

# **Epidemiology, treatment and outcome of out-of-hospital cardiac arrest**

**Thomas Werner Lindner**



Dissertation for the degree philosophiae doctor (PhD)  
at the University of Bergen

2015

Dissertation date: 26th of March





Faculty of Medicine

Department of Clinical Medicine

University of Bergen, Norway

Department of Anaesthesiology and Intensive Care



Stavanger University Hospital

Stavanger, Norway

## **Scientific environment**

The presented studies were performed at the Stavanger University Hospital, Department for Anaesthesiology and Intensive Care, in cooperation with the local emergency medical services and the Department of Medicine and in collaboration with the Department of Heart Disease, the Medical Intensive Care Unit and the Department of Anaesthesia and Intensive Care at Haukeland University Hospital. Additional collaborations were with the Department of Anaesthesiology, Division of Emergencies and Critical Care, at the Oslo University Hospital and the Department of Surgical Sciences, Anaesthesiology and Critical Care Medicine, Uppsala University, Sweden. This work was financially supported by the Regional Competence Centre for Emergency Medicine in Helse Vest and the Laerdal Foundation for Acute Medicine.

## Acknowledgements

First, I must thank my supervisor and friend Professor Eldar Søreide for his excellent guidance and motivation during this work. He was always supportive, and this dissertation would not have been possible without his contribution. I also want to thank my co-supervisors Professor Hans Morten Lossius and Odd Bjarte Nilsen for their help and guidance both in human factors and in the statistical analysis.

I also want to thank my co-authors H. Aarsetøy, C. Deakin, T. Draegni, J.K. Heltne, J. Langørgen, A.I. Larsen, J.T. Kvaløy, W.T. Mathisen, S. Rubertsson, K. Sunde and C. Vossius for their contribution to this thesis.

My family was always in my mind while I was occupied by thinking and writing, especially my bright and beloved daughters Wanda and Mathilda and, most of all, my wife Corinna Vossius. She was a sempiternal support for all matters of my life throughout this thesis. I wish to thank them with deep and humble gratitude.

---

# Contents

<b>SCIENTIFIC ENVIRONMENT</b> .....	<b>4</b>
<b>ACKNOWLEDGEMENTS</b> .....	<b>5</b>
<b>CONTENTS</b> .....	<b>6</b>
<b>LIST OF PUBLICATIONS</b> .....	<b>9</b>
<b>ABBREVIATIONS</b> .....	<b>10</b>
<b>ABSTRACT</b> .....	<b>12</b>
<b>1. INTRODUCTION</b> .....	<b>14</b>
<b>2. EPIDEMIOLOGY, TREATMENT AND OUTCOME</b> .....	<b>16</b>
<b>2.1 EPIDEMIOLOGY OF OUT-OF-HOSPITAL CARDIAC ARREST</b> .....	<b>16</b>
<b>2.2 TREATMENT OF OUT-OF-HOSPITAL CARDIAC ARREST</b> .....	<b>19</b>
2.2.1 History of out-of-hospital cardiac arrest treatment and resuscitation guidelines .....	19
2.2.2 Prehospital cardiopulmonary resuscitation .....	21
2.2.3 In-hospital treatment of out-of-hospital cardiac arrest patients .....	23
2.2.3.1 General treatment .....	23
2.2.3.2 Therapeutic hypothermia after out-of-hospital cardiac arrest .....	24
2.2.3.3 Percutaneous coronary intervention .....	25
<b>2.3 OUTCOME OF OUT-OF-HOSPITAL CARDIAC ARREST</b> .....	<b>26</b>
2.3.1 Outcome measures .....	26
2.3.2 Outcome numbers .....	26
2.3.3 Outcome and genetic factors in out-of-hospital cardiac arrest .....	27
2.3.4 Documentation of the incidence and outcome after out-of-hospital cardiac arrest .....	29
<b>3. AIMS OF THE THESIS</b> .....	<b>31</b>
<b>3.1 PAPER I</b> .....	<b>31</b>
<b>3.2 PAPER II</b> .....	<b>31</b>
<b>3.3 PAPER III</b> .....	<b>32</b>

---

3.4	PAPER IV.....	32
4.	<b>MATERIALS AND METHODS.....</b>	<b>33</b>
4.1	STUDY AREA AND RECEIVING HOSPITAL.....	33
4.2	PAPER I.....	34
4.2.1	EMS.....	34
4.2.1.1	Emergency dispatch centre.....	34
4.2.1.2	Emergency units.....	34
4.2.1.3	CPR guidelines.....	35
4.2.2	Patient inclusion, data collection and ethical approval.....	36
4.3	PAPER II.....	38
4.3.1	Study population.....	38
4.3.2	Ethical Considerations.....	39
4.3.3	Collection and analysis of genetic material.....	40
4.4	PAPER III.....	40
4.4.1	Study population and participating hospitals.....	40
4.4.2	Data collection and ethical approval.....	42
4.5	PAPER IV.....	43
4.5.1	Study population, EMS and receiving hospital.....	43
4.5.2	Data collection and ethical approval.....	44
4.5.3	Potential life years saved.....	44
4.5.4	Standardised mortality rates.....	44
4.6	STATISTICAL ANALYSES.....	45
5.	<b>MAIN RESULTS.....</b>	<b>47</b>
5.1	PAPER I.....	47
5.2	PAPER II.....	47

---

5.3	PAPER III .....	48
5.4	PAPER IV .....	49
6.	DISCUSSION.....	50
6.1	PAPER I AND II .....	50
6.2	PAPER III .....	54
6.3	PAPER IV .....	56
7.	LIMITATIONS OF THE STUDIES.....	58
8.	CONCLUSIONS AND FUTURE RESEARCH .....	60
9.	ERRATUM .....	62
10.	REFERENCES.....	63
11.	REPRINTS OF PAPER I-IV .....	79

---

## List of publications

The thesis is based on the following papers, which are referenced in the text using Roman numerals.

- I. Lindner TW, Søreide E, Nilsen OB, Torunn MW, Lossius HM.  
Good outcome in every fourth resuscitation attempt is achievable-an Utstein template report from the Stavanger region.  
**Resuscitation. 2011 Dec; 82(12):1508-13.**
- II. Lindner TW, Deakin CD, Aarsetøy H, Rubertsson S, Heltne JK, Søreide E.  
A pilot study of angiotensin converting enzyme (ACE) genotype and return of spontaneous circulation following out-of-hospital cardiac arrest.  
**Open Heart. 2014 Aug 14;1(1):e000138. doi: 10.1136/openhrt-2014-000138**
- III. Lindner TW, Langørgen J, Sunde K, Larsen A, Kvaløy J, Heltne J, Draegni T, Søreide E.  
Factors predicting the use of therapeutic hypothermia and survival in unconscious out-of-hospital cardiac arrest patients admitted to the ICU.  
**Critical Care. 2013 Jul 23;17(4):R147**
- IV. Lindner TW, Vossius C, Mathiesen WT, Søreide E.  
Life years saved, standardised mortality rates and causes of death after hospital discharge in out-of-hospital cardiac arrest survivors.  
**Resuscitation. 2014 May; 85(5):671-5.**

The papers are reprinted for this thesis with the permission of the publishers.

---

## Abbreviations

ACE	-	Angiotensin-Converting Enzyme
ALS	-	Advanced Life Support
AED	-	Automatic External Defibrillator
BLS	-	Basic Life Support
CCU		Cardiac Care Unit
CPC	-	Cerebral Performance Category
CPR	-	Cardiopulmonary Resuscitation
CVD	-	Cardiovascular Disease
EDC	-	Emergency Dispatch Centre
EMS		Emergency Medical System
ERC	-	European Resuscitation Council
GP	-	General Practitioner
HACA	-	Hypothermia After Cardiac Arrest Study Group
ICU	-	Intensive Care Unit
ILCOR	-	International Liaison Committee on Resuscitation
OHCA	-	Out-of-Hospital Cardiac Arrest
NSD	-	Norwegian Social Science Data Service
PAD	-	Public Access Defibrillator

---

PCI	-	Percutaneous Coronary Intervention
RCE	-	Regional Committee for Research Ethics
ROSC	-	Return of Spontaneous Circulation
SCA	-	Sudden Cardiac Arrest
SMR	-	Standardised Mortality Rate
STEMI	-	ST-Elevation Myocardial Infarction
TH	-	Therapeutic Hypothermia

## Abstract

**Introduction:** Every year in the Western world, emergency medical system (EMS) personnel attempt to resuscitate approximately 500,000 patients who experience out of the hospital cardiac arrest (OHCA). Reported incidences and outcomes numbers of OHCA show substantial variations. System and quality differences in the chain of survival and post resuscitation care may contribute to these variations. This thesis aims to update our knowledge about incidence and outcomes of OHCA in an area, which previously have reported high survival rates after OHCA.

**Aims:** The specific aims of this thesis are to present current epidemiology, outcomes and factors linked to survival in adult patients after OHCA, to examine the relationship between the angiotensin-converting enzyme (ACE) genotype and the return of spontaneous circulation (ROSC), study the use of therapeutic hypothermia (TH) after OHCA, estimate the life years saved by resuscitation efforts and present a calculation of the overall mortality risk after hospital discharge in OHCA survivors.

**Methods:** In paper I, we accessed a prospectively collected Utstein template database to identify all resuscitation attempts in patients with OHCA of cardiac origin and compared the outcomes during two periods (2001–2005 vs. 2006–2008). In paper II, we performed a prospective observational study of all OHCA of cardiac origin between 2007 and 2010. The ACE genotype was identified and used together with the Utstein template parameters to examine the relationship between ROSC and the ACE genotype. In paper III, we conducted a retrospective observational study of OHCA patients admitted to the ICU from 2004 to 2008 and examined the factors predicting the use of TH and survival. Paper IV was a retrospective observational study of long term survival of OHCA patients between 2002 and 2011 discharged from hospital.

---

We calculated the potential life years saved, the standardised mortality rates (SMR) and reported the causes of death after hospital discharge.

**Results:** In paper I, we found that the overall survival to discharge increased from 18% to 25% and in witnessed OHCA with shockable rhythm from 37% to 52%. There were no significant differences between the two time periods regarding age, sex distribution, OHCA location, proportion of shockable rhythms and ROSC rate. In paper II, we measured the ACE gene polymorphism distribution in OHCA patients to be similar to the general population, but no correlation to ROSC was found. In paper III, we found that TH was used in 70% of all unconsciousness OHCA patients. Witnessed arrest, bystander CPR, shockable rhythm and cardiac origin, were all positive predictors of TH use and survival. Increasing age, and within a subgroup female gender, predicted a lower utilisation of TH and lower survival. In paper IV, we found the mean number of potential life years saved per patient to be 23 years. The overall SMR in the study cohort was 2.3, and cardiac disease was the prominent cause of late deaths.

**Conclusions:** Overall, we found good outcome to be achievable in every fourth resuscitation attempt and in every second resuscitation attempt when patients have a shockable rhythm. No significant association between the ACE gene polymorphism and ROSC was demonstrated. TH was used in the majority of OHCA patients who were admitted to the ICU, with an observed underutilisation in some subgroups. The resuscitation of OHCA victims lead to a significant long-term benefit with respect to the number of life years saved. Cardiac disease was the main cause of death after hospital discharge. The reasons for overall improved outcomes are probably multi-factorial and related to improvements in all links of the chain of survival.

# 1. Introduction

The line between life and death is ephemeral and almost invisible. Throughout time, mankind has dreamed of reversing death. The concept of resurrection is found in all cultures and religions, from Orpheus and Eurydice to Lazarus. In human history, there have always been technical attempts to resuscitate perished human and non-human bodies. However, despite the more mystical approaches, practical manoeuvres are also described. Even 4000 years ago, insufflations of air were used to restore life in deceased loved ones. The first report of proper mouth-to-mouth ventilation is approximately 270 years old.[1-3] The first external chest compressions were performed by the physicians Hill and Maas in the late 18th century.[4, 5]

However, it was only approximately 50 years ago that practical treatment options for impending death from cardiac arrest were identified. Sudden cardiac arrest (SCA) is defined by unresponsiveness, apnoea (or agonal, gasping respirations), and the absence of signs of circulation due to lack of cardiac output.[6, 7] Current resuscitation guidelines recommend starting with chest compressions and ventilating the lungs, which is also referred to as cardiopulmonary resuscitation (CPR).[8]

Every year, emergency medical system (EMS) personnel in the Western world attempt to resuscitate approximately 500,000 adult patients in whom unexpected cardiac arrest occurs out of the hospital.[9-13] The incidence and outcome of out-of-hospital cardiac arrest (OHCA) have been reported for decades but still show substantial variation.[14-16]

The area in which the research for this thesis was conducted has previously reported high survival rates after OHCA.[17, 18] To follow up on these findings, identify possible contributing factors for survival, and gather more-detailed knowledge about OHCA patients, the plan for this thesis was

developed in 2008. This thesis presents current outcomes and factors that are linked to survival in adult patients after OHCA, contains a pilot study of the relationship between the angiotensin-converting enzyme (ACE) genotype and the return of spontaneous circulation (ROSC), examines the use of therapeutic hypothermia (TH) after OHCA, estimates the life years that are saved by resuscitation efforts, and presents a calculation of the overall mortality risk after hospital discharge in OHCA survivors.

## **2. Epidemiology, treatment and outcome**

### **2.1 Epidemiology of out-of-hospital cardiac arrest**

The term “epidemiology” was first used in the early 19<sup>th</sup> century [19] to describe the science of how frequently diseases occur in a population. Today, the term is also used to describe the rate of symptoms and disease-associated behaviours. To obtain epidemiological numbers by observation, both the disease or symptom and the observed population must be defined. The incidence is the number of new diseases or conditions that are diagnosed during a given period of time, while the prevalence is the number of diseases or conditions at a given point in time.

This thesis specifically focuses on adult patients in whom unexpected cardiac arrest occurs outside of the hospital. OHCA represents approximately 60% of all documented cardiac arrests and differs from in-hospital cardiac arrest.[20]

Our knowledge about the epidemiology and outcomes of patients with OHCA is mainly based on epidemiological studies, using the Utstein template for the uniform reporting of OHCA.[7, 21] According to the Utstein definition, the aetiology of an OHCA is immediately determined at the moment of treatment at the site where the OHCA occurs.[21, 22]

Currently, only estimates of the global epidemiology and incidence of OHCA are available. Exact statistics for larger areas or regions are not known, and the described populations are not always sufficiently defined. Variances in the reported numbers are seen both between different countries and between regional EMS departments.[16, 23, 24] The estimated overall incidence is between 60 and 100 OHCA patients per 100,000 inhabitants per year.[16, 24, 25] The incidence of OHCA is correlated with age. In persons younger than 50 years, the incidence is only 1 OHCA per 100,000 inhabitants per year, while in

---

the population of persons who are 80 years and older, the reported incidence is as high as 9 OHCA per 100,000 inhabitants per year.[25]

Both the causes of OHCA and the first documented electrocardiographic (ECG) rhythm are frequently reported epidemiological figures. The cause of OHCA can be divided into cardiac or non-cardiac origins. OHCA of non-cardiac origin includes conditions such as trauma, drowning, asphyxia, exsanguination, intoxication, drug overdose, suicide or any other non-cardiac cause as determined to the extent that is possible by the EMS.[7] A presumed cardiac aetiology of OHCA is usually determined by the absence of the listed non-cardiac origins. Thus, there is an inherent uncertainty in epidemiological estimates regarding the aetiology of OHCA. For example, some acute central nervous system diseases, such as intracranial haemorrhages, may be registered as an OHCA of cardiac origin. Furthermore, the presumed aetiology may be revised during a subsequent hospital stay or through a post-mortem examination, and if so, this more exact aetiology of the OHCA must be independently registered and clearly distinguished from the presumed diagnosis at the site of the OHCA.

Cardiac causes are the most common reason for OHCA. Ischemic heart disease accounts for the majority of OHCA of cardiac origin, even though modern treatment regimens have been able to reduce the prevalence of ischemic heart diseases.[26] In addition to ischemic heart disease, arrhythmias, inflammatory heart diseases, valvular diseases or other cardiac diseases may cause OHCA of presumed cardiac origin.

The first ECG rhythm is also important for the epidemiologic classification of OHCA. There are four different rhythm groups that are described in patients with cardiac arrest. In ventricular fibrillation (VF), all of the heart muscle cells contract in an irregular pattern without maintaining circulation but with a high energetic turnover. Ventricular tachycardia (VT) is a more regular electrical

activity but still does not generate sufficient cardiac output. Pulseless electrical activity (PEA) includes all other recorded ECG activity that does not result in a palpable pulse. Finally, ECG recordings with no electrical activity and therefore no heart muscle activity are defined as asystole. For epidemiological purposes, these rhythms are usually grouped as shockable rhythms (VF/VT) and non-shockable rhythms (PEA and asystole).[22]

## **2.2 Treatment of out-of-hospital cardiac arrest**

### **2.2.1 History of out-of-hospital cardiac arrest treatment and resuscitation guidelines**

The current treatment techniques for SCA emerged in the late 1950's.[27] Kouwenhoven, Jude and Knickerbocker combined methods for respiratory and circulatory support. These authors reported a case summary of 20 patients with SCA, in which 14 patients survived for a measurable time span. This work was continued and extended by Peter Safar and James Elam in the early 1960's. Safar published the first "chain of survival". He mentioned several treatment steps for patients with SCA, starting with chest compressions and ventilations and proceeding to intensive care treatment, including TH.[28-30] The combination of artificial ventilation and chest compression has since been known as CPR. To terminate the irregular electrical heart activity in VF/VT, a short (<50 msec.) and strong (<50 A and <4000 V) DC current is used. This defibrillation technique was developed in the early 1950's by Zoll; portable defibrillators have been available since the early 1960's.[31-33] The concept of the chain of survival has since been modified several times, always with the goal of increasing survival after OHCA.[34, 35]

The first international recommendations on resuscitation were made in 1961 after a conference on emergency resuscitation held in Stavanger, Norway.[36] This led to the standard treatment recommendations from the Cardiopulmonary Resuscitation Committee on CPR from the American Heart Association in 1966.[37] The European Resuscitation Council (ERC) was established in 1989 with participants from the European Society of Cardiology, the European Academy of Anaesthesiology, the European Society for Intensive Care Medicine, and several national societies. In 1992, the International Committee on Resuscitation (ILCOR) was founded.[38] The founding associations include the American Heart Association, the Australian

and New Zealand Committee on Resuscitation, the ERC, the Heart and Stroke Foundation of Canada, the Inter-American Heart Foundation, the Resuscitation Councils of Asia and the Resuscitation Councils of Southern Africa.[38] ILCOR provides the scientific background for treatment recommendations that form the bases for the development of national CPR guidelines. Due to economical, pedagogical and political reasons, the national guidelines may differ slightly around the world.

---

### **2.2.2 Prehospital cardiopulmonary resuscitation**

Prehospital CPR starts with the identification of an OHCA. The absence of circulation will, after up to six seconds, be accompanied by the loss of consciousness; after 20-40 seconds, the breathing pattern will be altered, the breathing will subsequently stop and the patient will collapse.[39]

A witnessed OHCA is defined as an OHCA in which the collapse was either seen or the sound of falling or the disappearance of breath sounds was heard by someone else. This person is supposed to call for help and then begin simple resuscitation manoeuvres, the so-called bystander CPR. Bystander CPR or basic life support (BLS) is defined as simple respiratory and circulatory support (providing airway patency, ventilations and chest compressions).[40] If an OHCA is not witnessed, and the patient is not found in the following minutes, additional signs of prolonged death will appear, making resuscitation efforts futile in the end.

In most countries, the emergency dispatch centre (EDC) will ask questions to determine whether the patient is suffering from an OHCA and will advise the bystander to start CPR and explain how to do so if necessary.[10, 18]

In some circumstances, an automatic external defibrillator (AED) may be available on the scene. Public access defibrillators (PADs) are AEDs that are placed to allow easy access for laypeople to perform CPR with defibrillation. The distribution of PADs is widespread. PADs can be located inside or outside private enterprises, shopping malls and public buildings. Usually, the information where PADs are located is rarely available and not updated at the local EDC.[10, 18] Although the use of PADs is in general life saving, the frequency of their use is low.[41] To have a potential life-saving effect, PADs must be placed in areas where a high number of persons at risk for OHCA are located or passing through, such as train stations, airports or casinos:[42]

PADs at golf courses and private/residential homes are very rarely used.[40, 43, 44]

After the CPR process is started by laypersons and the emergency call is made, the EDC will scramble the EMS, which will respond with several units.[10, 45, 46] These units are staffed with personnel who are capable of advanced life support (ALS). ALS includes securing the airway ventilations and providing drug therapy and post resuscitation care for OHCA patients where ROSC could be established.[8] ALS will also be immediately delivered in patients where the OHCA occurred in the presence of the EMS personal as EMS witnessed OHCA.

If ROSC could not be established, the deceased remains on the scene. Under special circumstances the OHCA patient may be transported to the receiving hospital with ongoing ALS.[47, 48] During this mission, mechanical chest compression devices may be used to ensure both adequate chest compressions and the safety for the EMS personal while driving.[49, 50]

At the receiving hospital, the OHCA patient is examined immediately by a team consisting of specialists in anaesthesia and cardiology, specially trained nurses and supportive staff.[45, 46]

---

### **2.2.3 In-hospital treatment of out-of-hospital cardiac arrest patients**

After the arrival of an OHCA patient at the hospital, the major goal is the stabilisation and normalisation of the body's functions, as well as the identification and treatment of the cause of the arrest. In recent years, the focus on the special needs of post-OHCA patients has increased.[12, 51]

#### **2.2.3.1 General treatment**

The general in-hospital treatment course obviously depends on the condition of the admitted OHCA patient. The patient may be awake or unconscious; he or she may have maintained circulation or may lack independent circulation and require continuous chest compressions.

Conscious OHCA patients should be transferred either to immediate PCI, when indicated or to a cardiac care unit (CCU where comprehensive cardiac diagnostics and supportive care are available.

If the OHCA victim remains unconscious, he or she should be admitted to the ICU directly or after PCI. For such patients who may have sustained general tissue damage from global hypoxia and from reperfusion, the reconstitution of cellular haemostasis is of primary importance. This metabolic phase after the OHCA requires the optimisation of cellular oxygenation with respiratory support, maintenance of sufficient circulation, normalisation of electrolyte abnormalities, and identification and, where possible, treatment of the cause of the OHCA.[52, 53] Furthermore, temperature management is a cornerstone of post-resuscitation treatment and will be discussed in the next chapter.

---

### 2.2.3.2 Therapeutic hypothermia after out-of-hospital cardiac arrest

TH after OHCA is defined as a reduced body temperature that is induced for therapeutic reasons.[54] TH as protection for the central nervous system from hypoxia damages due to reduced circulation was first mentioned in 1950. Since then, the use of TH has been reported in intracranial and cardiac surgeries and for SCA victims. However, no clear treatment method or protocol emerged, and serious side effects have been described.[55-59] In the 1980's, promising results from animal studies were published,[55-61] and small studies again indicated that TH may improve neurological outcomes after OHCA.[62-65] In 2002, two large randomised controlled trials paved the way for a general recommendation for the use of TH in the treatment of OHCA victims admitted to hospitals.[66-68]

The protective effects of TH on cell function and integrity are assumed to be due to a reduction in the metabolic and inflammatory reactions to hypoxic, ischemic and reperfusion damage during and after OHCA. Although the specific effects of TH are not fully understood, the theory is that a lowered core temperature contributes to the inhibition of pathophysiological cascades, allowing damaged cells to reconstitute or at least partly maintain their function.[54] These effects result in a better neurological outcome among OHCA victims who survive to discharge.[66, 67]

Since 2002, TH has been recommended by many major critical care societies and has been used in the hospitals that are studied in this thesis.[12, 51, 69]

### 2.2.3.3 Percutaneous coronary intervention

Coronary heart disease, also known as ischemic heart disease or coronary artery disease, presents with one or several stenosis in the arteries supplying the myocardium. Over the past 60 years, revascularisation therapy has been the basic treatment option for coronary heart diseases. Both surgical approaches, via aortic coronary bypass surgery and non-surgical treatments with PCI are used to supply the ischemic myocardium with more oxygen.[70, 71]

Twenty-five to 40% of patients suffering from acute coronary syndrome present with a so-called ST-segment elevation myocardial infarction (STEMI).[72] Emergency treatment paradigms for these patients have changed over time. In the late 1980's, the ISIS (International Studies of Infarct Survival and GISSI (Italian group for the study of the survival of Myocardial Infarction) trials demonstrated that intravenous streptokinase given within 0-4 hours of onset of myocardial infarction reduced mortality and improved outcome.[73, 74] Later, tissue plasminogen activator, tenecteplase, adjuvant heparin and low-molecular-weight heparin were studied and introduced to the primary lytic therapy of STEMI.[75-78] In the late 1990's, facilitated PCI was added to primary lytic therapy.[79-81] Since 2001, PCI has become a more-frequent first-line therapy for STEMI.[82, 83]

---

## **2.3 Outcome of out-of-hospital cardiac arrest**

### **2.3.1 Outcome measures**

The suggested outcome measures for OHCA in terms for survival are ROSC at the scene, hospital admission with ROSC, admission to an ICU/CCU, survival to discharge from hospital, and long-term survival over months or years. The numbers for survival to discharge and long-term survival are frequently combined with a simple neurological ranking, the cerebral performance score (CPC).[21]

### **2.3.2 Outcome numbers**

Large variations have been described in both short- and long-term survival after discharge, with reported survival to discharge rates varying widely.[16, 24] This large variation may be due to different inclusion criteria in the published studies. The reported subgroups are often sorted by the first recorded rhythms, if an OHCA was witnessed or the aetiology of the OHCA and may bear some uncertainty. Nevertheless, even in matching populations, the reported differences in survival to discharge are still striking. Reported survival to discharge aggregates from different continents, including OHCA patients with VF/VT as the first rhythm, which varies from 2%-11% and for OHCA patients where all origins are included from 1-15%.[16, 24] Some patients experience prodromal clinical signs before an OHCA and are able to contact the EMS dispatch centre. In such cases, an ambulance unit may arrive on the scene before the loss of circulation, and the OHCA is witnessed by EMS. The outcome of EMS-witnessed OHCA is usually higher than the general OHCA outcome.[11, 16]

There are several factors that impact the outcome of the OHCA. Most important, a positive predictor of survival is if the OHCA was witnessed and if

---

bystander CPR was performed. In addition, increased age and comorbidity are negative predictors for survival.[24, 84] Furthermore, differences in post resuscitation inpatient treatment also contribute to the observed variability in survival to discharge as an outcome.[12, 18, 26, 85] Gender may also be a predicting factor for OHCA survival but is most likely more prominent in the in-hospital course than as a predictor for ROSC.[86, 87]

Despite considerable scientific, educational and practical efforts, the aggregated survival rate has not improved in recent decades. Published results show a 7-8% survival to discharge rate for OHCA of all origins in which resuscitation attempts were made and approximately 20% survival to discharge for patients with an OHCA with VF/VT as the first recorded rhythm.[16, 24]

### **2.3.3 Outcome and genetic factors in out-of-hospital cardiac arrest**

Recent decades have seen an enormous expansion in the research, knowledge and understanding of the genetic basis of human variations and diseases.[88, 89] In many areas of medicine, genetic influences on health, disease progression and response to therapy have become more apparent. From single-gene alterations to genome-wide associations, several studies have established correlations between genetic alterations and an increased risk for disease development and adverse outcome.[90-92]

It is known that genetic factors are linked to heart disease [93, 94] and SCA,[95] and research is ongoing regarding the genetic factors that determine individual responsiveness to treatment and outcomes after OHCA.[96]

Genetic mutations alter cellular functions and the pathophysiological response. Thus, genetic polymorphisms affect the risk of OHCA. Genetic factors have been identified as underlying causes for cardiovascular disease (CVD) leading

---

to SCA.[97, 98] In addition, the following arrhythmias leading to OHCA have been identified as caused by genetic mutations: Brugada syndrome, long and short QT syndromes and catecholaminergic polymorphic ventricular tachycardia. Furthermore, patients with genetic alterations manifesting in abnormal cardiac ion channel function may have an increased risk of OHCA.[99-102] However, whether genetic alterations also have impact to the outcomes, such as ROSC or survival to discharge, remains unclear.

It is obvious that the development and severity of CVD have many contributing factors, including geography, socioeconomics, lifestyle, gender and genetics.[103, 104] Genetic polymorphisms in the development of CVD have been described for the renin-angiotensin system,[92] for the peroxisome proliferator-activated receptor gamma,[105] the Calpain 10 polymorphism[106] and others, indicating that many genetic factors contribute to SCA. However, difficulties in assessing individual risks remain.[107]

The peptide hormone angiotensin II is part of the renin-angiotensin-aldosterone system, which participates in blood pressure control.[108, 109] The ACE gene polymorphism has three genotypes: the insertion polymorphism (II), the insertion/deletion polymorphism (ID) and the deletion polymorphism (DD). This gene polymorphism has significant effects in adult respiratory distress syndrome and paediatric meningococcal infection; it has also been linked to survival after trauma and outcomes of traumatic brain injury.[110-113] There is a strong association between the ACE gene polymorphism and the plasma level of ACE. Genetic effects account for 47% of serum ACE levels.[108] Paradis et al reported that the vascular tone and the resulting blood pressure contribute to ROSC.[114] Therefore, the differences in ACE gene polymorphisms that influence the serum ACE levels and following vascular tonus may affect the outcome of OHCA by increasing the probability of achieving ROSC.

---

### **2.3.4 Documentation of the incidence and outcome after out-of-hospital cardiac arrest**

Reliable documentation of the OHCA incidence and outcome is essential for many aspects of care. Consistent documentation can be used for local EMS development and for the decision as to how to allocate national and international economic and scientific resources relative to other acute or chronic diseases. For these reasons, systematic, objective and reviewable documentation of the OHCA incidence is essential. This documentation should include essential medical and system-associated data points, such as the location of the OHCA, responding EMS units, patient identification data, arrest and outcome variables, and comprehensive timeframes describing events from the moment of the OHCA to ROSC, the termination of resuscitation, or admission to the receiving hospital. These databases should attempt to provide real-time, updated documentation to the fullest extent possible. Furthermore, such a template should be internationally developed, recognised and used.

To reach these goals, the resuscitation societies developed the Utstein template for uniform data reporting for OHCA. The initial Utstein-style template was developed in 1991 at a conference held at the Utstein Abbey on the island of Mosterøy, Norway, to promote the uniform and comparable reporting of OHCA incidence and outcomes.[21] This form has been used around the world, and in 2002, the original template was revised.[7, 21] This revision attempted to simplify the older template, tried to lessen logistical difficulties in the collection of core data, and addressed inconsistencies in the terminology between prehospital and in-hospital SCA registers.

The Utstein template includes whether the OHCA was witnessed and whether bystander CPR was performed. The location of the OHCA is also registered and categorised into three main groups: at home, in public or “other”. A public

localisation of the OHCA usually includes street, city park, shopping centre, sports stadium, entertainment centre, airport, railway station, church, beach, or office buildings. The location “other” may include places such as nursing homes/long-term care facilities, schools and hotel rooms. More-specific information is provided if necessary.[7]

The neurological status as part of the outcome documentation is reported at 30 days, 6 months and one year after the OHCA.[7] Documentation of the neurological status is challenging, but knowledge of the patient’s cognitive abilities is essential to providing insight regarding the entire chain of survival. The Utstein template uses the simple definition of neurological status that is provided by the CPC.

In every data register, precise and accurate control of the data input and adherence to the data field definitions must be ensured before the results can be analysed and interpreted, both for the purposes of reporting and for future research. These data-control procedures are extremely important for scientific progress and should be reported together with the results.

### **3. Aims of the thesis**

The overall aim of this thesis was to study the epidemiology and outcome of OHCA and possible contributing factors for the survival of OHCA patients in a region where high survival rates of OHCA victims have been previously reported. This thesis also describes the local chain of survival in detail and provides updated numbers for OHCA epidemiology and outcomes, including the effects of the ACE gene polymorphism distribution on ROSC (Papers I + II). In addition, this thesis addresses aspects of treatment and decision making in the receiving hospitals for OHCA patients (Paper III). Furthermore, this thesis provides an estimate of the life-years saved by a successful resuscitation process (Paper IV).

#### **3.1 Paper I**

The aim of paper I was to describe the epidemiology and outcomes of OHCA of cardiac origin from 2001-2008 in the study area. Two time periods with different resuscitation guidelines should be compared. We wished to identify the factors that are associated with the outcomes ROSC and survival to discharge.

#### **3.2 Paper II**

The aim of this study was to examine the distribution of the ACE gene polymorphism in patients with OHCA of cardiac origin and the influence of these genetic variations on ROSC. In addition, the aim was to demonstrate the feasibility of collecting blood samples from OHCA patients, even if they are not ultimately admitted to the receiving hospital, and to show how practical, legal and ethical challenges could be addressed.

### **3.3 Paper III**

The aim of the paper was to analyse patient characteristics and cardiac arrest factors that predicted the use of in-hospital TH and as well survival to discharge in unconscious OHCA patients who were admitted to the ICUs at three different Norwegian university hospitals.

### **3.4 Paper IV**

The aim of the study was to describe the long-term outcome of OHCA victims surviving to discharge from the same study hospital as in papers I and II. We wanted to estimate the life years that were saved by the resuscitation efforts. Furthermore, this study aims to examine the standardised mortality rates of OHCA survivors by comparing the long-term survival of OHCA victims to that of an age- and gender-matched general population.

## 4. Materials and methods

### 4.1 Study area and receiving hospital

Papers I, II and IV were conducted in the same study area, the Stavanger region. All of the OHCA patients were admitted to the same hospital, which was the only facility that admitted OHCA patients in the studied area. The Stavanger region is the catchment area of the Stavanger University Hospital, comprising the city of Stavanger in the centre and the surrounding 17 municipalities. The study area is situated on the west coast of Norway, and the combined area is approximately 5700 km<sup>2</sup>. The study area lies on the same circle of latitude as the southern tip of Greenland. The population in the studied area increased from approximately 273,000 inhabitants in 2001 to approximately 314,000 inhabitants in 2008.[18, 115] Approximately 15% of the inhabitants are immigrants.[116, 117] The Stavanger University Hospital is the only admitting hospital in the study area. Together with its primary and referral areas, the hospital covers a population of approximately 400,000 inhabitants.[18, 45] Patients who are admitted after OHCA are assessed by an intensive care physician and a cardiologist in the emergency department. TH has been offered for unconscious OHCA patients since 2002.[45] Primary emergency PCI has been available for patients with STEMI since 2004.[46] Before TH was introduced, unconscious OHCA patients were admitted to a general ICU for supportive care and two to three days of mechanical ventilation before a prognosis was determined, eventually leading to weaning or withdrawal of active treatment.[18, 45]

---

## 4.2 Paper I

This is a retrospective observational study of prospectively collected OHCA data.

### 4.2.1 EMS

#### 4.2.1.1 Emergency dispatch centre

The EMS in the study area is reachable via one toll-free, three-digit emergency number (113).[118] There is only one EDC in the study area. The call is received by a specially trained nurse who determines the urgency of the symptoms that are presented by the caller using a criteria-based index.[119] After the nurse decides that an OHCA is the cause of the presenting symptoms, the EDC will immediately dispatch the following resources: fire brigades as first responder units, one or two ambulance car units, one anaesthesiologist-staffed rapid response unit and a general practitioner (GP).[10] If the incident was not initially identified as an OHCA, the physician-staffed units may be called to the scene at a later time. Simultaneously, the nurse will provide advice to start CPR if it has not already been performed. In the study area, both chest compressions and mouth-to-mouth ventilation are recommended by the EDC nurse, following the Norwegian resuscitation council guidelines.[8, 119, 120] There were no systematic changes in this approach during the study period.

#### 4.2.1.2 Emergency units

There are 18 ambulance car units available at all times in the study area. These units are dispatched from six different ambulance stations. The ambulance car units are equipped to support ALS and are staffed with two health care professionals, at least one of whom is an ALS-certified paramedic.

---

This response to OHCA is supported by fire brigades who carry AEDs and act as first responder units. This collaboration between the EMS and the first responders began in 2000 and reached 17 units in 2008.

The anaesthesiologist-staffed unit can respond either by car or by helicopter. The crew includes a physician, a paramedic/nurse who is specially trained in rescue techniques, and a pilot.[10, 121] Pre-hospital TH treatment is initiated by the anaesthesiologist on scene if the OHCA patient has not regained consciousness after 10 minutes.[45] The GP responding to the OHCA is on call in the municipality emergency centre. He or she either follows in the ambulance or uses his or her own transportation.

#### 4.2.1.3 CPR guidelines

The resuscitation guidelines from 2000 and 2005 were used when the data for this work were collected. The 2000 Norwegian guidelines were similar to the ERC (ERC) guidelines.[122] These guidelines had been fully implemented when the data collection started. The 2005 resuscitation guidelines emphasise chest compressions and normalised ventilation in a comprehensive ratio of 30:2 and allow only one defibrillation per loop.[8, 40, 123] The 2005 Norwegian resuscitation guidelines are slightly different from the 2005 ERC guidelines.[8, 120] The Norwegian version recommends a three-minute loop between rhythm analyses and eventual defibrillation; pulse control is performed one minute after the heart rhythm analyses, followed by the administration of one mg of epinephrine if no palpable pulse is detected.

The implementation process of the 2005 guidelines took place simultaneously with the data collection. The implementation process included a training period of several weeks when both guidelines may have been used, but after this training period, only the 2005 guidelines were used.[124]

---

#### **4.2.2 Patient inclusion, data collection and ethical approval**

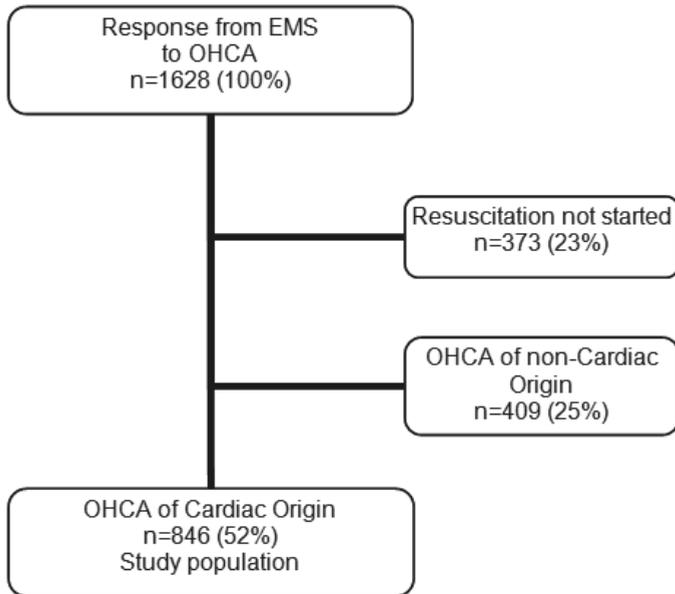
In 1996, the EMS established an Utstein template-based register for all OHCA. For this work, prospectively collected data from January 1<sup>st</sup>, 2001, to December 31<sup>st</sup>, 2008, were accessed. All EMS responses to OHCA patients were reported. Patients, for whom resuscitation (according to the Utstein definitions) was not initiated, as well as patients with a non-cardiac origin of OHCA, were excluded from the analysis.[7, 22] A resuscitation effort was only registered as such when medical measures, such as airway assistance, chest compressions, defibrillation or drug administration, were performed.[7, 22]

The presumed origin of the OHCA was determined on scene according to the Utstein definitions. A cardiac origin of the OHCA was determined based on the absence of any other cause for the OHCA, such as trauma, drowning or poisoning.[7, 22]

The Utstein data were registered by both the ambulance units and the physician-staffed rapid response unit. These data were crosschecked against each other before being entered into the study database. Outcomes, CPC scores and in-hospital data were obtained by reviewing the patient's hospital record. The data from 846 OHCA patients were analysed (Figure 1).

The scientific use of the data was approved by the Regional Committee for Research Ethics (RCE), the Norwegian Social Science Data Service (NSD) and the central office for national registration.

Figure 1: Inclusion of patients with OHCA from January 1, 2001, to December 31, 2008.



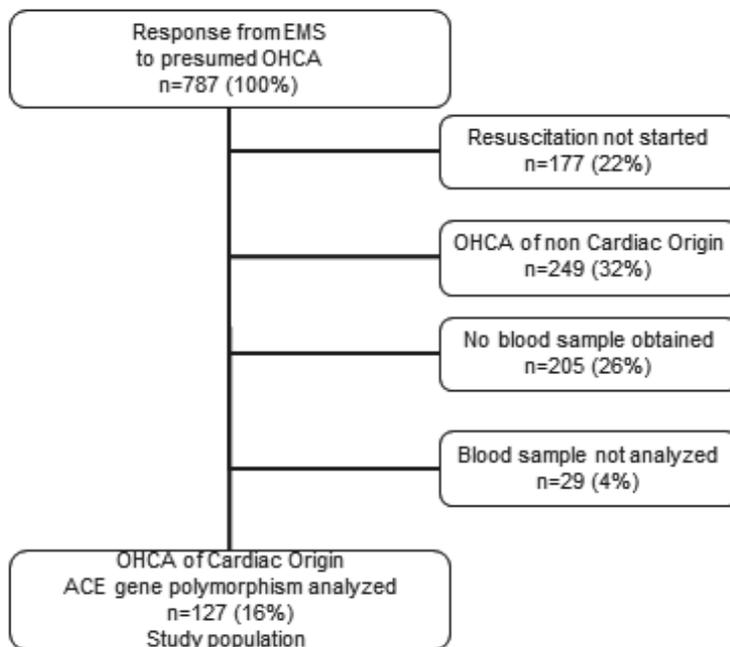
## 4.3 Paper II

This is a prospective observational study.

### 4.3.1 Study population

The study area is described in section 4.1.1.; the EMS response is described in section 4.1.2.1-2. During the study period, the 2005 ERC resuscitation guidelines (with Norwegian alterations) were followed.[40, 120] The Utstein data collection for this study was similar to the methods that are described in section 4.1.4. The study population is presented in Figure 2. Blood samples and datasets from 127 patients were further analysed.

*Figure 2: Inclusion of patients with OHCA between February 2007 and November 2010.*



---

### 4.3.2 Ethical Considerations

To analyse the impact of ACE polymorphisms on achieving ROSC, we collected blood samples from OHCA patients during the resuscitation process. This procedure leads to challenging ethical questions. In the proposal to the RCE, the questions of informed consent and consent obtained by the next-of-kin were addressed. In all scientific research, informed consent of the participating persons must be obtained.[125-127] In medical emergency situations in which immediate action is required, an undisturbed decision is not possible for the patient. In addition, the patient may be under physical and/or emotional distress or may even be unconscious. Therefore, it is not possible to obtain informed consent before blood samples are drawn. The RCE accepted that informed consent could be obtained retrospectively, either directly from the patients (if they regained the ability to consent) or from the next-of-kin (in cases where the patient did not survive or did not achieve an adequate neurological recovery). If the next-of-kin had to be contacted, this was done several weeks after the OHCA event to allow the patients' relatives to cope with the experience of the loss. In all cases, both oral and written information were given, and signed approval was obtained.

The EMS teams were continuously informed about and integrated into this process. Teaching sessions to describe the ethical and practical challenges of this research were performed for all participating EMS personnel. It was always emphasised that the blood-collection process should never disturb or delay established BLS, ALS or other operational procedures. If the resuscitation process was terminated because no ROSC could be established, the deceased was no longer within the scope of accountability of the EMS, and no blood samples could be collected after death was declared.

---

### **4.3.3 Collection and analysis of genetic material**

A peripheral vein was accessed, and 10-20 ml of blood was withdrawn. Blood samples were either drawn on scene or upon transport to the hospital (among patients with ROSC). These samples were transferred to the hospital, and special research personnel were called to register and prepare the blood samples for storage at -80 °C until analysis. Genetic analyses were conducted using all of the samples together after the termination of the study. The ACE polymorphism analysis was determined using polymerase chain reaction under standard conditions as described by Takemoto.[128] The presentation of the three ACE gene polymorphisms was performed separately but also aggregated into two groups; ACE II and ACE DD/ID, as described by Kehoe.[112]

## **4.4 Paper III**

This is a retrospective, observational study of prospectively collected OHCA data from three university hospitals using a standardised post-resuscitation treatment protocol.

### **4.4.1 Study population and participating hospitals**

This study was performed with in- and pre-hospital data from the University Hospitals in Bergen, Oslo and Stavanger. All three ICUs had standardised treatment protocols for unconscious OHCA patients, including TH and emergency PCI, where applicable.[12, 46] Prognostication was primarily based on clinical examination in the three ICUs.[129] The EMS in the Bergen and Oslo areas are comparable to the system that is described in section 4.1.2.1-3. From January 2004 to January 2008, all unconscious adult OHCA patients with ROSC that were admitted to the ICUs were included. Patients with OHCA



#### **4.4.2 Data collection and ethical approval**

All three of the study sites provided data from their pre-hospital OHCA registers, ICU and hospital quality assurance databases, and the Northern Hypothermia Network databases.[7, 45, 130] A study protocol including all of the data points and their definitions was composed. Each hospital was responsible for verifying and controlling data input according to the study protocol. The NSD and RCE approved the use of data for this study.

## 4.5 Paper IV

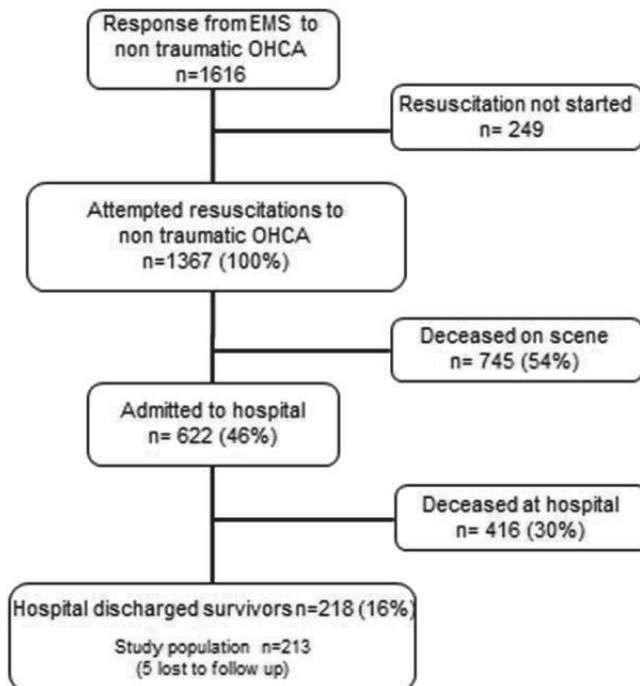
This is a retrospective observational study of prospectively collected OHCA data.

### 4.5.1 Study population, EMS and receiving hospital

The EMS, the receiving hospital and the implemented resuscitation guidelines are described in sections 4.1.2.1-3. and 4.1.3.

A total of 213 patients were examined in the study population as presented in Figure 4.

*Figure 4: Inclusion of patients in the study cohort between July 2002, and June 2011.*



### **4.5.2 Data collection and ethical approval**

Pre- and in-hospital data collection for this study was performed according to the methods that are described in section 4.1.4 (paper I). The date of death for patients who were discharged from the hospital was accessed from the Norwegian national register via the hospital data system. The causes of death, expected remaining lifetime and mortality rates were obtained via Statistics Norway.[131-133] The RCE approved the use of the data for this study.

### **4.5.3 Potential life years saved**

Potential life years saved were calculated based on the assumption that our cohort of survivors discharged after OHCA had the same life expectancy as the rest of the age and gender matched Norwegian population.

### **4.5.4 Standardised mortality rates**

The SMR describes the relative risk of death within a study cohort compared to the general population. The mortality rates for the general population in Norway are provided by Statistics Norway as the deaths per 100 000 Norwegians. We calculated the SMR for each year after the OHCA event and for the whole observation period based on the observed mortality in the study cohort, the time under risk of the study population and the mortality rates as given by Statistics Norway.

---

## 4.6 Statistical analyses

In the four papers that are presented in this thesis, the following statistical analyses were used where appropriate:

The chi-square test and Fischer's exact probability test were used to examine different proportions for categorical variables. The independent samples t-test, the Mann-Whitney U test and the Kruskal-Wallis test were used to identify between-group differences for continuous variables.

A multiple logistic regression analysis was used to model the effect of the explanatory variables on the dichotomous outcome variables. The goodness of fit was verified by the Hosmer-Lemeshow test. To evaluate the confidence intervals, bootstrapping was performed

In paper III, a propensity score was calculated, and the logarithm of the odds of the propensity score was added as a covariate in the multivariable logistic regression model that evaluated the outcome variables.

In paper IV, log-rank tests and a Kaplan Meier survival analysis were performed to analyse the survival of different populations.

The data were entered into FileMaker Pro databases (FileMaker Inc.; USA). The statistical analyses were performed in SPSS/PASW (SPSS Inc.; USA). The figures were constructed in SPSS and Microsoft Office (Microsoft Cooperation; USA). Two-sided p-values < 0.05 were considered statistically significant. Table 1 provides the exact descriptions of the statistical tests that were used in the individual papers.

*Table 1: Statistical methods that were used in the different papers*

<b>Test</b>	<b>Paper I</b>	<b>Paper II</b>	<b>Paper III</b>	<b>Paper IV</b>
Chi-square			X	X
Chi-square +Yates correction	X	X		
Fischer's Exact Probability				X
Independent samples t-test	X	X		X
Kaplan Meier analysis				X
Kruskal-Wallis			X	
Mann-Whitney U	X	X		
Hosmer-Lemeshow			X	
Multiple logistic regression models	X	X	X	
Multiple logistic regression models + Propensity score			X	
Bootstrap analysis				X

---

## 5. Main results

### 5.1 Paper I

The two time periods of 2001-2005 and 2006-2008 were examined, and no significant differences regarding age (71 and 70 years ( $p=0.309$ )), sex distribution (males 70% and 71% ( $p=0.708$ )), location of the OHCA (home 64% and 63% ( $p=0.732$ )), proportion of shockable rhythms (44% and 47% ( $p=0.261$ )), and ROSC (38% and 43% ( $p=0.136$ )) were found, respectively. The rate of bystander CPR increased significantly, from 60% to 73% ( $p<0.0001$ ), as did the overall rate of survival to discharge, from 18% to 25% ( $p=0.018$ ). The EMS response time increased significantly from eight minutes to nine minutes. In patients with a shockable first rhythm, the survival to discharge improved from 37% to 48%, and the share of patients with a CPC 1-2 increased from 87% to 99% ( $p=0.036$ ). In this patient group, the one-year survival increased from 30% to 43% ( $p=0.005$ ). In patients with a witnessed OHCA with a shockable rhythm, the survival to discharge increased from 37% to 52% ( $p=0.0105$ ). Based on the last three years of the study period, the OHCA incidence in the study area was approximately 38/100,000 inhabitants

### 5.2 Paper II

In this study population, the mean age was 67 years, 86% of the patients were males, the OHCA was witnessed in 79% of the cases, bystander CPR was performed in 80% of the cases, and a shockable first rhythm was detected in 62% of the cases. The ACE II polymorphism was found in 17% of the patients, the ACE ID polymorphism in 52%, and the ACE DD polymorphism in 31%. When using the descriptive grouping of ACE II versus ID/DD with a correction for other contributing factors in the multivariable analysis, we found no significant effect of ACE genetic polymorphisms on the likelihood of ROSC.

---

Comparing other ACE genotype groupings (II/ID vs DD or II vs DD) did not change the overall finding of a lack of impact of the ACE genotype on ROSC

### **5.3 Paper III**

In this study, the mean age was 61 years, 73% of the patients were males, and 73% of the patients had a cardiac origin of OHCA. TH was used in 70% of all of the OHCA patients. The overall survival to discharge was 42%.

Increasing age predicted a lower likelihood of TH use (OR, 0.96 [95% CI, 0.94 to 0.97]  $p < 0.001$ ), as well as lower survival rates (OR 0.96 [95% CI, 0.94 to 0.97]  $p < 0.001$ ). Patients older than 80 years had worse outcomes, with only 18% surviving to discharge compared to the overall survival of 42%.

Witnessed arrest, shockable first rhythm, cardiac origin and bystander CPR were positive predictors of the use of TH in the multivariable logistic regression model, while increasing age and female gender predicted a lower rate of TH use. This effect was also found in the subgroup of patients with shockable first rhythm but disappeared in the non-shockable patients.

Cardiac origin and a shockable first rhythm were positive predictors of survival, while increasing age, female gender and diabetes mellitus were negative predictors.

A propensity score for the use of TH was included in a multivariable analysis with survival to discharge as the outcome variable. However, the odds ratio for the effect of TH did not change in this analysis. In the subgroup of patients with a non-shockable first rhythm, age and cardiac origin were positive predictors of survival to discharge, while TH treatment had no effect.

---

## 5.4 Paper IV

In the study population, 81% of the patients were male, 91% had a cardiac origin of OHCA, and 80% had a shockable first rhythm. TH was used in 81% of patients and PCI in 78%. At discharge, CPC 1-2 was observed in 93% of all of the patients. On average, patients were observed for 4.3 years, yielding a total of 920 patient years. During the observation period, 25% of the patients died, with a mean age of 74 years. The main cause of death was cardiac disease. Taking age and gender of the study population into account, an average of 23 life years per patient were gained through the resuscitation effort. A Kaplan-Meier analysis revealed that OHCA patients had shorter observed survival times compared to those of an age- and gender-matched population. These findings were more prominent in patients with non-cardiac OHCA compared to those with cardiac-origin OHCA and for patients with non-shockable rhythms compared to those with shockable rhythms. An age- and gender-matched population would have had a mortality rate of 11%, while the observed mortality rate in the study population was 25%. Thus, the standardised mortality rate (SMR) was 2.3. Patients with non-cardiac OHCA had a higher SMR (5.0) [95% CI 2.3-51.5] than did those patients with cardiac-origin OHCA, who had an SMR of 2.1 [95% CI) 1.7-2.7].

We calculated the specific SMR for cardiac death by relating the observed number of deaths due to cardiac disease in the study cohort to the expected number of deaths based on the age- and gender-matched population in the county of Rogaland. A total of 20 males and 7 females died of heart disease after discharge from the hospital, while the expected number would have been 0.48 for males and 0.05 for females. Thus, the SMR for death due to cardiac disease was 42 in males and 140 in females.

## 6. Discussion

This thesis provides an updated and comprehensive overview of the epidemiology, treatment, and short- and long-term outcome of OHCA patients in a specific region in western Norway that previously have reported high survival rates after OHCA.

### 6.1 Paper I and II

In paper I, we reported that the survival to discharge increased from 18% to 25% in patients with an OHCA of cardiac origin and with a CPC 1-2 of 97% at discharge. Furthermore, we measured an OHCA incidence of 38/100,000 inhabitants. However, it is difficult to identify the exact incidence and survival ratios of OHCA in a population. The reported incidence and survival rates vary widely. Several reasons for this variance are quoted in the literature.[14, 24, 134-136] First, the denominator for the calculation may be chosen in accordance to the Utstein template and thus represent resuscitation attempts, or calculations might be based on the estimated incidence per population studied as the denominator. Usually, calculations based on the number of resuscitation attempts will generate a higher rate of survival than if based on the estimated incidence.[7, 16] Second, different interpretations of the Utstein template definitions and variations in missing data may contribute to the discrepancies in the reported ratios.[137] Recent years have observed an increase in the reported incidence of OHCA.[84, 138-140] The main reasons for this finding seem to be increased rates of bystander CPR and awareness of the EDC, where both factors may lead to an increased registration of OHCA in a database.[141] Patients with witnessed OHCA and dispatched EMS will usually be accounted for in the epidemiological group of “resuscitation started”, with or without executed bystander CPR. Similarly, patients with an unwitnessed OHCA but in whom bystander CPR was started

---

almost always trigger continued CPR by the EMS and will usually be registered in OHCA databases as a resuscitation attempt. Patients with an unwitnessed OHCA and no bystander CPR may be found so late after the OHCA that the EDC is able to unquestionably determine that no EMS response is necessary, and the patient will be lost for registration as an OHCA victim.[142] In papers I and II, we found an increase in the resuscitation attempts in our study area over the past decades. This result is in accordance with other published results[10, 18, 141], and the increased resuscitation attempts may indicate that our OHCA data registration is valid and reliable.[10, 18]

Outcomes in OHCA can be defined as the percent of ROSC, admittance to an ICU, survival to discharge, or long-term survival.[143] Improvements in these outcome rates are based on advances in every link of the chain of survival, such as, “Awareness for OHCA, public education in bystander CPR leading to increased performed bystander CPR, first responder teams equipped with AEDs, PAD availability, dedicated EMS teams that follow resuscitation guidelines, standardised post-resuscitation care in specialised centres and a rigorous and in-depth registration of OHCA-associated events, treatments and outcomes”. [12, 134, 144, 145]

During the two time periods that were compared in paper I, the percentage of ROSC increased slightly from 38% to 43%, although this difference was not significant. This finding is interesting because the two time periods correspond to two different resuscitation guidelines. Some research has demonstrated that the 2005 guidelines had a positive effect on the outcome,[146, 147] while other studies did not.[148-151] However, even if the implementation of the 2005 guidelines did not result in a higher rate of ROSC, there was a significant increase in the survival to discharge, and this finding might be contributed to the revised guidelines. Still, resuscitation guidelines are the subject of

---

research,[152] and the coming 2015 ACLS guidelines may help clarify some controversies in pre-hospital ACLS. Procedures, such as airway manoeuvres, mechanical chest compression devices and extracorporeal circulation devices and the use of medications are continuously being studied to establish their different impacts on the resuscitation process.[153-158]

ROSC as an outcome measure was also studied in paper II. We examined whether different ACE gene polymorphisms may impact ROSC after OHCA. No correlation was found, despite the relevance of the ACE gene polymorphism to major trauma and recovery from traumatic brain injury.[110, 112] The sample size of the study was likely too small to provide sufficient statistical power to detect differences in the ACE II, ID and DD proportions. This result is supported by the fact that the measured ACE genotype distribution in the study population was comparable with the expected distributions in a mainly Caucasian population.[159-162]

As reported above, the ROSC rates did not increase significantly during the time periods that were studied in paper I. However, the survival to discharge improved. We showed that the overall survival to discharge for OHCA of cardiac origin increased from 20% to 25%. For OHCA patients with a witnessed arrest and a shockable first rhythm, survival increased from 37% to 52%. In addition, 97% of all patients who were discharged from the hospital had a CPC of 1-2. These numbers are high compared to previous research.[16, 24, 135, 141, 163] In paper I, the rate of bystander CPR increased significantly from 60% to 73% during the two time periods that were examined. Furthermore, we also identified bystander CPR as a positive contributor for survival to discharge, similar to previous findings.[164-169] The increase in bystander CPR might be the main explanation for the improved survival to discharge, but all together, the high survival numbers may also reflect the permanent improvement efforts to the whole chain of survival that

---

have been conducted in the study area in recent years.[18, 45, 46, 118-121, 129, 170-177]

Paper II established a practical and ethically feasible way of collecting blood samples from OHCA patients in the pre-hospital setting. This approach can be used as an example for studies that require the collection of biological material in pre-hospital setting. The described collection procedures also included patients who later were declared dead on the scene, while most studies only include patients who were admitted to the hospital. The specified ethical details - such as preventing interference with the resuscitation process and the process of consent after the OHCA - are applicable to other research projects that are planned in the pre-hospital setting. The methods and the ethical challenges were accepted by the participating EMS personnel. The important rule that the blood sample collection should not interfere with the resuscitation process may in the future lead to the need for extra staff on scene whom are solely responsible for the collection of biological specimens. However, in this study, the regular EMS staff was used for the collection process.

Most of the OHCA patients and/or relatives provided informed consent for participation in the study, while one in five did not. If informed consent from relatives was refused, the most frequently quoted reason was the wish not to be reminded about the death of the deceased. Almost all of the patients who regained consciousness consented to the study.

---

## 6.2 Paper III

In paper III, factors that affect the decision to use TH and the related outcomes were examined. TH was used in 70% of the patients. We found that the use of TH was an independent predictor of improved survival in the entire study population. However, for the subgroup of patients with non-shockable rhythms, TH was not a significant predictor of survival. This outcome mirrors previous reports of lower expected survival rates and a decreased effect of TH treatment in this patient group.[178-180] In Norway, the use of TH is also recommended in OHCA patients with non-shockable first rhythms [69], but only 50% of these patients received TH treatment. These findings demonstrate the continuous need for further studies in OHCA populations and for subgroup analyses.[178, 179, 181]

Older age predicted the less-frequent use of TH and worse survival. This phenomenon is also found in previous research, indicating that older age might be an independent predictor of reduced efficacy of TH treatment.[175] Additionally, decreased willingness of physicians to allocate ICU resources to older patients has been described.[182, 183] In OHCA patients with a shockable first rhythm, female gender was a predicting factor both for decreased use of TH and lower survival rates, even when controlling for age and comorbidity. Studies on the effect of gender on the outcomes in the ICU and pre-hospital setting have reported conflicting results.[169, 184-186] Gender remains an important factor in OHCA survival, and these results may indicate that TH is underutilised in women. Furthermore, there are indications that the effect of TH treatment in woman is different from that in men, but our statistical analyses did not confirm this effect.[187] More research may improve the understanding of gender specific factors in the resuscitation of OHCA victims.[188]

---

The study site was an independent predictor of survival for the whole cohort in the logistic regression model. As far as we could evaluate, the in-hospital course was similar for all three sites, which may indicate differences in pre-hospital management in the different EMS catchment areas that were included in this study. The time to ROSC was a positive predictor of survival in patients with witnessed arrest. However, this finding is confined to this subgroup, and we do not know whether it is applicable to the entire study population. Still, the time to ROSC is an important factor in the resuscitation process when survival to discharge is the primary end point.[16, 189, 190]

In 2013, a multicentre multi-national randomised controlled trial including more than 900 OHCA patients (TTM trial) demonstrate no differences in the survival to discharge regarding the outcome between patients who had a core temperature of 33 °C versus 36 °C for 24 h in otherwise comparable groups of OHCA victims.[191] This study questions the appropriate temperature for TH treatment and whether the use of TH should be discontinued. Subsequently, ILCOR recommends that post-resuscitation centres should continue with their established practices while waiting for more data and revised formal guidelines.[181] A recent study indicates that the positive effects of TH may increase with the time to defibrillation and that this time could be interpreted as resuscitation time,[192] while other researchers report that longer resuscitation times are still associated with lower survival.[193] In addition, these results indicate that the questions of which patient groups are eligible for TH treatment, which is the optimal core temperature, the duration and onset of cooling and which cooling technique should be used are still not fully answered.[194-200]

---

### 6.3 Paper IV

The description of the chain of survival frequently ends with the survival to discharge numbers and CPC scores. Reporting the numbers of life years that were gained by the successful resuscitation of OHCA patients adds important socio-economic information to the resuscitation picture. In paper IV, 213 surviving patients were followed after discharge from the hospital. Almost 23 potential life years were gained per patient, with a 5-year survival rate of 76%. In the studied population, 90% had cardiac-origin OHCA. This rate is higher than reported from King County, Washington, and may explain the higher 5-year survival rate in Stavanger compared to the findings of US researchers (75% versus 64%).[201] When comparing these numbers, one should also account for the differences between the EMS systems in USA and Europe.[10, 18, 45, 46, 202, 203]. An earlier Norwegian study reported lower 5-year survival rates than those that were observed in paper IV.[204] This result may reflect the continuous improvement of the chain of survival in the study area. Patients with non-cardiac OHCA had lower survival compared to patients with cardiac-origin OHCA. This outcome is in accordance with previous findings.[13]

While brain injury is the major cause of death among OHCA patients during hospitalisation,[205] cardiovascular diseases were the leading cause of death during long-term observation after discharge. This outcome is in accordance with previously published results.[206] Comparing the study population in paper IV to a gender- and age-matched population, the study cohort had a two-fold higher mortality rate. However, the risk of dying of cardiovascular diseases increased by a factor of forty. This finding indicates a need for close follow-up after discharge from the hospital, as well as a need for further studies on the post-hospital course of OHCA patients who survive to discharge. This need for more follow up is supported by findings from patients

who were treated with PCI for STEMI. In these PCI-treated patients, those with STEMI and following OHCA have higher long-term mortality than patients with STEMI only.[207, 208]

## 7. Limitations of the studies

Use of registry-based data in retrospective, observational studies such as papers I, III and IV has several limitations. First, the reliability of the data entry must be secured. For all of the papers that were presented in this thesis, one designated research nurse was in charge of continuously collecting and cross-checking the data from different sources to reduce uncertainty and missing data (Paper III only at the Stavanger University Hospital). Second, there is always the possibility of undocumented changes in medical management and treatment in the study period that could not be detected or described in the papers that were presented in this thesis. Third, the CPC score was used as an outcome measure. This score is a crude measure and might not detect small differences. In addition, the scoring was based on a retrospective evaluation of the medical records and may contain uncertainties that cannot be controlled for. A prospective study design would have addressed some of these limitations.

Furthermore, in paper I, information about co-morbidity and ongoing medical treatments could not be included due to a lack of data. This approach reduces the strength of the described associations with ROSC and survival to discharge because co-morbidity is an important factor that is related to survival.[18] Other factors, such as different times to ROSC or a lower degree of hypoxic brain damage with the use of the 2005 guidelines, that might also influence the results the study design were not able to be accounted for.

In paper II, the major limitation of the study is the small sample size. Genetic studies often require sample sizes that are much larger than was possible in this setting.[209] This fact could also explain why factors that are known to have a positive association with ROSC did not show significant associations in this work. The demand that the blood sampling process would not interfere

with the CPR/ACLS process may have led to a non-representative study population. This rule may explain the high proportion of patients with ROSC and may thus have altered the results of the analyses.

For paper III, a research protocol was agreed upon that included the exact definitions of the different data points. However, data verification was performed on site and may have varied, thus representing a confounding factor. Furthermore, variations in the organisation of the three studied ICUs may impact the clinical outcome. There may have been differences in the diagnostic procedures, treatments or procedures for the withdrawal of life-sustaining therapy that may have altered the results and reduced the comparability of the institutions.

TH treatment was registered if the target temperature was reached. Thus, there may have been more patients in whom there was an intention to treat with TH but who were not registered as patients receiving TH treatment.

Paper IV is limited by a relatively small sample size and by variations in the observation period. Discharged OHCA patients were consecutively included during the study period, leading to variations in the observation time from one to ten years. This approach may have resulted in an overestimation of the number of life years that were saved.

## 8. Conclusions and future research

This thesis provides a detailed picture of the chain of survival, from the OHCA event to long-term survival, in the studied area. Good outcome was achievable in every fourth resuscitation attempt and in every second resuscitation attempt when patients had a shockable rhythm. We found that survival in patients with OHCA was strongly connected to the recognition of the OHCA and early CPR provided by bystanders. Only if these steps were taken, all of the other steps in the treatment chain may have their maximum effect. Even if no association between the ACE gene polymorphism and ROSC could be demonstrated, this thesis presents a method of acquiring biological specimens in the pre-hospital setting that is feasible and ethically acceptable and may be used in the future for new research questions.

In-hospital standardised treatment protocols are important. This thesis has demonstrated that in-hospital treatment for OHCA patients may vary, and that international recommendations may be interpreted and used differently. A widespread use of TH after OHCA is described in this work, however with lower utilisation in some subgroups.

This thesis also demonstrates that the studied chain of survival gained many life years in OHCA victims. In general, OHCA patients who were discharged alive from the hospital had good neurological outcomes, but also an elevated risk of early death due to cardiac causes compared to the normal population. This indicates a need for close follow-up of OHCA patients after hospital discharge.

This thesis describes a system with high survival rates after OHCA and the findings may contribute to a further development of the chain of survival. The discussion and limitations indicate areas where future research may increase the long-term outcome of all OHCA survivors. Expanded prehospital treatment

options, such as the use of mechanical chest compression devices and extracorporeal circulation, may contribute to increased survival but are presently not established or examined in the study area.

## **9. Erratum**

In paper IV, Table 2, second column, the word “Cardiac” is missing. It should be placed before “Origin”.

---

## 10. References

- [1] Fisher JM. The resuscitation greats. The earliest records. *Resuscitation*. 2000;44:79-80.
- [2] Ristagno G, Tang W, Weil MH. Cardiopulmonary resuscitation: from the beginning to the present day. *Critical care clinics*. 2009;25:133-51, ix.
- [3] Fothergill J. Observations on a Case Published in the Last Volume of the Medical Essays, &c. of Recovering a Man Dead in Appearance, by Distending the Lungs with Air. Printed at Edinburgh, 1744; by John Fothergill, Licent. Coll. Med. Lond. *Philosophical Transactions*. 1744;43:275-81.
- [4] Safar P, Nicholas G. B. Cardiopulmonary cerebral resuscitation: basic and advanced cardiac and trauma life support: an introduction to resuscitation medicine. WB Saunders Company, 1988.
- [5] Figl M, Pelinka LE, Mauritz W. Resuscitation great. Franz Koenig and Friedrich Maass. *Resuscitation*. 2006;70:6-9.
- [6] Chamberlain D, Cummins RO, Abramson N, et al. Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the 'Utstein style': prepared by a Task Force of Representatives from the European Resuscitation Council, American Heart Association, Heart and Stroke Foundation of Canada, Australian Resuscitation Council. *Resuscitation*, 22(1), 1-26.
- [7] Jacobs I, Nadkarni V, Bahr J, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Councils of Southern Africa). *Circulation*. 2004;110:3385-97.
- [8] Nolan JP, Deakin CD, Soar J, et al. European Resuscitation Council guidelines for resuscitation 2005. Section 4. Adult advanced life support. *Resuscitation*. 2005;67 Suppl 1:S39-86.
- [9] Hollenberg J, Herlitz J, Lindqvist J, et al. Improved survival after out-of-hospital cardiac arrest is associated with an increase in proportion of emergency crew-witnessed cases and bystander cardiopulmonary resuscitation. *Circulation*. 2008;118:389-96.
- [10] Langhelle A, Lossius HM, Silfvast T, et al. International EMS Systems: the Nordic countries. *Resuscitation*. 2004;61:9-21.
- [11] Fairbanks RJ, Shah MN, Lerner EB, et al. Epidemiology and outcomes of out-of-hospital cardiac arrest in Rochester, New York. *Resuscitation*. 2007;72:415-24.

- 
- [12] Sunde K, Pytte M, Jacobsen D, et al. Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. *Resuscitation*. 2007;73:29-39.
- [13] Franczuk P, Rewiuk K, Gasowski J, et al. Ten-year follow-up after in-hospital adult cardiac arrest. *Cardiology journal*. 2008;15:543-7.
- [14] Hollenberg J, Bang A, Lindqvist J, et al. Difference in survival after out-of-hospital cardiac arrest between the two largest cities in Sweden: a matter of time? *Journal of internal medicine*. 2005;257:247-54.
- [15] Nichol G, Thomas E, Callaway CW, et al. Regional variation in out-of-hospital cardiac arrest incidence and outcome. *JAMA : the journal of the American Medical Association*. 2008;300:1423-31.
- [16] Sasson C, Rogers MA, Dahl J, et al. Predictors of survival from out-of-hospital cardiac arrest: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes*. 2010;3:63-81.
- [17] Herlitz J, Bahr J, Fischer M, et al. Resuscitation in Europe: a tale of five European regions. *Resuscitation*. 1999;41:121-31.
- [18] Langhelle A, Tyvold SS, Lexow K, et al. In-hospital factors associated with improved outcome after out-of-hospital cardiac arrest. A comparison between four regions in Norway. *Resuscitation*. 2003;56:247-63.
- [19] de Villalba J. *Epidemiologia Espanola, o Historia cronologica de las Pestes, Contagios, Epidemias y Epizootias, que han acaecido en Espana desde la Venida de los Cartagineses hasta el ano 1801 (etc.): Villalpando; 1803.*
- [20] Herlitz J, Bang A, Ekstrom L, et al. A comparison between patients suffering in-hospital and out-of-hospital cardiac arrest in terms of treatment and outcome. *Journal of internal medicine*. 2000;248:53-60.
- [21] Cummins RO, Chamberlain DA, Abramson NS, et al. Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the Utstein Style. A statement for health professionals from a task force of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council. *Circulation*. 1991;84:960-75.
- [22] Cummins RO, Chamberlain D, Hazinski MF, et al. Recommended guidelines for reviewing, reporting, and conducting research on in-hospital resuscitation: the in-hospital 'Utstein style'. American Heart Association. *Circulation*. 1997;95:2213-39.
- [23] Atwood C, Eisenberg MS, Herlitz J, et al. Incidence of EMS-treated out-of-hospital cardiac arrest in Europe. *Resuscitation*. 2005;67:75-80.
- [24] Berdowski J, Berg RA, Tijssen JG, et al. Global incidences of out-of-hospital cardiac arrest and survival rates: Systematic review of 67 prospective studies. *Resuscitation*. 2010;81:1479-87.
- [25] Straus SM, Bleumink GS, Dieleman JP, et al. The incidence of sudden cardiac death in the general population. *Journal of clinical epidemiology*. 2004;57:98-102.

- 
- [26] Pell JP, Sirel JM, Marsden AK, et al. Presentation, management, and outcome of out of hospital cardiopulmonary arrest: comparison by underlying aetiology. *Heart (British Cardiac Society)*. 2003;89:839-42.
- [27] DeBard ML. The history of cardiopulmonary resuscitation. *Annals of emergency medicine*. 1980;9:273-5.
- [28] Kouwenhoven WB, Jude JR, Knickerbocker GG. Closed-chest cardiac massage. *JAMA : the journal of the American Medical Association*. 1960;173:1064-7.
- [29] Berman RA, Safar P. Mouth-to-mouth resuscitation. *Anesthesiology*. 1958;19:685-7.
- [30] Safar P. Closed chest cardiac massage. *Anesthesia and analgesia*. 1961;40:609-13.
- [31] Beck CS, Pritchard WH, Feil HS. Ventricular fibrillation of long duration abolished by electric shock. *J Am Med Assoc*. 1947;135:985.
- [32] Zoll PM, Linenthal AJ, Gibson W, et al. Termination of ventricular fibrillation in man by externally applied electric countershock. *The New England journal of medicine*. 1956;254:727-32.
- [33] Lown B, Amarasingham R, Neuman J. New method for terminating cardiac arrhythmias. Use of synchronized capacitor discharge. *JAMA : the journal of the American Medical Association*. 1962;182:548-55.
- [34] Cummins RO, Ornato JP, Thies WH, et al. Improving survival from sudden cardiac arrest: the "chain of survival" concept. A statement for health professionals from the Advanced Cardiac Life Support Subcommittee and the Emergency Cardiac Care Committee, American Heart Association. *Circulation*. 1991;83:1832-47.
- [35] Nolan J, Soar J, Eikeland H. The chain of survival. *Resuscitation*. 2006;71:270-1.
- [36] Poulsen H. Symposium on Mouth-to-Mouth R, External Cardiac R. Emergency resuscitation : proceedings of the Symposium on Mouth-to-Mouth Resuscitation and External Cardiac Resuscitation, Stavanger, August 21 - 24, 1961. Aarhus: Universitetsforlaget; 1961.
- [37] Paraskos JA. History of CPR and the role of the national conference. *Ann Emerg Med*. 1993;22:275-80.
- [38] Chamberlain D. The International Liaison Committee on Resuscitation (ILCOR)-past and present: compiled by the Founding Members of the International Liaison Committee on Resuscitation. *Resuscitation*. 2005;67:157-61.
- [39] Kabat H, Anderson JP. Acute arrest of cerebral circulation in man: Lieutenant ralph rossen (mc), u.s.n.r. *Archives of Neurology & Psychiatry*. 1943;50:510-28.
- [40] Handley AJ, Koster R, Monsieurs K, et al. European Resuscitation Council guidelines for resuscitation 2005. Section 2. Adult basic life support and use of automated external defibrillators. *Resuscitation*. 2005;67 Suppl 1:S7-23.

- 
- [41] Cairns KJ, Hamilton AJ, Marshall AH, et al. The obstacles to maximising the impact of public access defibrillation: an assessment of the dispatch mechanism for out-of-hospital cardiac arrest. *Heart (British Cardiac Society)*. 2008;94:349-53.
- [42] Cabanas JG, Lugo-Amador N. Automated external defibrillators in public places: an overview. *Boletin de la Asociacion Medica de Puerto Rico*. 2007;99:294-8.
- [43] Folke F, Lippert FK, Nielsen SL, et al. Location of cardiac arrest in a city center: strategic placement of automated external defibrillators in public locations. *Circulation*. 2009;120:510-7.
- [44] Fedoruk JC, Paterson D, Hlynka M, et al. Rapid on-site defibrillation versus community program. *Prehospital and disaster medicine*. 2002;17:102-6.
- [45] Busch M, Soreide E, Lossius HM, et al. Rapid implementation of therapeutic hypothermia in comatose out-of-hospital cardiac arrest survivors. *Acta anaesthesiologica Scandinavica*. 2006;50:1277-83.
- [46] Larsen AI, Melberg TH, Bonarjee V, et al. Change to a primary PCI program increases number of patients offered reperfusion therapy and significantly reduces mortality: a real life experience evaluating the initiation of a primary PCI service at a single center without on site heart surgery in Western Norway. *International journal of cardiology*. 2008;127:208-13.
- [47] Larsen AI, Hjørnevik AS, Ellingsen CL, et al. Cardiac arrest with continuous mechanical chest compression during percutaneous coronary intervention. A report on the use of the LUCAS device. *Resuscitation*. 2007;75:454-9.
- [48] Eisenburger P, Havel C, Sterz F, et al. Transport with ongoing cardiopulmonary resuscitation may not be futile. *British journal of anaesthesia*. 2008;101:518-22.
- [49] Olasveengen TM, Wik L, Steen PA. Quality of cardiopulmonary resuscitation before and during transport in out-of-hospital cardiac arrest. *Resuscitation*. 2008;76:185-90.
- [50] Axelsson C, Nestin J, Svensson L, et al. Clinical consequences of the introduction of mechanical chest compression in the EMS system for treatment of out-of-hospital cardiac arrest-a pilot study. *Resuscitation*. 2006;71:47-55.
- [51] Herlitz J, Castren M, Friberg H, et al. Post resuscitation care: what are the therapeutic alternatives and what do we know? *Resuscitation*. 2006;69:15-22.
- [52] Weisfeldt ML, Becker LB. Resuscitation after cardiac arrest: a 3-phase time-sensitive model. *JAMA : the journal of the American Medical Association*. 2002;288:3035-8.
- [53] Part 6: advanced cardiovascular life support. Section 1: introduction to ACLS 2000: overview of recommended changes in ACLS from the guidelines 2000 conference. *European Resuscitation Council*. *Resuscitation*. 2000;46:103-7.

- 
- [54] Bernard SA, Buist M. Induced hypothermia in critical care medicine: a review. *Critical care medicine*. 2003;31:2041-51.
- [55] Botterell EH, Lougheed WM, Scott JW, et al. Hypothermia, and interruption of carotid, or carotid and vertebral circulation, in the surgical management of intracranial aneurysms. *Journal of neurosurgery*. 1956;13:1-42.
- [56] Campos JM, Paniagua P. Hypothermia during cardiac surgery. *Best practice & research Clinical anaesthesiology*. 2008;22:695-709.
- [57] Safar P. Community-wide cardiopulmonary resuscitation. *Journal of the Iowa Medical Society*. 1964;54:629-35.
- [58] Benson DW, Williams GR Jr., Spencer FC, et al. The use of hypothermia after cardiac arrest. *Anesthesia and analgesia*. 1959;38:423-8.
- [59] Williams GR Jr., Spencer FC. The clinical use of hypothermia following cardiac arrest. *Annals of surgery*. 1958;148:462-8.
- [60] Sterz F, Safar P, Tisherman S, et al. Mild hypothermic cardiopulmonary resuscitation improves outcome after prolonged cardiac arrest in dogs. *Critical care medicine*. 1991;19:379-89.
- [61] Fay T. Observations on generalized refrigeration in cases of severe cerebral trauma. *Assoc Res Nerv Ment Dis Proc* 1943;24:611-9.
- [62] Hachimi-Idrissi S, Corne L, Ebinger G, et al. Mild hypothermia induced by a helmet device: a clinical feasibility study. *Resuscitation*. 2001;51:275-81.
- [63] Bernard SA, Jones BM, Horne MK. Clinical trial of induced hypothermia in comatose survivors of out-of-hospital cardiac arrest. *Annals of emergency medicine*. 1997;30:146-53.
- [64] Yanagawa Y, Ishihara S, Norio H, et al. Preliminary clinical outcome study of mild resuscitative hypothermia after out-of-hospital cardiopulmonary arrest. *Resuscitation*. 1998;39:61-6.
- [65] Zeiner A, Holzer M, Sterz F, et al. Mild resuscitative hypothermia to improve neurological outcome after cardiac arrest. A clinical feasibility trial. Hypothermia After Cardiac Arrest (HACA) Study Group. *Stroke; a journal of cerebral circulation*. 2000;31:86-94.
- [66] HACA Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *The New England journal of medicine*. 2002;346:549-56.
- [67] Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *The New England journal of medicine*. 2002;346:557-63.
- [68] Nolan JP, Morley PT, Vanden Hoek TL, et al. Therapeutic hypothermia after cardiac arrest: an advisory statement by the advanced life support task force of the International Liaison Committee on Resuscitation. *Circulation*. 2003;108:118-21.
- [69] Sunde K, Soreide E, Jacobsen D, et al. [Therapeutic hypothermia after cardiac arrest saves more lives!]. *Tidsskr Nor Laegeforen*. 2004;124:925-6.

- 
- [70] Haller JD, Olearchyk AS. Cardiology's 10 greatest discoveries. *Texas Heart Institute journal / from the Texas Heart Institute of St Luke's Episcopal Hospital, Texas Children's Hospital*. 2002;29:342-4.
- [71] Meier B, Bachmann D, Luscher T. 25 years of coronary angioplasty: almost a fairy tale. *Lancet*. 2003;361:527.
- [72] O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127:529-55.
- [73] ISIS Steering Committee. Intravenous streptokinase given within 0-4 hours of onset of myocardial infarction reduced mortality in ISIS-2. *Lancet*. 1987;1:502.
- [74] Maggioni AP, Franzosi MG, Fresco C, et al. GISSI trials in acute myocardial infarction. Rationale, design, and results. *Chest*. 1990;97:146S-50S.
- [75] Gersh BJ. Acute myocardial infarction. Results of the ASSENT-3 Trial. *Reviews in cardiovascular medicine*. 2002;3:111-5.
- [76] Van De Werf F, Adgey J, Ardissino D, et al. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. *Lancet*. 1999;354:716-22.
- [77] Van de Werf F, Cannon CP, Luyten A, et al. Safety assessment of single-bolus administration of TNK tissue-plasminogen activator in acute myocardial infarction: the ASSENT-1 trial. The ASSENT-1 Investigators. *American heart journal*. 1999;137:786-91.
- [78] Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. *Lancet*. 2001;358:605-13.
- [79] Cantor WJ, Ohman EM. 'Facilitated' PCI for Acute MI: PCI with Lysis and Platelet Inhibition. *Current interventional cardiology reports*. 2001;3:321-9.
- [80] Herrmann HC, Kelley MP, Ellis SG. Facilitated PCI: rationale and design of the FINESSE trial. *The Journal of invasive cardiology*. 2001;13 Suppl A:10A-5A.
- [81] Cannon CP. Bridging the gap with new strategies in acute ST elevation myocardial infarction: bolus thrombolysis, glycoprotein IIb/IIIa inhibitors, combination therapy, percutaneous coronary intervention, and "facilitated" PCI. *Journal of thrombosis and thrombolysis*. 2000;9:235-41.
- [82] Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) investigators. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. *Lancet*. 2006;367:569-78.

- 
- [83] Velianou JL, Al-Suwaidi J, Mathew V. Optimizing the use of abciximab and intracoronary stents in patients with acute ST elevation myocardial infarction. *American journal of cardiovascular drugs : drugs, devices, and other interventions*. 2002;2:315-22.
- [84] Gaul GB, Gruska M, Titscher G, et al. Prediction of survival after out-of-hospital cardiac arrest: results of a community-based study in Vienna. *Resuscitation*. 1996;32:169-76.
- [85] Engdahl J, Abrahamsson P, Bang A, et al. Is hospital care of major importance for outcome after out-of-hospital cardiac arrest? Experience acquired from patients with out-of-hospital cardiac arrest resuscitated by the same Emergency Medical Service and admitted to one of two hospitals over a 16-year period in the municipality of Goteborg. *Resuscitation*. 2000;43:201-11.
- [86] Pell JP, Sirel J, Marsden AK, et al. Sex differences in outcome following community-based cardiopulmonary arrest. *European heart journal*. 2000;21:239-44.
- [87] Wigginton JG, Pepe PE, Bedolla JP, et al. Sex-related differences in the presentation and outcome of out-of-hospital cardiopulmonary arrest: a multiyear, prospective, population-based study. *Critical care medicine*. 2002;30:S131-6.
- [88] Lander ES, Linton LM, Birren B, et al. Initial sequencing and analysis of the human genome. *Nature*. 2001;409:860-921.
- [89] Zhao LP, Hsu L, Davidov O, et al. Population-based family study designs: an interdisciplinary research framework for genetic epidemiology. *Genetic epidemiology*. 1997;14:365-88.
- [90] Bartsch H, Dally H, Popanda O, et al. Genetic risk profiles for cancer susceptibility and therapy response. Recent results in cancer research *Fortschritte der Krebsforschung Progres dans les recherches sur le cancer*. 2007;174:19-36.
- [91] Richardson M, Powell E, Barrie HD, et al. A combination of genetic polymorphisms increases the risk of progressive disease in chronic hepatitis C. *Journal of medical genetics*. 2005;42:e45.
- [92] Wang JG, Staessen JA. Genetic polymorphisms in the renin-angiotensin system: relevance for susceptibility to cardiovascular disease. *European journal of pharmacology*. 2000;410:289-302.
- [93] Weinshilboum R, Wang L. Pharmacogenomics: bench to bedside. *Nature reviews Drug discovery*. 2004;3:739-48.
- [94] Siest G, Jeannesson E, Berrahmoune H, et al. Pharmacogenomics and drug response in cardiovascular disorders. *Pharmacogenomics*. 2004;5:779-802.
- [95] Royse SD. Implications of genetic testing for sudden cardiac death syndrome. *British journal of nursing (Mark Allen Publishing)*. 2006;15:1104-7.
- [96] Norrgard, K. "Genetic variation and disease: GWAS." *Nature Education* 1.1 2008

- 
- [97] Prutkin JM, Sotoodehnia N. Genetics of sudden cardiac arrest. *Progress in cardiovascular diseases*. 2008;50:390-403.
- [98] O'Donnell CJ, Cupples LA, D'Agostino RB, et al. Genome-wide association study for subclinical atherosclerosis in major arterial territories in the NHLBI's Framingham Heart Study. *BMC medical genetics*. 2007;8 Suppl 1:S4.
- [99] Lehnart SE, Ackerman MJ, Benson DW Jr., et al. Inherited arrhythmias: a National Heart, Lung, and Blood Institute and Office of Rare Diseases workshop consensus report about the diagnosis, phenotyping, molecular mechanisms, and therapeutic approaches for primary cardiomyopathies of gene mutations affecting ion channel function. *Circulation*. 2007;116:2325-45.
- [100] Friedlander Y, Siscovick DS, Weinmann S, et al. Family history as a risk factor for primary cardiac arrest. *Circulation*. 1998;97:155-60.
- [101] Jouven X, Desnos M, Guerot C, et al. Predicting sudden death in the population: the Paris Prospective Study I. *Circulation*. 1999;99:1978-83.
- [102] Dekker LR, Bezzina CR, Henriques JP, et al. Familial sudden death is an important risk factor for primary ventricular fibrillation: a case-control study in acute myocardial infarction patients. *Circulation*. 2006;114:1140-5.
- [103] Kang AK, Miller JA. Effects of gender on the renin-angiotensin system, blood pressure, and renal function. *Current hypertension reports*. 2002;4:143-51.
- [104] Guilbert JJ. The world health report 2002 - reducing risks, promoting healthy life. Education for health (Abingdon, England). 2003;16:230.
- [105] Hara K, Okada T, Tobe K, et al. The Pro12Ala polymorphism in PPAR gamma2 may confer resistance to type 2 diabetes. *Biochemical and biophysical research communications*. 2000;271:212-6.
- [106] Turner MD, Cassell PG, Hitman GA. Calpain-10: from genome search to function. *Diabetes/metabolism research and reviews*. 2005;21:505-14.
- [107] Podrid PJ, Myerburg RJ. Epidemiology and stratification of risk for sudden cardiac death. *Clinical cardiology*. 2005;28:13-11.
- [108] Rigat B, Hubert C, Alhenc-Gelas F, et al. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. *The Journal of clinical investigation*. 1990;86:1343-6.
- [109] Tiret L, Rigat B, Visvikis S, et al. Evidence, from combined segregation and linkage analysis, that a variant of the angiotensin I-converting enzyme (ACE) gene controls plasma ACE levels. *American journal of human genetics*. 1992;51:197-205.
- [110] Ariza M, Matarin MD, Junque C, et al. Influence of Angiotensin-converting enzyme polymorphism on neuropsychological subacute performance in moderate and severe traumatic brain injury. *The Journal of neuropsychiatry and clinical neurosciences*. 2006;18:39-44.

- 
- [111] Harding D, Baines PB, Brull D, et al. Severity of meningococcal disease in children and the angiotensin-converting enzyme insertion/deletion polymorphism. *American journal of respiratory and critical care medicine*. 2002;165:1103-6.
- [112] Kehoe AD, Eleftheriou KI, Heron M, et al. Angiotensin-converting enzyme genotype may predict survival following major trauma. *Emergency medicine journal : EMJ*. 2008;25:759-61.
- [113] Marshall RP, Webb S, Bellingan GJ, et al. Angiotensin converting enzyme insertion/deletion polymorphism is associated with susceptibility and outcome in acute respiratory distress syndrome. *American journal of respiratory and critical care medicine*. 2002;166:646-50.
- [114] Paradis NA, Martin GB, Rivers EP, et al. Coronary perfusion pressure and the return of spontaneous circulation in human cardiopulmonary resuscitation. *JAMA : the journal of the American Medical Association*. 1990;263:1106-13.
- [115] Statistics-Norway. Population Figures Statistics Norway 2009. [http://www.ssbno/english/subjects/02/befolkning\\_en](http://www.ssbno/english/subjects/02/befolkning_en)
- [116] Statistics-Norway. Population Figures Norway 2010. <https://www.ssb.no/statistikkbanken/SelectVarVal/saveselections.asp>
- [117] Statistics-Norway. Population Figures Norway. 2010. <https://www.ssb.no/a/kortnavn/folkendrkv/2010k2/hittil11.html>
- [118] Vaardal B, Lossius HM, Steen PA, et al. Have the implementation of a new specialised emergency medical service influenced the pattern of general practitioners involvement in pre-hospital medical emergencies? A study of geographic variations in alerting, dispatch, and response. *Emergency medicine journal : EMJ*. 2005;22:216-9.
- [119] Medicine TLFfA. Norwegian Index of Emergency Medical Assistance. Norwegian Medical Association: 21st edition Stavanger. 2005.
- [120] Lexow K, Sunde K. Why Norwegian 2005 guidelines differs slightly from the ERC guidelines. *Resuscitation*. 2007;72:490-2.
- [121] Lossius HM, Soreide E, Hotvedt R, et al. Prehospital advanced life support provided by specially trained physicians: is there a benefit in terms of life years gained? *Acta anaesthesiologica Scandinavica*. 2002;46:771-8.
- [122] de Latorre F, Nolan J, Robertson C, et al. European Resuscitation Council Guidelines 2000 for Adult Advanced Life Support. A statement from the Advanced Life Support Working Group(1) and approved by the Executive Committee of the European Resuscitation Council. *Resuscitation*. 2001;48:211-21.
- [123] Hazinski MF, Nadkarni VM, Hickey RW, et al. Major changes in the 2005 AHA Guidelines for CPR and ECC: reaching the tipping point for change. *Circulation*. 2005;112:IV206-11.

- 
- [124] Baskett PJ, Nolan JP, Handley A, et al. European Resuscitation Council guidelines for resuscitation 2005. Section 9. Principles of training in resuscitation. *Resuscitation*. 2005;67 Suppl 1:S181-9.
- [125] Human D, Crawley F. Revised declaration of Helsinki. WMA will continue to revise policy as medicine and research changes. *BMJ (Clinical research ed)*. 2001;323:283-4.
- [126] Rid A, Schmidt H. The 2008 Declaration of Helsinki - first among equals in research ethics? *The Journal of law, medicine & ethics : a journal of the American Society of Law, Medicine & Ethics*. 2010;38:143-8.
- [127] World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. *Bulletin of the World Health Organization*. 2001;79:373.
- [128] Takemoto Y, Sakatani M, Takami S, et al. Association between angiotensin II receptor gene polymorphism and serum angiotensin converting enzyme (SACE) activity in patients with sarcoidosis. *Thorax*. 1998;53:459-62.
- [129] Busch M, Soreide E. Prognostication after out-of-hospital cardiac arrest, a clinical survey. *Scandinavian journal of trauma, resuscitation and emergency medicine*. 2008;16:9.
- [130] Errson A, Friberg H. Therapeutic hypothermia. *Scand J Trauma Res Emerg Med* 2004; 12: 1
- [131] StatisticsNorway. Expected remaining lifetime, table 05375. *Statistics Norway*; 2012.
- [132] StatisticsNorway. Mortality according to gender and age groups per 100 000 population, Table 05381. *Statistics Norway*; 2012.
- [133] StatisticsNorway. Cases of death per 100 000 population, according to gender and detailed cause of death (per county), Table 08881. *Statistics Norway*; 2012.
- [134] Nolan JP. Optimizing outcome after cardiac arrest. Current opinion in critical care. 2011;17:520-6.
- [135] Nehme Z, Andrew E, Bernard S, et al. The impact of partial resuscitation attempts on the reported outcomes of out-of-hospital cardiac arrest in Victoria, Australia: Implications for Utstein-style outcome reports. *Resuscitation*. 2014;85:1185-91.
- [136] Perkins GD, Cooke MW. Variability in cardiac arrest survival: the NHS Ambulance Service Quality Indicators. *Emergency Medicine Journal*. 2012;29:3-5.
- [137] Nishiyama C, Brown SP, May S, et al. Apples to apples or apples to oranges? International variation in reporting of process and outcome of care for out-of-hospital cardiac arrest. *Resuscitation*. 2014;85:1599-609.
- [138] Kentsch M, Schlichting H, Mathes N, et al. Out-of-hospital cardiac arrest in north-east Germany: increased resuscitation efforts and improved survival. *Resuscitation*. 2000;43:177-83.

- 
- [139] Ro YS, Shin SD, Song KJ, et al. A trend in epidemiology and outcomes of out-of-hospital cardiac arrest by urbanization level: a nationwide observational study from 2006 to 2010 in South Korea. *Resuscitation*. 2013;84:547-57.
- [140] Sakai T, Iwami T, Tasaki O, et al. Incidence and outcomes of out-of-hospital cardiac arrest with shock-resistant ventricular fibrillation: Data from a large population-based cohort. *Resuscitation*. 2010;81:956-61.
- [141] Stromsoe A, Svensson L, Axelsson AB, et al. Improved outcome in Sweden after out-of-hospital cardiac arrest and possible association with improvements in every link in the chain of survival. *European heart journal*. 2014. Epub ahead of print
- [142] Fukuda T, Matsubara T, Doi K, et al. Predictors of favorable and poor prognosis in unwitnessed out-of-hospital cardiac arrest with a non-shockable initial rhythm. *International journal of cardiology*. 2014;176:910-5
- [143] Whitehead L, Perkins GD, Clarey A, et al. A systematic review of the outcomes reported in cardiac arrest clinical trials: The need for a core outcome set. *Resuscitation*. 2014. Epub ahead of print
- [144] Rea TD, Dumas F. Resuscitation science: a role for observation? *Resuscitation*. 2012;83:281-2.
- [145] Rea TD, Page RL. Community approaches to improve resuscitation after out-of-hospital sudden cardiac arrest. *Circulation*. 2010;121:1134-40.
- [146] Steinmetz J, Barnung S, Nielsen SL, et al. Improved survival after an out-of-hospital cardiac arrest using new guidelines. *Acta anaesthesiologica Scandinavica*. 2008;52:908-13.
- [147] Hinchey PR, Myers JB, Lewis R, et al. Improved out-of-hospital cardiac arrest survival after the sequential implementation of 2005 AHA guidelines for compressions, ventilations, and induced hypothermia: the Wake County experience. *Annals of emergency medicine*. 2010;56:348-57.
- [148] Olasveengen TM, Vik E, Kuzovlev A, et al. Effect of implementation of new resuscitation guidelines on quality of cardiopulmonary resuscitation and survival. *Resuscitation*. 2009;80:407-11.
- [149] Berdowski J, ten Haaf M, Tijssen JG, et al. Time in recurrent ventricular fibrillation and survival after out-of-hospital cardiac arrest. *Circulation*. 2010;122:1101-8.
- [150] Jost D, Degrange H, Verret C, et al. DEFI 2005: a randomized controlled trial of the effect of automated external defibrillator cardiopulmonary resuscitation protocol on outcome from out-of-hospital cardiac arrest. *Circulation*. 2010;121:1614-22.
- [151] Robinson S, Swain AH, Hoyle SR, et al. Survival from out of hospital cardiac arrest in New Zealand following the 2005 resuscitation guidelines changes. *Resuscitation*. 2010;81:1648-51.
- [152] Avalli L, Mauri T, Citerio G, et al. New treatment bundles improve survival in out-of-hospital cardiac arrest patients: a historical comparison. *Resuscitation*. 2014;85:1240-4.

- 
- [153] Henlin T, Michalek P, Tyll T, et al. Oxygenation, ventilation, and airway management in out-of-hospital cardiac arrest: a review. *BioMed research international*. 2014;2014:376871.
- [154] Wang CH, Huang CH, Chang WT, et al. Biphasic versus monophasic defibrillation in out-of-hospital cardiac arrest: a systematic review and meta-analysis. *The American journal of emergency medicine*. 2013;31:1472-8.
- [155] Nolan JP, Perkins GD. Is there a role for adrenaline during cardiopulmonary resuscitation? *Current opinion in critical care*. 2013;19:169-74.
- [156] Wang CH, Chen YS, Ma MH. Extracorporeal life support. *Current opinion in critical care*. 2013;19:202-7.
- [157] Rubertsson S, Lindgren E, Smekal D, et al. Mechanical chest compressions and simultaneous defibrillation vs conventional cardiopulmonary resuscitation in out-of-hospital cardiac arrest: the LINC randomized trial. *JAMA : the journal of the American Medical Association*. 2014;311:53-61.
- [158] Wik L, Olsen JA, Persse D, et al. Manual vs. integrated automatic load-distributing band CPR with equal survival after out of hospital cardiac arrest. The randomized CIRC trial. *Resuscitation*. 2014;85:741-8.
- [159] Cambien F, Poirier O, Lecerf L, et al. Deletion polymorphism in the gene for angiotensin-converting enzyme is a potent risk factor for myocardial infarction. *Nature*. 1992;359:641-4..
- [160] Danser AJ, Schalekamp MA, Bax WA, et al. Angiotensin-Converting Enzyme in the Human Heart Effect of the Deletion/Insertion Polymorphism. *Circulation*. 1995;92:1387-8.
- [161] Marian A, Yu Q, Workman R, Greve G, et al. Angiotensin-converting enzyme polymorphism in hypertrophic cardiomyopathy and sudden cardiac death. *The Lancet*. 1993;342:1085-6.
- [162] Schunkert H, Hense H-W, Holmer SR, et al. Association between a deletion polymorphism of the angiotensin-converting-enzyme gene and left ventricular hypertrophy. *New England Journal of Medicine*. 1994;330:1634-8.
- [163] Bray JE, Di Palma S, Jacobs I, et al. Trends in the incidence of presumed cardiac out-of-hospital cardiac arrest in Perth, Western Australia, 1997-2010. *Resuscitation*. 2014;85:757-61.
- [164] Lick CJ, Aufderheide TP, Niskanen RA, et al. Take Heart America: A comprehensive, community-wide, systems-based approach to the treatment of cardiac arrest. *Critical care medicine*. 2011;39:26-33.
- [165] Stromsoe A, Andersson B, Ekstrom L, et al. Education in cardiopulmonary resuscitation in Sweden and its clinical consequences. *Resuscitation*. 2010;81:211-6.
- [166] Wnent J, Bohn A, Seewald S, et al. [Bystander resuscitation: the impact of first aid on survival]. *Anesthesiologie, Intensivmedizin, Notfallmedizin, Schmerztherapie : AINS*. 2013;48:562-5.

- 
- [167] Murakami Y, Iwami T, Kitamura T, et al. Outcomes of out-of-hospital cardiac arrest by public location in the public-access defibrillation era. *Journal of the American Heart Association*. 2014;3:e000533.
- [168] Hollenberg J, Svensson L, Rosenqvist M. Out-of-hospital cardiac arrest: 10 years of progress in research and treatment. *Journal of internal medicine*. 2013;273:572-83.
- [169] Adielsson A, Hollenberg J, Karlsson T, et al. Increase in survival and bystander CPR in out-of-hospital shockable arrhythmia: bystander CPR and female gender are predictors of improved outcome. Experiences from Sweden in an 18-year perspective. *Heart (British Cardiac Society)*. 2011;97:1391-6.
- [170] Larsen AI, Hjørnevik A, Bonarjee V, et al. Coronary blood flow and perfusion pressure during coronary angiography in patients with ongoing mechanical chest compression: a report on 6 cases. *Resuscitation*. 2010;81:493-7.
- [171] Aarsetoy H, Ponitz V, Nilsen OB, et al. Low levels of cellular omega-3 increase the risk of ventricular fibrillation during the acute ischaemic phase of a myocardial infarction. *Resuscitation*. 2008;78:258-64.
- [172] Bjorshol CA, Lindner TW, Soreide E, et al. Hospital employees improve basic life support skills and confidence with a personal resuscitation manikin and a 24-min video instruction. *Resuscitation*. 2009;80:898-902.
- [173] Bjorshol CA, Soreide E, Torsteinbo TH, et al. Quality of chest compressions during 10min of single-rescuer basic life support with different compression: ventilation ratios in a manikin model. *Resuscitation*. 2008;77:95-100.
- [174] Bjorshol CA, Sunde K, Myklebust H, et al. Decay in chest compression quality due to fatigue is rare during prolonged advanced life support in a manikin model. *Scandinavian journal of trauma, resuscitation and emergency medicine*. 2011;19:46.
- [175] Busch M, Soreide E. Should advanced age be a limiting factor in providing therapeutic hypothermia to cardiac arrest survivors? A single-center observational study. *Therapeutic hypothermia and temperature management*. 2011;1:29-32.
- [176] Eikeland Husebo SI, Bjorshol CA, Rystedt H, et al. A comparative study of defibrillation and cardiopulmonary resuscitation performance during simulated cardiac arrest in nursing student teams. *Scandinavian journal of trauma, resuscitation and emergency medicine*. 2012;20:23.
- [177] Vaga A, Busch M, Karlsen TE, et al. A pilot study of key nursing aspects with different cooling methods and devices in the ICU. *Resuscitation*. 2008;76:25-30.
- [178] Sandroni C, Cavallaro F, Antonelli M. Therapeutic hypothermia: is it effective for non-VF/VT cardiac arrest? *Critical care (London, England)*. 2013;17:215.

- 
- [179] Vaahersalo J, Hiltunen P, Tiainen M, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest in Finnish intensive care units: the FINNRESUSCI study. *Intensive care medicine*. 2013;39:826-37.
- [180] Xiao G, Guo Q, Shu M, et al. Safety profile and outcome of mild therapeutic hypothermia in patients following cardiac arrest: systematic review and meta-analysis. *Emergency medicine journal : EMJ*. 2013;30:91-100.
- [181] Jacobs I, Nadkarni. Targeted temperature management following cardiac arrest An update. 2013. <http://www.ilcor.org/news/news-archive/ttm>
- [182] Garrouste-Orgeas M, Boumendil A, Pateron D, et al. Selection of intensive care unit admission criteria for patients aged 80 years and over and compliance of emergency and intensive care unit physicians with the selected criteria: An observational, multicenter, prospective study. *Critical care medicine*. 2009;37:2919-28.
- [183] Sprung CL, Artigas A, Kesecioglu J, et al. The Eldicus prospective, observational study of triage decision making in European intensive care units. Part II: intensive care benefit for the elderly. *Critical care medicine*. 2012;40:132-8.
- [184] Bray JE, Stub D, Bernard S, et al. Exploring gender differences and the "oestrogen effect" in an Australian out-of-hospital cardiac arrest population. *Resuscitation*. 2013;84:957-63.
- [185] Mahmood K, Eldeirawi K, Wahidi MM. Association of gender with outcomes in critically ill patients. *Critical care (London, England)*. 2012;16:R92.
- [186] Nachtigall I, Tafelski S, Rothbart A, et al. Gender-related outcome difference is related to course of sepsis on mixed ICUs: a prospective, observational clinical study. *Critical care (London, England)*. 2011;15:R151.
- [187] Kim MJ, Shin SD, McClellan W, et al. Neurological prognostication by gender in out-of-hospital cardiac arrest patients receiving hypothermia treatment. *Resuscitation*. 2014;85:1732-8
- [188] Wigginton JG, Perman SM, Barr GC, et al. Sex- and Gender-specific Research Priorities in Cardiovascular Resuscitation: Proceedings from the 2014 Academic Emergency Medicine Consensus Conference Cardiovascular Resuscitation Research Workgroup. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine*. 2014;21:1343-9.
- [189] Oddo M, Ribordy V, Feihl F, et al. Early predictors of outcome in comatose survivors of ventricular fibrillation and non-ventricular fibrillation cardiac arrest treated with hypothermia: a prospective study. *Critical care medicine*. 2008;36:2296-301.
- [190] Tomte O, Andersen GO, Jacobsen D, et al. Strong and weak aspects of an established post-resuscitation treatment protocol-A five-year observational study. *Resuscitation*. 2011;82:1186-93.
- [191] Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. *The New England journal of medicine*. 2013;369:2197-206.

- 
- [192] Drennan IR, Lin S, Thorpe KE, et al. The effect of time to defibrillation and targeted temperature management on functional survival after out-of-hospital cardiac arrest. *Resuscitation*. 2014;85:1623-8.
- [193] Kim WY, Giberson TA, Uber A, et al. Neurologic outcome in comatose patients resuscitated from out-of-hospital cardiac arrest with prolonged downtime and treated with therapeutic hypothermia. *Resuscitation*. 2014;85:1042-6.
- [194] Lin S, Scales DC, Dorian P, et al. Targeted Temperature Management Processes and Outcomes After Out-of-Hospital Cardiac Arrest: An Observational Cohort Study\*. *Critical care medicine*. 2014;42:2565-74.
- [195] Polderman K, Nielsen N, Graffagnino C, et al. Therapeutic Hypothermia in Post-Cardiac Arrest. *Therapeutic hypothermia and temperature management*. 2014;4:154-8.
- [196] Ferreira Da Silva IR, Frontera JA. Targeted temperature management in survivors of cardiac arrest. *Cardiology clinics*. 2013;31:637-55, ix.
- [197] Polderman KH, Varon J. We should not abandon therapeutic cooling after cardiac arrest. *Critical Care*. 2014;18:130-1.
- [198] Pittl U, Schratte A, Desch S, et al. Invasive versus non-invasive cooling after in- and out-of-hospital cardiac arrest: a randomized trial. *Clinical research in cardiology : official journal of the German Cardiac Society*. 2013;102:607-14.
- [199] Deakin CD, Morrison LJ, Morley PT, et al. Part 8: Advanced life support: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Resuscitation*. 2010;81 Suppl 1:e93-e174.
- [200] Nunnally ME, Jaeschke R, Bellingan GJ, et al. Targeted temperature management in critical care: a report and recommendations from five professional societies. *Critical care medicine*. 2011;39:1113-25.
- [201] Dumas F, Rea TD. Long-term prognosis following resuscitation from out-of-hospital cardiac arrest: role of aetiology and presenting arrest rhythm. *Resuscitation*. 2012;83:1001-5.
- [202] Key CB. Operational issues in EMS. *Emergency medicine clinics of North America*. 2002;20:913-27.
- [203] Pozner CN, Zane R, Nelson SJ, et al. International EMS systems: The United States: past, present, and future. *Resuscitation*. 2004;60:239-44.
- [204] Naess AC, Steen PA. Long term survival and costs per life year gained after out-of-hospital cardiac arrest. *Resuscitation*. 2004;60:57-64.
- [205] Lemiale V, Dumas F, Mongardon N, et al. Intensive care unit mortality after cardiac arrest: the relative contribution of shock and brain injury in a large cohort. *Intensive care medicine*. 2013;39:1972-80.
- [206] Rea TD, Crouthamel M, Eisenberg MS, et al. Temporal patterns in long-term survival after resuscitation from out-of-hospital cardiac arrest. *Circulation*. 2003;108:1196-201.

[207] Siudak Z, Birkemeyer R, Dziewierz A, et al. Out-of-hospital cardiac arrest in patients treated with primary PCI for STEMI. Long-term follow up data from EUROTRANSFER registry. *Resuscitation*. 2012;83:303-6.

[208] Zimmermann S, Flachskampf FA, Alff A, et al. Out-of-hospital cardiac arrest and percutaneous coronary intervention for ST-elevation myocardial infarction: long-term survival and neurological outcome. *International journal of cardiology*. 2013;166:236-41.

[209] Bernstein KE, Ong FS, Blackwell WL, et al. A modern understanding of the traditional and nontraditional biological functions of angiotensin-converting enzyme. *Pharmacological reviews*. 2013;65:1-46.