using active cooling garments in five patients, ice bags and cold towels in one patient, and ice bags alone in one patient.

3.4 Outcomes

Paper I

The primary end point was survival to hospital discharge.

Paper II

The primary end point was cognitive impairment as measured by the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Cambridge Cognition, Tunbridge Court, Tunbridge Lane, Bottisham, Cambridge CB25 9TU). Secondary outcome was health-related quality of life as measured by the EQ-5D-5L questionnaire (EuroQol Group, Marten Meesweg 107, 3068 AV Rotterdam, the Netherlands).

Paper III

The primary end point was restricted mean survival time, defined as the number of days alive after CA limited to a maximum value of 365 days. The secondary end point was mean CPC score.

3.5 Data acquisition

Paper I

Utstein plots supplied by the helicopter emergency medical service provided data in the majority of OHCA. Data regarding IHCA was primarily obtained from the electronic patient journal. Several sources were screened in order to identify missing

cases and to find missing data. Resuscitations occurring physically on hospital grounds were allocated to the in-hospital group according to Utstein criteria.[5]

Paper II

The Hospital Anxiety and Depression rating Scale (HADS) (Ageing and health, Oslo University Hospital, Ullevål, Bygn. 37, 0407 Oslo, Norway) and the EQ-5D-5L were sent by post to all eligible patients, along with written information about the study, a consent form and a pre-paid return envelope. Participants who returned the initial forms were contacted by telephone to schedule cognitive testing. Participants who did not return the forms were contacted by telephone for consent. If consent was given, they were reminded to return the forms and cognitive testing was scheduled. CANTAB test sessions took place at Haukeland University Hospital and lasted approximately one hour. For participants unable to travel to the hospital, testing was arranged at a health facility closer to their residence.

Paper III

Data were collected retrospectively from the patient medical journals and local quality registries between 2009 and 2011.

3.6 Statistics

Paper I

Numerical data are presented as median (inter-quartile range) with analysis using the Students t-test if normally distributed or the Mann-Whitney U-test if not normal. *P*-values < 0.05 were considered significant. Proportions were analysed using the chi-squared test or the Fischer exact test where any values were 5 or less.

Paper II

Mean scores are reported with the 95% confidence interval in brackets. Categorical data were analysed using chi-squared tests without continuity correction, and confidence intervals for the difference between proportions were calculated using the Agresti-Caffo method.[80] Correlations were calculated using Pearson's product-moment correlation. Simple and multiple regressions were performed to investigate whether cognitive function could be predicted. Survival data were retrieved from the electronic patient journal and compared to Norwegian life tables.[81] Life tables for 2009 were used for subsequent years since more recent tables were unavailable at the time of analysis. All statistical analyses were conducted in R version 3.1.1.[82]

Paper III

Initial comparisons between treatment groups were performed using *t*-tests for continuous variables and chi-squared test for discrete variables. All baseline variables affecting both treatment and outcome are potential confounders and were considered for inclusion in the propensity score model. Due to the small data set, variables only weakly associated with outcome were excluded.[83] Potential confounders included in the analysis were: age, gender, shockable primary rhythm, witnessed CA, bystander CPR, time from CA to professional CPR, time from CA to ROSC, smoking status, known diabetes mellitus, known hypertension, and previous myocardial infarction. Because of low counts in some categories, smoking was recoded from four to three categories and hypertension from three to two categories. Time from CA to ROSC was winsorised to 60 minutes (i.e. longer times were replaced by 60 minutes).

For predictors with less than 10 missing values, the observations with missing data were discarded. For continuous predictors with more than 10 missing values, missing values were replaced by fixed values and indicator variables for 'missing' were included in the model. For categorical predictors with more than 10 missing values,

'missing' was treated as a separate category.[84, 85] See Figure 5 for a flowchart of the data used.

The propensity score was modelled using logistic regression. To ensure that the model was flexible enough to accurately predict treatment, we used second-degree polynomial terms for all three continuous variables. The distribution of the propensity score in the treatment groups was examined to ensure adequate overlap. Balance checks were based on examining means, proportions, and distributions of predictors before and after matching.[83]

Non-treated subjects were matched 1:1 to treated subjects within callipers, using a best-first ('greedy') algorithm. The calliper width for matching was set to 10% of the standard deviation of the logit of the propensity score since the common rule of 20% did not adequately balance the predictors.

Survival was compared using mean values restricted to a maximum of 365 days.[86] The treatment effect was estimated using a linear mixed-effects model with a random intercept for each matching pair. For comparison purposes, we also report the results from a naïve *t*-test (ignoring any confounders), and from an ordinary least-squares model, where we adjust for confounders by including the same predictors in the same form as in the propensity score model.

Stata SE version 14.0 (StataCorp LP, Texas, USA) and R version 3.2.3 with the 'nonrandom' package version 1.42 were used for data analysis.[87, 88]

3.7 Ethics

Paper I

The study was conducted with the approval of the Norwegian Directorate of Health [08/6690; 12 November 2008], the Norwegian Social Science Data Services [18919/2/LT; 5 May 2008] and the Regional Ethics Committee [REK Vest, Universitetet i Bergen, Det medisinske fakultet, Postboks 7804, 5020 Bergen;

protocol number 073/08; 8 April 2008]. Patients surviving to hospital discharge gave their informed consent.

Paper II

The study was conducted in accordance with the protocol approved by the Regional Committee for Medical and Health Research Ethics (2012/1701/REK Vest). Written consent was obtained from all subjects.

Paper III

The study was approved by the privacy ombudsman in Helse Bergen Hospital Trust and judged not to need approval in the regional ethics committee. (Approval no. 2014/20465)

4. Synopsis of results

4.1 Paper I

A total of 430 patients were considered for inclusion, of which 380 were finally included. (Figure 3) The study population included six patients under the age of 18; the youngest patient aged six at the time of CA. The incidence of CA was 60.6 per 100.000 person-years for OHCA and 2.10 per 1000 admissions for IHCA. The helicopter emergency medical service unit responded to 128 of 226 OHCA (56.6%). The OHCA population was significantly younger and had a wider age span than the IHCA population. No significant differences were found in terms of gender, shockable primary rhythms or presumed cardiac aetiology. The proportion of patients with pulseless electric activity (PEA) was smaller for OHCA compared with IHCA.

IHCA was more often witnessed and had higher proportions of professional first rescuers. Bystander CPR and bystander DC shock before arrival of CAT or EMS were also higher for IHCA. The median time from CA to start of CPR and the duration of professional resuscitation for IHCA was significantly shorter than the corresponding values for OHCA. Termination of resuscitation due to comorbidity was more frequent for IHCA compared with OHCA.

There was a higher proportion of any ROSC for IHCA compared with OHCA. There were no differences between the groups regarding sustained ROSC or survival to hospital discharge. There was no difference in survival for subgroups VF/VT, CA of cardiac aetiology, or witnessed CA. The majority of survivors in both groups had a

favourable neurological outcome as defined by Cerebral Performance Category ≤ 2 at hospital discharge.[64]

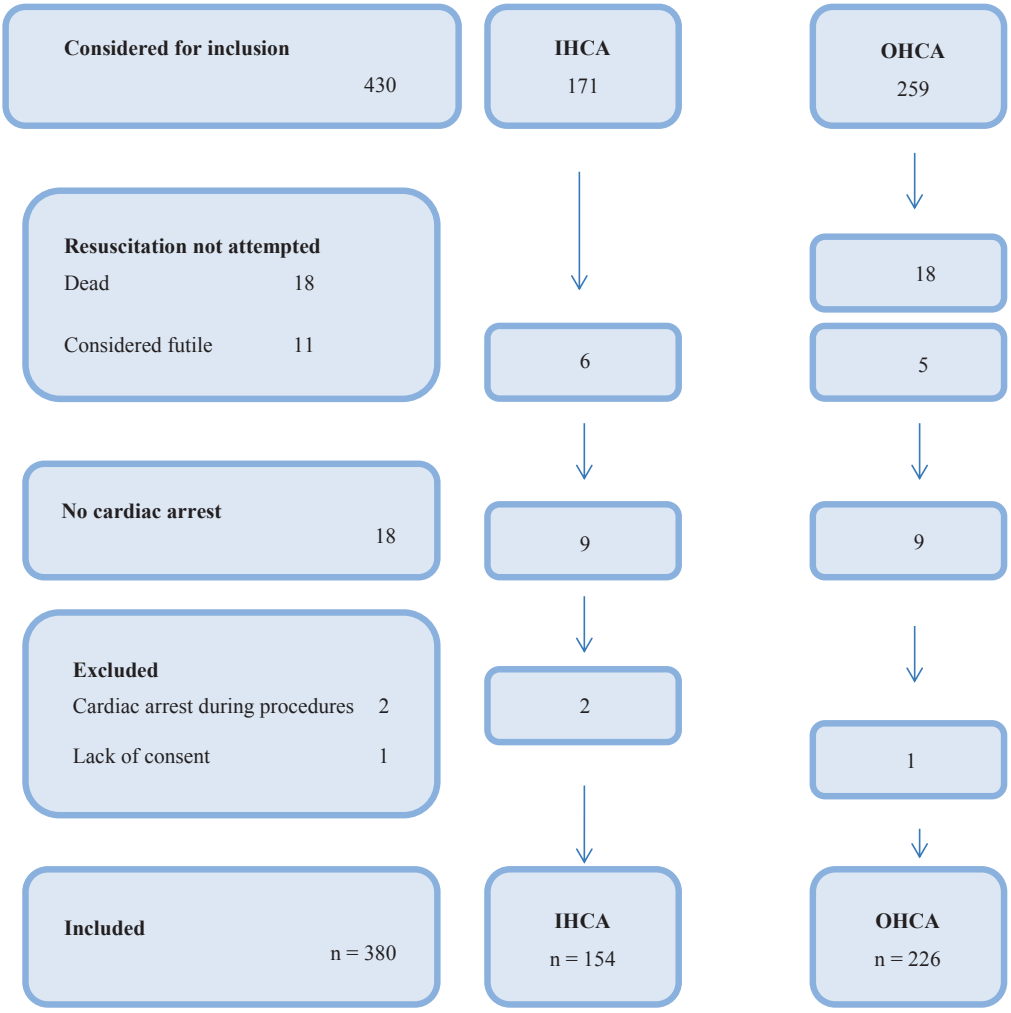

Fig. 3. Flow chart showing included and excluded patients in Paper I.

4.2 Paper II

Of the initial 61 CA survivors, one's identity was unknown. 46 of the remaining 60 were alive at the start of the study. Four had CPC > 2 on hospital discharge, one could not be reached, and 11 declined to participate. (Figure 4)

Of the 30 included patients, 24 had coronary angiography performed during their hospital stay, while 16 had percutaneous coronary intervention performed. One patient had coronary artery bypass grafting performed, and seven were treated with TTM. The duration of resuscitation was longer among the included patients than among the patients who declined to participate or could not be reached.

At the start of the study, 14 of 55 Norwegian patients with CPC ≤ 2 discharged alive with known identity were deceased. The expected number of deaths in an age and gender-matched Norwegian population was 5.0 (standardised mortality ratio: 2.8; 95% CI: 1.6–4.5; $p<0.001$).[81]

The mean score for EQ-VAS was 70.6 (95% CI: 63.4 to 77.8), compared with 80.0 (95% CI: 79.1 to 80.9) for an age and gender-matched Danish normal population.[89] The mean score for the EQ-index was 0.85 (95% CI: 0.79 to 0.90), compared with 0.86 (95% CI: 0.85 to 0.87) for the same reference population.

According to the criteria, 29% (8/28; 95% CI: 15%–47%) of the patients were cognitively impaired.[90] In the multiple regression analysis, OHCA was a statistically significant predictor, with OHCA indicating better cognitive function. For reversal stages (stages 5, 7 and 9) of the Intra-/ Extradimensional set shift (IED), the mean number of errors was 18.7. For non-reversal stages (stages 4, 6 and 8), the mean number of errors was 16.1 (95% CI for difference: −1.4 to 6.5; $p = 0.20$). The total number of trials in IED intradimensional shift (ID, stage 6) was 6.5 versus 24.8 for the extradimensional shift (ED, stage 8) (95% CI for difference: 11.8 to 24.8; $p < 0.001$) For the Delayed Matching to Sample (DMS) percentage correct at 0 seconds delay, the mean was 81.4 (95% CI: 75.4 to 87.5), whereas, at 12 seconds delay, the mean was 68.2 (58.8 to 77.6) (n=28).

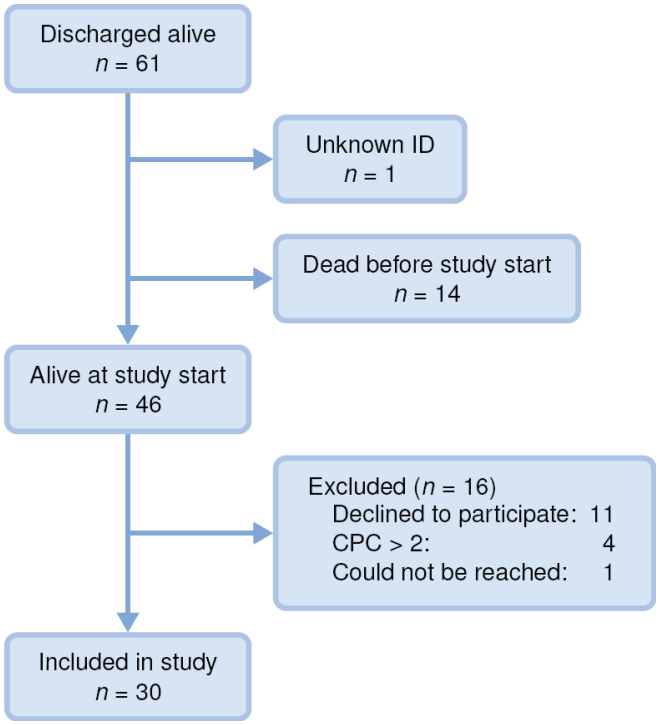

Fig. 4. Flow chart showing included and excluded patients in Paper II.

4.3 Paper III

A total of 403 comatose CA patients were available for TTM in the study period. Exclusions due to study criteria numbered 57, while exclusions due to missing data numbered 10. (Figure 5) This left 336 patients eligible for inclusion in the propensity score model, 183 (54%) of them TTM-treated cases and 153 non-TTM controls. A crude comparison between treated cases and controls revealed significant differences in age, gender, primary rhythm, presumed cause of arrest, resuscitation, and medical history. The propensity score model developed to balance these differences satisfied the overlap assumption, i.e. treated cases and controls with similar propensity scores were available for matching. We successfully matched 96 treated cases with controls. The propensity scores had similar distributions in cases and controls after matching, and most baseline covariates were sufficiently matched. This indicates that the propensity score model was adequately specified and suited for causal inference. The estimation of treatment effects revealed that survival in the first year after CA (restricted mean comparison) increased by 57 days (95% CI: 12–103, $p = 0.01$) in TTM-treated cases. The mean CPC value at discharge was reduced by 0.5 (95% CI: 0.1–1.0, $p = 0.02$) in TTM-treated cases.

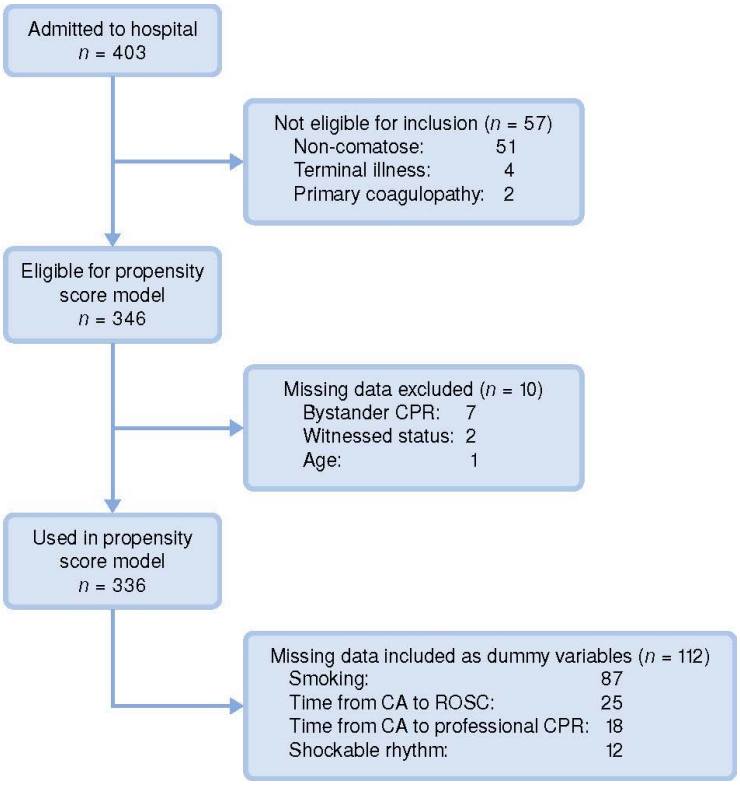

Fig. 5. Flow chart illustrating patients included in the propensity score model in Paper III.

5. Discussion

This dissertation demonstrates similarities between IHCA and OHCA in terms of survival to hospital discharge. We present evidence that TTM in clinical practice had beneficial effects for comatose CA patients in terms of increased survival. When investigating long-term cognitive function in CA survivors, we found impaired short-term memory similar to amnestic mild cognitive impairment (MCI).

5.1 Epidemiology

The incidence of EMS treated OHCA in paper I at 60.6 per 100.000 person-years is between the two most recent European estimates, and in line with recent registry publications from the US and Scandinavia.[23, 24, 91, 92] The incidence of CA treated by the CAT was 2.10 per 1000 admissions. This is lower than in the US, but higher than in the UK.[27, 35] In order to create OHCA and IHCA incidence rates which are easier to compare, we converted incidence per 1000 admissions to incidence per 100.000 person-years in the general population served by Helse Bergen Hospital Trust. The 171 IHCA correspond to an incidence of 41.3 per 100.000 person-years. When the numbers are presented this way, they communicate the relative incidence of OHCA and ICHA in a more understandable way.

As mentioned in sections 1.2 and 1.7, it is not valid to directly compare crude estimates. In order to compare incidence rates, they should as a minimum be standardised to match the age composition of a reference population. Adjustment according to gender composition is desirable, as well as adjustment according to socioeconomic status. The latter, however, is difficult in European populations due to a lack of publicly available reference populations. Such information has proven beneficial in explaining county-level variation in survival in the US.[93]

Knowing the prevalence of risk factors for cardiovascular disease in the research population would further help comparison. Several studies document the impact of reductions in cardiovascular risk factors on CA incidence and outcome. One study

found that favourable changes in cholesterol, smoking, physical activity and blood pressure reduced the incidence of coronary heart disease and out-of-hospital sudden death.[94] Another study reported that smoking legislation had an impact on CA incidence.[95] Next to standardisation to match a reference population, controlling for cardiovascular risk factors may help in discovering whether differences in CA incidence and outcomes between health systems are due to population differences, or differences in the health care provided.

The proportions of shockable primary rhythms between IHCA and OHCA (Paper I) were remarkably similar, at 26.3% for IHCA and 25.9% for OHCA. Proportions of presumed cardiac aetiology were also similar, at 71.2% for IHCA and 65.3% for OHCA. The OHCA group has traditionally been dominated by acute myocardial infarction, which commonly presents with initial shockable rhythms.[96] Improved prevention and an increasing use of implantable cardioverter defibrillators have reduced both incidence and severity of acute myocardial infarction.[75, 94, 97-100] As a consequence, the OHCA group is less dominated by coronary disease, and probably more similar to the ICHA group now than previously.

Many resuscitations from IHCA are undertaken in patients unlikely to survive.[101] Hence, policy on when not to attempt resuscitation will influence both IHCA incidence and outcome. There is an ongoing discussion in the UK regarding whether the initial presumption for CPR should remain, or if it may be better to replace it with a positive recommendation for CPR in a minority of patients.[102] Such an alteration of policy would probably have a dramatic effect on CA incidence and outcome. In order to control for resuscitation policy, the ratio of IHCA incidence to total hospital mortality could be an indicator of interest. Hospital effectiveness in preventing and treating CA in specific high-risk populations, like patients admitted for acute coronary syndromes, is another indicator to consider.[103]

5.2 Treatment

Paper III shows that intensive care treatment including TTM in ordinary clinical practice compared to intensive care treatment without TTM may have a beneficial effect in terms of increased survival. The patients were treated with TTM at 33˚C for 24 hours followed by rewarming to 37˚C at a rate of 0.5˚C per hour. Intensive care treatments included endotracheal intubation with mechanical ventilation, sedation in order to tolerate treatment and reduce oxygen consumption, haemodynamic optimization, treatment of seizures and prevention of pyrexia. Left ventricular assist devices in the form of impella or intra-aortic balloon pump were used for circulatory support when indicated at the discretion of the treating physician.

The optimal duration and target temperature for TTM is unknown, but there is consensus that TTM to some degree is indicated in comatose OHCA survivors.[45] A recent registry study found no benefit from TTM in IHCA, recommending a randomized trial in order to explore the question.[104] It may be that TTM has effect only in patients who have suffered global brain ischemia. Recent trials have included patient groups with short periods of anoxia, where TTM is less likely to be of benefit.[104, 105] An effect might be seen in patients with longer resuscitation times.

To what extent improved outcomes from CA over the past decade are due to better intensive care treatment, standardized treatment protocols, introduction of TTM, or PCI is debated.[106, 107] At present, there are probable but uncertain effects from TTM as well as primary PCI in CA. We may be back to the discoveries of Peter Safar and colleagues in the 1990s.[108] They found an effect of hypertensive hemodilution and TTM combined, but no isolated effect of either. This may be the case in contemporary clinical research as well. The effects of available treatment on coarse indicators of outcome like mortality may be small, and easily offset by Hawthorne effects in clinical trials. One way to make treatment effects substantial enough to measure in a clinical setting is to combine several treatments in a bundle.[109] A treatment bundle involving PCI, TTM, and general intensive care treatment improved survival, but gave no indication as to which factors contributed the most.[110]

Paper III is an example of how health registry data may be used to move the discussion forward by investigating causality based on registry data. Propensity score matching is a robust method, its advocates claiming that a well performed observational study closely resembles a randomized controlled trial.[111] A prerequisite for matching is that some patients receive the treatment in question and others do not. These two populations differ because treatment is based on indications, a problem which has hampered observational studies and made policy makers reluctant to include them in systematic reviews. Matching methodology reduces the problem of differing populations by creating pairs or groups of subjects, one treated and one not treated, which are similar except for the treatment. After successful matching, the data may be used to infer causality. Propensity score matching uses the probability for treatment calculated from baseline covariates as the matching criterion. Baseline covariates must be measured before the start of treatment and must be likely to affect outcome. Although baseline covariates differ between two subjects, they may still be matched as long as the probability for treatment is similar. The result is two groups of patients, one treated and one not treated, in which the probability of treatment, i.e. the propensity score, is the same. The key feature of the propensity score is that the differences in baseline covariates between treatment and control patients in the unmatched sample tend to balance in the matched sample.[111] Comparison of outcomes between the two groups therefore evaluates treatment effect and establishes causality. Critics of the method argue that confounders may exist which are unknown or unmeasured, and therefore not included in the model. These hidden confounders may either be responsible for or hide treatment effects. In order to reduce confounding, there are strict demands to methodology in propensity score analyses. All known confounders must be measured at baseline, before treatment allocation, and included in the analysis. Even so, observational studies will never be free of the potential confounder. This is why randomised studies are rated more highly than observational studies when grading the level of evidence.

Survival from IHCA in paper I was similar to that of OHCA even though the IHCA population was older and presumably less healthy. We suspect that the immediate professional treatment of IHCA documented in the study is beneficial. If so, bringing

the experience and technology available in hospitals to the pre hospital stage might improve survival from OHCA. A recent meta-analysis comparing paramedic-led CPR to physician-led CPR showed increased survival for physician-led CPR.[112] Whether this is due to the physicians knowledge or to her technical skills is not known.

There is evidence that hospitals admitting more than 50 CA patients per year have better survival rates than hospitals with fewer admissions.[113] This implies that adequate monitoring of circulation and experience with optimizing circulation in a setting with circulatory compromise is of importance. Further studies are needed to ensure that the effect is not due to selection bias, hospital or ICU size, or simply an artefact of the availability of more sophisticated treatment options.

5.3 Outcome

5.3.1 Survival

In paper I, survival to hospital discharge from OHCA was 16.8%, or 10.2 per 100.000 person-years, while survival from IHCA was 16.2%, or 6.7 per 100.000 person-years. As discussed previously, comparison of crude survival to hospital discharge between health systems is not generally advisable. Apart from differences in discharge policy, the lack of standardisation to a population norm causes bias. Further problems due to selection bias in terms of systematic exclusions and missing inclusions are discussed below in the section on limitations.

Pooled mortality from CA in our community was 85.0 per 100.000 person-years, accounting for approximately two-thirds of the estimated cardiovascular mortality in our community.[58, 114] The major remaining causes of cardiovascular mortality are heart failure and cerebrovascular disorders.

Long-term survival (Paper II) was markedly decreased for patients discharged alive. Standardized mortality ratio from hospital discharge to start of the second study, compared with an age- and gender-matched Norwegian population, was 2.8. Most deaths occurred within the first six months after discharge. (Figure 6)

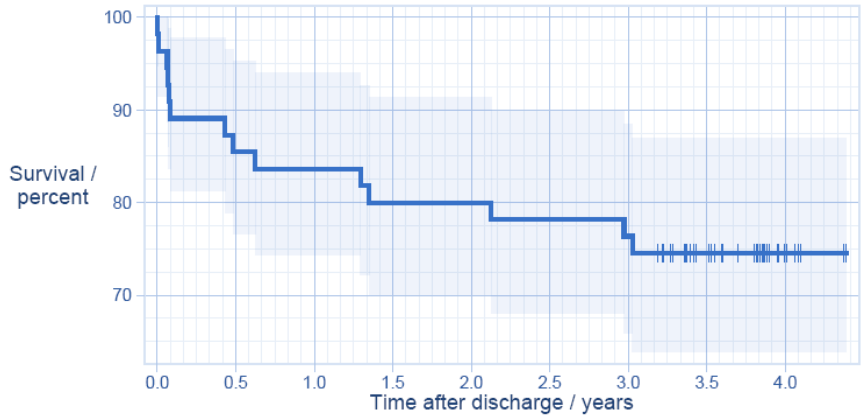

Fig. 6. Survival after hospital discharge with 95 % pointwise confidence intervals.*

* Vertical lines indicate time of censoring.

The reported increase in mortality is corrected for age and gender, but we know that cardiovascular risk factors and socioeconomic factors are likely to contribute.[94, 99, 100] Cardiovascular risk factors like smoking, obesity, diabetes mellitus, and physical inactivity are more prevalent in parts of society with lower socioeconomic status. Consequently, if socioeconomic status in the study sample was lower than the general Norwegian population, it could account for some of the increased mortality. One must also bear in mind possible effects of comorbidity in addition to risk factors and socioeconomic status.

As there is a substantial number of deaths the first six months after discharge, some of them may be attributed to CA. A further aspect is that intensive care patients, regardless of the diagnosis which precipitates intensive care, have a higher mortality after hospital discharge compared to an age- and gender-matched normal population.[115] It may be that some early deaths after discharge are due to intensive care treatment rather than CA.

The choice of restricted mean survival time as the outcome measure in paper III complicates interpretation of the treatment effect. Restricted mean survival time was chosen because unlike hazard ratios, which are commonly used in similar studies, it does not depend on the proportional hazards assumption. Hazard ratios estimate

survival at a single point in time: the time of follow-up. They assume, therefore, that the treatment effect is stable so that hazards do not change with time. If hazards do, in fact, change with time, the hazard ratio will depend on the time to follow-up. Consequently, the estimated treatment effect will depend on the chosen time to follow-up. Restricted mean survival time is more robust because survival during the entire period from inclusion to follow-up influences the mean. We chose to restrict survival time to 365 days after CA on the assumption that survival beyond one year likely depends more on other factors than CA.

The question of whether a 57-day increase in restricted mean survival time is clinically significant remains, however. An impression of the magnitude of the difference can be gained from a study comparing the restricted mean survival time to hazard ratios in well-known cancer studies.[116] The hazard ratios in the RE01 trial in advanced kidney cancer, the GOG111 trial in advanced ovarian cancer, and the IPASS trial in lung cancer were 0.73 / 0.75 / 0.73, respectively. Restricted mean survival times in the same three studies were 0.9 months / 3 months / 9 months, respectively, with corresponding follow-up times of 4 years / 7 years / 1.5 years. This indicates that the increase in restricted mean survival time of 57 days is clinically significant.

5.3.2 Cognitive function

When investigating long-term cognitive function in CA survivors in paper II, we identified MCI in 29% of patients with good cerebral function at hospital discharge according to the CPC classification. There is no general consensus regarding diagnostic criteria for MCI. However, the concept of MCI as a measurable deficit in at least one cognitive domain beyond that of normal aging with the absence of dementia is well established.[117, 118] When defining cognitive impairment we used the Jackson criteria, classifying cognitive impairment as two out of ten results two standard deviations below the mean or three out of ten results 1.5 standard deviations below the mean.[90]

Cognitive testing revealed reduced episodic memory and a probable impact on executive function in CA survivors compared to the norm. Our findings correlate with the physiological substrate of damage to oxygen-sensitive neurons in the medial temporal lobe.[119] Similar results from cognitive testing have been shown both over the short- and long-term using traditional neurocognitive tests, and over the short-term using computerized tests.[68, 120, 121] Rehabilitation of executive functioning is possible, whereas treatment of amnesia is limited.[122] This might explain why executive functions were less affected than memory four years after CA.

We assessed cognition using the CANTAB, a tablet-based computerized neuropsychological assessment device. Following its introduction by Sahakian and Robbins in the 1980s it has been increasingly used. Even so, there is discussion regarding computerized neuropsychological assessment devices compared with standard neuropsychological tests.[123] Since CANTAB is a stand-alone solution there are no issues with compatibility with other software packages. Construct validity has been established in a Norwegian population, and we have chosen tests with high test-retest correlations to achieve robustness.[124-127]

The question of what CANTAB really measures remains, however. Studies investigating correlations between CANTAB and traditional neuropsychological test batteries find poor correlations between CANTAB tests purportedly assessing specific cognitive domains and their traditional neuropsychological counterparts.[128] It is suggested that interaction with the computer interface may account for the discriminant ability of computerized neuropsychological assessment devices due to impairments in visual processing skills in MCI.[129] Therefore, the most appropriate use of computerized neuropsychological assessment devices in CA survivors is as a screening tool in patients where MCI is suspected.[124]

5.4 Strengths and limitations

One strength of this dissertation lies in its attempt to combine emergency medicine, intensive care, epidemiology, and neuropsychology. These fields of research are

distinctly different with their own bodies of knowledge and differing methodologies. Data collection for papers I and II was prospective and thorough, using several data sources in order to identify cases and collect complete data sets. A further strength is the statistical methods used to evaluate treatment effect.

It is a limitation that data for paper I, and in part for paper III, was collected from patient records. This is a problem affecting clinical research in general. The optimal solution in terms of data quality is to collect data prospectively and for study purposes only. This may be accomplished by making data collection forms and protocols for how to fill in each data point prior to the start of the study. The drawback is that compliance of clinical staff to fill in such forms is low, increasing the likelihood of both missing cases and missing data. Hiring staff dedicated to data collection is a possible solution, though not well suited to low incidence emergency conditions such as CA. Basing data collection on standard clinical documentation is another solution. This bypasses problems with compliance, but data not considered clinically relevant may be missing. The likelihood of inter-observer variability is also higher due to the lack of a strict protocol defining data elements. Our solution when collecting data for paper I was a hybrid between these two alternatives. Data collection forms for CA with protocols for their use existed as a standard in our patient journals. Nurses, physicians, and EMS personnel responsible for the documentation of CA were taught how to fill in these forms, and expected to do so for every CA. Personnel dedicated to the study checked that forms were filled in for relevant patients and that the data in each form was correct. This reduced the likelihood of both missing cases and missing data, while at the same time ensuring a protocol guided collection of data.

Paper I is biased due to systematic exclusions because CA of less than three minutes' duration during invasive cardiologic procedures were excluded due to methodological concerns. There are also few IHCA in the ICU and operative wards in the data set for paper I. This makes us suspect missing inclusions of IHCA in specialised wards.

It would have been advantageous if all data sets contained information about socioeconomic status, comorbidity, and cardiovascular risk factors. Such information would make comparison with other publications possible, and it would be possible to standardize the results according to these factors. Papers I and II would also have benefited from a better survival analysis.

One may question the use of Z-scores to define cognitive impairment in paper II due to the small sample size and the fact that Fig. 2 in paper II suggests that the distributions may be skewed. A direct comparison of means would have been better. However, Z-scores are the only option for norms comparison in CANTAB.[130] As a means of ascertaining the results from the t-tests, we conducted a bootstrap analysis as a sensitivity test.

Lack of Norwegian population norms has led us to use Danish norms for EQ-5D and British norms for CANTAB, both of them close approximations of the parent population, in our opinion.

The lack of temperature traces in paper III is a limitation, since the magnitude and profile of temperature differences between cases and controls is unknown to us.

5.5 Perspectives

The effects of cardiovascular risk factors, comorbidity, and socioeconomic status on CA incidence and survival need to be investigated further. This may be accomplished by monitoring IHCA and OHCA in a single population over time, and might also give insights into how prevention strategies and advances in treatment influence incidence and outcome from CA.

The effects of physician-led CPR in OHCA should be further investigated as to whether increased survival is due to knowledge or technical skills.[112] One could imagine that the physician has a better capability to diagnose the precipitating cause of CA than other health professionals. This is of particular importance when resuscitation is not successful during the first few cycles. The next natural step for a

physician would be to administer treatment based on the most probable diagnosis. A protocol which rapidly identifies the most likely precipitating cause of CA and tailors treatment accordingly could increase survival if good quality CPR is not lost. In order to aid diagnostic accuracy, one should consider the use of diagnostic tools during resuscitation. One such tool is ultrasonography, which is suggested to aid treatment of reversible causes of CA.[131, 132] Continuous capnography readings might provide both diagnostic and prognostic information.[133, 134] While mechanical chest compressions are not recommended as a standard initial setup, there is evidence of benefit later in the resuscitation phase.[135] A setup with capnography in conjunction with controlled mechanical ventilation and controlled chest compressions would allow better standardization of respiratory minute volume and cardiac output. A pilot study, perhaps including autopsy, could indicate whether capnography in this setting provides information about the cause of CA or aids in prognostication. Analyses of arterial pH, lactate, and potassium would be of further interest in prognostication.

An interesting development is the use of ECMO in CA, either as a bridge to treatment for a precipitating cause or as a bridge to recovery. Research in the field is, however, predominantly observational studies of low to moderate quality, rendering the effect of the intervention largely unknown. Due to the low number of available patients, comparison of ECMO CPR with standard CPR is initially best undertaken as registry studies using matching methodology in order to establish causality.

Even though there seems to be no difference between TTM at 33˚C compared with 36˚C, there are still questions to be answered regarding TTM. One question currently being investigated is the effect of early induction of TTM versus standard induction after admission. Currently, no strong evidence exists in favour of either.[136] Studies on other methods for rapid induction of TTM are ongoing.[137] A study investigating TTM of 48 hours' duration compared with TTM of 24 hours' duration is completed but not yet published.[138]

There is some interest in the neuroprotective properties of inhaled agents. Xenon has shown neuroprotective properties in animal studies. In a recent human study, MRI

showed less white matter damage compared with controls, but there was no difference in survival or cognitive function.[139] There is also an interest in the potential ameliorating effect of NO inhalations on cerebral and myocardial ischemia – reperfusion injuries that often follow CA.[140]

Keeping in mind that recent randomized controlled studies of single interventions have failed to identify treatment effects, it may be that this is not the best method to identify improvements in the treatment of CA. One path to investigating the field further may be to conduct randomised controlled studies which investigate bundles rather than single treatments.[109] A treatment bundle is a collection of evidence-based interventions applied to a patient category in order to improve outcome.[141-143] Bundles of care rather than single interventions may increase the magnitude of treatment effects so that they are discernible from Hawthorne effects and other spurious effects which are difficult to control in a clinical setting.[144]Another path would be to look for natural opportunities to conduct high quality observational studies.[145] When they are well designed, observational studies come close to randomized controlled trials in establishing causality.[111]

Cognitive function and quality of life in CA survivors is a field where much is yet to be uncovered. In order to move forward, however, one has to establish consensus regarding which tools to use for measuring cognitive function and quality of life. At present the diversity of approaches hinders progress. The selected tools must be well validated, easy to use, and calibrated so that floor and ceiling effects are avoided. After selection of appropriate tools CA survivors should be compared to relevant control groups. For instance, survivors from CA with a cardiac cause could be compared to an age- and gender-matched population admitted to the ICU and treated for acute coronary syndrome during the same time period. Such a study could assess the temporal development of cognitive function and quality of life in CA survivors. If properly designed, the study could also investigate the effects of cognitive training.[146]

An interesting consequence of recent discoveries linking the mental maps which aid spatial navigation with memory is the potential for physical activity in cognitive

rehabilitation.[147-149] Position cells in the hippocampus and grid cells in the entorhinal cortex aid navigation, but they are also instrumental in creating memories.[148] This link between memory and spatial perception might be a factor in explaining why visual processing skills are affected in MCI.[146] The link also provides a theoretical basis for promising research regarding the cognitive abilities of MCI patients as a result of combined physical and cognitive training.[149, 150]

6. Conclusions

Paper I

The majority of CA in Helse Bergen Hospital Trust occurred out-of-hospital. Survival to hospital discharge was similar whether CA was out-of-hospital, or in-hospital.

Paper II

Four years after CA, cognitive impairment persisted in 29% of CA survivors with good neurological outcome at hospital discharge.

Paper III

In comatose CA survivors, intensive care treatment with TTM compared to intensive care treatment without TTM significantly increased the restricted mean survival by 57 days.

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8. Appendix

8.1 Utstein data template

Utstein data templates: summary of changes[5]

1991 Name	2004 Name	2004 Definition	1991 Status	2004 Status
1. Population served by EMS system	Removed	Total population of service area of EMS system	Core	Supplementary
2. Confirmed cardiac arrests considered for resuscitation	Absence of signs of circulation and/or considered for resuscitation	Number of cardiac arrests defined by absence of signs of circulation	Core	Core
3. Resuscitations not attempted	Unchanged	Total number of cardiac arrests in which resuscitation was not attempted and number of these arrests not attempted because	Core (total not attempted)	Core
		A DNAR order was present	None (DNAR and futile status)	
		Attempt was considered futile (or meaningless)		
		Signs of circulation were present		
4. Resuscitations attempted	Unchanged	Total number of resuscitations attempted and number of these resuscitations that included	Core (total attempted)	Core
		Any defibrillation attempt		
		Chest compressions	None (defibrilla-tion, chest compres-sions, and ventila-tions)	
		Ventilations		

1991 Name	2004 Name	2004 Definition	1991 Status	2004 Status
5. Cardiac aetiology	Aetiology	Number of resuscitations in which etiology of arrest was Presumed cardiac Trauma Submersion Respiratory Other Unknown	Core	Core
6. Noncardiac aetiology	Merged with aetiology	See aetiology	Core	See aetiology
	Arrest witnessed/monitored	Total number of resuscitation attempts and number of arrests witnessed by Laypersons Healthcare providers	None	Core
7. Arrest witnessed by bystanders	See arrest witnessed/monitored	Number of resuscitation attempts in which arrest was witnessed by laypersons	Core	Core
8. Arrest not witnessed	See arrest witnessed/monitored	Number of resuscitation attempts in which arrest was not witnessed by anyone	Core	Core
9. Arrest witnessed by EMS personnel	See arrest witnessed/monitored	Number of resuscitation attempts in which arrest was witnessed by healthcare personnel	Core	Core
	First monitored rhythm shockable	Total number of resuscitation attempts in which first monitored rhythm was shockable and identified as: VF VT Unknown AED shockable rhythm	None	Core
10. Initial rhythm VF	See monitored rhythm shockable	Number of resuscitation attempts in which first	Core	Core

1991 Name	2004 Name	2004 Definition	1991 Status	2004 Status
		monitored rhythm after arrest was VF		
11. Initial rhythm VT	See monitored rhythm shockable	Number of resuscitation attempts in which first monitored rhythm after arrest was VT	Core	Core
	First monitored rhythm nonshockable	Total number of resuscitation attempts in which first monitored rhythm was nonshockable and rhythm was identified as Asystole PEA Bradycardia Other Unknown AED nonshockable rhythm	None	Core
12. Initial rhythm asystole	See first monitored rhythm nonshockable	Number of resuscitation attempts in which first monitored rhythm after arrest was asystole	Core	Core
13. Other initial rhythms	See first monitored rhythm nonshockable	Number of resuscitation attempts in which first monitored rhythm after arrest was unshockable	Core	Core
14. Determine presence of bystander CPR: yes or no for each subset	CPR before EMS	Number of resuscitation attempts in which CPR (chest compression) was performed before EMS arrival	Core	Core
	Rhythm analysis or defibrillation before EMS	Number of resuscitation attempts in which either AED rhythm analysis or defibrillation was performed before EMS arrival	None	Core
15. Any ROSC	Any ROSC	Number of resuscitation	Core	Core

1991 Name	2004 Name	2004 Definition	1991 Status	2004 Status
		attempts in which any ROSC was present Yes No Unknown		
16. Never achieved ROSC	See any ROSC	See any ROSC	Core	See Any ROSC
17a. Efforts stopped: patient died en route to hospital	Removed	Number of resuscitation attempts in which all resuscitative efforts were discontinued and patient died before arriving at hospital	Core	Supplementary
17b. Efforts stopped: patient died in ED	Removed	Number of resuscitation attempts in which all resuscitative efforts were discontinued and patient died in ED	Core	Supplementary
18. Admitted to ICU/ward	Survived event to ED/ICU	Number of resuscitation attempts in which patient regained signs of circulation and was admitted to ED or ICU	Core	Core
19a. Died in-hospital total	Removed	Number of resuscitation attempts in which patient regained signs of circulation and was admitted to ED/ICU but died in hospital	Core	Supplementary
19b. Died in hospital within 24 hours	Removed	Number of resuscitation attempts in which patient regained signs of circulation and was admitted to ED/ICU but died in hospital within 24 h	Core	Supplementary
20. Discharged alive	Unchanged	Number of resuscitation attempts in which patient regained signs of circulation,	Core	Core

1991 Name	2004 Name	2004 Definition	1991 Status	2004 Status
		was admitted to ED/ICU, and was discharged from hospital alive		
21. Died within 1 year of hospital discharge	Removed	Number of resuscitation attempts in which patient regained signs of circulation, was discharged alive from hospital but died within 1 year from hospital discharge	Core	Supplementary
22. Alive at 1 year	Removed	Number of resuscitation attempts in which patient regained signs of circulation, was discharged alive from hospital, and was/is alive at 1 year from hospital discharge	Core	Supplementary
	Neurological outcome at discharge	Number of resuscitation attempts in which patient regained signs of circulation, was discharged alive from hospital, and had a CPC score of 1 or 2 3 or 4 or unknown	None	Core
	Location of arrest: out-of-hospital	Total number of resuscitations that took place out-of-hospital and number of resuscitation attempts that took place within Home/residence Industrial/workplace Sport/recreation event Street/highway Public building Assisted living/nursing home Educational institution Other Unspecified/unknown	None	Core (EMS only)

1991 Name	2004 Name	2004 Definition	1991 Status	2004 Status
	Location of arrest: in-hospital	Total number of resuscitation attempts that took place in-hospital and number of resuscitation attempts that took place within Ward ED Operating room ICU Other Unknown	None	Core (hospital only)