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OUT-OF-HOSPITAL CARDIAC ARREST

A study on factors associated with cardiopulmonary resuscitation, early defibrillation and survival

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Out-of-hospital cardiac arrest

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"It's not that I'm afraid to die, I just don't want to be there when it happens."
Woody Allen (b. 1935-)

To my family

ABSTRACT

Cardiac disease is the most common cause of mortality in the Western World and the majority of these cardiac deaths is due to out-of-hospital cardiac arrest (OHCA). In Sweden, an estimated 5,000-10,000 people suffer an OHCA annually. The objective of this thesis is to study patient characteristics and survival in patients with OHCA, to explore the importance of pre-hospital factors and in-hospital factors and to investigate the benefits of an early defibrillation program.

Methods and results: Most data in this thesis are based on patient material collected by the Swedish Cardiac Arrest Register. Other data come from case records from patients admitted alive and time measurements from the emergency dispatch centre and defibrillators.

In ***Study I,*** 969 cases of OHCA in Stockholm and 398 cases of OHCA in Göteborg between January 2000 and June 2001 were compared. The two groups were similar in terms of age, gender and various factors at resuscitation. All pre-hospital time intervals were longer in Stockholm and the proportion of patients found in ventricular fibrillation (VF) was 18% compared to 31% in Göteborg ($p<0.0001$). 1-month survival was significantly lower in Stockholm (2.5% vs. 6.8%; $p<0.001$).

To evaluate the relative roles of pre-hospital and in-hospital factors, 1,542 OHCA in Stockholm and 546 in Göteborg between January 2000 and June 2002 were investigated in ***Study II***. Survival after OHCA was again lower in Stockholm (3.3% vs. 6.1%; $p=0.01$). Significantly longer time intervals and a lower proportion of VF OHCA were found in Stockholm compared to Göteborg. Patient demography, medical history, in-hospital investigations and interventions as well as in-hospital mortality (78% in Göteborg, 80% in Stockholm) did not differ between the two groups.

To describe temporal trends in 1-month survival after OHCA in Sweden, 38,646 patients between 1992-2005 were investigated in ***Study III***. The proportion of patients surviving to hospital admission increased from 15.3% in 1992 to 21.7% in 2005 (p for trend<0.0001). The corresponding figures for patients being alive after 1 month were 4.8% and 7.3% (p for trend<0.0001). Factors related to the improved survival were an increase in crew-witnessed cases from 9% in 1992 to 15% in 2005 (p for trend <0.0001) and, to a lesser degree, more frequent bystander CPR which rose from 31% in 1992 to 50% in 2005 (p for trend <0.0001).

In ***Study IV,*** specially trained fire-fighters equipped with automated external defibrillators were dispatched in addition to traditional medical responders to suspected cases of OHCA in Stockholm from December 2005 to December 2006. 863 OHCA patients were enrolled during the intervention and 657 OHCA from 2004 served as historical controls. Among dual dispatches, fire-fighters assisted with CPR in 94% of cases and arrived first on scene in 36% of cases. The median time from call to arrival of first responder decreased from 7.5 to 7.1 minutes ($p=0.004$). 1-month survival rose from 4.4% to 6.8% ($p=0.047$; adjusted OR: 1.6; 95% C.I: 0.9-2.9). 1-month survival among witnessed cases of OHCA rose from 5.7% to 9.7% ($p=0.029$; adjusted OR: 2.0; 95% C.I: 1.1-3.7).

Conclusions: Survival after OHCA was significantly lower in Stockholm than in Göteborg during 2000-2002 and this difference was associated with pre-hospital factors only rather than with in-hospital factors or patient characteristics. Survival after OHCA in Sweden increased significantly from 1992 to 2005. The increase was particularly marked among patients found with a shockable rhythm and is associated with an increase in the proportion of crew-witnessed cases and, to a lesser degree, an increase in bystander CPR. A dual dispatch early defibrillation program in Stockholm has decreased response times and is likely to have improved survival in patients with OHCA. This increase in survival is believed to be associated with improved CPR and shortened time intervals.

Key words: *out-of-hospital cardiac arrest; sudden cardiac death; ventricular fibrillation; cardiopulmonary resuscitation (CPR); automated external defibrillators; return of spontaneous circulation; fire department*

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

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

I Hollenberg J, Bang A, Lindqvist J, Herlitz J, Nordlander R, Svensson L, Rosenqvist M. Difference in survival after out-of-hospital cardiac arrest between the two largest cities in Sweden: a matter of time?
J Intern Med. 2005;257:247-54.

II Hollenberg J, Lindqvist J, Ringh M, Engdahl J, Bohm K, Rosenqvist M, Svensson L. An evaluation of post-resuscitation care as a possible explanation of a difference in survival after out-of-hospital cardiac arrest.
Resuscitation. 2007;74:242-52.

III Hollenberg J, Herlitz J, Lindqvist J, Riva G, Bohm K, Rosenqvist M, Svensson L. Improved survival after out-of-hospital cardiac arrest associated with an increase in proportion of crew-witnessed cases and bystander CPR.
Submitted

IV Hollenberg J, Riva G, Bohm K, Larsen R, Herlitz J, Pettersson H, Rosenqvist M, Svensson L. Dual dispatch early defibrillation program in out-of-hospital cardiac arrest – the SALSA-project.
Submitted

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ABBREVIATIONS

ACE	angiotensin converting enzyme
ACLS	advanced cardiac life support
AED	automated external defibrillator
AHA	American Heart Association
AMI	acute myocardial infarction
B-CPR	bystander cardiopulmonary resuscitation
BLS	basic life support
CA	cardiac arrest
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CPC	cerebral performance category
CPR	cardiopulmonary resuscitation
D-CPR	defibrillator cardiopulmonary resuscitation
ECG	electrocardiogram
EDC	emergency dispatch centre
EMS	emergency medical system
ERC	European Resuscitation Council
ICD	implantable cardioverter-defibrillator
ICU	intensive care unit
IHD	ischaemic heart disease
NS	non-significant (statistically)
OHCA	out-of-hospital cardiac arrest
OR	odds ratio
PAD	public access defibrillation
PCI	percutaneous coronary intervention
PEA	pulseless electrical activity
ROSC	return of spontaneous circulation
SALSA	SAving Lives in the Stockholm Area
SCAR	Swedish Cardiac Arrest Register
SCA	sudden cardiac arrest
SCD	sudden cardiac death
VF	ventricular fibrillation
VT	ventricular tachycardia

1. INTRODUCTION

Sudden cardiac arrest (SCA), also referred to as sudden cardiac death (SCD), is the sudden, unexpected loss of heart function, breathing and consciousness. It is a medical emergency that, if not treated immediately, is fatal.

1.1 History

Cardiopulmonary resuscitation (CPR) today includes both mouth-to-mouth ventilation and chest compressions. The roots of resuscitation extend back for centuries, with descriptions of different techniques (many of them inadequate) including varying types of management of airways, breathing and circulation. Some claim that the earliest recorded reference to artificial breathing can be found in the Old Testament (book of Kings), where the prophet Elisha restored the life of a boy through a technique that included placing his mouth on the mouth of the child [2 Kings]. After that, however, little is mentioned about artificial ventilation or attempts to restore circulation for somewhere around 2000 years. The first record of use of electricity for successful human resuscitation was made in 1774 by Squires who described a child who became pulseless and to "all appearance dead" after falling out of a window. He wrote that "Upon transmitting a few shocks through the thorax I perceived a small pulsation; in a few minutes the child began to breathe" [Squires 1774]. Even though this remarkable success gives Squires a place in the history of resuscitation, he was never heard from again. Only one year later, in 1775, Abildgard described having shocked a chicken into lifelessness and on repeating the shock, bringing the bird back to life [Lown 2002].

A short historical overview of modern resuscitation during the 20th century includes the first American closed-chest cardiac massage by Crile in 1904, the initiation and termination of ventricular fibrillation (VF) with electric shocks in 1933 by Kouwenhoven, mouth-to-nose ventilation of polio patients by Elan in 1946 and Beck's successful defibrillation of a 14-year old boy using open-chest massage and an AC defibrillator in 1947 [Ornato 2005]. Three very important contributors to the development of modern CPR are Zoll, Safar and Kouwenhoven [Cooper 2006, Acosta 2005, Ornato 2005]. In 1955, Zoll performed and recorded the first successful closed-chest human defibrillation on a man with recurrent syncope and VF. In the 1950s Safar methodically investigated techniques for airway management and showed that the optimal position for CPR was achieved with the patient's neck extended, the mandible supported (jaw thrust) and an oropharyngeal tube introduced to deliver oxygen. Closed chest cardiac massage and external defibrillation was developed and described during the 1950s and 1960s by Kouwenhoven, Knickerbocker and Jude and improved the outcome of patients with SCA.

1.2 Definition of cardiac arrest

Over time, many different definitions of cardiac arrest (CA) have been used [Kuller 1966, Paul 1971, Biörck 1972, Goldstein 1982, Oliver 1985, Roberts 1986, Myerburg 1987, Demirovic 1994]. These have varied in several aspects including the duration of the condition, whether the event was witnessed or not, if it was expected or not, and furthermore its etiology. The problems associated with defining the mode of death have been a matter of concern for many authors [Hinkle 1982, Pratt 1996]. As of today, SCD is most often defined as follows: "Natural death due to cardiac causes, heralded by abrupt loss of consciousness within one hour of the onset of acute symptoms; pre-existing heart disease may have been known to be present, but the time and mode of death are unexpected." [Myerburg 1997b]. There are many causes and mechanisms that could lead to a clinical presentation defined as SCD. Key concepts thus included in the definition today are that the condition is of non-traumatic nature and that it is unexpected. Sudden cardiac arrest occurring outside hospital is referred to as out-of-hospital cardiac arrest (OHCA) and include all-rhythm cardiac arrests due to different underlying etiologies.

1.3 Epidemiology

Death from cardiac disease is the single most common cause of mortality in the Western World [Myerburg 1993, Myerburg 1997a, Salomaa 2003]. Cardiovascular disease represents around 40% of all causes of mortality in Europe [Sans 1997]. The majority of these cardiac deaths are considered to be due to OHCA [Zheng 2001]. It has been approximated that the number of emergency medical services (EMS) treated OHCA amounts to around 275,000 cases in Europe annually [Atwood 2005]. In the USA, somewhere between 200,000 [Rea 2004] up to > 400,000 cases [Zheng 2001] of OHCA occur each year. In Sweden, an estimated 5,000-10,000 people suffer an OHCA annually [Anonymous 2006].

Incidence numbers for OHCA vary widely in the literature, one reason being the difficulty of defining OHCA. Incidence rates from 17 per 100,000 to 128 per 100,000 inhabitants per year have been described [Becker 1993b, Gaul 1996, Vreede-Swagemakers 1997, Rea 2004]. These studies only include patients resuscitated by the EMS and may therefore be an underestimate of the true incidence of OHCA in the population.

It seems that men have a significantly higher incidence of OHCA than women [Escobedo 1996, Vreede-Swagemakers 1997, Zheng 2001]. This is in all probability due to the higher incidence of coronary heart disease in men [McGovern 1996, Anonymous 2005c], which by far is the most common cause of OHCA.

1.4 Causes and risk factors

There are numerous causes of CA. Establishing the etiology of the condition is, however, difficult. As the vast majority of patients suffering from OHCA also die outside hospital or in emergency departments, many do not undergo an autopsy, and in a large proportion of cases information about co-morbidity and medication is absent. Furthermore, data regarding possible symptoms prior to the collapse are usually lacking. Only about 60-70% of all OHCA are witnessed [Vreede-Swagemakers 1997, Fredriksson 2003], and circumstances in the remaining cases are often unknown. Also, diagnostication of cause of OHCA differs depending on such factors as the availability of autopsy reports, medical history, ECG-findings, in-hospital data and interviews with relatives.

It has, however, been established that a cardiac condition is by far the most common cause of OHCA [Myerburg 1993, Zipes 1998]. Structural coronary heart disease is the underlying condition in the vast majority of cases, accounting for some 90% of all cardiac causes [Wennerblom 1984, Davies 1992]. Several autopsy studies of patients suffering from OHCA have been performed. Wennerblom and co-workers found that 51% of 1,073 autopsied OHCA patients (all causes) were due to ischaemic heart disease [Wennerblom 1984], Fornes and colleagues found that 61% of OHCA patients (all causes) had coronary heart disease [Fornes 1993]. Virmani and co-workers furthermore described that approximately 60% of

Table 1.1

Cardiac causes of cardiac arrest
Ischaemic cardiac disease (coronary artery disease)
Ischaemic cardiomyopathy
Dilated cardiomyopathy
Hypertrophic cardiomyopathy
Non-atherosclerotic disease of coronary arteries
Valvular heart disease
Arrhythmogenic right ventricular cardiomyopathy
Infiltrative and inflammatory myocardial disease
Congenital heart disease
Primary cardiac electrical abnormalities

sudden coronary deaths are caused by coronary thrombosis, the remainder having severe coronary disease in the absence of thrombosis [Virmani 2001]. The second most common cardiac cause of OHCA is dilated or hypertrophic cardiomyopathy [Zipes 1998]. Cardiac causes of OHCA are listed in Table 1.1.

In three studies, non-cardiac causes among all OHCA were judged to account for 34% of cases [Wennerblom 1984], 27% [Fredriksson 2003] and 18% [Pell 2003], respectively. OHCA from non-cardiac causes seem to be associated with worse crude survival than arrests from cardiac causes [Kuisma 1997, Pell 2003]. Non-cardiac causes of OHCA are listed in Table 1.2.

Table 1.2

Non-cardiac causes of cardiac arrest
Bleeding (non-traumatic)
Pulmonary embolism
Lung disease
Electrolyte abnormalities
Subarchnoid haemorrhage
Drug overdose
Suffocation
Drowning
Sudden infant death syndrome

There are numerous risk factors for OHCA. It is for example well established that the risk of sudden death from cardiac causes is increased in patients with *previous myocardial infarction* and *reduced left ventricular systolic function* [Solomon 2005]. A number of reports (especially epidemiological population based studies) have attempted to identify risk factors that may specifically predict OHCA. *Age* has been shown to be a risk factor for SCD [Wannamethee 1995]. *Hypertension* [Kannel 1988, Weijenberg 1996] and *left ventricular hypertrophy* [Haider 1998] are other factors that have been associated with an independently higher risk of SCD. There is an association between elevated levels of *LDL-cholesterol* and all manifestations of ischaemic heart disease including OHCA [Burke 1997, Tsuji 1999]. *Absence of physical activity* might also increase the risk of OHCA [Lemaitre 1999]. *Smoking* as an independent risk factor for SCD has been confirmed in several community-based studies [Wannamethee 1995, Jouven 1999, Engdahl 2000a]. It furthermore seems that *excessive alcohol intake* increases the risk of OHCA [Lithell 1987] while moderate alcohol intake was associated with a reduction in case fatality of a first major coronary event in the prospective British Regional Heart Survey [Wannamethee

1995]. *Increased heart rate* has been reported as an independent risk factor for SCD in several studies [Algra 1993, Jouven 2001]. Evidence is conflicting on the issue of *diabetes mellitus* as a risk factor for SCD. Most studies have found diabetes to be a strong risk factor [Jouven 1999, Balkau 1999] while others have not [Wannamethee 1995]. Inherited genetic abnormalities affecting key proteins of the heart may lead to OHCA. Hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, Long QT Syndrome and Brugada Syndrome are examples of diseases with genetic predisposing for OHCA. Jouven and co-workers demonstrated parental sudden death as an independent risk factor for sudden death in middle-aged men [Jouven 1999].

1.5 Location of cardiac arrest

Most cases of OHCA occur at home. Several reports indicate that the proportion of cases occurring at home is somewhere between 60% and 80% [Litwin 1987, Engdahl 2005, Iwami 2006]. The importance of describing the location of CA has increased over the last years as the feasibility of out-of-hospital defibrillation has emerged. Furthermore, the location of arrest gives information of the population at risk. Several investigations during the last decade have described the relationship between public location of OHCA and its association with survival. Eisenburger and co-workers found that CA in a public location is independently associated with a better outcome [Eisenburger 2006] and Iwami and colleagues described that patients with OHCA in public or at work place had a higher chance of being found to have VF and survive than those in private residences [Iwami 2006]. Others have investigated the locations of OHCA in relation to where automated external defibrillators (AEDs) should be placed. Most of these studies have found 15-20% of OHCA to be suitable for public access defibrillation (PAD) [Becker 1998, Pell 2002, Engdahl 2005] according to different criteria. The guidelines for CPR from the European Resuscitation Council (ERC) published in 2005 state that "suitable sites might include those where the probability of cardiac arrest occurring is at least once in every 2 years (e.g., airports, casinos, sports facilities)" [Anonymous 2005a] while the AHA Emergency Cardiovascular Care Committee, Council on Clinical Cardiology, Office of State Advocacy and others wrote in 2006 that "AEDs should be placed where there is a high likelihood of sudden cardiac arrest. In the PAD trial, such locations had the equivalent of ≥250 adults >50 years of age present for 16 hours per day or a history of an average of ≥1 witnessed sudden cardiac arrest every 2 years" [Aufderheide 2006].

1.6 Initial arrhythmia and symptoms

In real life, it is impossible to acquire information about the initial arrhythmia that culminates in an OHCA as these persons are nearly always unmonitored. Instead, the arrhythmia first recorded by the EMS crews has served as a marker for comparisons. *Ventricular fibrillation*, *asystole* and *pulseless electrical activity* (PEA) are the three main electrical pathophysiological mechanisms that lead to CA.

The mechanisms of *VF* are still not fully understood but certainly involve a complex interaction between different structural and functional components (substrates) in combination with interacting (often transient) stimuli. Most commonly, VF is caused by a re-entry tachycardia evolving from an ischaemic zone close to dead tissue cased by myocardial infarction. Findings from long term ECGs and implantable cardioverter-defibrillators (ICD) indicate that VF is usually preceded by ventricular tachycardia (VT) which sooner or later deteriorates into a more chaotic rhythm [Bayes de Luna 1989]. There are many different factors that can enhance the vulnerability of the myocardium and lead to fibrillation.

Although difficult, a few studies have tried to estimate the proportion of patients having VF at the time of collapse. One of these investigations, performed by Holmberg and co-workers, points to an incidence of VF at the time of cardiac arrest of 60-70% in all patients and 80-85% in cases with probable heart disease [Holmberg 2000]. VF is generally present in about 25-50% of OHCA patients as the first registered arrhythmia [Cobb 2002, Rea 2004, Herlitz 2004] and is one of the strongest predictors of survival in OHCA as has been demonstrated in several studies [Holmberg 2000, Rewers 2000, Herlitz 2005a, Fridman 2007]. During the last decade a trend towards increased survival rates among VF patients has been observed but at the same time a decline in the proportion of patients with VF as the presenting rhythm has been found [Kuisma 2001, Rea 2003, Herlitz 2005b, Kette 2007].

Even if a few patients present with *asystole* at the time of collapse, most patients found in asystole have, at the time of collapse, initially had VF. With time, VF slowly deteriorates into fine VF (from coarse VF) and then finally to asystole [Bayes de Luna 1989, Huikuri 2001]. Asystole is therefore regarded as a sign of dying or even as a sign of a dead heart. The reasons for this perception are also based on the fact that survival is extremely low in patients found with asystole. Studies have demonstrated zero or only up to at most 5% of patients surviving an asystolic OHCA [Silfvast 1990, Weston 1997, Engdahl 2000b, Eisenberg 2001].

PEA is a condition with absence of a detectable pulse in the presence of some form of electrical activity other than VF or VT. Several conditions (both cardiac and non-cardiac) can generate PEA [Anonymous 2000b, Anonymous 2005b] even though non-cardiac causes seem to be more common in PEA OHCA than in VF OHCA. Survival after PEA OHCA is almost as low as it is with asystole, with most authors reporting survival in 2-6% of patients [Pepe 1993, Weston 1997, Engdahl 2001].

Previous investigations have shown that a majority of patients suffering from OHCA do have symptoms prior to the arrest [Muller 2006, Vreede-Swagemakers 1997]. The most common symptoms include angina pectoris, dyspnea, nausea/vomiting and dizziness or syncope.

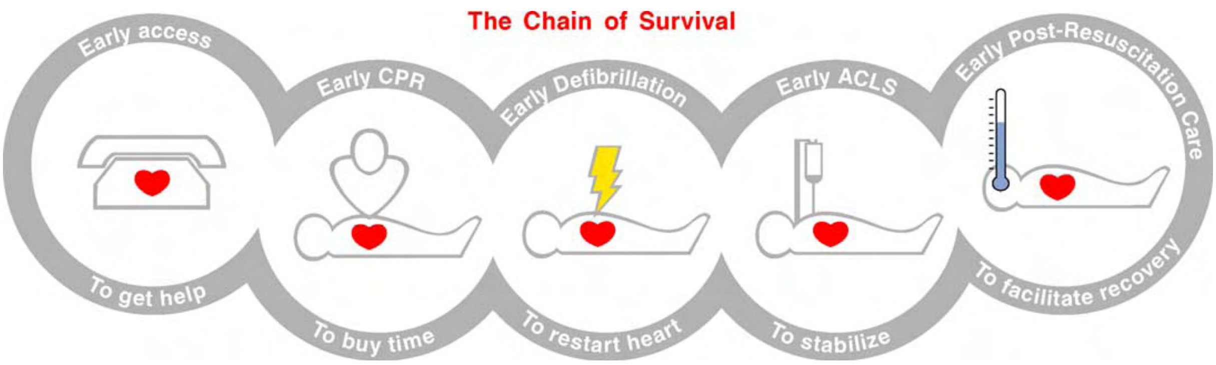
1.7 Treatment of OHCA (*chain-of-survival*)

Treatment of OHCA can be divided into two principal groups: prevention and resuscitation.

Prevention of OHCA can subsequently be divided into primary prevention and secondary prevention. Primary prevention stands for prevention of the first event (i.e. CA) while secondary prevention stands for prevention of a recurrence of a CA among patients surviving their first episode. Prevention of OHCA includes such measures as the reduction of known risk factors for ischaemic heart disease, the use of anti-arrhythmic drugs and other medical treatment for ischaemic heart disease (such as aspirin, beta-blocking agents, statins, ACE-inhibitors), the use of ICDs and catheter-based or surgical revascularization. The different aspects regarding primary and secondary prevention are beyond the scope of this introduction.

Resuscitation of the OHCA patient has been the focus of much work during the last decades. The "chain-of-survival" concept [Cummins 1991a] is nowadays well established, comprising early access, early CPR, early defibrillation and early advanced cardiac life support (ACLS). Furthermore, during the last few years, patient management during the in-hospital phase has also been addressed. This has led to the proposition of an additional fifth link to the "chain-of-survival" in the form of post-resuscitation care. The five links of the "chain-of-survival" concept are illustrated in Figure 1 and described in detail below.

Figure 1 Updated chain-of-survival



1.7.1 Early access

This first step in the chain-of-survival concept involves quick identification and localization of the CA victim and consequent notification to the dispatch centre. The effects of early access on survival are difficult to measure. However, three studies strongly support the hypothesis that early access has a positive effect on survival [Valenzuela 1997, Anonymous 2002a, Herlitz 2003]. Early access is also important for the optimal use of CPR guidance by telephone from dispatchers to bystanders, an area which has been gaining increasing interest during the last few years [Rea 2001, Bohm 2007b, Harve 2007].

1.7.2 Early CPR

The effects of early CPR on survival have been repeatedly demonstrated. It is believed that early CPR doubles or even triples survival after OHCA [Lund 1976, Larsen 1993, Herlitz 2005a, Herlitz 2005c]. It has also been established that bystander CPR improves survival rates in patients with pre-hospital VF [Cobb 1999, Waalewijn 2002]. The explanation for this is believed to be that CPR extends the time period during which effective defibrillation can be performed, working as a bridge to defibrillation by increasing VF-amplitude [Eftestol 2004].

During the last two decades the CPR protocol has been slightly modified and the ventilation/compression ratio has changed from 2 ventilations/15 compressions to 30 compressions/2 ventilations [Anonymous 2000a, Anonymous 2005a]. Also, during the last few years, investigators have addressed the method of compressions-only CPR as an alternative to standard CPR in OHCA [Kern 2002, Sanders 2002] and two large population-based, observational register studies have demonstrated no significant differences in 1-month survival among patients with OHCA with either standard CPR or chest compressions only [Bohm 2007a, Iwami 2007]. At the time of the present publication, the American Heart

Association issued a statement including so-called "hands-only" CPR, recommending that "bystanders who witness the sudden collapse of an adult should activate the EMS system and provide high-quality chest compressions by pushing hard and fast in the middle of the victim's chest, with minimal interruptions" [Sayre 2008]. Immediately after the American publication, the European Resuscitation Council adopted a more cautious attitude and concluded that there is insufficient evidence to make any changes at this time [Koster 2008]. At present, two large independent, prospective and randomized trials are ongoing in the United States and the other in Finland and Sweden where dispatchers randomize patients to either standard CPR or compressions-only CPR.

Furthermore, the use of mechanically aided chest compressions has come into focus following the development of new devices for this purpose. While a few case reports [Steen 2005] and animal studies [Ikeno 2006] have indicated positive outcomes with these devices, two larger randomized trials using two different devices have revealed unchanged [Axelsson 2006] or even worsened [Hallstrom 2006] survival rates compared with manual CPR. Device design or implementation strategies therefore require further evaluation.

1.7.3 Early defibrillation

The only effective treatment for VF is defibrillation as VF in man hardly ever is self-terminating. Defibrillation interrupts the uncoordinated depolarisation-repolarisation process that occurs during VF [Anonymous 2005a]. If not too much time has passed from collapse, the normal pacemaker cells will then resume their function and produce an effective rhythm and restore adequate circulation.

Early defibrillation has been shown to improve survival after OHCA by several authors [Stiell 1999, Valenzuela 2000, Holmberg 2000, Page 2000] with survival numbers as high as 74% in witnessed patients defibrillated within 3 minutes after arrest in casinos [Valenzuela 2000]. For every minute without CPR or defibrillation in witnessed VF, the probability of survival to hospital discharge decreases by about 10% [Valenzuela 1997, Waalewijn 2001]. Hardly any patients survive if CPR or defibrillation is not attempted within 15 minutes after the collapse.

1.7.4 Early advanced cardiac life support

Early ACLS stands for advanced airway management (endotracheal intubation) and intravenous drug therapy. There is, however, considerable controversy regarding the use of drugs in this context. The administration of for example adrenaline during resuscitation of

OHCA has been used for decades although several observational studies during the end of the last decade have failed to demonstrate differences in survival rates with the use of adrenaline in this setting [Mitchell 1997, Rainer 1997, Mitchell 2000]. Adrenaline, however, is still recommended in the most recent guidelines for ACLS [Anonymous 2005b] even though the same guidelines acknowledge that there are no placebo-controlled studies showing that the routine use of any vasopressor at any stage during the management of OHCA increases survival. Nor has any anti-arrhythmic drug given during OHCA resuscitation been shown to increase survival, even though amiodarone has been shown to increase survival to hospital admission [Kudenchuck 1999, Dorian 2002]. More recently, Stiell and co-workers confirmed that the addition of advanced-life-support interventions did not improve the rate of survival after OHCA in a previously optimized EMS system of rapid defibrillation [Stiell 2004]. They recommend that in order to save lives, health care planners should make CPR by citizens and rapid-defibrillation responses a priority for the resources of EMS systems. Moreover, a recent literature review, comparing basic life support (BLS) to ACLS, demonstrated that in cardiac arrest studies, ACLS does not provide additional benefits over BLS and defibrillation care [Isenberg 2005]. Further studies are needed to prove the superiority of ACLS to BLS.

1.7.5 Early post-resuscitation care

Historically, few studies have focused on in-hospital mortality after OHCA and only a handful have managed to demonstrate in-hospital factors as having a direct effect on survival. However, during the last few years greater attention has been directed towards the post-resuscitation phase of OHCA. This fifth phase in the "chain-of-survival" concept addresses different aspects of the treatment of the successfully resuscitated patient. Following the publication of two investigations that demonstrated improved neurological outcome in comatose survivors after VF with therapeutic mild hypothermia [Bernard 2002, Anonymous 2002b] this treatment has become implemented in clinical practice. Other in-hospital factors found to be associated with (poor) survival are high body temperature, elevation of blood glucose, acidosis, seizures [Langhelle 2003], high age, long delay before sustained return of spontaneous circulation, elevated potassium concentration and low use of beta-blocking agents [Skrifvars 2003]. Therapeutic possibilities can be divided into 4 groups [Herlitz 2006]:
1) Optimising physiology (body temperature, blood pressure, blood glucose, acid-base status, electrolytes).
2) Revascularisation (thrombolysis, PCI, CABG).
3) Antiarrhythmic therapy (ICD, beta-blocking agents, amiodarone).
4) Anticonvulsant therapy.

1.8 Survival after OHCA

Reported survival after OHCA has varied considerably. To some extent this is related to the type of cardiac arrest population. Most of cardiac arrest studies have reported on OHCA from cardiac causes only, some have studied all OHCA while others have reported on witnessed and/or on VF arrests only. Also, differences in survival may be due to differences in EMS activation and threshold for care (i.e. guidelines for when to start or not start

Table 1.3 Studies with data on survival among patients with OHCA

Location of study (year of publication)	No. of OHCA	All-rhythm incidence	All-rhythm survival (%)	VF OHCA survival (%)
Milwaukee County, USA (1989) [Stueven]	4216	44.9	12.6	21.9
Chicago, USA (1993) [Becker]	6451	119.5	1.8	3.3
Houston, USA (1993) [Pepe]	2404	63.3	8.0	15.4
New York, USA (1994) [Lombardi]	2329	63.5	2.2	6.5
San Francisco, USA (1996) [Callaham]	544	81.4	5.9	14.6
King County, USA (2001) [Eisenberg]	5222	48.2	16.0	30.0
Miami-Dade County, USA (2002) [Myerburg]	738	17.0	6.9	13.7
Alachua County, FL, USA (2003) [Layon]	145	68.6	4.1	5.7
Rochester, NY, USA (2007) [Fairbanks]	539	-	6.9	10.3
Stockholm, Sweden (1978) [Erhardt]	319	-	3.8	-
Stockholm, Sweden (1987) [Jakobsson]	307	119.5	3.6	6.4
West Yorkshire, UK (1990) [Wright]	1196	20.4	5.4	14.0
Helsinki, Finland (1996) [Kuisma]	255	49.4	19.6	32.5
Vienna, Austria (1996) [Gaul]	249	16.5	10.8	20.5
St-Etienne, France (1996) [Giraud]	113	19.8	7.1	17.8
South Glamorgan, UK (1997) [Weston]	712	66.5	6.3	16.3
Bonn, Germany (1997) [Fischer]	464	48.3	16.0	26.7
Amsterdam, Netherlands (1998) [Waalewijn]	1046	37.1	12.8	-
Ljublijana, Slovenia (1998) [Tadel]	337	28.3	5.6	12.5
Copenhagen, Denmark (2000) [Rewers]	703	50.4	11.7	17.9
Göteborg, Sweden (2003) [Fredriksson]	3871	44.2	8.8	-
Katowice, Poland (2004) [Rudner]	147	43.5	10.2	-
Syndey, Australia (2006) [Cheung]	2011	52.6	12.6	-
Taipei, Taiwan (2007) [Ma]	1423	53.7	5.6	21.3

resuscitation). Thus, the large variation in populations makes direct comparisons between studies difficult to perform. A selection of OHCA studies is presented in Table 1.3, in which survival for all-rhythm OHCA ranged between 1.8% and 19.6%.

Long-term survival among patients who have undergone rapid defibrillation after OHCA is similar to that among age-, sex- and disease-matched patients without previous OHCA [Bunch 2003]. One recent study confirmed this finding and concluded that long-term survival after OHCA in a physician-staffed emergency system was comparable to survival after myocardial infarction with 46% of patients being alive after ten years [Holler 2007]. It also seems probable that the long-term outcome is somewhat better if the CA occured in connection with acute myocardial infarction compared with OHCA due to other causes [Cobb 1975, Goldstein 1985, Kimman 1994].

Several studies have reported on the quality of life in OHCA survivors and found it to be favourable [Bunch 2003, Khan 2004]. New data confirm this and indicate that patients discharged from hospital after surviving OHCA have summary scores of quality of life not significantly different from the national norm, with signs of dementia being uncommon [Horsted 2007].

1.9 Automated external defibrillators and defibrillation outside hospital

In 1979, 24 years after the first recorded successful closed-chest human defibrillation, the first portable AED was developed with shocking electrodes on the abdomen and tongue and a simple algorithm to detect abnormal rhythms which automatically delivered defibrillation shocks if necessary [Cooper 2006]. Placement of AEDs in public places was recommended by the American Heart Association in the early 1990s [Weisfeldt 1995]. In Sweden, as late as in the first years of the 21st century, no other group besides health care personnel and ambulance personnel performed defibrillation. Automated external defibrillators are today small and portable devices (weighing only a few kilos) with the capacity to instruct the user to perform defibrillation or CPR when appropriate via voice prompts (based on the rhythm registered). AEDs interpret short segments of the rhythm measuring frequency, slope, shape and amplitude of the wave forms. The algorithms used to define shockable rhythms have been continuously refined. Specificity (the true exclusion of VF) has been found to be very high almost reaching 100%, while sensitivity is somewhat lower, in most analyses between 90-95% [Macdonald 2001, Ko 2005]. Modern AEDs have the capability to capture data such as ECG, blood pressure and time intervals.

Some strategies to increase survival after OHCA involve the spread of the concept of defibrillation beyond conventional EMS and ambulances crews also to non-medical persons. Hence, three types of groups can be identified:

1) Untrained lay rescuers using public access defibrillation (PAD).
2) Trained lay people using PAD.
3) First responders via (theoretically) simultaneous paired dispatches from central dispatch centres.

Only a few studies have reported on untrained lay rescuers with promising results on survival [Whitfield 2005]. Others have shown improved survival with the use of trained lay rescuers as in the PAD-trail [Hallstrom 2004], defibrillation in casinos [Valenzuela 2000] and in airplanes [Page 2000]. Most reports, however, have used first responders for intervention.

First responder AED programs have varied regarding the type of *intervention*, type of *control* and CA *population*. Most first responder AED programs have used police officers as first responders [White 1998, Mosesso 1998, Groh 2001, Myerburg 2002, Capucci 2002], some have used both police and fire departments simultaneously [van Alem 2003, White 2005, Sayre 2005] and a few have used fire departments as the sole first responder [Stiell 1999, Smith 2002]. Most AED studies have used historical controls for comparisons, whereas more recent investigators have leaned towards comparing first responder cases with concurrent EMS. Also, study populations have varied. Most authors have included all OHCA [Mosesso 1998, Stiell 1999, Groh 2001, Myerburg 2002, Smith 2002, Capucci 2002] while others have reported only on witnessed arrests [van Alem 2003], VF arrests [White 1998, White 2005] or OHCA with cardiac etiology only [Sayre 2005]. These large variations and combinations of these three important parameters make direct comparisons between studies difficult. The most important first responder studies are summarized in Table 1.4.

Table 1.4 First responder studies

Authors *Journal* (Year)	Country	Time period	No. of patients (intervention)	Population	Main control-group	Type of first responder	Main findings / Conclusions
Mosesso et al. *Ann Emerg Med* (1998)	USA	1992-1995	317	All OHCA	Historical controls	Police	Police first on scene in 59% of cases. Shorter time intervals and non-significant increase (14% vs. 6%) in VF-group. AED use was an independent predictor of survival.
Stiell et al. *JAMA* (1999)	Canada	1994-1999	1641	All OHCA	Historical controls	Fire dept, new routines etc.	Significant improved survival (5.2% vs. 3.9%) compared to historical controls. Improved time intervals.
Groh et al. *Acad Emerg Med* (2001)	USA	1995-1999	388	All OHCA	Historical controls	Police	Police first on scene in only 6.7% of cases. Non-significant increase in survival despite shorter time intervals.
Myerburg et al. *Circulation* (2002)	USA	1999-2001	420	All OHCA	Historical controls	Police	Police first on scene in 56% of cases. Significant increase in VF-group (17%) compared to historical VF EMS-group (9%) but not in overall survival (7.6% vs. 6.0%).
Smith et al. *Med J of Australia* (2002)	Australia	2000-2001	420	All OHCA	EMS	Fire dept.	Fire department provided defibrillation in 26.5%. No difference in survival between patients treated by fire dept. and EMS-service.
Capucci et al. *Circulation* (2002)	Italy	1999-2001	354	All OHCA	EMS	Police, lay staffed ambulances and PAD.	Experimental group treated 40% of cases. Shorter time intervals and tripled survival in experimental group compared with EMS (10.5% vs. 3.3%).
van Alem et al. *BMJ* (2003)	Holland	2000-2002	243	Witnessed OHCA only	EMS	Police and Fire dept.	Trend towards increased survival (18% vs. 15%; NS) in experimental areas. Higher proportion of patients with ROSC, admittance to hospital, shorter time delays.
White et al. *Resuscitation* (2005)	USA	1990-2003	193	VF OHCA only	EMS Historical controls	Police and Fire dept. (since 1998)	Police/Fire dept. first in 52% of cases. High survival in police/fire dept. group (43%) and in EMS-group (40%). Difference non-significant.
Sayre et al. *Resuscitation* (2005)	USA	1997-1999	154	Cardiac etiology OHCA only	EMS	Police (Fire dept. already with AEDs)	Police first on scene in 9.1%, fire department almost always first. Non-significant increase in survival in interventional group (7.1% vs. 3.8%).

1.10 Rationale for this thesis

In Göteborg, mass medial campaigns about heart disease, symptoms and cardiac arrest were performed during the 1980s and 1990s. Interest in the issue of OHCA in Göteborg was re-inforced by the development of local research groups and the establishment of the Swedish Cardiac Arrest Register which, as a consequence, has led to several important reports on OHCA. The last study on OHCA in Stockholm was published in 1989 [Jakobsson 1989] despite major advances in both pre-hospital interventions, primary and secondary prevention of coronary heart disease and rapid advances in the hospital treatment including catheter-based revascularization and implantable cardioverter-defibrillators. This thesis therefore analyses the epidemiology, patient characteristics, pre-hospital time intervals, rhythms, in-hospital treatment and survival of patients suffering OHCA. Furthermore, to address the unsatisfactory situation of low survival numbers following OHCA in Stockholm, as confirmed in studies I and II, a dual dispatch early defibrillation project entitled SALSA (SAving Lives in the Stockholm Area) was designed and evaluated.

2. AIMS OF THE THESIS

- To evaluate survival after OHCA in Stockholm and Göteborg, and to analyse any differences in mortality by comparing pre-hospital and in-hospital factors as well as patients characteristics (I, II).

- To explore the temporal trends of survival after OHCA in Sweden with regard to factors mainly related to the pre-hospital phase and resuscitation (III).

- To explore whether an intervention with the use of trained fire-fighters and security officers equipped with AEDs as a parallel resource to the existing EMS organisation could decrease response-times after OHCA and whether this could lead to a higher proportion of patients found in shockable rhythms and to more patients surviving OHCA in Stockholm (IV).

- To describe patient characteristics and factors affecting survival in patients with OHCA in Stockholm and Sweden (I, II, III, IV).

3. METHODS AND PATIENTS

The majority of data in this thesis is based on patient material collected by the Swedish Cardiac Arrest Register, SCAR (I, II, III, IV). Missing or uncertain data concerning survival were checked with the Swedish National Register of Deaths (I, II, III, IV). Other data were obtained from medical records including laboratory results and ECGs from patients admitted alive to hospital as well as from death certificates (II). Time measurements were obtained from the emergency dispatch centre (EDC) and defibrillators (IV). For study IV special forms were developed for completion by the fire-fighters and security officers. All data from Stockholm in study IV were manually double checked by the investigators.

3.1 Description of dispatch centre and EMS system

SOS Alarm (central emergency dispatch centre) receives all emergency telephone calls in Sweden. Every day, 18 geographically well-spread EDCs respond to about 10,000 calls from around the country which has 9 million inhabitants. The organization employs about 600 emergency medical dispatchers. The EDC in Stockholm collaborates with all 43 fire stations and all 55 ambulances. The EDC has 113 medical dispatchers and annually receives about 190,000 emergency calls, of which approximately 1,000 concern OHCA.

The EMS (ambulance) organizations in Stockholm and Göteborg work according to a two-tier system, i.e. for each call judged as a CA one mobile coronary care unit (if available), as well as an ambulance are dispatched. During studies I, II and III ambulances did not generally carry nurses but were equipped with specialized ambulance personnel trained in basic CPR and the use of defibrillators. During study IV a large proportion of ambulances did carry nurses. The educational programme for the ambulance personnel is the same in both cities. Mobile coronary care units in both cities carry a registered nurse trained in anaesthesiology with additional courses in advanced cardiac life support. All ambulances (and mobile coronary care unit when in use) have been equipped with defibrillators since the 1980s. The ambulances in Stockholm and Göteborg are stationed throughout the two cities and not predominantly at the hospitals. The pre-hospital (ambulance) pharmacological treatments do not differ between Göteborg and Stockholm or other parts of Sweden.

3.2 Swedish OHCA Register

The SCAR is a joint venture between the Federation of Leaders in Swedish Ambulance and Emergency Services and the Swedish Council for Cardiopulmonary Resuscitation. Since 1993 the register is funded by the Swedish National Board of Health and Welfare. This voluntary register was started in 1990 and covers some 70% of the population in Sweden which amounts to 9 million. Larger cities (including all major cities) as well as sparsely populated areas are represented in the register that has a geographical distribution covering the vast majority of Sweden. The ambulance organizations not reporting to the register are not different in terms of education or guidelines.

For each case of OHCA the ambulance crews (mostly two persons) completed a form with relevant information such as age, place of arrest, bystander CPR (a bystander is defined as someone starting CPR before the arrival of the first ambulance, regardless of profession), witnesses, resuscitation procedure, probable cause of arrest, intervention times, defibrillation, intubation, drug treatment, type of initial rhythm, and clinical findings at first contact. To estimate the time of cardiac arrest in witnessed cases, the ambulance crews were instructed to interview bystanders about the delay from arrest to call. It was stressed in written instructions that a maximum effort was to be made to obtain these times. The ambulance crew also classified the probable cause of the arrest by nine different diagnostic categories (heart disease, lung disease, trauma, drug overdose, suicide, drowning, suffocation, sudden infant death syndrome and other) based on clinical assessment and bystander information. Their diagnosis was accepted for the present investigations and no further control was made among initial survivors during hospitalization with an exception in study II. It was emphasized in written instructions to the ambulance personnel to extract as much information as possible from relatives and witnesses about what had happened before the CA (chest pain? sudden tachypnea? sudden headache?). In ambulances with manual defibrillators, the first recorded rhythm was defined either as VF, PEA or asystole. For AEDs, the rhythm was defined as shockable or non-shockable.

The forms were completed during and immediately after the acute event. Each form was sent to the medical director with a copy to SCAR in Göteborg. Another copy was subsequently sent with additional information about whether the patient was dead or alive after one month. Any uncertainty about survival was checked with the National Register of Deaths. All data were computerized at a database in Göteborg and later in a database in Stockholm.

3.3 Description of intervention and study design of the SALSA-project

Study I and study II in this thesis demonstrated markedly low survival rates following OHCA in Stockholm. To address this unsatisfactory situation the SAving Lives in the Stockholm Area (SALSA) project was designed (Study IV). Prior to 2005 no other group besides health care personnel and ambulance personnel performed defibrillation in Stockholm. With the introduction of the SALSA-project, all 43 fire stations in the Stockholm area were equipped with AEDs. Fire-fighters received an 8-hour course approved by The National Board of Health and Welfare in the use of AED and D-CPR (Defibrillator - Cardio Pulmonary Resuscitation). Fire brigades had a crew of 2-5 fire-fighters during assignments. Simultaneously, 65 public venues (including larger malls, stations for public transportation, sport stadiums and two major airports) were equipped with AEDs and their local security guards were trained in the use of AEDs and D-CPR.

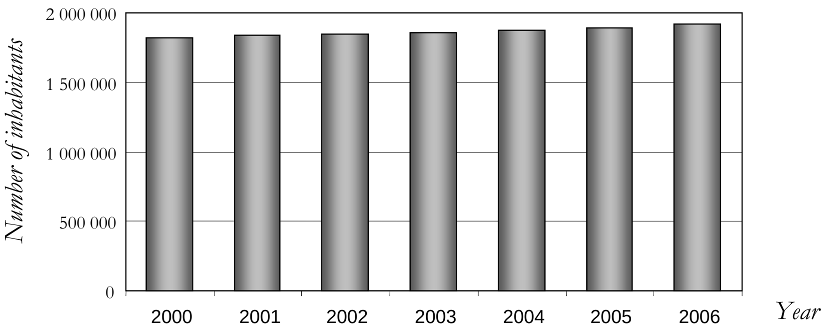
At the EDC in Stockholm a structured policy was applied as to when the fire-fighters were to be dispatched. In cases of suspected cardiac arrests, the EDC alerted the nearest available ambulance/emergency vehicle first and thereafter contacted the closest available fire engine via a special unit at the EDC using a computer-mediated alarm code. The fire brigade dispatch was intended to happen simultaneously with the EMS dispatch. The first rescuer to arrive at the victim's side was responsible for performing a quick medical assessment. If the patient was unresponsive and pulseless, CPR was started and the AED was attached. The EMS worked in the same manner as prior to the SALSA-project and took over the full responsibility for the treatment as soon as they reached the patient regardless of weather the fire-fighters where there before or not. Security guards at the public venues were not alerted from the EDC, but instead via local alarm logistics developed at respective location.

Study IV describes the PILOT part of the SALSA-project. The primary outcome measures were time intervals from call for assistance at the EDC to the time of arrival of first responder (fire brigade or ambulance) and the proportion of OHCA cases to which fire-fighters arrived first. The secondary outcome measures were time intervals from call to first defibrillatory shock for patients in VF, the proportion of patients found in VF, survival to hospital admission, survival to one month and an evaluation of dispatch logistics. This trial is a prospective cohort study and therefore not randomized, primarily for ethical considerations. Results are presented according to the Utstein-template [Cummins 1991b].

3.4 Patients

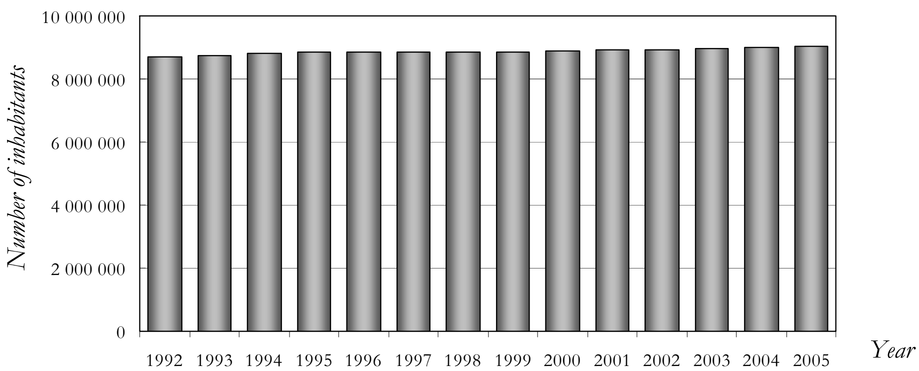
Every patient suffering from OHCA to whom an ambulance is called is included in SCAR with the exception of patients who had obviously been dead for a long time and whose bodies are therefore not taken to hospital by the ambulance crew. Only cases where any type of resuscitation measure (airway assistance, chest compressions, administration of drugs, intubation and defibrillation) was started were included in any of the studies. Patients were enrolled regardless of cause of arrest or age with the exception of study IV in which traumatic OHCA and patients ≤ 8 years old were excluded. In-hospital cardiac arrests were not included in the present investigations. Patients admitted alive were defined as patients admitted alive from an Emergency Department to a hospital ward and who, accordingly, had not been declared dead in the Emergency Rooms. A crew-witnessed cardiac arrest was defined as a cardiac arrest that occurred after the arrival of the ambulance crew.

Figure 3.1 Population in Stockholm over time



Most of the patient material in this thesis is based on the population in the county of Stockholm. Stockholm is the capital of Sweden and is also the largest city in the country. Since the year of 2000, an increase in population has occurred (Figure 3.1). In studies I and II comparisons with the population of the municipality of Göteborg were performed, which on December 31, 2000 had a population of 466,990 inhabitants with a population density of 1,036 inhabitants/square kilometres compared with a population of 1,823,210 inhabitants

Figure 3.2 Population in Sweden from 1992 to 2005



with a population density of 280 inhabitants/square kilometres in Stockholm. Göteborg is the second largest city in Sweden. The proportion of men in both Stockholm and Göteborg was just below 50% during studies I and II. In study III, all patients suffering from OHCA in Sweden in whom CPR was attempted between 1992-2005 were included. The change in population size in Sweden is described in Figure 3.2. In the preparations for study IV, a geographic pre-study was performed to determine the sites of OHCA in Stockholm. All OHCA from June, 2003 to June, 2004 were positioned on a map and assigned with a black dot as shown in Figure 3.3.

3.5 Ethics

The Ethics Committee at the University of Göteborg approved the protocols for Study I, II and III following regular applications. The Ethics Committee at the Karolinska Institutet approved the protocols for Study IV following regular application.

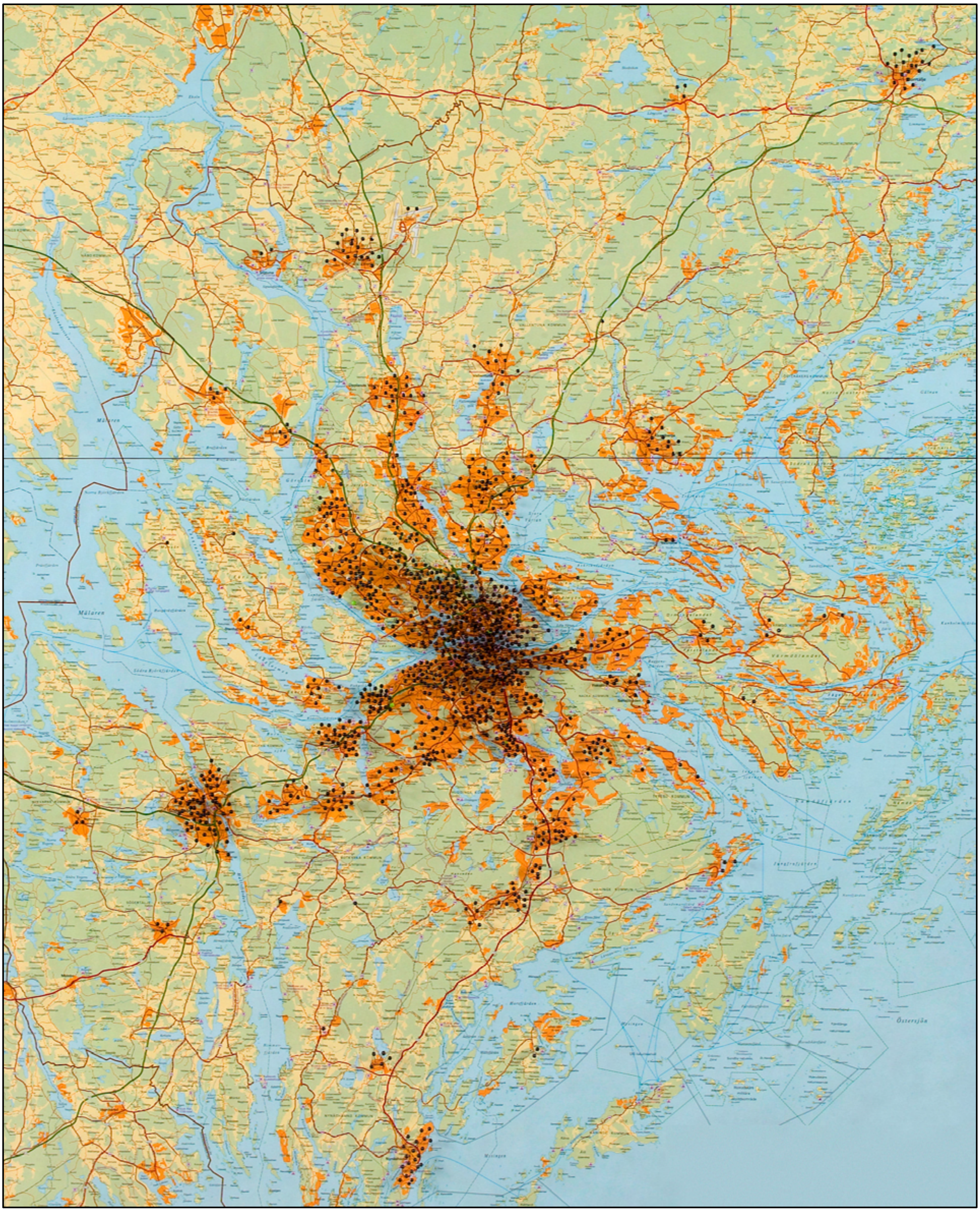
3.6 Statistical methods

A summary of chosen statistical methods is presented in Table 3.1. For further details regarding statistical methods, see respective study. All p-values are two-tailed and considered significant if below 0.05.

Table 3.1 Statistical analyses used in Study I-IV in the thesis

	Study I	Study II	Study III	Study IV
COMPARISONS BETWEEN TWO GROUPS:				
Dichotomous variables:				
Fisher's exact test	X	X		X
Continuous variables:				
Fisher's non-parametric permutation test	X	X		
Wilcoxon rank-sum test				X
MULTIVARIATE ANALYSIS TO STUDY ASSOCIATIONS BETWEEN VARIABLES AND ADJUST FOR CONFOUNDERS:				
Logistic regression	X	X	X	X
TREND TESTS:				
Dichotomous variables:				
Mann-Whitney U test			X	
Continuous variables:				
Spearman's rank statistic			X	

Figure 3.3 A map of the county of Stockholm with all OHCA occurring during one year



1 black dot = 1 OHCA. Urban areas in orange.

4. RESULTS

4.1 Study I: Difference in survival after OHCA between Stockholm and Göteborg

All cases of OHCA in Stockholm and Göteborg between January 1, 2000 and June 30, 2001 were included. There were 969 OHCA in Stockholm and 398 in Göteborg. The two groups were similar in terms of age, gender and various factors at resuscitation with exception of VF on initial ECG, which was more common in Göteborg (Table 4.1).

Table 4.1 Main results from Study I showing differences in time intervals and survival

	Stockholm	Göteborg	P-value
Age (years, mean)	67.7	68.2	NS
Gender, male (%)	70	69	NS
Witnessed arrest by bystanders (%)	54	57	NS
Witnessed arrest by ambulance crew (%)	11	13	NS
Cardiac arrest at home (%)	60	59	NS
CPR started prior to arrival of ambulance (%)	36	34	NS
VF on initial ECG (%)	18	31	<0.0001
Time intervals (median, min):			
Cardiac arrest to call	5.0	3.0	0.002
Call to arrival of ambulance	7.0	5.0	<0.0001
Call to first defibrillation (VF only)	10.0	6.0	<0.0001
Survival to 1 month (%)	2.5	6.8	0.0008
Survival to 1 month, bystander-witnessed (%)	2.9	9.2	0.016

p-values denoted only if < 0.1. NS = non significant.

The time intervals were generally longer in Stockholm. Almost 55% of victims in Göteborg were reached by an ambulance within 5 min after call versus 20% in Stockholm (Figure 4.1) and less than 5% of patients found with VF in Stockholm were defibrillated <5 min after call versus 40% in Göteborg (Figure 4.2). The number of ambulances per million inhabitants differed between the two cities. During the daytime (7 am-10 pm), Stockholm had on average 31 ambulances per million inhabitants, versus 41 in Göteborg. During night (10 pm-7 am), Stockholm had 19 ambulances per million inhabitants, whereas Göteborg had 30.

Figure 4.1 Cumulative percentage of patients reached by the ambulance within various time intervals after call for an ambulance.

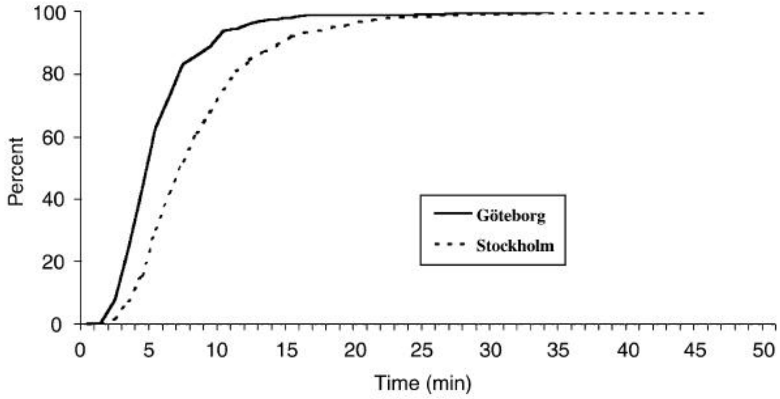
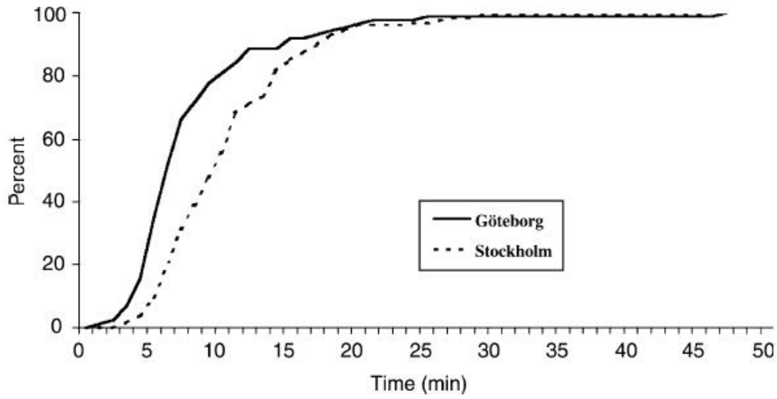


Figure 4.2 Cumulative percentage of patients found in VF who were defibrillated within various time intervals after call for an ambulance.



In Stockholm, 2.5% of OHCA patients survived to 1 month, versus 6.8% in Göteborg (p=0.0008). In a multivariate analysis, only VF on initial ECG appeared as an independent predictor for an increased chance of survival (odds ratio 15.0; 95% CI 5.3–53.3).

4.2 Study II: An evaluation of post-resuscitation care as a possible explanation of a difference in survival after OHCA

Study I thus revealed a large difference in survival between the two largest cities in Sweden. In study II, we wanted to evaluate the relative contribution of *pre-hospital factors*, *co-morbidity* and *patient characteristics* among admitted patients and *in-hospital treatment* to the difference in survival. In order to include more patients, the study period was extended with 12 months. All patients with OHCA between January 1, 2000 and June 30, 2002 were included, regardless of cause of arrest or age.

In all, 1,542 OHCA in Stockholm and 546 OHCA in Göteborg occurred during the study period. 16% of patients with OHCA were admitted alive in Stockholm in contrast to 28% in Göteborg ($p<0.0001$). The two groups of admitted patients were found to be similar in terms of age, sex and medical history prior to the index event. Almost identical percentages of smokers and chronic alcoholics were observed. Furthermore, the use of long-term medication at the time of CA was similar in the two groups.

Several pre-hospital differences were observed in this investigation. Almost all important pre-hospital time intervals were significantly longer in Stockholm, both when comparing all patients or those admitted to hospital only. Sixty-two percent of all victims in Göteborg were reached by an ambulance within 5 min after call versus 29% in Stockholm ($p<0.0001$). VF as the initial rhythm registered was more frequently encountered in Göteborg (29% versus 19%, $p<0.0001$). The majority of CA in both cities occurred at home and during day-time. Furthermore, the two groups were similar in terms of the proportion of witnessed arrests.

Table 4.2 Results from Study II focusing on in-hospital interventions and survival

	Stockholm	Göteborg	P-value
Intervention/Investigation, admitted pat. only			
Thrombolysis (%)	7	5	NS
Coronary angiography (%)	12	16	NS
PCI (%)	7	10	NS
CABG (%)	2	3	NS
Echocardiography (%)	33	38	NS
Exercise stress test (%)	5	3	NS
Electrophysiological testing (%)	2	3	NS
ICD (%)	3	4	NS
Time intervals (median, min):			
Call to arrival of ambulance, all patients	7.0	5.0	<0.0001
Call to arrival of ambulance, admitted pat. only	7.0	4.0	NS
In-hospital mortality (%)	80	78	NS
1-month survival, all patients (%)	3.3	6.1	0.01

p-values denoted only if < 0.1. NS = non significant.

No significant in-hospital differences were found between the two groups regarding acute investigations such as coronary angiography and echocardiography or acute interventions such as thrombolysis, percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) (Table 4.2). When comparing only patients with good cerebral performance or moderate cerebral disability (CPC 1-2), the proportion of patients undergoing acute interventions was evidently higher, but the absence of differences between the two cities remained.

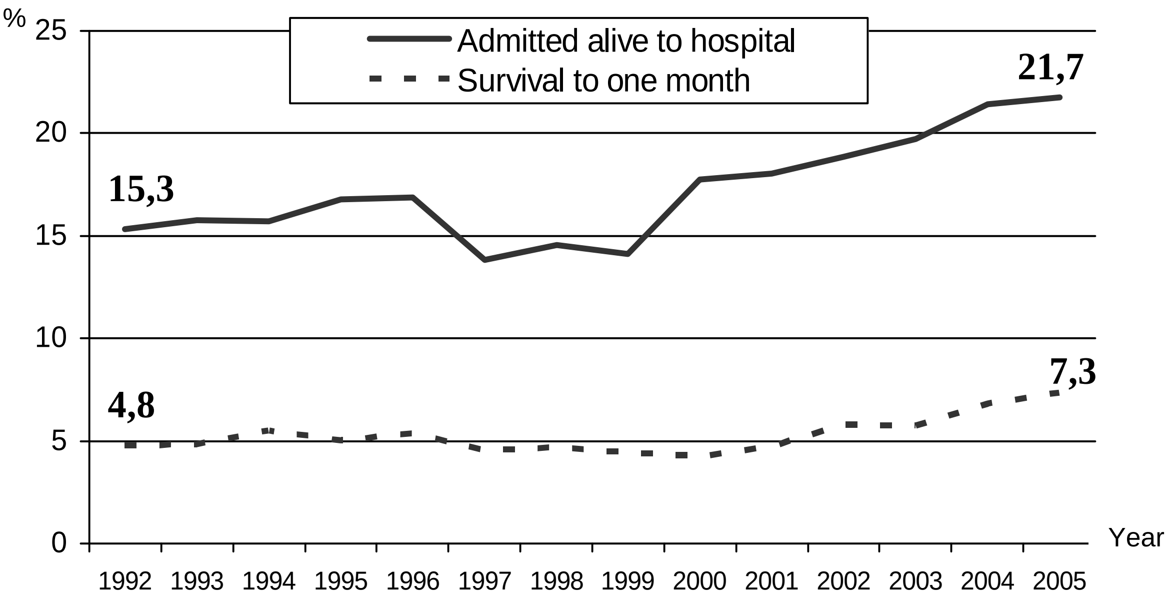
Total survival to discharge after OHCA during the study period was 6.1% in Göteborg and 3.3% in Stockholm (p=0.01). The significant difference in survival remained at a 3-year follow up: 5.5% versus 2.3% (p=0.0007). Of the patients admitted alive to hospital, 20% survived to discharge in Stockholm versus 22% in Göteborg (NS).

4.3 Study III: Improved survival after OHCA in Sweden between 1992 and 2005

To describe temporal trends in 1-month survival after OHCA in Sweden, 38,646 patients between 1992-2005 were included in this study. The proportion of patients receiving bystander CPR prior to arrival of the ambulance (crew-witnessed cases excluded) increased significantly from 31% in 1992 to 50% in 2005 (p for trend<0.0001). A significant increase in the proportion of witnessed OHCA was observed (p for trend<0.0001) which, in turn, was due to an increase in crew-witnessed cases from 9% in 1992 to 15% in 2005. A decrease in patients presenting with VF as the first recorded rhythm from 33% in 1992 to 26% in 2005 (p for trend<0.0001) was noted. Most CA occurred at home and their proportion did not change during the study period. The proportion of patients with a presumed cardiac cause declined from 73% in 1992 to 63% in 2005 (p for trend<0.0001). The time interval from call to arrival of ambulance (median) increased from 6 minutes in 1992 to 8 minutes in 2005 (p for trend<0.0001). There was a similar increase during both day and night.

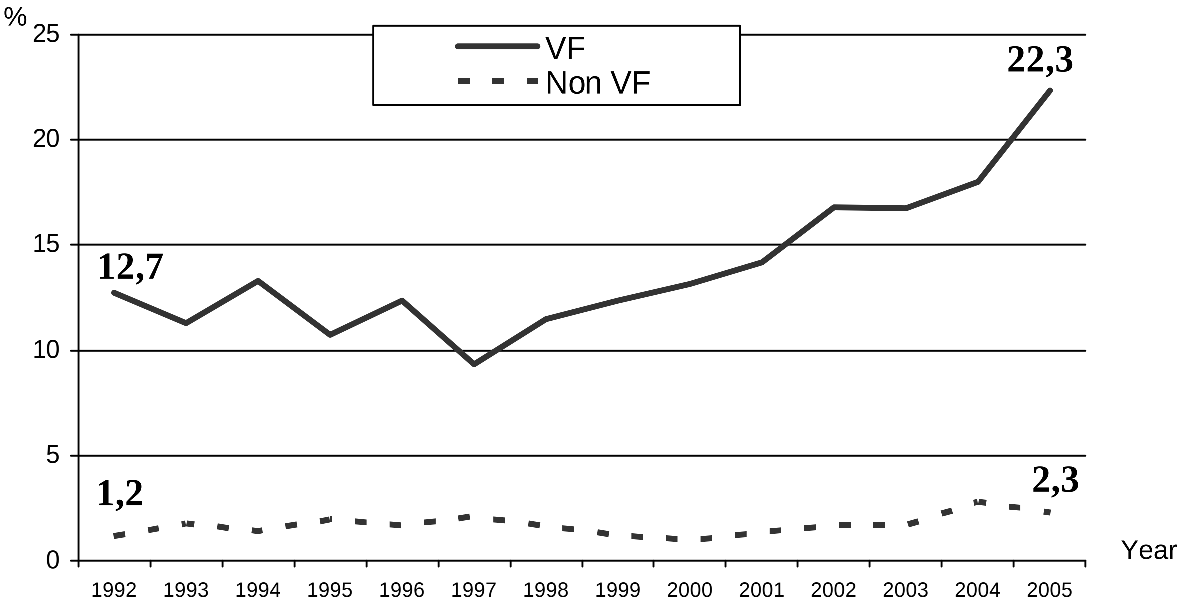
There was an increase in the proportion of patients who were admitted alive to hospital from 15.3% in 1992 to 21.7% in 2005 (p for trend<0.0001). The corresponding figures for the proportion of patients alive after one month rose from 4.8% to 7.3% (p for trend<0.0001; Figure 4.3). The increase in survival to one month was particularly marked among

Figure 4.3 Admission to hospital and survival to one month



patients who hade been found in a shockable rhythm (increase from 12.7% to 22.3%; p for trend<0.0001; Figure 4.4). In-hospital survival did not increase significantly during the investigation, ranging from 32.6% in 1992 to 34.8% in 2005. (NS).

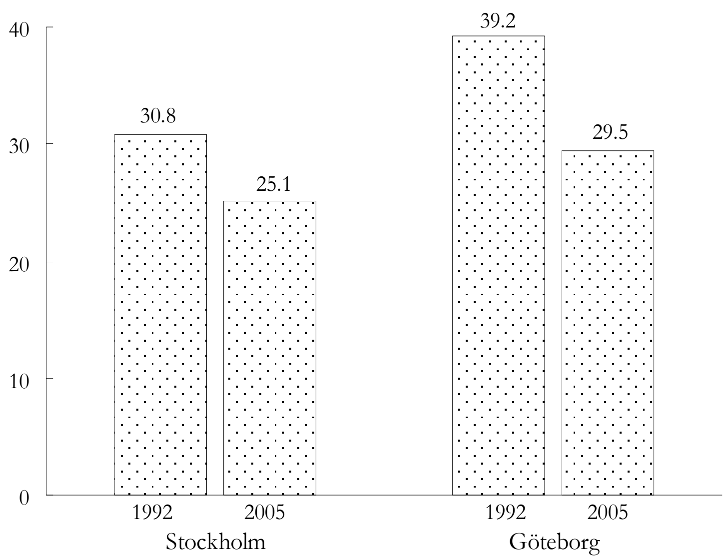
Figure 4.4 Survival in relation to VF



The year of OHCA (i.e. as estimate of time) remained significantly associated with 1-month survival after adjustment for potential baseline risk factors. The factor which had the largest impact on the estimate of time regarding the increase in survival was crew-witnessed OHCA. Bystander CPR also affected the estimate of time in the same direction, although to a lesser extent. When excluding crew-witnessed cases, the factor with the largest corresponding impact was bystander CPR. Thus, out of eight baseline characteristic factors studied, two appeared to contribute to the increase in 1-month survival over time, i.e. crew-witnessed cases and, to a lesser degree, bystander CPR.

A noteworthy observation was that from 1992 to 2005, the number of ambulances per million inhabitants decreased significantly by 19% in Stockholm and 25% in Göteborg, respectively (Figure 4.5).

Figure 4.5 Number of ambulances per million inhabitants

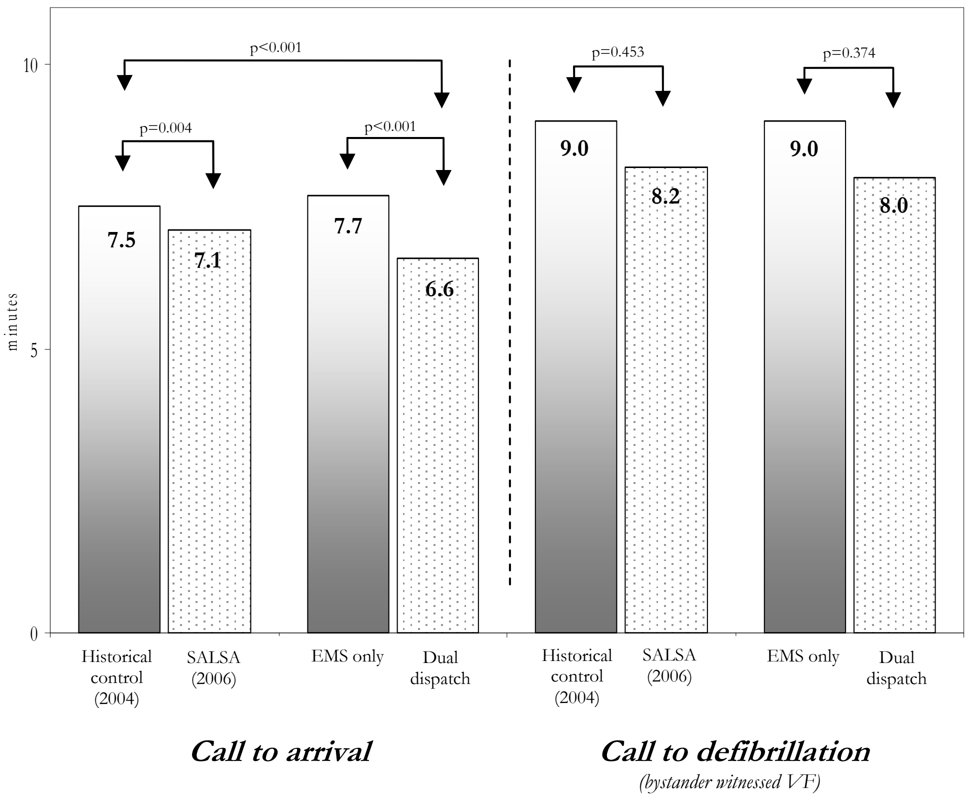


4.4 Study IV: Dual dispatch early defibrillation program in OHCA – the SALSA-project

To address the unsatisfactory situation with low survival rates following OHCA in Stockholm that were observed in studies I and II, a dual dispatch early defibrillation project (SALSA) was designed (see page 27). All adult patients suffering an OHCA in the Stockholm area from December 1, 2005, to December 31, 2006, were included resulting in 863 cases. A control group of all 657 cases in Stockholm from 2004 were included to serve as historical controls.

Of dual dispatches, the fire-fighters assisted with CPR in 94% of all cases and arrived first on scene and initiated treatment in 36% of cases. EMS arrived before the fire department in 50% and they arrived simultaneously in 14%. No fire brigade dispatch had to be recalled for other assignments. Baseline characteristics and demographic data did not differ notably between patients included in the interventional and historical parts of the study. The time interval from call to arrival of first responder decreased significantly but modestly from 7.5 minutes before the implementation of the SALSA-project to 7.1 minuets during the project (p=0.004). A more marked time difference from call to arrival was found when comparing cases with dual dispatch with those where the fire department was not dispatched (6.6 vs. 7.7 minutes respectively; p<0.001). Fire brigades were dispatched to only 66% of the treated CA (crew-witnessed cases excluded). For reasons regarding dispatch failure of fire brigades, see page 45.

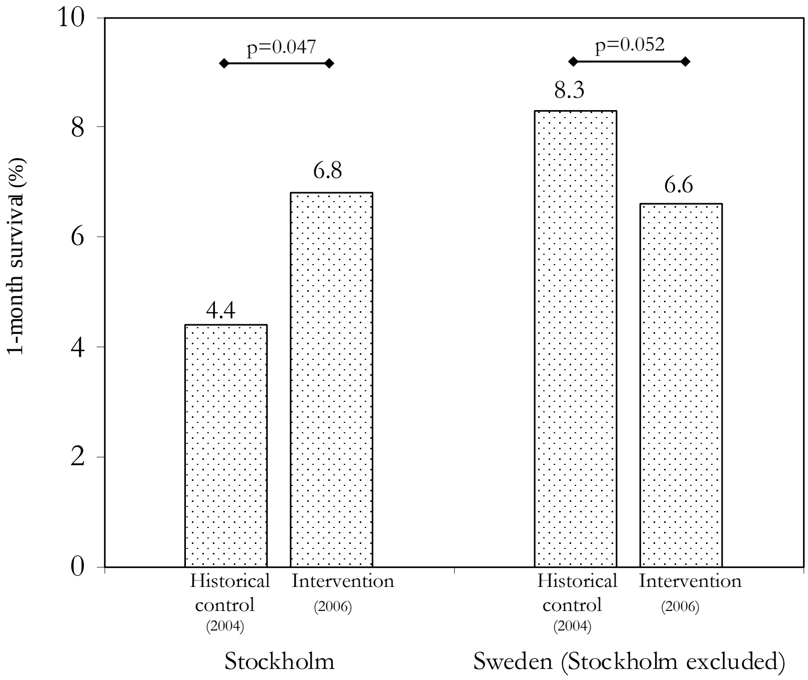
Figure 4.6 Time interval comparisons for first responders before and after implementation of SALSA and in relation to success or failure of dual dispatch



No major variation was observed in the time interval from call to defibrillation among patients presenting with VF as the first recorded rhythm in either comparisons between intervention and historical controls or between groups of first responder.

No increase in the proportion of patients admitted alive to hospital was observed with 22.3% of patients being admitted in 2004 and 22.7% during the intervention. However, the corresponding proportions of patients alive after 1 month rose significantly from 4.4% to 6.8% (p=0.047). The odds ratio (OR) for survival during the intervention (vs. historical control) was 1.6 (95% CI. 1.0-2.5). After adjustment for factors associated with survival the OR for survival remained at 1.6 (95% CI. 0.9-2.9) but the confidence interval widened. The difference in survival to 1 month was particularly marked among patients with witnessed cardiac arrests in whom an increase from 5.7% to 9.7% was observed (adjusted OR: 2.0; 95% C.I: 1.1-3.7). Data from SCAR show that survival after OHCA in Sweden (Stockholm patients excluded) declined from 8.3% to 6.6% during the same time period (unadjusted OR: 0.8; 95% CI: 0.6-1.0) (Figure 4.7).

Figure 4.7 Survival over time from 2004 to 2006 (2005 excluded)



Only three OHCA occurred at public venues that were equipped with AEDs. Two of these CA occurred at Stockholm international airport and the third case in a car on a highway north of Stockholm. None of these three cardiac arrests survived to hospital discharge.

5. DISCUSSION

Sudden OHCA is a leading cause of death in the Western World and is a condition that is generally associated with a poor prognosis. Previous reports have demonstrated low survival rates following OHCA in Sweden with less than 4% of patients surviving in the 1970s and 1980s [Erhardt 1978, Jakobsson 1987]. It is our hope that the results of these four studies will increase the knowledge about OHCA in general and to be of relevance for decision making in health-care management. Our data are, however, to a large extent observational and uncontrolled which has to be taken into account when drawing conclusions.

1. Are the patients included in the thesis representative of OHCA in Sweden?
Reported incidence numbers for OHCA vary widely. To some extent this is a consequence of the difficulty of defining OHCA. The studies in this thesis only include patients resuscitated by the emergency medical services (EMS) and may therefore underestimate the true incidence of OHCA in the population. Comparisons with other studies should, however, not be affected as most of these also only include EMS resuscitated patients.

2. Is the Swedish Cardiac Arrest Register reliable?
The Swedish Cardiac Arrest Register (SCAR) is a voluntary register that was started in 1990 and covers some 70% of the population in Sweden. Larger cities (including all major cities) as well as sparsely populated areas are represented in the register that has a geographical distribution covering most of Sweden. The ambulance organizations not reporting to the register do not differ in terms of education or guidelines. We can only speculate on to what extent SCAR is truly representative and reliable, but based on the above we consider it to be a fair representative of the OHCA population in Sweden. There are two points that should be stressed within the context of reliability. First, most studies based on registers have limitations in terms of potential bias such as lack of information on risk factors and absence of randomization. Data in registers may be biased by selection, incompletion (i.e. lack of information on some variables), recall and input error. Second, in a register of OHCA, the information gathered regarding several factors such as time intervals, witnessed status, symptoms may be somewhat unreliable due to the highly stressful nature of the situation in which information is obtained. Throughout the investigations included in the thesis, it was stressed in written instructions that a maximal effort was to be made to obtain the correct time intervals and to extract as much information as possible from relatives and witnesses.

3. Has survival after OHCA in Stockholm increased over time?

Previous reports have demonstrated low survival rates following OHCA in Stockholm with 3.8% of patients surviving in 1978 [Erhardt 1978] and 3.6% in 1987 [Jakobsson 1987]. Results from studies I and II furthermore show that survival in Stockholm after OHCA had not improved during the last two decades. According to the results of study IV, following the implementation of the dual dispatch early defibrillation program, a large relative survival increase was found compared to the older two studies as well as compared to 2004, with 6.8% of patients surviving during the SALSA-intervention. This survival number is thus high in a historical perspective and acceptable in a national perspective [Anonymous 2006] but still rather low in an international perspective [Rea 2004, Atwood 2005].

4. Is survival after OHCA similar in Stockholm and Göteborg?

According to the results of studies I and II, overall survival data after OHCA in Stockholm and Göteborg differ greatly. Study I showed that 1-month survival was almost three times higher in Göteborg than in Stockholm and study II demonstrated that 1-month survival in Göteborg was almost double that of Stockholm. Survival within different subgroups (i.e. VF OHCA, witnessed OHCA) differed in a corresponding manner with better results in Göteborg. Direct comparisons between Stockholm and Göteborg have not been reported previously. However, an investigation on CA in Göteborg from 1980 to 1990 demonstrated an overall survival rate of 7% [Ekström 1994], indicating that differences in survival between the two cities were present also during the 1980s. Data for Stockholm in 2006 (study IV) show that 6.8% of OHCA survived to 1 month and preliminary data for 2006 (unpublished results) indicate an overall survival rate of 7.4% in Göteborg, pointing to almost equalized survival rates.

5. What are the pre-hospital reasons for differences in survival between Stockholm and Göteborg?

The rather dramatic difference in survival after OHCA between two cities with similar rescue organizations demands explanation. Demographic data did not differ between the two cities as shown in study I and study II. All pre-hospital time intervals that were analysed were, however, longer in Stockholm. In Stockholm (study I), 18% of the patients were initially found in VF. This is low in comparison with both national and international reports [Cobb 2002, Rea 2003, Herlitz 2004]. VF as the first registered rhythm is one of the absolute strongest predictors for survival in OHCA [Holmberg 2000, Rewers 2000, Herlitz 2005a, Fridman 2007]. The observation that only half as many patients in Stockholm had a shockable rhythm on the first ECG recording than in Göteborg is likely to be due to the longer time intervals in Stockholm and may well explain the difference in survival. The strong association between short time intervals, VF and survival was demonstrated by Valenzuela and colleagues who showed that among witnessed OHCA patients defibrillated within 3 minutes after their arrest an impressive 74% survived to discharge [Valenzuela 2000]. For every minute without CPR or defibrillation in witnessed VF, it has been estimated that the probability of survival to discharge decreases by around 10% [Valenzuela 1997, Waalewijn 2001]. If CPR or defibrillation is not attempted within 15 minutes after collapse, hardly any patients survive. Other causes besides long time intervals, such as differences in patients selection and quality of CPR are other possible reasons that may affect survival. There were, however, no indications in studies I or II that this was the case.

6. Why are time intervals prior to treatment longer in Stockholm?

All important time intervals in studies I and II were longer in Stockholm. It is possible that the large difference in land area between Stockholm and Göteborg is important in this context. However, the percentage of arrests that occurred <10 km from an ambulance station was similar in both cities and differences in distances to the ambulance stations did not further appear to influence mortality data. Among several possible factors explaining the differences in time intervals the most probable is undoubtedly the higher ambulance density per capita in Göteborg. During the daytime in study I, Stockholm had on average 31 ambulances per million inhabitants versus 41 in Göteborg. Corresponding numbers during the night were 19 ambulances per million inhabitants in Stockholm versus 30 in Göteborg. Increase in traffic congestion in urban areas did, however, not contribute to the differences in time interval from call to arrival and survival, as these differences were similar during day and night. Finally, the difference in the estimated time from CA to call could perhaps be a consequence of a higher alertness to respond among the general population in Göteborg (due to mass medial campaigns about cardiac disease, CA and CPR that have been offered to large parts of the population in Göteborg in the 1990s), even if this hypothesis is not supported by any data.

7. Is the difference in survival after OHCA between Stockholm and Göteborg associated with pre-hospital factors only or with in-hospital factors or patient characteristics?

In study II, we evaluated the contribution of pre-hospital factors compared to the potential contribution of differences in co-morbidity and patient characteristics and/or in-hospital treatment, to the difference in survival between Stockholm and Göteborg.

Once again a large difference in survival was found to the advantage of Göteborg. The two groups of patients admitted alive were very similar in terms of age, sex, (previous) medical history and chronic medication prior to the index event. Patient characteristics were also similar to CA groups studied previously in Sweden. Smoking incidence or chronic alcoholism did not differ between the two cities. Moreover, no significant differences were found regarding patients subjected to acute or subacute investigations and interventions such as coronary angiography (including PCI), thrombolysis, echocardiography, exercise testing, electrophysiological testing, CABG or ICD-implantation following the index event. In-hospital survival did accordingly not differ. A logistic regression analysis indicated a lower in-hospital mortality in the Stockholm region after adjustment for independent predictors of survival. In spite of this, total mortality was significantly higher in Stockholm (once again in parallel with longer pre-hospital response intervals in Stockholm) indicating that pre-hospital factors played the predominant role for the difference in mortality.

Following two studies that demonstrated improved neurological outcome in comatose survivors after VF with therapeutic mild hypothermia [Bernard 2002, Anonymous 2002b] this has become implemented in clinical practice. Hypothermia was established in Stockholm and Göteborg after study I and II and was fully implemented prior to study IV. Other in-hospital factors found to be associated with (poor) survival are high body temperature, elevation of blood glucose, acidosis, seizures [Langhelle 2003], high age, long delay before sustained return of spontaneous circulation, elevated potassium concentration and low use of beta-blocking agents [Skrifvars 2003]. These analyses were, however, not available in our database. Our results neither support nor contradict the concept of the importance of the fifth phase in the "chain-of-survival" concept that addresses different aspects of the treatment of the successfully resuscitated patient. We do however, consider that the difference in survival after OHCA between Stockholm and Göteborg is associated with pre-hospital factors only, rather than with in-hospital factors or patient characteristics.

8. Why did overall OHCA survival in Stockholm not improve from 1978 to 2002?

We have no clear understanding or data explaining the fact that survival following OHCA in Stockholm was, if anything, worse in 2000-2002 (studies I and II) than in the 1970s and 1980s. Clearly, cardiac treatment such as anti-arrhythmic drugs, medical treatment for ischaemic heart disease (exemplified by aspirin, statins, ACE-inhibitors), ICDs and catheter-based or surgical revascularization has improved over the years. Also, the chain-of-survival concept has come into practice and all ambulances in Stockholm have been supplied with defibrillators. In contrast to a decrease (or absence of an increase) in survival following OHCA, survival in patients with AMI (without OHCA) has clearly improved since the mid 1990s [Anonymous 2005c], mainly believed to be an effect of the above mentioned treatments. This paradox may perhaps be explained by the fact that while prevention and in-hospital treatment have improved, pre-hospital time intervals in Stockholm remain long and have not decreased since the 1980s. In a study from 1989, the mean time interval from call to arrival of ambulance was 7.5 minutes [Jakobsson 1989], which may be compared with the 9 minutes found in study II. The long time intervals in Stockholm are to some extent explained by the fact that from 1992 to 2005 the number of ambulances per million inhabitants has decreased by 19%. An additional possible explanation includes the decline in the proportion of VF OHCA. This finding has also been observed by others [Kuisma 2001, Rea 2003, Bunch 2004, Polentini 2006, Kette 2007].

9. Has OHCA survival increased over time in Sweden?

Recent studies from the United States [Rea 2003, Fox 2004] and Europe [Moore 2006, Kette 2007] point to unchanged or slightly better survival rates after OHCA during the last two decades. The SCAR which was started in 1990 today includes survival data for around 50,000 OHCA patients. A previous report from 2003 based on the register [Herlitz 2005b] did not reveal any increase in survival after OHCA. In study III, however, we found a significant increase in survival after OHCA in Sweden over the last 14 years. This increase was particularly prominent during the last few years and mainly encountered among patients found in a shockable rhythm.

10. Why has OHCA survival increased over time in Sweden?

The increase in survival was observed in spite of the fact that important factors (pre-hospital time intervals, VF incidence, presumed cardiac cause) known to be associated with an increased chance of survival worsened over time. Nor did in-hospital survival increase significantly over time. Instead, the increase in survival is associated with a higher proportion of crew-witnessed cases and, to a lesser degree, an increase in bystander CPR.

A noteworthy increase in the proportion of crew-witnessed cardiac arrests was thus observed, rising from 8% in 1992 to 15% in 2005. Two probable reasons explaining this finding may be that patients and relatives over time have become more active to call to the emergency dispatcher for an ambulance after the onset of symptoms as well as the fact that ambulance personnel stay with the patient longer on scene. Previous investigations have shown that the large majority of patients suffering from OHCA do have symptoms prior to the arrest [Vreede-Swagemakers 1997, Muller 2006]. Data from Sweden and USA point to unchanged time intervals between onset of symptoms and arrival at the Emergency Departments (ED) for patients suffering from AMI during the last 10 years [Anonymous 2005c, McGinn 2005]. At the same time, we know that more investigations and treatments such as tele-ECG and fibrinolysis have been transferred from the hospital to the pre-hospital arena [Morrison 2000, Svensson 2003] during the last decade indicating that ambulance personnel stay with the patient longer on scene. This together with unchanged time intervals between onset of symptoms and arrival at ED indicates that EMS is called upon earlier today, than previously. Increased proportions of patients surviving crew-witnessed cardiac arrest have been observed also by other groups [Pell 2006].

The considerable increase in the proportion of patients receiving bystander CPR prior to the arrival of ambulance (from 31% in 1992 to 50% in 2005; crew-witnessed cases excluded) found in study III is very satisfying. This increase may be an effect of the extensive CPR training of health personnel and lay persons in Sweden and the use of CPR guidance by telephone from dispatchers to bystanders which started in 1997.

11. Has the introduction of a dual dispatch early defibrillation program been successful?
The introduction of a dual dispatch early defibrillation program has led to shortened response times for patients with OHCA in Stockholm. Although only intended as a pilot-study, our data suggest that our intervention also has improved survival. This seems especially to be the case for patients with witnessed OHCA in whom survival rates almost doubled. Survival after OHCA in Sweden (Stockholm patients excluded) did not increase during the corresponding time period. The increase in survival is mainly believed to be associated with improved CPR which in part may be due to more persons treating the patient with ongoing CA and shortened time intervals. When comparing dual dispatches (fire vehicles were not dispatched to all OHCA during the intervention, see question 12 below) with EMS dispatch only, a larger difference in time interval and adjusted survival was found. Somewhat surprisingly, the increase in survival was not related to a corresponding increase in the proportion of patients presenting with VF as the initial rhythm (our results show unchanged or only slightly higher proportion of VF OHCA). Other studies, including study III, have indicated a decline in VF arrests during the last decade [Kuisma 2001, Rea 2003, Kette 2007].

12. Which are the main problems when changing dispatch logistics?

Despite efforts during the implementation phase (a structured policy was applied as to when the fire-fighters were to be dispatched) to minimize time loss at the EDC, a 2.0 minute delay (median) was found when comparing the interval from dispatch of EMS to the dispatch of fire brigades in corresponding cases. Furthermore, fire brigades were dispatched to only 66% of the cardiac arrests (crew-witnessed cases excluded) where dual dispatch was intended. The most common reason for both the delay and dispatch failure proved to be difficulties at the EDC to rapidly identify true cases of OHCA. This uncertainty resulted in traditional immediate dispatches of an EMS vehicle following which the fire department was either not alerted at all or only after some hesitancy. Similar experiences have been encountered in Göteborg, where 45% of all true OHCA were dispatched with other alarm codes than "possible cardiac arrest" or "unconsciousness" [personal communication Christer Axelsson]. The most common alarm codes in these cases in Göteborg were "chest pain" or "dyspnoea". Also, signs of breathing (agonal breathing) are often mistaken for normal breathing and are a recognised cause of delay in the diagnosis of CA [Bohm 2007b]. Delays from arrival of call to dispatch of first responders have been described also by others. Van Alem and co-workers concluded that much of the potential benefit of dispatched first responders using AEDs was limited by time lost in decision making, incorrect decisions at the EDC and delays in communication between dispatch centres [van Alem 2003]. With improved routines at the EDC and smaller delays a higher proportion of patients will receive the best treatment (dual dispatch) earlier.

13. Why is the proportion of OHCA presenting with VF as the initial registered rhythm decreasing while an increase in survival among VF patients is observed?

VF as the first registered rhythm is one of the absolutely strongest predictors for survival in OHCA [Weston 1997, Holmberg 2000, Herlitz 2005a, Fridman 2007]. In the present investigations the proportion of patients found in VF varied in Stockholm from 18 and 19% (studies I and II) to 22% (study IV), and from 33% in 1990 to 26% in Sweden (study III).

Several groups have pointed to a decreasing proportion of patients found in VF during the last two decades. Bunch and colleagues found a clearly decreasing incidence of VF OHCA in Minnesota from 1989-2002 [Bunch 2004] and Polentini and co-workers found similar results in Wisconsin from 1992-2002 [Poleniti 2006]. Rea and co-workers in Seattle [Rea 2003], Kette and colleagues in north-east Italy [Kette 2007] and Kuisma and co-workers in Finland [Kuisma 2001] have also reported on a decline in the proportion of patients with VF as presenting rhythm, all in accordance with the results of study III. In parallel with a decrease in the proportion of OHCA presenting with VF as the initially registered rhythm, an increase in survival among VF patients was observed in our investigations. Results from both study III and IV indicate that the increase in survival was mainly encountered in patients who had been found with a shockable rhythm and in whom survival almost doubled. In study III, this increase was observed even though the time interval between call and defibrillation did not decline over time. The reasons for a decline in the proportion of patients found in VF in combination with the increased survival in this group are not fully understood. Suggested causes of a decline in VF OHCA include the decreasing incidence of coronary heart disease [Kuisma 2001], as well as the presumption that more patients today (with updated therapeutic regimes including new medications, earlier revascularization and ICD implantation) reach an "end stage" heart disease prior to CA [Herlitz 2004, Bunch 2005]. One might thus speculate that OHCA-patients nowadays to a larger proportion present with non-shockable rhythms as part of heart failure [Luu 1989]. Furthermore, the decline of patients with cardiac etiology in study III might have contributed, even if corresponding declines have not been observed by others [Herlitz 2000]. Possible contributory explanations for the improvement in survival in VF OHCA could be the higher proportion of patients receiving bystander CPR, working as a bridge to defibrillation by increasing VF-amplitude [Eftestol 2004], a selection of patients with a better chance of survival within this group (due to a decline in the proportion of VF OHCA) as well as an increasing proportion of crew-witnessed cases.

14. Why was the increase in 1-month survival (SALSA-project) not associated with a corresponding increase in the proportion of patients admitted alive to hospital?

A rather surprising finding in study IV is an increase 1-month survival without a corresponding increase in hospital admissions. Similar findings have been observed recently [Bobrow 2008]. In-hospital survival has, accordingly, increased significantly over time and one might argue that this is mainly due to the contribution of in-hospital factors such as therapeutic hypothermia, revascularization and better medication [Bernard 2002, Anonymous 2002b, Skrifvars 2003, Sunde 2007]. However, the guidelines for in-hospital treatment have not changed between the historical control period and the intervention. For example, hypothermia and primary PCI for STEMI were standard treatments already before 2004. Furthermore, if in-hospital factors would have contributed to a large extent, a corresponding increase in survival in the rest of Sweden (Stockholm excluded) would also be expected. Survival after OHCA in the rest of the country did, however, not increase during the study period. The more probable reason explaining the improved in-hospital survival in Stockholm during the intervention is that patients due to altered pre-hospital interventions arrive at the emergency rooms in a better clinical condition. It is, however, not possible at this stage of a pilot-study to fully exclude the possible contribution also of in-hospital factors to the increase in survival.

15. Where should out-of-hospital defibrillators be placed?

There is an ongoing discussion on the clinical effectiveness, public health impact and cost-effectiveness of PAD. Some authors consider PAD to be cost-effective in locations with high incidences of cardiac arrest [Gold 2007] while others have adopted a more reluctant approach concluding that a more widespread PAD to sites with lower incidences of cardiac arrest is unlikely to be cost-effective in comparison to other healthcare interventions in coronary artery disease [Pell 2007].

Within the concept of spread of defibrillation to others than conventional EMS and ambulance personnel, three groups are becoming discernible: (1) untrained lay rescuers using PAD, (2) trained lay people using PAD and (3) first responders via paired dispatches from central dispatch centres. Only a handful authors have reported on untrained lay rescuers [Whitfield 2005] with promising results on survival, whereas others have observed improved survival rates with the use of trained lay rescuers as in the PAD-trail [Hallstrom 2004], casinos [Valenzuela 2000] and airplanes [Page 2000]. Most investigations have used first responders as their intervention. In the SALSA-project we chose dual dispatch defibrillation by first responders and PAD performed by trained lay security officers. No lives were saved by the latter. However, the use of defibrillators and the length of the intervention were limited and a longer evaluation is clearly needed to draw final conclusions of the potential benefit of PAD. By contrast, our data strongly support that patients with OHCA benefit from a dual dispatch early defibrillation program using fire-fighters as a complement to traditional medical responders.

16. Has ambulance density changed over time and what are the consequences?

To find the causes of the long time delays in Stockholm the overall and relative numbers of ambulances in Stockholm and Göteborg were scrutinised. As presented on page 31 there were marked differences in favour of the latter city. Furthermore, the number of ambulances per million inhabitants was reduced in both cities between 1992 and 2005 (by 19% in Stockholm and 25% in Göteborg) and these decreases coincided with an increase in the time interval between call to arrival of ambulance at the scene of OHCA as shown in studies III and IV. However, in an analysis of the time interval from call to arrival of first responder (ambulance *or* fire brigade) in Stockholm in study IV, a decline was instead observed pointing to the beneficial effects achieved by the addition of fire brigades. Ambulance number per capita, accordingly, has had an impact on important pre-hospital time intervals in this patients group. One might even suggest that the fire vehicles acted as "additional" ambulances during study IV. However, we have no data regarding the use of and the priority of ambulances in different types of conditions (i.e. acute, subacute or non-acute) in these situations.

17. Implications for the future?

Survival after OHCA has improved in Stockholm and in Sweden since the beginning of this decade. This is a positive and longed-for development. However, survival in Stockholm remains low in an international perspective. We believe that the main reason for this is due to long time intervals before treatment (i.e. CPR and defibrillation). Many lives could probably be saved if patients with sudden worsening of chest pain and dyspnea were to receive medical treatment and observation more rapidly. There are two principal methods to achieve this: (1) earlier calls to the emergency dispatch centres and (2) shorter time intervals from CA to treatment. Education of patients and relatives and mass medial campaigns must continue to be ways to reach the first group, whereas improved dispatch routines, increased use of CPR guidance by telephone from dispatchers to bystanders, PAD and first responder defibrillation are ways to obtain the latter. Presently, CPR performance out in the field is poor [Wik 2005]. It seems evident that patients suffering OHCA should be treated by more hands during the first crucial 10-15 minutes after the collapse. It is most likely that the addition of 2-5 persons via dual dispatch greatly improves CPR with fewer pauses and better chest compressions.

The field of OHCA is wide. It covers aspects of the pre-hospital and the intra-hospital arena as well as prevention and treatment. Promising approaches within this context are new groups of first responders such as taxi drivers, improved and more widespread CPR skills in the population, SMS (short-message-system)-guided dispatch of rescuers, the increasing importance of chest compressions, the quality of CPR and different aspects of post-resuscitation care. In brief, it is particularly obvious that with early CPR and early defibrillation a larger number of patients with OHCA can be saved. The most clearly identifiable example supporting this argument comes from Valenzuela and colleagues who demonstrated that 74% of OHCA who received their first defibrillation within three minutes after a witnessed collapse survived to discharge [Valenzuela 2000]. Therefore, decreasing the pre-hospital time intervals should become a high priority for all health care providers.

6. CONCLUSIONS

- Survival after OHCA in Stockholm was only between 2.5% and 3.3% between 2000-2002 and had not increased since the last measurements 20 years earlier.

- During 2000-2002 survival after OHCA was significantly lower in Stockholm than in Göteborg and this difference was associated with pre-hospital factors only (predominately in the form of prolonged time intervals in Stockholm), rather than with in-hospital factors or patient characteristics.

- Survival after OHCA in Sweden increased significantly from 1992 to 2005. The increase was particularly marked among patients found with a shockable rhythm and is associated with an increase in the proportion of crew-witnessed cases and, to a lesser degree, an increase in bystander CPR.

- A dual dispatch early defibrillation program in Stockholm has decreased response times and is likely to have improved survival in patients with OHCA. This increase in survival is believed to be associated with improved CPR and shortened time intervals.

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9. ORIGINAL PUBLICATIONS