# The fight against time in prehospital cardiac arrest

## – a true medical emergency


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# The fight against time in prehospital cardiac arrest

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Sweden

## ABSTRACT

**Background:** The chances of survival after an out-of-hospital cardiac arrest (OHCA) are one in ten. The majority of survivors have no or relatively mild neurological sequelae. Interventions are time critical and well-timed management is challenging. All aspects of resuscitation in an OHCA are based on knowledge of clinically important actions and their timing in OHCA management.
Randomised trials face ethical and legal barriers. The victim is unable to give informed consent and obtaining consent from a legal surrogate delays resuscitation actions. This highlights the need for observational efforts in cardiac arrest research, together with the further exploration of clinically relevant factors and their importance to survival chances in OHCA.

**Methods:** Study *I* describes the importance of the number of defibrillations in OHCA and their association with survival chances. It is based on data from the Swedish Registry of Cardiopulmonary Resuscitation (SRCR). Study *II* describes the implementation and feasibility of a direct pathway to immediate coronary angiography after OHCA and its outcome. Patients were screened in the field by ambulance crews and referred to the catheterisation laboratory after consultation with the interventionalist. Study *III* examines the effect of a basic manoeuvre (passive leg-raising, PLR) in cardiopulmonary resuscitation (CPR) in an observation comparing PLR with standard CPR. Study *IV* determines the association between ambulance response time and survival after an OHCA, based on data reported to the SRCR.

**Results:** *Study I:* Between 1990 and 2015, 19,519 patients with a shockable rhythm were reported to the SRCR and included in the study. The chances of survival decreased as the number of defibrillations required increased. Among patients found in a shockable rhythm, 7.5% required more than 10 shocks. Among the witnessed cases, we identified 12 factors associated with survival to 30 days, one of which was the number of shocks that were delivered. *Study II:* Prehospital screening identified 86 OHCA patients, but only 58% fulfilled the given criteria for pathway activation. Among these, the angiography procedure was started within an hour after collapse in half the cases and the majority had a culprit lesion. Thirty per cent of the patients survived to 30 days and 92% of the survivors presented with a shockable rhythm. All survivors had a good cerebral performance or sufficient function to manage activities of daily life independently. *Study III:* The PLR manoeuvre was performed in 44% of the n=3,554 OHCA patients included in the study. Survival to 30 days was 7.9% among patients who received PLR and 13.5% among those who did not (OR 0.55; 95% CI 0.44-0.69; $p < 0.0001$). When matching 1:1 on a propensity score, the difference in 30-day survival between the two groups disappeared (OR 1.07; CI 0.80-1.44; $p = 0.65$). The matched comparison showed a 30-day survival rate of 8.6% in the PLR group versus 8.2% in the control group. *Study IV:* Survival chances after a witnessed OHCA decreased as ambulance response times increased. This was seen independently of the initial rhythm and whether or not CPR was performed before EMS arrival. The chances of survival to 30 days was 19.5% when the EMS crew arrived within 0-6 minutes in an OHCA situation, as compared with 9.4% if the crew arrived within 10-15 minutes.

**Conclusion:** *I)* The chances of survival after an OHCA decreased for each defibrillatory shock administered. *II)* The prehospital activation of a pathway to immediate coronary angiography in OHCA showed limited feasibility. The criteria for the prehospital initiation of a pathway of this kind have to be clear and simple in this time-critical situation. The initial rhythm could be an accurate criterion for prehospital screening to immediate coronary angiography after OHCA. *III)* We found no indications that the PLR manoeuvre during CPR was beneficial when performed by the EMS crew within five minutes of arriving on the scene. *IV)* The ambulance response time is important to survival chances in OHCA. Possible actions to reduce EMS response times need to be considered urgently, as this can be lifesaving for future OHCA patients.

**Keywords**: cardiac arrest, cardiopulmonary resuscitation, out-of-hospital.

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# SAMMANFATTNING PÅ SVENSKA

När en människa drabbas av plötslig livlöshet och andningen upphör eller blir onormal, så rekommenderas omedelbar hjärtlungräddning för att rädda personen till livet. Nästan 90% av de som drabbas av hjärtstopp utanför sjukhus dör. Detta sker trots att andelen överlevare har ökat under många år. Det beror bland annat på allt fler livräddaringripanden, där närstående eller förbipasserande påbörjar hjärt-lungräddning. Fler defibrillatorer utplacerade i samhället, många HLR-utbildade i civilsamhället och mobiltelefonbaserad teknik som förbättrar hjärt-lungräddningsinsatsen på plats är viktiga förbättringar under senare år. Trots detta är chanserna att överleva ett hjärtstopp som inträffar utanför sjukhus alltså ungefär en på tio.

Ökande överlevnadschanser vid hjärtstopp är en följd av insatser i förloppets alla led, när någon drabbas. Allt arbete för att utveckla och förbättra omhändertagandet vid hjärtstopp, bygger på kunskap; aktuell kunskap kring vad som påverkar patientens möjligheter att överleva.

Ny kunskap om bästa möjliga behandling vid hjärtstopp får vi till stor del genom att analysera stora grupper av patienter. Jämförande studier mellan tex två behandlingsalternativ, eller olika sätt att utföra hjärt-och lungräddning, är ofta inte möjliga att genomföra av etiska eller praktiska skäl. Att lotta mellan två olika behandlingsmöjligheter i en situation där detta inte får påverka tiden till insats är svårt. Patienten har heller inte möjlighet att lämna sitt samtycke till forskning, och att tillfråga anhöriga och avkräva omedelbart svar i en situation med pågående återupplivningsinsats är sällan försvarbart.
Detta gör att mycket av vår kunskap och dess landvinningar kommer från observationer och analyser som är gjorda i efterhand. Tillförlitliga analyser av insamlade data bygger på en noggrann och välfungerande registrering av information från varje enskild hjärtstoppshändelse. Sedan 1990 registrerar ambulanspersonal data efter varje hjärtstoppshändelse i Svenska Hjärt-lungräddningsregistret. Sammanställd information från hela landet finns sedan tillgänglig genom registrets årsrapport och via en webapplikation där parametrar kan följas och jämföras.

Två av studierna i den här avhandlingen bygger helt på data från Svenska Hjärt-lungräddningsregistret, och i ytterligare en av studierna används registret som verktyg för att undersöka ett behandlingsalternativ som införts i ett antal ambulansdistrikt.

Vid hjärtstopp och hjärtlungräddning så har ungefär en fjärdedel av de drabbade ett s.k kammarflimmer. Det innebär att hjärtat är drabbat av ett elektriskt kaos och dess pumpförmåga har upphört. En del av dessa patienter kan då räddas genom att hjärtats elektriska kaos snabbt återställs med en strömstöt från en hjärtstartare (defibrillator).

I vår första studie undersöks sambandet mellan antalet defibrilleringar (strömstötar från en hjärtstartare) och chanserna att överleva vid ett hjärtstopp som inträffar utanför sjukhus. Det visade sig att överlevnadschansen minskar för varje defibrillering som måste utföras. Över tid ökade dock andelen överlevare efter hjärtstopp, oberoende av hur många defibrilleringar som krävdes. Ytterligare 11 faktorer visade sig korrelera med överlevnadschansen efter hjärtstopp, bland annat tid från kollaps till ambulansens ankomst och tid från kollaps till påbörjad HLR och defibrillering.

I den andra studien beskrivs och analyseras ett direktspår till kranskärlsröntgen för patienter som drabbats av hjärtstopp utanför sjukhus. Vi fann att kranskärlsröntgen ofta kan påbörjas inom en timma från kollaps och merparten av patienterna hade allvarliga kranskärlsförändringar. Alla överlevande patienter hade bärande cirkulation vid ankomst till sjukhuset, och nästan alla (92%) hade kammarflimmer som första registrerade hjärtrytm.
I den tredje studien undersöktes effekten av passivt benlyft för att förbättra blodcirkulationen i samband med hjärt-lungräddning vid hjärtstopp utanför sjukhus. Vi fann inget som talar för att passivt benlyft utfört av ambulanspersonalen, inom 5 minuter från ankomst till patienten, skulle öka överlevnadschanserna vid hjärtlungräddning.

Den sista studien undersöker effekten av ambulansens responstid på möjligheterna att överleva efter inträffat hjärtstopp. Responstiden mäts från det att larmcentralen sänder uppdraget till ambulansen till det att besättningen är framme hos patienten. Ambulansens responstid vid hjärtstopp har fördubblats under de sista 30 åren, till att vara i genomsnitt 11 minuter år 2018 (mediantid). Det visade sig att chanserna att överleva efter ett hjärtstopp minskar när ambulansens responstid ökar. Detta samband var oberoende av om hjärtlungräddning utfördes innan ambulansens ankomst eller inte. Sambandet var också oberoende av vilken första EKG-rytm som registrerades efter det att hjärtstopp inträffat. Resultatet belyser vikten av att arbeta för kortare ambulansresponstider vid hjärtstopp. Under 2018 räddades 609 människor som drabbats av hjärtstopp utanför sjukhus, och ambulansens responstid var i genomsnitt 11 minuter i Sverige.
I en matematisk modell baserad på studieresultatet, fann vi att 1194 människor kunde ha räddats till livet efter hjärtstopp om ambulansens responstid varit maximalt sex minuter. Modellen har brister, men åtgärder för att minska ambulansens responstid kan öka möjligheterna att överleva vid ett hjärtstopp som inträffar utanför sjukhus.

# LIST OF PAPERS

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

I. Johan Holmén, Jacob Hollenberg, Andreas Claesson, Maria Jiménez Herrera, Youcef Azeli, Johan Herlitz, Christer Axelsson. **Survival in ventricular fibrillation with emphasis on the number of defibrillations in relation to other factors at resuscitation.**
*Resuscitation 2017 Apr;113:33-38. doi: 10.1016/j.resuscitation.2017.01.006. Epub 2017 Jan 18.*

II. Johan Holmén, Johan Herlitz, Christer Axelsson. **Immediate coronary intervention in prehospital cardiac arrest - Aiming to save lives.**
*Am Heart J. 2018 Aug;202:144-147. doi: 10.1016/j.ahj.2018.05.008. Epub 2018 May 22.*

III. Johan Holmén, Johan Herlitz, Maria Jimenez-Herrera, Thomas Karlsson, Christer Axelsson. **Passive leg raising in out-of-hospital cardiac arrest.**
*Resuscitation 2019 Apr;137:94-101. doi: 10.1016/j.resuscitation.2019.02.017. Epub 2019 Feb 18.*

IV. **Shortening ambulance response time increases survival in out-of-hospital cardiac arrest.** *Submitted manuscript*

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# ABBREVIATIONS

| | |
|---|---|
| AED | Automated external defibrillator |
| AHA | American Heart Association |
| CPR | Cardiopulmonary resuscitation |
| CPC | Cerebral Performance Category |
| DAG | Direct acyclic graph |
| ECG | Electrocardiogram |
| E-CPR | Extracorporeal CPR |
| EMS | Emergency medical service |
| ERC | European Resuscitation Council |
| LUCAS | Lund University Cardiopulmonary Assist System |
| OHCA | Out-of-hospital cardiac arrest |
| OR | Odds ratio |
| PCI | Percutaneous coronary intervention |
| PLR | Passive leg raising |
| pVT | Pulseless ventricular tachycardia |
| ROSC | Return of spontaneous circulation |
| SRC | Swedish Resuscitation Council |
| SRCR | The Swedish Registry of Cardiopulmonary Resuscitation |
| STEMI | ST-elevation myocardial infarction |
| VF | Ventricular fibrillation |

# INTRODUCTION

The purpose of this work is to save lives by improving the treatment of the apparently dead patient. Sudden cardiac arrest is a condition with insufficient or absent blood flow, respiration and consciousness. There may be many causes. Left untreated, cardiac arrest results in dying cells due to lack of oxygen. As time passes, if blood flow is not re-established, cells in the brain and other organs are damaged and finally die, due to lack of oxygen. Brain cells are particularly vulnerable and, within minutes without blood flow and oxygen, permanent brain damage starts to evolve.

Even though Hippocrates stated in 400 BC that "*Those who are subject to frequent and severe fainting attacks without obvious cause die suddenly"*[1], the first more modern scientific attempt in the field of resuscitation is from the late 18th century. In 1792, James Curry, M.D, published his *Popular Observations on Apparent Death from Drowning, Suffocation etc.* in which he describes three patients with temporary recovery after apparent death. Here he uses the term "recoverable apparent death" and describes this as "death lies only dormant" in contrast to absolute death "in which the vital principle is completely extinguished". This brilliant description is still accurate and in fact covers the complete clinical spectrum of conditions that we currently treat and define as cardiac arrest. In fact, apparent death is probably more accurate, as it does not refer to the cause but simply describes the condition.

Despite the variety of possible causes, successful treatment in cardiac arrest has one initial and common denominator: time. Immediate efforts to support blood flow and respiration are crucial. Instant chest compressions and artificial breathing constitute the very foundation in saving the life of a cardiac arrest victim, together with the opportunity for immediate defibrillation. Without this first effort, more specific treatment of the underlying cause will be useless, as interrupted blood flow instantly implies damaged brain cells. Cardiopulmonary resuscitation (CPR) offers some, albeit insufficient, blood flow. Nevertheless, CPR buys some time and allows the rescuers to attempt the treatment of an underlying cause. Sometimes, CPR and life support can restore circulation and even more time is gained to find and treat the underlying cause of the cardiac standstill.

In many cases, chest compressions, eventual defibrillation and artificial breathing are unable to immediately restore cardiac function. This leaves the rescue team with only a short period of time to identify and treat the underlying cause of the cardiac arrest. This is extremely challenging and most often not possible.

Huge efforts and progress have been made in cardiopulmonary resuscitation over the last 40 years. To allow this improvement to continue, and to save more cardiac arrest victims, we need to know where to invest our efforts. Healthcare resources are not endless and only knowledge can guide us in obtaining the greatest possible value in return for our efforts.





# BACKGROUND

## SETTING THE SCENE

The medical team around the unconscious patient with abnormal breathing is under maximum pressure. Resuscitation demands both immediate CPR and an immediate search for the underlying cause. Effective CPR is complex teamwork, achieved using individual skills, team training and perceptive leadership. When a person collapses outside a hospital, the first ambulance crew on the scene faces not only a patient without signs of life but also observing fellow humans, bystander rescuers, relatives, children, family and curious spectators. The immediate start of high-quality CPR and attaching the defibrillator is the first priority for the first ambulance crew to arrive. When the second team arrives, the search for an underlying cause can be intensified, while intravenous or intraosseous access is established, and drugs are prepared. What is behind this collapse? Who can provide information on the circumstances of the collapse, indicating a myocardial infarction, a foreign body airway obstruction or intoxication? Potential hypothermia, pregnancy or an implanted pacemaker or cardioverter-defibrillator have to be considered. Is there a severe, end-stage disease making further attempts pointless? Meanwhile, CPR interruptions have to be minimal and the crew member performing chest compressions has to be replaced continuously to ensure optimal compressions. Only a few minutes after these initial actions, the question of transportation has to be considered. When is the right time to accept the inevitable impairment in resuscitation quality associated with loading the patient into the vehicle? Which hospital is the preferred destination for our patient? What can this hospital add in terms of diagnostics and treatment and how long is the transfer?

## DEFINITION – WHAT IS AN OUT-OF-HOSPITAL CARDIAC ARREST?

This straightforward question is, in fact, complex and deserves attention. The main issue is that the biological and physiological definition differs from the practical, clinical definition used by both healthcare in general and field researchers.

Biological definitions are fairly direct and the following has been suggested:

- “The loss of functional cardiac mechanical activity in association with an absence of systemic circulation, occurring outside of a hospital setting” [2].

- “Cardiac arrest is the cessation of cardiac mechanical activity, as confirmed by the absence of signs of circulation” [3].

- “A sudden, sometimes temporary, cessation of heart function resulting in hemodynamic collapse” (Cardiac arrest MC82, as defined by the World Health Organisation’s International Classification of Diseases, ICD-11[4]).

In the clinical approach, these definitions do not have to be true. International guidelines state that: “the victim who is unresponsive and not breathing normally is in cardiac arrest and requires CPR” [5]. In practice, we do not know that this condition represents a cardiac standstill, as there can be many causes of unresponsiveness and abnormal breathing. What we do know, from both science and proven experience, is that this patient is in urgent need of CPR to stand a chance of survival.
This is the clinical background to the fact that all patients treated with CPR are documented as cardiac arrests in both emergency medical service (EMS) and hospital records, as well as in the cardiac arrest registries.

An international consensus on how to report out-of-hospital cardiac arrest (OHCA) data was proposed in 1991 [6] and it is now well established and often referred to as “Utstein style”. In June 1990, an international meeting was held at Utstein Abbey close to Stavanger, Norway. The heterogeneous nomenclature and the lack of conformity in reporting OHCA data were addressed and a recommendation for uniform reporting was presented. This landmark document has the following definition of a cardiac arrest:

- “Cardiac arrest is the cessation of cardiac mechanical activity, confirmed by the absence of a detectable pulse, unresponsiveness and apnoea (or agonal, gasping respirations)”.

The original Utstein criteria have been supplemented with in-hospital definitions [7] and was updated in 2004 [8] and 2014 [9]. The Utstein guidelines provide a framework to compare cardiac arrest care in different EMS systems.

Since the criteria for starting CPR do not necessarily meet the theoretical definition of a cardiac arrest, it is important to note that we use the term





“cardiac arrest” when the true meaning is that a CPR attempt has been performed.

For this thesis and its papers, we use the following definition of OHCA: Each time an ambulance is called and CPR and/or defibrillation is initiated by the EMS crew, another dispatched unit or any bystander at scene, it is regarded as a cardiac arrest. All incidents occurring anywhere outside hospital are regarded as OHCAs.

*Figure 1. Utstein Abbey, anonymous painter (photo by: Frode Inge Helland).*

# EPIDEMIOLOGY

Out-of-hospital cardiac arrest is a global, common and lethal event. At least 17 individuals/day suffered an OHCA with CPR attempts in Sweden in 2018 [10]. Around 12 of them collapsed in their homes (69%).

More than 6,000 CPR attempts were reported in Sweden in 2018 [10]. With a population of 10.2 million in 2018, the incidence of cardiac arrest was 60 per 100,000 inhabitants.

Large amounts of data are available from North America and Europe. A well-founded estimation is that the incidence of cardiac arrest in these regions is approximately 50-100 per 100,000 person-years, in the general population [11].

The European Resuscitation Council (ERC) has declared that, depending on the definition of a cardiac arrest, about 55-113 per 100,000 inhabitants, or 350,000-700,000 individuals a year, suffer a cardiac arrest in Europe every year [5, 12]. In a population of 21.4 million people in 10 different North American regions, the median incidence of EMS-treated OHCAs was 52 per 100,000 person-years, as reported by the North American Resuscitation Outcomes Consortium (ROC-Epistry Cardiac arrest). Regional variations were considerable in terms of both incidence and outcome [13].

Beck et al. report from the Australian Resuscitation Outcomes Consortium (Aus-ROC) and the New Zealand OHCA Epistry for 2015. This survey reported a crude incidence rate of 47.6 attempted resuscitation OHCA cases per 100,000 population a year [11].

The European Registry of Cardiac Arrest (EuReCa) TWO study collected registry data from 28 European countries for a three-month period in 2017 and report an overall incidence of OHCA (in which CPR was attempted) of 56 per 100,000 population a year [14].

Comparisons of cardiac arrest and CPR attempt incidences between regions or countries require a common definition of the numerator “cardiac arrest/CPR attempt”, as well as the denominator “population at risk”. Despite the widespread Utstein criteria, this is rarely the case. Serious attempts have been made [12] and they conclude that there is a 10-fold global variation in reported OHCA incidences and outcome.

The most obvious confounding factor when comparing incidences and outcome between countries is differences in age distribution. In many cases





differences in the distribution of other factors, like pre-existing co-morbidities and in-hospital interventions, also have to be taken into account when seeking to explain these differences in inter-country comparisons.

Attempts have been made to make adjusted inter-country comparisons [15], indicating that variations other than the already well-known predictors of OHCA outcome are important. This questions the reliability of aggregated comparative studies of OHCA outcome between countries. It also highlights the need for continuing cardiac arrest research as an instrument to guide and evaluate the development of cardiopulmonary resuscitation and the chain of survival.

# OHCA – THE CLINICAL PRESENTATION

If a person suddenly collapses, international consensus guidelines tell us to initiate CPR if the person is unresponsive and not breathing normally [5]. Despite the variety of triggers and causes behind the need for CPR, the clinical presentation is essentially the same. Unconsciousness is the first and most obvious sign. The assessment of breathing is more difficult. Deep, slow breaths can be “rescue breaths”, generated by the brain stem (agonal breathing) and withheld for several minutes after a circulatory arrest. This gasping breathing is common in the first minutes after a cardiac arrest and is associated with an increased chance of survival [16].

Checking for a pulse has been proven to be difficult and is an inadequate method to confirm the absence of circulation [17]. This is why current consensus recommendations rely on unresponsiveness and abnormal breathing only as a reason to advise CPR. Any movement, cough or other signs of life as a response to CPR prompt the cessation of CPR attempts and a re-evaluation.

In many situations, the medical history provides essential guidance to find the underlying cause of a condition. Out-of-hospital cardiac arrest is no different in this respect. Information from an OHCA witness is of great value to the EMS crew caring for the patient. Many patients who suffer an OHCA have symptoms preceding the collapse. Dyspnoea, chest pain and a change in consciousness are the most frequent warning symptoms [18-20]. Chest pain is primarily a sign of myocardial ischemia and often precedes a coronary-related OHCA [21].

# AETIOLOGY

Any condition causing sudden and unexpected unresponsiveness and abnormal breathing should lead to a prompt CPR attempt. Both healthcare systems and resuscitation registries will then register this incident as a cardiac arrest.

There may be many possible causes and a cardiac aetiology has traditionally been regarded as the most frequent. According to the Utstein templates for resuscitation registries, “an arrest is presumed to be of cardiac aetiology unless it is known or likely to have been caused by trauma, submersion, drug overdose, asphyxia, exsanguination, or any other non-cardiac cause as best determined by rescuers” [8].

Estimations of the proportion of OHCAs with a cardiac aetiology are linked to both the exact definition of a cardiac arrest and the criteria for selecting the population of OHCA cases. When seeking to improve cardiac arrest care, the patients of interest are mainly the ones in whom CPR has been attempted.

In a Japanese study based on 1,042 perimortem computed tomographies, the proportion of non-cardiac aetiology was found to be 62.5 % [22].

In the pioneering study from Paris by Spaulding et al., 84 consecutive OHCA survivors underwent an immediate coronary and left ventricular angiography [23]. The inclusion criteria were 30-75 years of age, OHCA within six hours of the onset of symptoms in patients who were previously leading a normal life and no obvious non-cardiac cause of arrest. More than 70% of the patients had a coronary lesion, with more than a 50% reduction in luminal diameter. A coronary occlusion was seen in 48% of the cases. This work has been regarded as important proof of the mechanism with a rupture of an atherosclerotic plaque causing myocardial ischaemia and cardiac arrest. Interestingly, 42% of the patients had neither chest pain nor ST-segment elevation, highlighting the poor predictive value of these parameters. More recent work reports similar findings [24].

Similar results have been reported from apparently healthy victims of OHCA in the Swedish population [25]. Seven hundred and eighty-one (781) patients with no hospital visit and no documented prescription of any medication for the last two years were identified. More than 70% of the 658 non-survivors underwent autopsy. Fifty-nine per cent of these patients were assessed as having a cardiac aetiology to the OHCA and 70% as having any cardiovascular cause. Pre-event ECGs were available in 182 of the patients, showing abnormalities in only 22%. In eight per cent, a ruptured aortic aneurysm was





the underlaying cause and for nine per cent of the patients the OHCA was caused by an accident. Only five per cent were assessed as having an underlying pulmonary cause of the arrest.
According to the Swedish Registry of Cardiopulmonary Resuscitation (SRCR), 60-70% of the patients with an OHCA have an underlying cardiac aetiology [10]. This figure refers to the assessment made by the attending EMS crew, reporting to the SRCR.

Despite the existing evidence of a high frequency of coronary lesions in OHCA patients, the subject is complex. In a series of 72 consecutive survivors of OHCA undergoing immediate coronary angiography on hospital arrival, 64% had at least one coronary lesion > 50%. This finding is in line with the reports described above. However, only 38% had clinical or angiographic evidence of an acute coronary syndrome due to a coronary occlusion, plaque rupture or thrombus [24]. Verifying myocardial ischaemia as a direct cause in OHCA remains challenging.

All the above has to be considered in relation to the population studied. In the work by Spaulding et al., the mean age was 56 years and, in the SRCR, the overall median age is 71 years. In younger age groups, trauma and drowning are more frequent causes of OHCA [26, 27]. In the paediatric cases, the mechanisms behind OHCA are primarily respiratory and cardiac causes are less frequent [28].

# CURRENT CONCEPTS IN CPR – “THE CHAIN OF SURVIVAL”

Recognising the symptoms and knowing what to do when someone collapses are crucial skills for everyone in society, in the struggle against mortality in OHCA.
A large proportion of patients who suffer an OHCA have well-known risk factors like cardiac conditions, smoking or diabetes [29, 30]. Warning symptoms preceding the collapse are present in the majority of patients with an OHCA and often for a relatively long time [29]. The chances of surviving an OHCA have proven to be considerably better if it occurs in the presence of an ambulance crew [31, 32] and the importance of early recognition and calling for help is decisive and life-saving.

When a person collapses, an immediate call for help and the initiation of CPR are critical and well known to be firmly associated with the chances of survival

[33-38]. In Sweden in 2018, the median time from collapse to EMS arrival was 11 minutes [10]. During this time, bystander-initiated CPR and the use of semi-automated defibrillators (AEDs) are essential to survival chances.

Calling for help and CPR were presented as the first links in “the chain of survival” metaphor by the American Heart Association (AHA) in 1991 [39]: “More people can survive sudden cardiac arrest when a particular sequence of events occurs as rapidly as possible”, Figure 2.

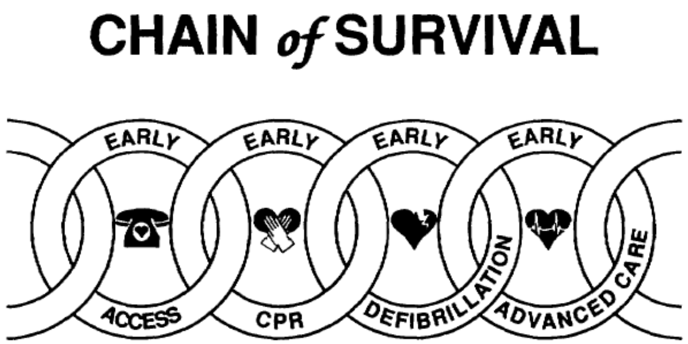


*Figure 2. The metaphor as graphically presented by the AHA in 1991 [39].*

The chain of survival concept has evolved over the years, but it still communicates a clear picture of the vital actions needed for successful resuscitation (Figure 3).

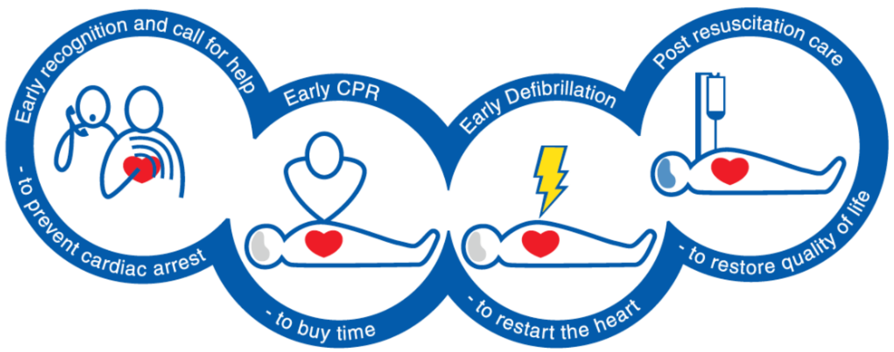


*Figure 3. The chain of survival concept as presented by the ERC in 2015 CPR guidelines [5].*





As scientific evidence grows, the importance of the first and second link has become more and more explicit. An early call for the EMS after cardiac arrest has been shown to be associated with an increased chance of survival [40].
An early call and immediate alert enable the emergency medical dispatcher to give instructions on performing CPR. Dispatch-assisted CPR has been found to improve survival chances compared with no CPR performance before EMS arrival [41, 42].

The second link in the chain refers to early CPR. CPR performed before EMS arrival more than doubles the chances of survival compared with no CPR before the ambulance crew arrives [33].
The great impact of bystander-initiated CPR on survival has been described in several populations [34, 38, 43].
Bystander-initiated CPR provides, to some extent, the delivery of oxygen to the cells. This enables the brain to cope with the situation of a cardiac arrest for a short period of time. It also prolongs the time span when the heart is viable and responsive to defibrillation and treatment.

Another important piece of evidence demonstrating the efficiency of CPR is the fact that some patients regain consciousness when high-quality CPR is performed. Many experienced CPR providers have been in the situation in which the collapsed patients start to show signs of life when CPR is performed. An Australian group report an incidence of 0.23% of CPR-related consciousness in OHCA patients. Of the reported 52 patients with CPR-related consciousness, 18 presented with combativeness/agitation [44].

The third link refers to early defibrillation. This is an important, well-established factor improving survival in OHCA [36, 45, 46]. The use of AEDs enables defibrillation by people other than the EMS personnel and the evidence in favour of improved survival due to the use of AEDs and early defibrillation is unquestionable [46-49].

Among the survivors after an OHCA, the vast majority have an initial rhythm that is shockable [50]. Many studies confirm the positive effect of early defibrillation in OHCA with a shockable rhythm [48, 51-53]. Lay rescuers using AEDs, alerted by text messages, are under development [54], as well as drone-delivered defibrillators [55, 56].

The SRCR reports that around 25% of witnessed OHCAs in Sweden have a shockable rhythm on initial rhythm analysis [10], Figure 4.

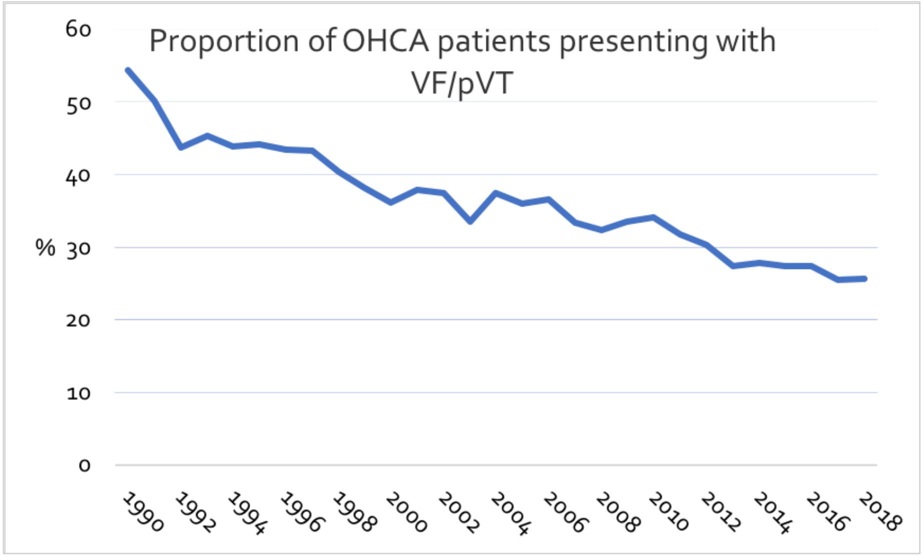


*Figure 4. Proportion of OHCA patients presenting with VF or pulseless ventricular tachycardia (pVT) on the first recorded ECG.*

Other centres report similar frequencies [57]. There has been a marked decrease in the proportion of patients with OHCA presenting with a shockable rhythm since 1990, as shown in Figure 4. This phenomenon appears to be widespread around the globe [57-62]. The potential causes of this declining trend are still unclear.

It is also not known whether this decline in shockable rhythm is caused by fewer shockable rhythms causing the collapse in OHCA, a shorter duration of the shockable rhythm after the collapse or simply an increase in the delay to the first ECG registration. All three mechanisms are possible explanations, considering that ventricular fibrillation (VF) is an extremely energy-consuming condition, eventually dissolving into a low-voltage VF and then asystole. This pattern is well illustrated in the famous study by Valenzuela et al., where the use of AEDs in casinos showed that n=105 of n=148 patients with an OHCA presented with a shockable rhythm in a setting with very short delays [63]. Another example is reported by Wiesfeldt et al., showing that VF occurs as the initial rhythm in 51% of OHCA cases in public places, compared with 22% in residential locations [64].

Based on registry data from the Netherlands, Hulleman et al. report no difference in the rates of VF dissolution when comparing patients from two time periods (1995-1997 versus 2006-2012). The researchers conclude that the





decline in VF is explained by the occurrence of fewer OHCA cases presenting with VF [65].
However, a recent study comprising patients from Amsterdam, Oslo, Copenhagen and Stockholm reports a decline in initial shockable rhythm for OHCAs taking place in a residential location but not for OHCAs in public places. Independent of where the OHCA took place, the proportion of patients with OHCA found in a shockable rhythm decreased as the time from EMS call to defibrillator connection increased [66].

It has been suggested that beta-blockers and angiotensin converting enzyme inhibitors reduce the duration of a VF [67]. Both drugs are widely used in the primary and secondary prevention of ischaemic heart disease and could reduce the incidence of VF as the first detected rhythm in sudden cardiac arrest in patients treated with these drugs.
Beta blockade is well known to reduce the risk of sudden cardiac death in patients who have suffered a myocardial infarction, as well as in patients with heart failure [68] and patients undergoing haemodialysis [69]. There are reports indicating the beneficial effects of beta blockade in patients with cardiac arrest presenting with VF/VT resistant to electrical therapy [70]. Recurrent multiple VF episodes, often referred to as an electrical storm, have been successfully treated with sympathetic blockade (beta-blocker or a left-side stellate ganglion blockade) in a comparison with anti-arrhythmic treatment based on CPR guidelines [71].
An increase in secondary prevention using implantable cardioverter defibrillators, is yet another possible contributory factor to the decrease in VF [57].

There is some evidence indicating that the decline in initial shockable rhythms has ended [72], or at least subsided [66]. This has not been observed in Sweden, where data from the SRCR indicate an ongoing decline (Figure 4).

The fourth link in the chain of survival refers to post-resuscitation care, including hospital interventions. Echocardiography, percutaneous coronary interventions, cardiac surgery and mechanical circulation, as well as therapeutic hypothermia and modern ventilator treatment in intensive care, are under constant development.
The complexity of post-OHCA care is increasing and dedicated cardiac arrest centres have been discussed as a future strategy [73, 74] and a fifth link in the chain of survival [75].

Post-resuscitation care, the fourth link in the chain of survival, is wide and complex. In addition to drugs and airway management, the questions of mechanical chest compressions, the timing of coronary angiography and targeted temperature management are important.

## ADVANCED LIFE SUPPORT

The effect of early advanced life support (ALS) in OHCA and CPR has been heavily debated for a long time. The ALS concept normally covers the administration of drugs and advanced airway management in CPR.

In 2019, Vargas et al. presented a meta-analysis of randomised clinical trials (RCTs) evaluating adrenaline in OHCA [76]. This review includes the landmark PARAMEDIC2-trial [77], in which n=8,014 patients with OHCA in the UK were randomised and treated with adrenaline versus placebo. Both reports conclude that adrenaline improves survival to 30 days or discharge from hospital, compared with placebo, but does not improve neurological outcome at discharge.

One possible limitation, when it comes to randomised, placebo-controlled trials of drugs in OHCA, is that the administration of any drugs has a possible timely impact on all other actions performed by the ambulance crews. The possibility that the preparation and administration of intravenous drugs in the OHCA situation affects adherence to guidelines cannot be ruled out. In a setting with two to four crew members resuscitating an OHCA victim, one of the team members has to deal with venous access, drug preparation and dose calculations. This increases the risk of interruptions in chest compressions, reduced quality of chest compressions from prolonged periods without a provider change, as well as delays in actions such as airway management and transportation. Out-of-hospital resuscitation differs from intra-hospital resuscitation in that staff and helpers are normally readily available in the hospital environment.
The prehospital resuscitation scenario completely omitting venous access and drugs has been compared with standard CPR guidelines, by Olasveengen et al. [78]. This trial found no improvement in survival to hospital discharge when intravenous drugs were used. Nor were there any differences between groups regarding chest compression rate, hands-off ratio, or pre-shock pause in chest compressions. The authors highlight this and state that the administration of intravenous drugs did not appear to interfere with CPR quality.

The best method of airway management is another hot topic in OHCA care [79]. In attempts to compare different methods, the time for each specific intervention is critical. Respiratory support is always initiated by mouth-to-mouth, mouth-to-mask or bag-valve-mask ventilation, as these methods are





fast and offer immediate ventilation. If laryngeal masks, laryngeal tubes or endotracheal tubes are used, they always follow one of these basic methods. This means that the more advanced methods enter later in the course of resuscitation, when some of the survivors have already regained circulation and respiration and further airway actions are not needed. Observational study designs risk suffering from time as a confounding factor, as well as an undocumented mix of airway methods used during resuscitation attempts.

There is some evidence suggesting that advanced airway manoeuvres impair the chances of survival to discharge and neurologically intact survival in OHCA [80]. However, the problem of confounding by indication is a crucial limitation to observational studies that show an association between advanced airway management and poor outcome in OHCA [81]. A randomised trial comparing supraglottic airway management with endotracheal intubation found no difference in survival to 72 hours, favourable functional outcome at discharge from hospital or complications from regurgitation and aspiration [82].

Well-established and effective actions in OHCA are high-quality CPR with minimal interruptions, immediate defibrillation and the identification and treatment of any underlying cause. As long as ventilation is established, it is possible that advanced manoeuvres, like endotracheal intubation, will compete with theses more important, time-critical interventions. However, these conclusions are drawn from a population perspective, including a variety of underlying causes of the OHCA. In the one third of all OHCA victims without a cardiac cause, ventilation is more likely to have high priority and intubation can sometimes be necessary to establish and secure ventilation.

## MECHANICAL CHEST COMPRESSIONS

To improve the effect of chest compressions in CPR, devices for mechanical chest compressions have been developed. The most frequently used devices today are LUCAS (Lund University Cardiopulmonary Assist System, Stryker) and AUTOPULSE (AutoPulse Resuscitation System, ZOLL), where LUCAS is the one partly implemented in Swedish EMS organisations. The obvious advantages are compressions with minimal interruptions and constant depth and frequency.

In 2002, the LUCAS device was compared with manual compressions in a swine model. Cardiac output, coronary perfusion pressure and end-tidal $pCO_2$ levels were significantly higher using the LUCAS device, compared with manual compressions, after inducing a VF in n=100 Swedish pigs with a mean

weight of 22 kilos [83]. The LUCAS device has a suction cup providing active decompression of the chest during CPR and has been shown to decrease the right atrial pressure during the decompression phase in pigs [84].
In 2009, Axelsson et al. found that average end-tidal $pCO_2$ levels were higher (3.26 kPa vs 2.69 kPa) using LUCAS compared with manual compressions after the cluster randomisation of 126 patients suffering an OHCA [85].

The LUCAS device has since been evaluated in randomised trials, with no evidence of improved survival in clinical practice compared with manual chest compressions [86, 87].

A more recent meta-analysis confirms these results [88] and a Cochrane report from 2018 states the following: "We conclude on the balance of evidence that mechanical chest compression devices used by trained individuals are a reasonable alternative to manual chest compressions in settings where consistent, high-quality manual chest compressions are not possible or dangerous for the provider (e.g. limited rescuers available, prolonged CPR, during hypothermic cardiac arrest, in a moving ambulance, in the angiography site and during preparation for extracorporeal CPR)" [89].
This is an effective summary of how the device is spread and used in Sweden today. Many EMS organisations use LUCAS during displacements and transport and it is widely used in catheterisation laboratories.

## CORONARY ANGIOGRAPHY IN OHCA

Myocardial ischaemia is likely to be the most important cause of OHCA, as discussed in the aetiology section. Immediate coronary angiography and percutaneous coronary intervention (PCI), to re-establish blood flow in the affected coronary artery, can resuscitate myocardium and cardiac function and reduce the risk of arrhythmias.

In patients who are resuscitated after an OHCA and present with an ST-elevation myocardial infarction (STEMI), the indication for emergency coronary angiography and PCI is clear. Among these patients, more than 85% have been estimated to have an acute thrombotic coronary occlusion or culprit lesion causing the OHCA [90].

Current European [91] and American [92] guidelines both recommend reperfusion therapy in all patients with STEMI and symptoms of ischaemia of < 12 h duration. Fibrinolysis is only recommended if the time from STEMI diagnosis to PCI is expected to exceed 120 minutes.



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When it comes to patients who are resuscitated after an OHCA and present at the hospital without obvious on-going myocardial ischaemia, the situation is less straightforward. There are observational studies supporting early coronary angiography in patients without acute ST elevations after an OHCA [93-96], as well as the opposite [97, 98]. An observational post-hoc analysis from the hallmark targeted temperature management (TTM) study reports no association between early coronary angiography and survival in patients without acute ST elevations after an OHCA [99]. The prevalence of an acute thrombotic coronary occlusion in OHCA patients with an initial shockable rhythm and without post-resuscitation STEMI has been estimated at 3-30% [100].
The 2015 ERC guidelines recommended consideration of emergent coronary angiography after the return of spontaneous circulation (ROSC) in patients without ST elevation after an OHCA, but with a high risk of a coronary aetiology [101]. The American Heart Association has similar recommendations, stating that emergency coronary angiography is reasonable for the electrically or haemodynamically unstable patient who is comatose after an OHCA of suspected cardiac origin, even without ST elevation on the electrocardiogram [102].

In 2019, a large randomised, multicentre trial reported no difference in survival to 90 days when comparing immediate coronary angiography (within two hours) with a delayed strategy among immediate survivors after an OHCA [103]. This trial comprised n=552 patients who were successfully resuscitated in the years 2015-2018, with an initial shockable rhythm, no signs of ST elevation and no obvious non-coronary cause. To date, this is the only randomised trial of immediate coronary angiography in OHCA patients.

Many centres report on cardiac arrest during catheterisation procedures [104], but initiating coronary angiography when CPR is already ongoing is less well described [105-107].

## TARGETED TEMPERATURE MANAGEMENT

Temperature management is another important part of the fourth link in the chain of survival. A period of post-cardiac arrest fever is common and the association with poor outcome is well documented [101]. There are no randomised trials comparing the treatment of fever episodes with no temperature control and it is possible that the fever itself only represents more severe brain damage. The prevailing clinical approach is to treat hyperpyrexia after an OHCA.

When it comes to targeted temperature management, two trials from 2002 reported improved neurological outcome at discharge from hospital or after six months, following an OHCA and VF, when compared with normothermia [108, 109]. After randomisation, Bernard et al. [108] compared n=43 patients treated with a core temperature of 33° for 12 hours with normothermia (n=34). Twenty-one (n=21) of the TTM-treated patients had no or only a moderate disability, compared with nine of the controls. There were n=22 non-survivors in the TTM group compared with n=23 in the normothermia group. The second randomised trial comprised n=275 patients and demonstrated a reduction in mortality from 55% to 41% in patients treated with 32-34° for 24 hours compared with normothermia [109]. Targeted temperature management with 33° was compared with 36° (36 hours) in the large multicentre TTM trial published in 2013 [110]. A number of n=950 unconscious OHCA survivors were included, irrespective of the initial rhythm, and a temperature of 33° was not found to be beneficial compared with 36°. Fever was well prevented in both groups.
To summarise, cooling to 32-36° is the established recommendation when TTM is applied after an OHCA [101].

### SCIENTIFIC EFFORTS AND THE CHAIN OF SURVIVAL

The scientific focus on hospital interventions in OHCA merits a discussion. Despite the fact that the first three links in the chain of survival have shown an extreme impact on the chances of surviving an OHCA, scientific efforts have largely focused on hospital interventions [111]. Most researchers and physicians are hospital based and this is the most straightforward explanation of this, despite the growing body of prehospital research and clinically active prehospital physicians [112, 113].
It is important to note that measures to reduce delays to activate the first three links in the chain of survival have all demonstrated a substantial impact on the chances of survival.

## CPR IN PREHOSPITAL AND TRANSPORTATION MEDICINE

Prehospital care is essential to emergency medicine and it is evolving in many respects towards an extension of the hospital's emergency department.





Modern prehospital care has many of the same opportunities to treat a patient in cardiac arrest as the hospital emergency department. Technical resources like defibrillators, electrocardiography (ECG) and its interpretation by a cardiologist, mechanical chest compression devices, monitoring (oxygen saturation, end-tidal $CO_2$, blood glucose) and drug therapies have been routine in many EMS systems for a long time. The addition of resources from cardiac arrest care in the emergency room, compared to prehospital care, is mainly a complete cardiac arrest team. It can be argued that a team that enters this time-critical situation at such a late stage risks delaying highly specialised, potentially life-saving procedures such as PCI or mechanical circulation [114]. The outcome in OHCA patients who still require CPR when arriving at the emergency department is poor [80].

Initiatives to add highly specialised competence to the out-of-hospital assessment are in progress [115]. The development towards reliable technical and digital solutions for telemedicine and video support is rapid.

## PASSIVE LEG RAISING – FROM INTENSIVE CARE TO PREHOSPITAL CPR

The passive leg raising (PLR) test has been the subject of lively debate in the context of predicting fluid responsiveness in the haemodynamically unstable patient [116-119]. The idea here is that PLR recruits a volume load of around 300 ml [120]. In potential fluid responders, this increase in venous return temporarily increases stroke volume and cardiac output [121]. In non-responders, the potentially harmful administration of fluid can hereby be avoided. The optimal manoeuvre for testing fluid responsiveness has been described as lowering the patient's trunk from a 45-degree angle and raising the legs at the same time, by tilting the bed [117, 122].

The idea of using PLR in CPR has been described in older CPR guidelines [123] and is sometimes identified as a means of increasing efficiency in CPR [124]. The physiological rationale behind PLR in CPR is that the increase in venous return would increase the output generated by manual chest compression. This would result in higher coronary perfusion pressure and increase the chances of ROSC.

In 2010, Axelsson et al. reported that PLR during uninterrupted CPR resulted in a significant increase in end-tidal levels of carbon dioxide [125], suggesting that PLR actually increases cardiac output from chest compressions.

In 2012, Dragoumanos et al. induced VF in 20 healthy piglets and randomly assigned them to CPR with PLR versus conventional CPR [126]. To allow a standardised manoeuvre, a 45-degree triangular device was used to elevate the hips, knees and ankles of the pigs. They were left untreated for eight minutes and then resuscitated according to the 2005 ERC guidelines. An arterial line was placed in the aorta via the common carotid artery. A Swan-Gantz catheter was placed in the right atrium via the internal jugular vein. Coronary perfusion pressure was then calculated as the difference between the minimal diastolic pressure in the aorta and the simultaneously measured diastolic pressure in the right atrium. Coronary perfusion pressure was found to be higher in the PLR group (22.8 ± 9.5 vs 10.6 ± 6.5 mm Hg, $P < 0.004$). Measurements were made just prior to the first defibrillation attempt. The return of spontaneous circulation was achieved in nine out of the 10 piglets resuscitated with PLR and six of the pigs in the control group.
This work indicates that PLR could be beneficial in CPR in humans.
To our knowledge, there are no trials investigating the effect of PLR in CPR in humans.

## THE SWEDISH AMBULANCE SERVICES

Healthcare in Sweden is decentralised. Sweden is divided into 290 municipalities and 21 regions. All the municipalities and regions have their own self-governing local authorities. The ambulance service is a regional responsibility. Prehospital activity can either be run by the regions themselves, or publicly procured and run by private contractors. In 2018, 15 of the Swedish regions had an in-house ambulance organisation. Two regions used exclusively private contractors and four regions had a mix [127]. In the region Västra Götaland, the ambulance service has been in house since 2012. Co-operation has been developed between the regions and the national dispatch centre has the opportunity, in an emergency like an OHCA, to use EMS crews from a nearby region if they are likely to have a shorter response time.
Even though half the regions (nine of 21) have a helicopter emergency service, the vast majority of all OHCA cases are treated and transported by car-bound EMS units.

National guidelines for resuscitation in OHCA are formulated by the Swedish Resuscitation Council (SRC), based on international guidelines from the ERC and the AHA. These guidelines are implemented in all EMS organisations through the national educational programme, designed by the SRC. The use of





mechanical chest compression varies over the country, but no device other than LUCAS is used.

According to reported data from 11 of the 21 regions, 65-90% of the EMS personnel were registered nurses and 40-90% of the EMS nurses had some kind of supplementary training [128].

## THE SWEDISH REGISTRY OF CARDIOPULMONARY RESUSCITATION – SRCR

The aim of the SRCR is to identify factors affecting survival after cardiac arrest and to guide the development of cardiac arrest care. The SRCR was instituted in 1990, by Dr Stig Holmberg. Dr Holmberg (1927-2019) was a leading force and a main strength in the evolvement of cardiac arrest care in Sweden. Apart from the SRCR, he also started the national movement of CPR training, resulting in the fact that today more than half of Sweden's population has participated in some kind of CPR training.

Coverage has gradually increased and today all ambulance organisations in Sweden report to the SRCR. For registration in the SRCR, the following criteria apply:

- The patient is unconscious and has absent or abnormal breathing.
- Chest compressions have been initiated and/or defibrillation has been performed.

Registration is performed by the EMS crew in all cases where CPR is initiated, by bystander rescuer, fire brigade, police or the crew themselves. All registrations are made online and this first part (Appendix A) is normally done in close connection with the event, by the first crew attending the scene. There is no common electronic charter in Sweden, but many districts have a digital link from their charter system to the registration website.

Patients suffering an OHCA where CPR has been initiated before the arrival of an EMS crew are included in the SRCR if resuscitation attempts are continued by EMS personnel, or if the patient has already regained spontaneous circulation on EMS arrival. In some cases, in which CPR is initiated before EMS arrival, the arriving crew find definitive signs of death and do not continue resuscitation attempts. These patients are not included in the SRCR.

A dedicated person in each region performs regular medical record searches to identify any missing cases. These searches are based on a list of words commonly used in the medical documentation of a cardiac arrest. Identified cases are registered retrospectively.

The follow-up registration is performed after the patient has been discharged from hospital (Appendix B). Survival is measured as survival to 30 days after the OHCA. In the original papers (I-IV) and the text of this thesis, the term "survival" refers to survival at 30 days after the OHCA. This is the outcome measurement used in all four papers.
The neurological performance of the survivors is assessed on discharge from hospital, by reviewing medical records. Their classification according to the scale of cerebral performance category (CPC) is recorded in the SRCR. The Utstein guidelines recommend the CPC score for neurological follow-up, together with the modified Rankin Scale [9]. This is a simple, well-established scale for quantifying cognitive and functional performance [129]. Cerebral performance category one refers to a good cerebral performance, a retained ability to work and only minor deficits are accepted. Category two signifies moderate disabilities in a conscious patient, with sufficient function to manage activities of daily life independently. Category three covers patients with a severe cerebral impairment, dependent on others for daily support. The unconscious patient in a vegetative state scores CPC four. Cerebral performance category five refers to brain death.

In relation to the follow-up registration, all survivors receive written information about their participation in SRCR. This information also present the opportunity for each survivor to apply for a copy of their personal information stored in the SRCR, as well as the possibility to withdraw their data from the registry.

The SRCR issues an annual report and, since 2018, this report has been digital [10]. All variables reported to the SRCR are described in Appendices I (part I) and II (part II).





# AIM

The overall aim of this work was to explore, identify and describe important survival factors in OHCA. In an attempt to widen the approach, both advanced techniques and a basic manoeuvre were examined, together with the aim of determining the importance of time and delay in treatment efforts. The aims of each specific paper are listed below.

I) The primary aim was to evaluate the distribution and characteristics of patients found in VF/pulseless ventricular tachycardia (pVT) in relation to the number of shocks delivered. Secondly, we wanted to describe and determine the association between various factors at resuscitation and 30-day survival with the emphasis on the number of shocks delivered.

II) The aim of this study was to describe the feasibility and determine the outcome of a direct pathway to an immediate coronary angiography among patients with OHCA and a good chance of survival. A secondary aim was to evaluate the feasibility of using mechanical chest compressions as a bridge to revascularisation among patients who did not attain ROSC at the scene.

III) The primary aim of the study was to determine whether PLR, when added to standard treatment after OHCA, would increase survival to 30 days.

IV) We aimed to determine the effect of ambulance response time on 30-day survival after OHCA. Secondly, we attempted to describe the association between ambulance response time and the usefulness of CPR before EMS arrival (bystander-initiated CPR).

# METHODS

This thesis is based on four observational papers (Table 1). Due to ethical considerations, many aspects of cardiac arrest treatment are very difficult, or impossible, to evaluate in randomised trials. Prior consent to performing any intervention in unconscious patients is required by Swedish law.

Papers I and IV are observational registry studies. Paper II is an observational feasibility study of a pathway for patients with OHCA. Paper III is an observational evaluation of an interventional manoeuvre implemented in eight ambulance districts in western Sweden.

| | Paper I | Paper II | Paper III | Paper IV |
|---|---|---|---|---|
| Design | Observational registry-based | Observational evaluation of introduced intervention | Observational evaluation of introduced intervention | Observational registry-based |
| Population | OHCA. National registry 1990-2015, n=19519 | OHCA. Sahlgrenska Univeristy hospital, Göteborg 2013-2015, n=86 | OHCA. Region Västra Götaland, 2012-2015, n=3554 | OHCA. National registry, 2008-2017 |
| Ethical approval Swedish Ethical Review Authority | DNR: 43116 | DNR: 953-17 | DNR: Ö 11-2011 | DNR: 2019-01094 |
| Main independent variable | Number of defibrillations in shockable OHCA | Immediate coronary angiography in OHCA | PLR | EMS response time |
| Primary outcome | Survival to 30 days | Survival to 30 days | Survival to 30 days | Survival to 30 days |

*Table 1. Methodological summary of Papers I-IV.*

# PAPER I

The first paper (I) is observational and is based exclusively on data from the SRCR. Associations between the number of defibrillations and both patient and resuscitation characteristics are described in a population of n=19,519 patients with either a witnessed or an unwitnessed OHCA in Sweden, between 1990 and 2015. Factors found to be correlated to the number of defibrillations were included in a multivariable logistic regression model. Unwitnessed cases were now excluded, since the time from collapse to CPR, defibrillation and EMS arrival was included in the model and this information was not available





in unwitnessed OHCA cases. New national CPR guidelines were introduced four times during the 25-year study period and analyses were performed for each five-year guideline period, as well as for the complete study period.

# PAPER II

The second paper (II) is a feasibility study of a direct pathway for patients with OHCA from the prehospital setting to immediate coronary angiography at the tertiary Sahlgrenska University Hospital. The pathway was implemented in clinical practice from 1 November 2013 to 31 October 2015. During this two-year period, pathway activation was considered by each EMS crew encountering a patient with an OHCA. The pathway was introduced as a quality improvement project and was available for activation 24 hours a day, seven days a week. The protocol was strictly clinical, aiming at the best possible cardiac arrest care.

During the pathway period, the Gothenburg EMS consisted of some 20 ambulances around the clock, where all the crews included at least one specialist nurse. In addition, there were three non-patient-carrying units in the system; two nurse-staffed, single-responder units and one physician-staffed support unit.

Information about the protocol was presented to all the EMS stations in Gothenburg, as well as the catheterisation laboratory unit, before the clinical introduction of the pathway. Written guidelines were available for all EMS staff during the period.

The EMS crew made an immediate on-the-scene evaluation according to a set of criteria. Since the decision to activate the pathway had to be instant, complete conformity with the criteria was not verified or imperative. The set of criteria aimed to provide the best possible support for the decision-making by the EMS crew.

## ACTIVATION AND EXCLUSION FROM THE PATHWAY

We stipulated three criteria for pathway activation in OHCA. The fulfilment of one of the criteria was considered sufficient for pathway activation:

- Collapse witnessed by EMS crew or crew from the Fire and Rescue Department (inclusion criterion 1)
- Bystander-witnessed collapse occurring < 3 minutes before EMS arrival and high-quality CPR performed, or cardiac arrest immediately defibrillated to return of spontaneous circulation by a public access defibrillator or at a primary care centre (inclusion criterion 2)
- Collapse occurring < 3 minutes before EMS arrival and retained spontaneous (or agonal) respiration on EMS arrival (inclusion criterion 3)

Two exclusion criteria were formulated:

- High biological age
- Presumed non-cardiac cause

Neither of the two exclusion criteria was specified in more detail and the assessment of a high biological age, as well as the likelihood of cardiac origin, was left to the EMS crew.

When the EMS crew decided to activate the pathway, the catheterisation laboratory interventionalist was contacted by telephone (often through a co-ordinator at the coronary care unit) as soon as possible. A decision was made over the phone by the interventionalist and the patient was accepted for immediate coronary angiography or not. Accepted patients were taken directly to the catheterisation laboratory with minimal delay. Mechanical chest compressions with the LUCAS device was used to ensure withheld CPR quality and EMS crew safety during loading and transportation. Patients not accepted for coronary angiography were taken to the emergency department, according to prior routine procedure. Resuscitation was performed by the EMS crews according to local CPR guidelines, irrespective of the in-hospital destination.

EMS crews activated the pathway, by contacting the catheterisation laboratory interventionalist, on 86 different occasions. All data were collected through reviews of both pre- and intrahospital medical records and evaluated by a descriptive analysis. For comparison, both regional and national data were retrieved from the SRCR.
We reviewed all 86 cases and matched data from EMS files with inclusion and exclusion criteria.





# PAPER III

Passive leg raising was introduced as a routine treatment in the CPR guidelines, in eight ambulance districts in western Sweden.
An application for a randomised trial to evaluate the effect of PLR in OHCA was rejected and an observational approach was suggested by the central ethical review board (see discussion). The study period was from 1 April 2012 to 31 March 2015.

All EMS crews were informed beforehand, through educational meetings, an instructional video and written instructions. The desirable feet elevation (20-45 degrees) was achieved using either a standard chair, or the ambulance backpack, supporting the feet.

A previous study of 44 endotracheally intubated patients, suffering an OHCA and receiving CPR, had demonstrated an increase in end-tidal $CO_2$ from PLR [125]. In this work, an angle of 20-degree leg elevation was chosen to standardise the PLR according to the equipment brought by the ambulance crew. At this time, the EMS crews in Gothenburg carried a defibrillator with a height of 35 centimetres and measurements showed that a 35-centimetre feet elevation corresponds to a 20-degree hip joint flexion in a 170- to 175-centimetre tall person. Dragoumanos et al. [126] reported in 2012 that a 45-degree passive leg raise during CPR in piglets significantly increased coronary perfusion pressure in the minute prior to the first shock.
Based on this knowledge, PLR between 20 and 45 degrees was considered desirable. The seat of a standard chair places the feet around 45 cm above the floor and was regarded as ideal. The ambulance backpack was equal in height to a chair and was regarded as satisfactory for the PLR manoeuvre.

The instructions for PLR recommended immediate leg elevation. If PLR was not performed within five minutes from arrival and the start of CPR, the patient was registered as being resuscitated without PLR.

The EMS systems in western Sweden used mechanical chest compressions (LUCAS) and all the crew members were trained to use the device. During the study period, not all ambulances carried LUCAS all the time, due to resource issues in some services. The dispatch centre routinely alerts two EMS crews in the case of an OHCA or a suspected OHCA. The procedure is to dispatch the closest unit available, followed by an additional unit carrying LUCAS.

All data collection was made via the SRCR, where PLR was added as a dichotomous variable (PLR yes/no) during the study period.

# PAPER IV

This study is based on data reported to the SRCR from 2008 to 2017. During this time, n=48,325 patients with an OHCA were reported to the registry. All unwitnessed cases were excluded, to ensure that the EMS response time corresponded to the time spent from collapse to EMS arrival. Paediatric cases assessed by the EMS crew as sudden infant death syndrome (SIDS) were excluded and the remaining number of paediatric cases 0-16 years of age were n=284.
The total number of patients included in the study was n=20,420.

The starting point for the EMS response time is when the dispatch call is sent from the dispatch centre to the radio units of the EMS crew. The endpoint of the response time is slightly more complex. The SRCR collects two different time stamps, one when the vehicle arrives at an address, as reported by the electronic positioning system in the vehicle, and one estimation from the crew of the time of arrival at the patient's side. Normally, the crew member filling in the registry report makes an estimation of the time spent from vehicle arrival at the address, provided electronically by the dispatch centre, until the crew reaches the patient. The time spent from parking the vehicle to reaching the patient depends on all eventual difficulties involved in finding and reaching the exact location of the patient. Crowded environments, very remote locations not accessible by vehicle, harsh weather conditions or large, complex buildings making it difficult to find the way are just some examples of what the crew may encounter after parking the vehicle.
This exact procedure for identifying the time of EMS crew arrival with the OHCA patient is not uniform or validated nationally and regional comparisons cannot easily be made.

To describe and quantify the relationship between survival to 30 days and EMS response time, we used logistic regression to model odds ratios (ORs). To identify possible confounding factors, a directed acyclic graph (DAG) was constructed (Figure 5). Factors were regarded as true confounders and were only adjusted for in the regression model if they were associated with survival, associated with EMS response time and not a link in the causal chain.

The time from collapse to CPR and from collapse to defibrillation, as well as the initial rhythm, were regarded as possible proxies for EMS response time and links in the causal chain and were not adjusted for in the overall model. Instead, we stratified the material for shockable and non-shockable rhythms.





This selection process generated a logistic regression model adjusted for age, gender, calendar year and place of arrest.

Hospital interventions were regarded as possible confounding factors, in the sense that a relatively long response time could result in poorer conditions for the patient on hospital arrival and thereby affect intra-hospital actions. We have no indications that there would be a systematic imbalance in hospital interventions between the different groups of EMS response time. To make sure that improved hospital interventions during the study period did not confound our results, we stratified by calendar year to verify consistency.

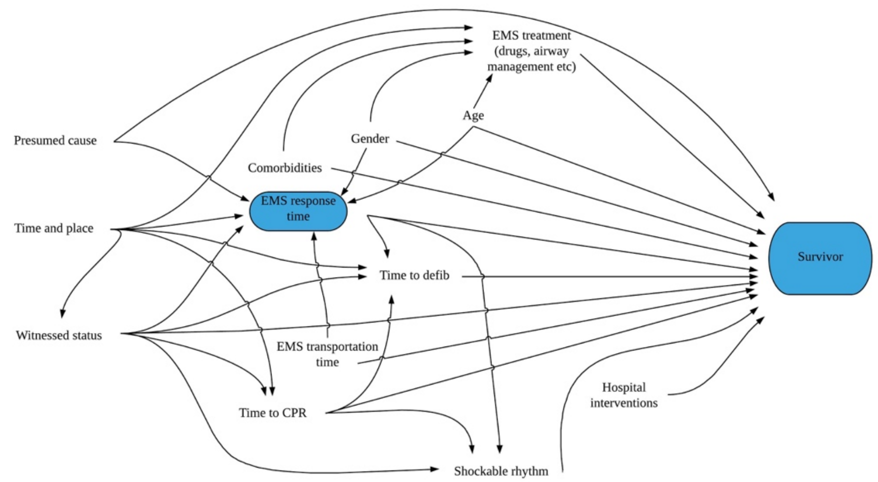


*Figure 5. The directed acyclic graph used to identify covariates for regression modelling.*

| | Paper I | Paper III | Paper IV |
|---|---|---|---|
| Univariable analysis | Mann-Whitney U test<br>Spearman's rank correlation | Fisher's exact test<br>McNemar's test<br>Mann-Whitney U test<br>Wilcoxon's signed rank test | |
| Multivariable analysis | Logistic regression | Logistic regression | Logistic regression |
| Other | | Propensity score<br>Multiple imputation | Multiple imputation |

*Table 2. Summary of statistical methods applied in Papers I, III and IV.*

# RESULTS

## PAPER I

Among the 19,519 patients with an OHCA presenting with a shockable rhythm, survival to 30 days decreased with each added shock, regardless of witnessed status and time period during the 25-year study period.
Ten or more shocks were delivered in 7.5% of all cases with VF/pVT and more than three shocks were delivered in 45% of all cases.

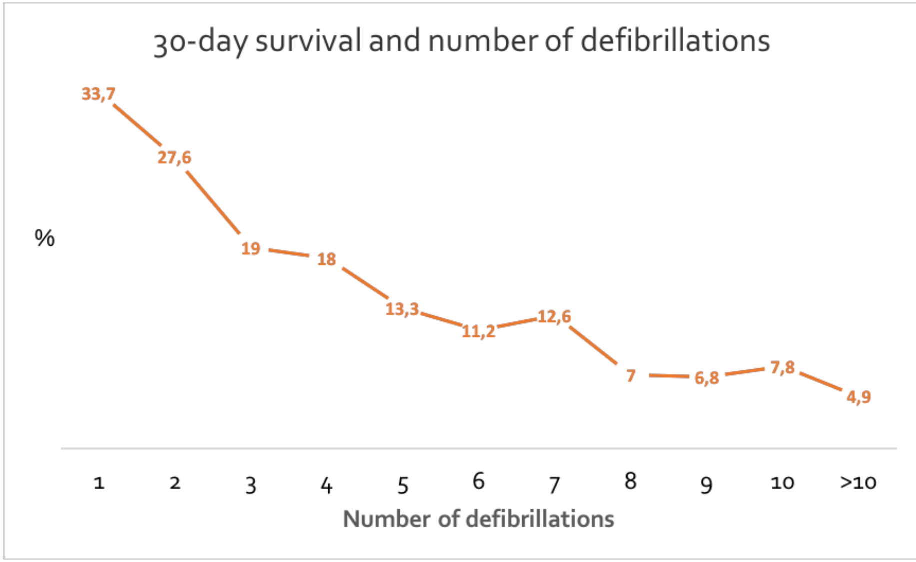


*Figure 6. Thirty-day survival in relation to the number of defibrillations.*

CPR guidelines were revised every five years during our study period and we used stratification to address this problem. Patients were grouped according to the number of defibrillations they received (1-3, 4-10 and > 10) and they were then stratified for the five different time periods corresponding to the changes in national guidelines. Survival increased for every new five-year period in all three groups of defibrillations according to Figure 7.





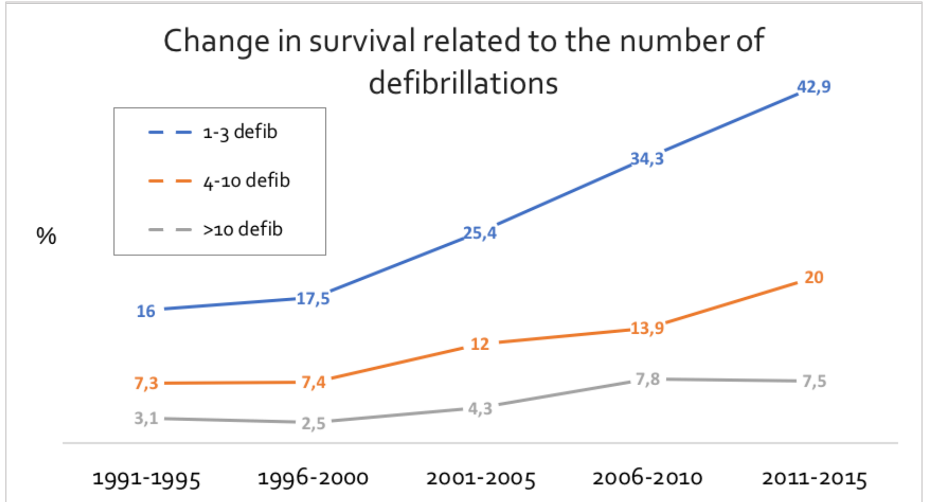


*Figure 7. Thirty-day survival for each five-year guideline period, in relation to the number of shocks delivered.*

In the multivariable analysis of the complete study period (1990-2015), we identified 11 further factors associated with 30-day survival, together with the number of shocks delivered (Figure 8). The four factors identified as predictors of an increased likelihood of 30-day survival were CPR before EMS arrival, cardiac aetiology, female gender and the year the cardiac arrest occurred.

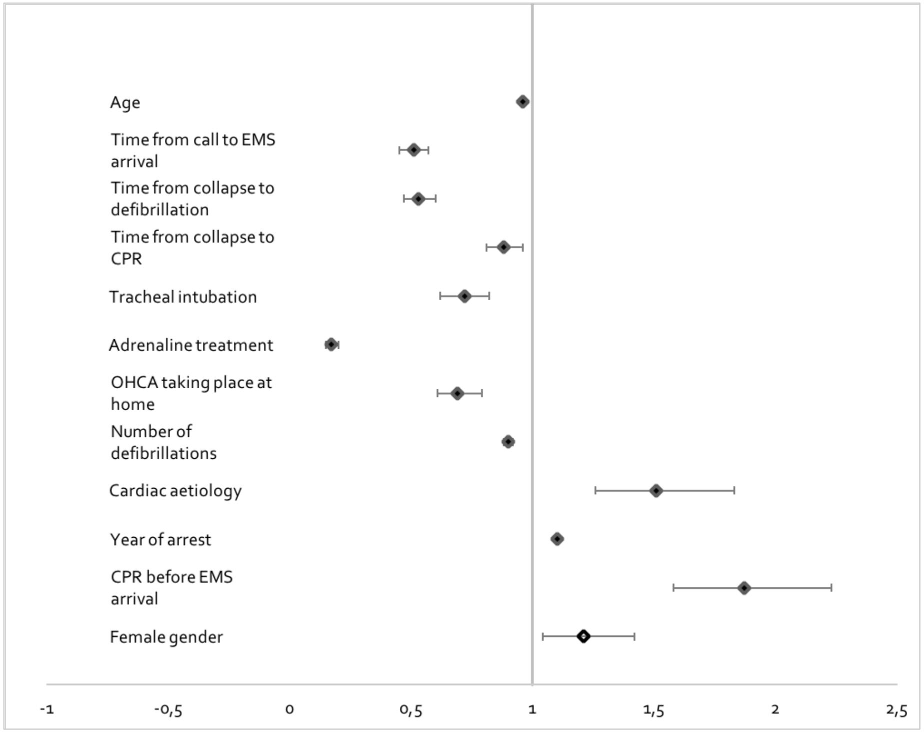


*Figure 8. Odds ratios and their 95% CI for factors found to be associated with 30-day survival.*

The following eight factors emerged as predictors of a decreased likelihood of 30-day survival: adrenaline treatment, increasing time from call to EMS arrival, increasing time from collapse to defibrillation, OHCA taking place at home, tracheal intubation, increasing time from collapse to CPR, number of defibrillations and age.

To deal with the potential confounding effect of the different guidelines during the study period, we performed a multivariable analysis in each subgroup corresponding to a five-year guideline period (1990-1995, 1996-2000, 2001-2005, 2006-2010, 2011-2015). After adjustment, it was confirmed that the number of defibrillations was associated with 30-day survival in all five time periods. The same was true for the variables of age, CPR before EMS arrival, time from collapse to defibrillation and use of adrenaline.





# PAPER II

We organised an EMS screening for immediate coronary angiography in selected patients with an OHCA and evaluated an intention-to-treat analysis, as well as a per-protocol analysis (Figure 9). Patient selection was extensive and aimed to identify particularly advantageous conditions. Eighty-six patients were screened by the EMS and 38 were accepted for immediate angiography by the interventionalist. Twenty of these patients had a coronary intervention. The per-protocol analysis showed that only 58% of the patients actually met the inclusion criteria without any exclusion criteria being fulfilled.

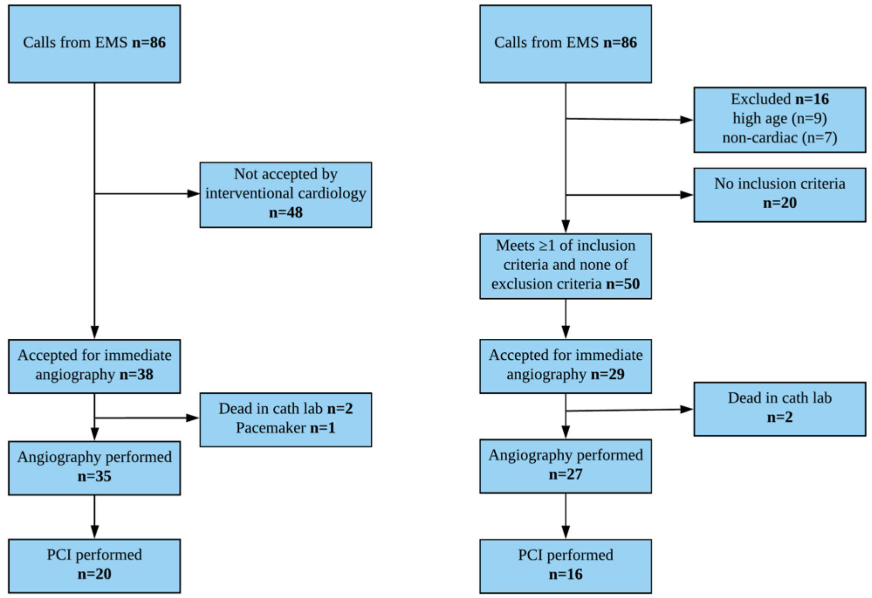


*Figure 9. Flowchart representing the chain of actual events in the intention-to-treat analysis (left) and the per-protocol analysis (right) of the n=86 OHCA cases.*

The overall survival to 30 days was 30%. All survivors (100%) had a good cerebral performance (CPC 1: 92%) or sufficient cerebral function for independent activities of daily life (CPC 2: 8%). Ninety-two per cent of the survivors were found in a shockable rhythm and all the survivors had ROSC on hospital arrival.

The median time from collapse to the start of a coronary angiography procedure was 63 minutes and the fastest procedure was initiated 28 minutes after collapse.

# PAPER III

We introduced PLR in addition to standard CPR in patients with an OHCA and found no evidence that prehospital PLR was able to increase survival to 30 days.

The treatment was introduced in eight ambulance districts and n=1,551 patients were compared with n=2,003 control patients from the same districts, who did not receive PLR for various reasons. Survival to 30 days was 7.9% among patients who received PLR and 13.5% among those who did not (OR 0.55; 95% CI 0.44-0.69; $p < 0.0001$), but there was a considerable imbalance between the two groups at baseline.
The control group was characterised by more EMS crew-witnessed patients and a prolonged delay from collapse to calling for the EMS, the start of CPR and defibrillation. Confounding factors were handled primarily by adjustment in a multivariable logistic regression model.

A regression model was used to construct a propensity score for receiving PLR. Patients were then matched 1:1, according to whether or not they had received PLR. This comparison showed a 30-day survival rate of 8.6% in the PLR group versus 8.2% in the control group (OR 1.07 CI 0.80-1.44, $p = 0.65$). These results were verified by using the propensity score as a covariate in a multiple regression model (OR 1.05 CI 0.81-1.37, $p = 0.69$) and by performing a multivariable analysis adjusted for same variables as those included in the propensity score (OR 1.07 CI 0.81- 1.42, $p = 0.64$).



Johan Holmén

| 30-day survival, PLR versus no PLR | n | OR | 95% CI | p-value |
|---|---|---|---|---|
| | | | | |
| Crude model (all pts) | 3554 | 0.55 | 0.44-0.69 | <0.0001 |
| Crude model (propensity score pts) | 3273 | 0.53 | 0.42-0.67 | <0.0001 |
| Multivariable model | 3273 | 1.07 | 0.81-1.42 | 0.64 |
| Matched on propensity score | 2524 | 1.07 | 0.80-1.44 | 0.65 |
| Regression adjusted for propensity score | | | | |
| Propensity score continous | 3273 | 1.05 | 0.81-1.37 | 0.69 |
| Propensity score deciles | 3273 | 1.04 | 0.80-1.36 | 0.76 |

*Table 3. ORs for 30-day survival (PLR versus no PLR) in all models used for analysis.*

Introducing PLR within five minutes from the start of CPR after an OHCA did not show any evidence of improved survival to 30 days compared with standard CPR according to guidelines.

# PAPER IV

We analysed the association between EMS response time and survival to 30 days in patients suffering an OHCA. After careful reasoning to identify possible confounding factors, the model adjusted for age, gender, calendar year and place of the arrest was chosen to demonstrate the effect of ambulance response time on survival to 30 days (Figure 10). The unadjusted results were found to be similar.

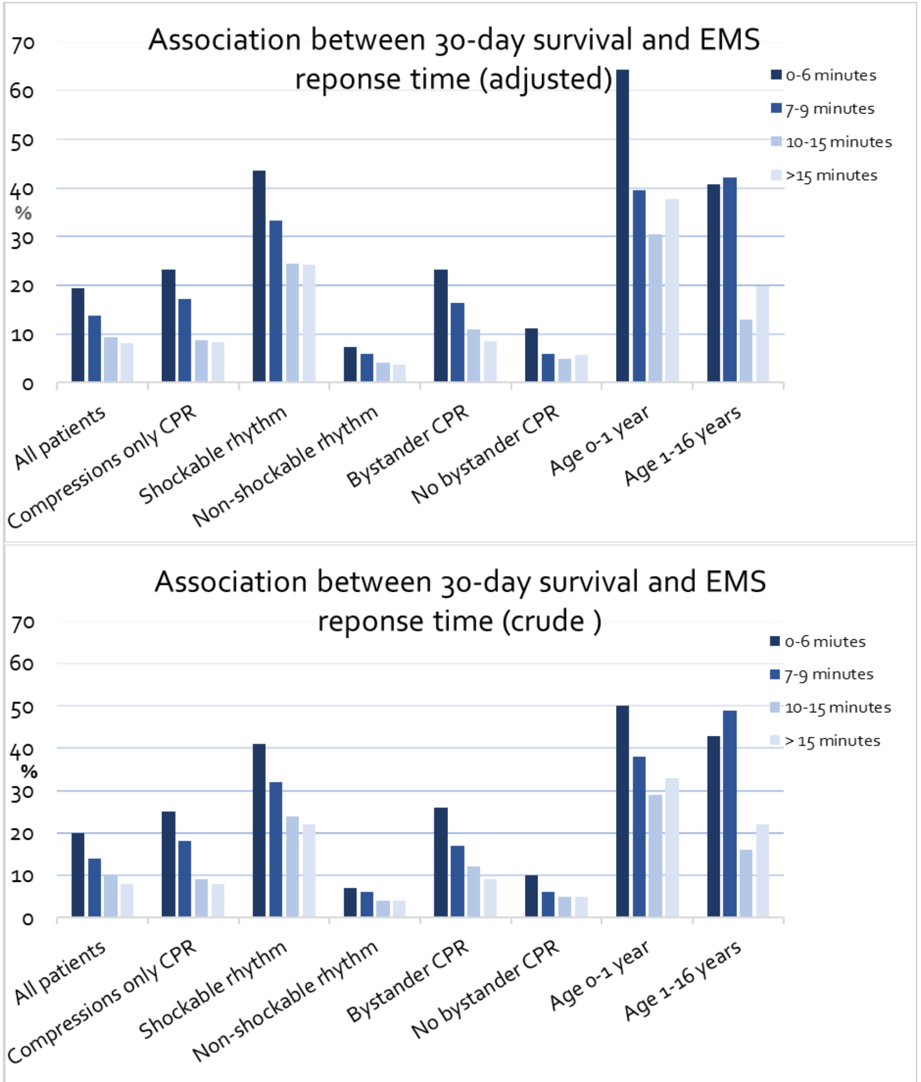


*Figure 10. Adjusted (top) and unadjusted (bottom) analyses of the association between EMS response time and survival to 30 days, stratified for crucial survival factors. An adjustment was made using age, gender, calendar year and place of the arrest as covariates in a logistic regression model.*

Bystander-initiated CPR and an initial shockable rhythm are factors of great importance for survival chances, as seen in the fully adjusted model (Figure 11). Both subgroups were analysed separately and, regardless of both the initial rhythm and whether or not CPR was performed before EMS arrival,





survival chances decreased with an increasing EMS response time (Figure 10).

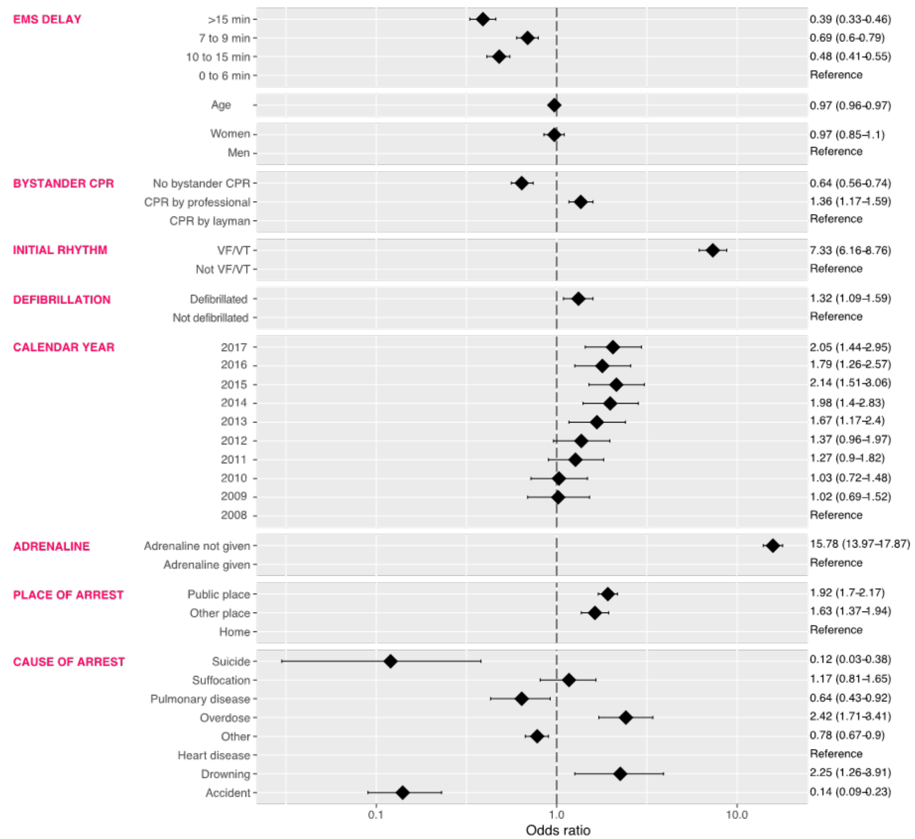


*Figure 11. The fully adjusted model.*

Among OHCA patients receiving bystander-initiated CPR (n=13,047), 21% were subject to compressions-only CPR. Survival dropped from 23% to 9% when the EMS response time increased from 0-6 minutes to 10-15 minutes in this subgroup. The corresponding drop for all OHCA patients receiving bystander-initiated CPR was 23% to 11% (Figure 10).

Paediatric OHCA patients were analysed separately, demonstrating a similar association between EMS response time and survival to 30 days as in the overall material (Figure 10).

About 90% of the survivors were assessed as having cerebral performance category one or two on discharge from hospital (Figure 12). We found similar proportions of CPC 1 and 2 in the four groups of EMS response time. The results do not indicate a correlation between EMS response time and CPC outcome among survivors.

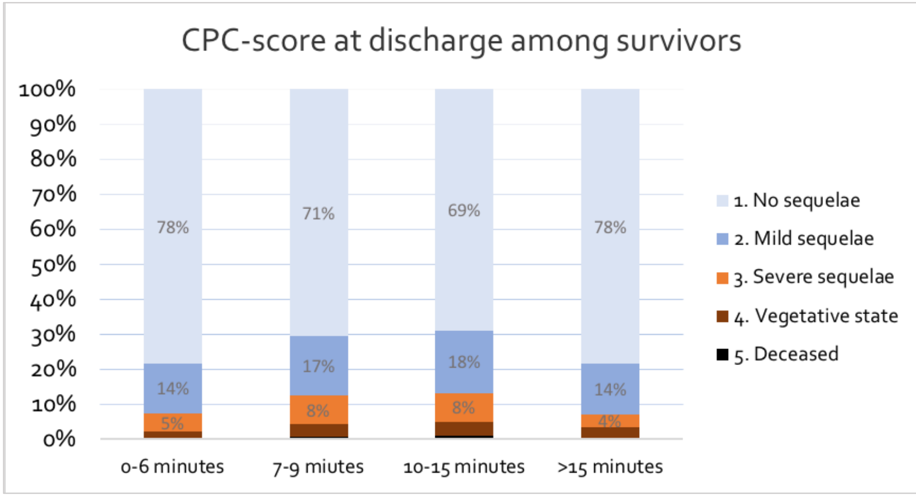


*Figure 12. CPC-score among survivors in relation to EMS response time.*





# DISCUSSION

## PAPER 1

**OHCA patients found in a shockable rhythm have a decreasing chance of survival for every defibrillatory shock added. What are the clinical implications of this finding?**

The clinical implication correlates to the delicate question of when to initiate the loading and transportation of the patient found in an OHCA with a shockable rhythm. We know that the chances of a successful countershock after an OHCA presenting with a shockable rhythm are improved not only by a minimal delay to CPR and defibrillation but also by high quality-CPR. In practice, it is reasonable to believe that on-the-scene CPR (normally on the floor/ground) is superior to CPR during loading and, at least for manual compressions, during transportation. The decision to initiate loading and transportation means temporarily reducing both CPR quality and the chance of the following defibrillation being successful. This has to be taken into account when deciding on the exact time for loading the OHCA patient in the ambulance.

During 2020, the Swedish Resuscitation Council launched an algorithm for decision support in adult OHCA and CPR situations [130]. This recommendation, in an OHCA patient with a shockable rhythm, is to perform three two-minute treatment cycles at the scene and then consider transportation with ongoing CPR. Three treatment cycles mean three or four defibrillations, as CPR is normally initiated immediately and ongoing as the first defibrillation is prepared.

This recommendation is well in line with our results, showing that the decrease in survival was more marked for the first three defibrillations and less pronounced for cases in which more than 10 defibrillations were administered.

Yet another aspect is the possibility of extracorporeal CPR (E-CPR). Mechanical circulation in cardiac arrest is normally provided by femoral cannulation. Extracorporeal membrane oxygenation and blood flow is then provided by an oxygenator and a centrifugal blood pump. In shock-resistant cases, E-CPR has been shown to be useful [131]. A prehospital approach, with out-of-hospital cannulation, has been suggested and has been applied by mobile intensive care units in Paris since 2011, with some success [114]. Our results demonstrate that, after seven or more defibrillations, the chances of

survival are low (Figure 6). After as many as seven unsuccessful defibrillations, there is a need for something else, in addition to CPR according to guidelines, to improve the patient's chance of surviving.
In selected settings and situations, E-CPR allows more extensive diagnostics, treatment and a possible bridge to recovery.
Both the distance to and the potential E-CPR capacity at the receiving centre have to be considered when deciding on the exact time to initiate loading and transportation. In our second study (Paper II), we noted that, among patients with an OHCA selected for immediate coronary angiography, no patient with ongoing CPR on hospital arrival survived. Six patients from this cohort of n=86 received ECMO, but none of them survived to 30 days or hospital discharge. This poor outcome may reflect the lack of more aggressive E-CPR at the receiving hospital during the study period for Paper II.

Terminating CPR despite an ongoing VF/pVT is unlikely to be ethical in a setting in which E-CPR is available. As always, biological age and co-morbidities have to be taken into consideration when deciding on highly invasive interventions with a long and demanding recovery.

**Is CPR still meaningful after as many as > 10 defibrillations?**

Time is crucial, but, even after more than 10 shocks we found that the survival chances were as high as 4.9% in our material. During the study period, the chances of survival more than doubled (3.1% in 1991-1995 versus 7.5% in 2011-2015) for patients in need of > 10 defibrillations. The proportion of patients requiring > 10 defibrillations decreased from 13 % in 2001-2005 to 5.4% in 2011-2015. One important limitation in our study was that neurological function after the OHCA was not considered. We do not know how the number of defibrillations correlate to neurological impairment among the survivors.

Our conclusion that survival remains possible even after a large number of shocks and that the number of shocks is independently associated with poorer survival (Paper I) has now been confirmed by other researchers [132].

The important distinction between shock-resistant VF and recurrent VF is not clear cut throughout the literature [133]. This complicates the evaluation of many of the studies, as well as Paper I in this thesis. The recurrent VF, re-appearing after it has been terminated, might result from a different pathophysiology than the shock-resistant fibrillation not responding to defibrillations. Paper I includes both categories of patient suffering from a VF, as does much of the research in this field. We do not know whether > 10 defibrillations in a shock-resistant VF has the same chances of survival as the





patient with repeated episodes of VF in combination with short periods of ROSC or asystole/PEA.
In many cases, we assume that CPR is meaningful even after > 10 defibrillations. However, this decision demands a careful assessment of each specific case. The patient's entire situation, including biological age, co-morbidities and capacity to recover, has to be considered in all prolonged resuscitations. There is no general guideline that can cover all possible scenarios and be valid for all patients. Nevertheless, knowledge acquired from a large group of patients can still be a valuable piece of information in the search for the best possible management in each situation.

**The use of adrenaline was one of the factors associated with a poorer outcome (together with the time from collapse to defibrillation, the number of defibrillations and high age). This was seen in all five-year periods between 1991 and 2015, corresponding to guideline changes. Why?**

The use of adrenaline in an OHCA has been questioned for decades. In 2018, a hallmark, randomised trial from the UK concluded that "the use of epinephrine resulted in a significantly higher rate of 30-day survival than the use of placebo, but there was no significant between-group difference in the rate of a favourable neurologic outcome because more survivors had severe neurologic impairment in the epinephrine group" [77]. It is important to note that the overall 30-day survival rate was 3.2 % (adrenaline) and 2.4 % (placebo) in this study, including adult OHCA patients from 2014 to 2017. During the same time period in Sweden, the overall survival to 30 days was slightly more than 11%, based on data from the SRCR [10]. This may indicate that OHCA care is not easily comparable between Sweden and the United Kingdom (UK) and that the effect of adrenaline in CPR under UK conditions is not necessarily the same as in Sweden. On the other hand, the UK study cohort was extremely selected and we are unable to exclude the possibility that the survival figures would have been just as low if the trial had been performed in Sweden.

Many observational studies present the same finding as we do in Paper I: adrenaline treatment is associated with poorer outcome. The median time from emergency call to adrenaline and placebo administration was 22 and 21 minutes respectively in the UK study [77]. There is a long way from association to causality and the most obvious reason for our finding is that adrenaline comes as a relatively late intervention, when many of the survivors have already been resuscitated (confounding by indication). In addition, the probability of receiving adrenaline increases with the duration of resuscitation attempts, along with a decreasing chance of survival as resuscitation proceeds.

By using adrenaline according to guidelines, we have identified the patients with the lowest chance of survival after an OHCA.

**If the number of defibrillations is just a proxy for time spent resuscitating, why is their correlation to the chances of survival important?**

Time without circulation causes death and all interventions in OHCA are related to time. An analysis aiming to describe an OHCA intervention independently of time is simply unrealistic. Nor is it of any clinical importance, since CPR guidelines for the treatment of cardiac arrest with a shockable rhythm state that every defibrillation should be followed by two minutes of CPR [5, 134].

When resuscitation is performed according to guidelines and each defibrillation is delivered at a predetermined time from the previous defibrillation, the number of defibrillations can never be independent of the time spent resuscitating the patient. Based on perfect guideline adherence, the additional two minutes spent for every defibrillation added would theoretically allow an estimation of the time spent resuscitating the patient, from the number of defibrillations administered. In practice, the time between defibrillations is likely to vary substantially and there might be many reasons for this. For example, it is possible that the arrested patient's initially shockable rhythm turns to a non-shockable rhythm. This could be temporary, with a recurrent shockable rhythm later in the course.

The association between the number of defibrillations and the chances of survival is not necessarily equally important during the course of resuscitation. Describing this association in detail could be important to the timing of other actions, such as when to prioritise applying mechanical chest compressions or when to initiate loading into the ambulance vehicle.

One possible way to acquire further knowledge on this matter would be a technical solution allowing real-time documentation – for example, a sound-recording device, activated by the EMS crew when turning on the defibrillator. Simple spoken commands to confirm specific interventions (defibrillations, ventilation, airway manoeuvres etc.) could then be read from the recording and exact time notations for every defibrillation would be possible.

At present, we do not know whether the association between the number of defibrillations and the chance of survival is explained simply by time or whether there are other explanations as well.





**Ambulance response time was included as an explanatory variable in the model for survival after a witnessed OHCA. How important was the EMS response time?**

In a multivariable analysis of factors associated with survival to 30 days, the EMS response time demonstrated an OR of 0.51 (CI 0.45-0.57). This means that the chances of survival declined as the EMS response time increased in this model. The EMS response time showed a larger impact on survival to 30 days than both the time from collapse to CPR (OR 0.88, CI 0.81-0.96) and the time from collapse to defibrillation (OR 0.53, CI 0.47-0.60).

However, fewer than half the witnessed cases were included in the multivariable analysis, as the amount of missing data was considerable. Even though this model has limitations, this was interpreted as an indication that the EMS response time is an independent and important survival factor. This correlation was further explored in Paper IV of this thesis.

## PAPER II

**Is it feasible to establish an EMS-activated pathway for immediate coronary angiography in OHCA?**

The answer to this question is yes. One of the main findings from evaluating the pathway to immediate coronary angiography (Paper II) is that prehospital decision-making and logistics can be rapid. In half the patients, the angiography procedure was initiated within 63 minutes of collapse (tenth to 90th percentile: 42-87 minutes). The fastest procedure was started 28 minutes after collapse.

None of the survivors among the patients selected for the pathway (n=86) had a CPC score of > 2. This supports the fact that the actual selection still identified patients with favourable conditions, despite poor compliance with the set criteria.
The limited feasibility we found was primarily a matter of the selection of patients, as the initial screening procedure was not accurate enough. It needs to be simpler.

**Many of the OHCA patients selected for immediate angiography by the EMS crews did not fulfil the given pathway criteria (42%). Why?**

We can only speculate about the answer to this question. In informal discussions with EMS crews and from personal experience of managing patients within the pathway, the criteria for inclusion were too complex. The OHCA situation is always time critical and decision-making has to be rapid. Complex criteria for inclusion/exclusion exerted added pressure on the EMS crew in this situation and it is possible that a fear of excluding patients from a potentially beneficial pathway pushed selection towards accepting the patient for the pathway rather than the opposite.
Another recurrent issue was the inclusion criterion stating that collapse should have been witnessed within three minutes of EMS arrival. Estimating a three-minute time period is neither easy nor reliably made in an OHCA situation. It is reasonable to assume that this timeframe was in fact extended to more than three minutes, with the aim of not jeopardising inclusion.

**Which OHCA patients appear to benefit most from an EMS-initiated immediate coronary angiography and which are the suggested criteria for this pathway?**

According to our results, an initial shockable rhythm is more likely to be an accurate and simple criterion for prehospital screening and subsequent pathway activation. This statement is based on the fact that 92% of the survivors (Paper II) had a shockable initial rhythm. However, our data were based on 86 patients and further research is needed to address this question satisfactorily.

**A randomised trial might have been more informative when it came to exploring the value of EMS-initiated immediate coronary intervention in OHCA. For what reasons was this not possible?**

Several reports support immediate coronary angiography in patients successfully resuscitated after an OHCA, regardless of ECG characteristics [23, 135, 136].
When it comes to coronary angiography and PCI during CPR, successful cases have been described [105, 106]. Immediate coronary angiography is currently recommended in OHCA after ROSC, in the presence of STEMI [137-139]. It has been suggested that the prevalence of an acute coronary occlusion after an OHCA with a likely cardiac cause is around 40% [140]. A study reporting on early coronary angiography in witnessed OHCA patients without ST elevation





on the primary ECG found that 14 of 38 patients (37%) had a culprit lesion on angiography [141].

With this state of knowledge, the overall assessment was that optimal treatment for the patients fulfilling pathway criteria should be CPR according to guidelines, followed by immediate coronary angiography and PCI when indicated. When this pathway was first implemented, it was regarded as a pilot study, as experience was very limited and the number of eligible patients in Gothenburg was fairly small.
The pathway was activated prehospitally to minimise the time to angiography procedure and ROSC on hospital arrival was not required. Mechanical chest compressions using the LUCAS device were regarded as the best way to ensure high-quality CPR and EMS crew safety during loading and transport. Under these circumstances, a randomised trial with a control group which was not offered immediate coronary angiography was considered ethically unjustifiable.

More recently, based on multiple small studies with consistent results, early coronary angiography (< 24 hours after cardiac arrest) has been found to be associated with a significantly higher survival and better neurological outcomes in a systematic review from 2018 [96].

The desired timing of coronary angiography and intervention among immediate survivors of an OHCA is still unclear. In a multicentre trial from 2020, including n=552 patients successfully resuscitated after an OHCA and found in a shockable rhythm, Lemkes et al. [103] conclude that “Among patients who had been successfully resuscitated after OHCA and had no signs of STEMI, a strategy of immediate angiography was not found to be better than a strategy of delayed angiography with respect to overall survival at 90 days”.
At present, there is an ongoing randomised, clinical trial in Sweden, evaluating the appropriate timing of coronary angiography among immediate survivors of an OHCA with a presumed cardiac aetiology and no signs of STEMI [141]

# PAPER III

**What circumstances prevented a randomised trial to evaluate the effect of PLR in out-of-hospital CPR?**

In 2011, we applied for the ethical approval of a randomised trial evaluating the effect of PLR during CPR on survival to 30 days after OHCA. This application was primarily assessed by the regional ethical review board in Gothenburg, who were unable to agree on this matter and the application was referred to the central ethical review board in Sweden. The central board stated that patient consent in OHCA is impossible and consent from a relative would risk delaying and interfering with CPR and resuscitation. Further, they concluded that there is no legal scope for research in an unconscious patient without consent. The application was therefore rejected, with a suggestion for an observational approach. The central review board considered PLR harmless and potentially beneficial. They mentioned the possibility of the implementation of PLR as a routine procedure followed by an observational evaluation, which would not require any further approval by the ethical board.

The central ethical review board added that they had turned to the Swedish government, in October 2010, calling for an amendment. In the rejection letter, the board stated that they were sending our application and its final decision to the Swedish government, as an example of the disadvantages of the current regulation.

**PLR was implemented in CPR guidelines for eight ambulance districts. Despite this, only 44% of the eligible OHCA patients received PLR. Why?**

Knowledge and training in CPR are widespread in Swedish EMS systems and have a long tradition. Adherence to guidelines is generally regarded as essential. We do not know the extent to which the addition of the PLR manoeuvre was actually accepted among the EMS personnel as being potentially beneficial to the OHCA patient. It is possible that, if more extensive information on PLR had been given to the EMS personnel, the study would have had a greater impact and compliance would have been higher.

Another possible contributory factor is that the PLR manoeuvre was forgotten, or considered not to be a priority, in OHCA situations which were more mentally demanding for the EMS crew. This hypothesis is supported by the fact that only slightly more than one third of the crew-witnessed OHCA patients included in the study received PLR. A cardiac arrest witnessed by the





EMS is likely to be a more stressful situation for the crew. It is possible that this contributed to PLR being less frequently performed among crew-witnessed cases.
Yet another possibility is that some patients, who suffered from a VF witnessed by the EMS crew, were very rapidly defibrillated to ROSC with no time for PLR.
Patients who received PLR were slightly older (median age of 72 years versus 70) and included a smaller proportion of crew-witnessed cases (12.6 % versus 17.7 %) than those who did not receive PLR.

**Patients who received PLR during CPR were more frequently treated with adrenaline, amiodarone and endotracheal intubation. This could be interpreted as a prolonged course of resuscitation. Did the patients treated with PLR have worse conditions before EMS arrival, causing a more extended resuscitation attempt?**

First, most of the survivors of OHCA regain circulation early after the collapse. The chances of survival are reduced for every minute of delay to CPR and defibrillation [35, 142]. A lower survival rate is therefore of necessity associated with the prolonged duration of a CPR attempt. One study inclusion criterion was that PLR should be performed within five minutes of EMS arrival. The sooner the patient regained circulation, the shorter the time to perform the PLR manoeuvre. From this perspective, the higher chance of survival found in the crude data analysis (Paper III, Table 1) among the patients who did not receive PLR is not surprising.

Our results indicate worse conditions for the OHCA patients treated with PLR: higher age, a smaller proportion of crew-witnessed cases and patients receiving bystander-initiated CPR, as well as a smaller proportion taking place in public places (Paper III, Table 1). This imbalance between groups highlights an important limitation in observational studies and furthermore the importance of adequate statistical analysis and a thoughtful interpretation.

**The PLR manoeuvre was evaluated in comparison with a group of OHCA patients not receiving PLR. There was a marked imbalance between the two groups. How was this imbalance addressed?**

Various statistical approaches were used to address this problem. The main analysis was performed using propensity score matching, where factors identified as important for the likelihood of receiving PLR were included in the score. The two groups were then matched on the basis of this propensity score and compared regarding 30-day survival, demonstrating no significant difference between groups (OR 1.07, CI 0.80-1.44, for PLR patients in relation to those not receiving PLR).

In addition, a standard multiple logistic regression analysis with the variables included in the propensity score above as covariates was performed, yielding an almost identical result (OR 1.07, CI 0.81-1.42) as in the matched propensity score analysis (Table 3). To further verify the result, we used the propensity score, both as a continuous variable and divided into deciles, as an adjustment variable in a multiple regression model, again yielding similar results (OR 1.05, CI 0.81-1.37 and OR 1.04, CI 0.80-1.36 respectively). Finally, we used multiple imputations to address the problem of missing data for several of the variables; this, too, produced a similar result (OR 1.10, CI 0.84-1.44). One limitation to the main analysis in this study is that only 71% of the patients were matched in terms of propensity score.

**Is there a future for the PLR manoeuvre in OHCA?**

We studied a large number of patients and the representativeness of the study cohort is likely to be very high. It is unlikely that PLR in OHCA, initiated within five minutes of EMS arrival, is beneficial. However, it is possible that the time from collapse, or from the initiation of CPR, to PLR is important. A positive effect of PLR performed earlier in the resuscitation procedure, for example, as a dispatcher-assisted manoeuvre in addition to bystander CPR, cannot be ruled out. Yet another possibility is that the degree of leg elevation is important and that the degree of PLR that was applied in our study was not enough. A more aggressive manoeuvre, generating a more marked increase in venous return, is still to be explored.

# PAPER IV

**Ambulance response time has been increasing since the early 1990s. What are the possible reasons for this?**

There are no available data on national ambulance density in Sweden. This is mainly due to the fact that ambulance services are a regional responsibility and all regions are self-governing. There is a report from 2008, indicating that the number of ambulances per one million inhabitants decreased by 19% in Stockholm and 27 % in Gothenburg from 1992 to 2005 [143].
Both the actual number of vehicles and the extent to which each vehicle is available for dispatch are likely to affect the response time.





The availability of an ambulance for an OHCA is not easily measured. In informal discussions with several EMS crews in Gothenburg, one recurring opinion is that the degree of vehicle occupancy has increased over the years. To the best of our knowledge, there is no complete compilation of national data in this area.

According to data from 14 of the 21 regions in Sweden [128], the number of available ambulance hours per 1,000 inhabitants did not increase substantially in any region during the time period 2014-2018 (Figure 14, Appendix C).

However, the number of priority-one dispatches per 1,000 inhabitants is available from a national database covering all regions [144]. There is a considerable increase in the number of priority-one dispatches per 1,000 inhabitants, as shown in Figure 13. If the number of ambulances has not increased, this indicates that ambulance availability for the OHCA patient has decreased.
Dispatches with a lower priority are likely to be of less importance for ambulance availability for the OHCA patient. In many cases, a priority-two or -three dispatch can be withdrawn, as long as there is no patient loaded in the vehicle, making already dispatched units available for a priority-one mission, like an OHCA.

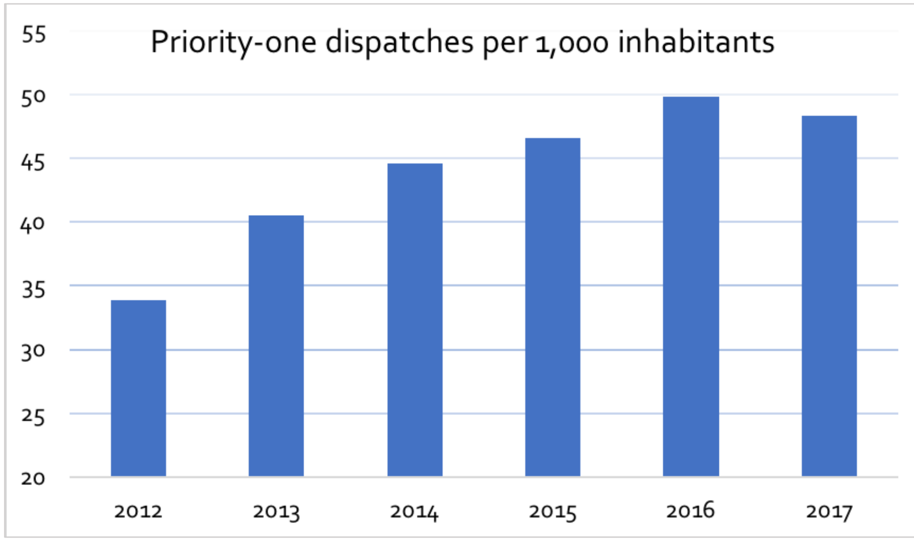


*Figure 13. The number of priority-one dispatches per 1,000 inhabitants from 2012 to 2017.*

One major issue that indisputably affects EMS response time is the overall traffic situation. The number of both cars and trucks increased substantially during the study period. There was an increase of more than half a million cars and 130,000 trucks registered in Sweden from 2008 to 2017. These data were provided by the contractor appointed by the government as being responsible for official statistics in the areas of transport and communications [145] (for complete data during the study period, see Figure 15-16 in Appendix C).
Another aspect is the extent to which other drivers tend to pull over for an ambulance to pass. Several crews report the impression that an increasing number of vehicles do not pull over when approached by an ambulance with lights and sirens going. If this is the case, it could be due to difficulties hearing the approaching emergency vehicle from a modern, more silent car. It could also be due to a general attitude towards emergency vehicles in society. These questions are still to be explored.

The development of prehospital care comprises both competence and equipment. The proportion of registered nurses working in the EMS organisations has increased over the years [128]. Together with technical developments, this permits advanced monitoring and treatment in the prehospital setting. The EMS is increasingly becoming an extension of the hospital's emergency department. It is possible that this development has increased the time spent on each dispatch. However, we have not found any data to support this speculation.

A number of pathways to promote rapid hospital admissions have evolved in recent decades. Obvious cardiac conditions, suspected stroke and suspected femoral fracture in older patients are some examples of conditions benefiting from pathways aiming to minimise delay and the time spent in the emergency department. It has been demonstrated that this incorporation of the EMS crew in hospital interventions affects EMS availability [146], since the pathway claims more time from the involved EMS crew.

Another possible contributory factor is that the general severity of the priority-one dispatches decreased during the study period 2008-2017. If this is the case, it is possible that the EMS crews adapt to the more frequent scenario where the priority-one dispatch is not as urgent as an OHCA. A report by Thang et al. found that patients transported by the EMS in Gothenburg, Sweden, were more likely to be hospitalised in 1986-1987 than in 2008 [147]. The same study revealed that the proportion of patients with chest pain using the EMS increased over a period of 20 years. This indicates that patients with symptoms like chest pain tend to use the EMS more frequently today than a few decades ago. In the 1980s, educational campaigns were run in the community and they





may have influenced both healthcare providers and citizens to call the EMS more frequently [148].
Some dispatch systems have developed a differentiation of priority-one dispatches, in an attempt to separate the immediate life-threatening events from the less urgent ones.

The number of ambulance stations and their location is another factor that is likely to affect the EMS response time. To the best of our knowledge, there are no reports highlighting the importance of the physical distance between the inhabitants of Sweden and the ambulance stations.

However, the increasing EMS response time is a problem that requires a solution rather than a more extensive analysis of its causes. Increased ambulance availability and strategically located ambulance stations are obvious and straightforward points of attack.

**What are the possible reasons for the strong association between EMS response time and survival after an OHCA?**

The potential gain from shortening EMS response time has been previously suggested by others [149-153], but there are conflicting results [154].

The most important survival factors in OHCA are immediate and effective CPR, uninterrupted, high-quality chest compressions and early defibrillation for shockable rhythms. All these can be promptly provided by an EMS crew arriving in close connection to the collapse. Effective compressions, airway management with ensured ventilation and immediate defibrillation are all provided by the EMS crew, as well as advanced post-resuscitation care if the patient regains circulation. The OHCA patient resuscitated and/or defibrillated by people other than EMS personnel always has an urgent need for the monitoring and support of vital functions to prevent further damage and an eventual re-arrest.

Bystander-initiated CPR is a well-known survival factor in OHCA. However, performing CPR is exhausting and replacing the rescuer is important to sustain CPR quality [155]. EMS crew arrival ensures sustainable high-quality CPR. Our results indicate that the effect of bystander-initiated CPR in OHCA with a probable cardiac cause is limited to cases where EMS arrival is less than 15 minutes. After this, the confidence intervals overlapped when comparing victims who did and did not receive CPR before EMS arrival (Figure 17, Appendix C). This highlights the association between EMS response time and survival chances.

**All ambulance drivers are not all equally fast. A driver spending more time reaching the patient, is probably likely to spend more time transporting the patient to the hospital. Does this matter?**

This is a classic confounding factor. The delay from loading the patient into the vehicle to arrival at the hospital is likely to be associated with the response time. The correlation between EMS response time and the return time to hospital has been demonstrated for trauma patients [156].
The lower chances of survival observed when response times are longer could be explained to some extent by an increased delay from collapse to hospital arrival, which introduces a systematic error.
However, there is not much evidence to support the idea that early hospital arrival has an important effect on survival chances. As previously discussed, in the chain of survival section, the importance of the early activation of the first three links in the chain of survival is well described.
To our knowledge, the importance of the time spent transporting the OHCA patient from the location of collapse to hospital has not been highlighted in the literature.

**The effect of EMS response time on survival is probably dependent on the receiving hospital to some extent. The large diversity of geographical and logistic prerequisites in Sweden could also be important. Do we need local or regional analyses of the effect of response times?**

A study of EMS response times during 11 major marathons in the US revealed that patients with OHCA and myocardial infarction had longer ambulance transport times and higher 30-day mortality compared with patients hospitalised on non-marathon dates. Only patients ≥65 years of age were included in this study, as they were unlikely to be marathon participants. No significant differences were found with respect to where the patients were hospitalised or the treatment they received in hospital [157]. It is possible that a very small receiving hospital with fewer resources could limit the positive effect of shorter EMS response times on survival. The smaller emergency department might not have decisive resources to add to a situation managed by a modern, resourceful EMS unit.
There is a long-term trend towards fewer emergency hospitals in Sweden. There were 115 Swedish emergency hospitals in 1970. In 1994, Sweden had 90 emergency hospitals and today (2020) there are 70 [127]. This dramatic reduction has most likely markedly increased the time from the scene to hospital arrival.





**What are the most important limitations when analysing observational data and the effect of ambulance response time on survival after OHCA?**

Not all priority-one dispatches are equally urgent. Many circumstances in a dispatch call are undetectable and cannot easily be measured, documented or analysed. A dispatch to an address close to a schoolyard perhaps adds pressure to the situation, the language and voice of the dispatcher and the number of dispatched units are all examples of available information, interpreted by the EMS crew. This informal and inevitable triage means that the ambulance crew responds more quickly in certain selected, more urgent, situations. These factors bias and dilute our estimate of the effect of response time on the outcome. When the EMS crews adapt their response time to adequately suit the situation, the effect of the response time on outcome will become more difficult to detect.
Wilde et al. addressed this problem using an instrumental variable [153]. The straight-line distance from the incident address to the nearest ambulance station was used instead of response time, as an independent variable. This distance correlates with response time but not with incident severity. Distance was positively and significantly correlated with mortality and the authors report a strong relationship between response time and mortality. However, this study included all categories of EMS calls and did not analyse OHCA patients separately.

In some cases, the emergency call and dispatch were due to chest pain, or other symptoms, and the cardiac arrest occurred later in the course but before EMS arrival. These events have a relatively long response time but advantageous conditions for resuscitation and could dilute the association between response time and outcome still further.

Furthermore, there are occasional areas in which EMS access to the patient is limited for security reasons. Situations such as demonstrations, riots or other potentially violent environments often require police assistance or escort. This introduces a delay from EMS dispatch to arrival in a few, albeit selected, cases.

It is not possible to quantify and measure all the aspects of an emergency call and a dispatch. This highlights the fact that knowledge based on conclusions from samples of patients can never be mechanically applied in a specific medical emergency.

**In Paper IV, regression modelling was used to describe the association between EMS response time and survival. Only four variables (age, gender, calendar year and place of OHCA) were used in addition to EMS response time to describe survival chances. Why?**

When interpreting these observational data, the handling of confounders is crucial. An overly complex regression model, adjusted for a large number of covariates in relation to the size of the data set, may tend to reflect random variations in our sample rather than a true association. This phenomenon, often referred to as overfitting, makes the selection of explanatory variables delicate. Many factors are associated with EMS response time, as well as the outcome. The established method is adjusted regression modelling, to quantify the association between the confounders and outcome. A valid model depends on the purposeful selection of explanatory variables. Several mechanical variable selection algorithms are in use [158]. A stepwise mathematical procedure then identifies the explanatory variables to include in the model, as in Paper III of this thesis. Before applying a mathematical method to variable selection, it is necessary to decide which factors are clinically relevant confounders. In OHCA research, this is challenging and seldom clear-cut. There are many variable interactions of different importance, as illustrated in Figure 5. Overlooking any biologically plausible variable in this process severely affects model validity.

**There did not appear to be an association between EMS response time and neurological outcome among survivors, but this was not further analysed. Why?**

Unfortunately, there is still a relatively large proportion of survivors for whom information on CPC score at hospital discharge is not available from medical records. Eighty-seven per cent of the survivors had a follow-up registration after discharge from hospital and 74% had a complete CPC score, based on a medical record review.

Although the CPC score is still a recommended method to assess cerebral function among survivors after OHCA [9], it can be criticised.
Neurological recovery may continue for a long period of time after an OHCA. In the SRCR, the CPC score is estimated at the time of discharge from hospital and by reviewing medical records. It is possible that an additional, later follow-up could be useful for a clinically more relevant assessment of neurological outcome.





**Do EMS crews always initiate resuscitation when they reach the OHCA patient?**

No. Under certain conditions, when there are clinical signs of death and resuscitation is assessed as futile, the crew makes the decision not to initiate CPR attempts. This introduces a selection bias where prolonged EMS response times might be associated with increased survival. This is one possible explanation of the slight increase in survival that we noted in EMS response times > 15 minutes among patients not receiving CPR before EMS arrival (Figure 10).

# METHODOLOGICAL CONSIDERATIONS FROM A REGISTRY PERSPECTIVE

**Is a registry for cardiopulmonary resuscitation the same as a cardiac arrest registry?**

This question may appear semantic, but it deserves to be addressed. The inclusion criterion for being reported to the SRCR is that CPR has been started. This is not the same as a circulatory arrest. According to guidelines, CPR should be commenced when there is no, or abnormal, breathing together with the absence of signs of life. The cause of a condition like this is not necessarily a circulatory arrest, even if it merits CPR. As a result, the population in the SRCR have received CPR, but, whether these patients have had a cardiac arrest or not is, strictly speaking, unknown. This might be important when considering the external validity of the conclusions drawn from the SRCR population. We often think of the typical OHCA patient as having a cardiac aetiology, predominantly a coronary cause, of the OHCA. The SRCR population is far more heterogeneous and our typical OHCA patient has to be regarded as a sub-group in this population.

**Is the quality of data in the SRCR good enough?**

All associations have three possible explanations: coincidence, systematic errors and a true association. P-values and confidence intervals tell us how likely it is that coincidence is affecting our results. Systematic errors are more difficult to identify and quantify. The careful and thorough work on the registration of OHCA incidents, done by the EMS crews, is the very foundation of data quality. This effort relies on confidence in a well-controlled registry contributing to improved OHCA care. Feeding back data compilations and knowledge to the healthcare workers who delivered the data is an important part of keeping a cardiac arrest registry.

The SRCR publishes an annual report [10] and a web application for comparisons and predictions based on collected data [159] is available to the public. Swedish EMS personnel are highly trained in CPR and their awareness of the importance of data quality in reporting to the SRCR is likely to be very high.

In spite of this, there are many difficulties involved in the documentation in a cardiac arrest situation and time perception in particular poses uncertainty. The work of developing and improving the SRCR is a constant struggle aiming to minimise systematic errors and loss. Uniform reporting is a crucial factor for data quality. It is important to identify and overcome possible inconsistencies, like the estimation of the exact time of EMS crew arrival discussed in the methods section (Paper IV).

One major strength in research based on data from the SRCR is the external validity. All EMS organisations in Sweden report to the registry and coverage is close to 100%. This guarantees a large sample size that effectively represents the population of all OHCA patients in Sweden where the EMS is alerted and resuscitation is attempted.

**Some OHCA patients are possibly not included in the SRCR, despite large efforts. Could this population differ from registered OHCA patients?**

We do not have the answer to this question. It is possible that there are OHCA patients in whom CPR is not initiated and where the dispatch centre is not alerted. People living alone, suffering an unwitnessed OHCA, will not be part of the SRCR.

Further, Sweden has an unknown number of undocumented immigrants. In this group, it has been shown that only one third of all deaths take place within a hospital environment [160]. This could indicate that alerting the EMS system in a life-threatening situation is less usual among undocumented immigrants living in Sweden, compared with the overall Swedish population.

It is reasonable to assume that both people living alone and undocumented immigrants differ from the rest of the SRCR population in several respects.

Strömsöe et al. examined OHCA cases from the period 2008-2010, reported to the SRCR [161]. This investigation covered one third of Sweden and found





that 25% of OHCA patients were not reported prospectively by the EMS crews but were identified and registered retrospectively. Since then, basically all cases that are not prospectively reported to the registry by the EMS crew are reported later and retrospectively by a local regional co-ordinator.
The same study demonstrated that the retrospectively registered patients were older, had a lower rate of bystander-initiated CPR and a higher survival rate compared with the prospectively reported cases.

**Comparisons in registry-based data often show relatively low p-values. What does this mean?**

Statistical significance in large cohorts is important in the interpretation of the data analysis. In large samples, even small differences can have statistical significance, when applying established criteria like a p-value of $< 0.05$. For example, the difference in age between our groups based on the number of defibrillations (Paper I, Table 1) is considered to be statistically significant, with $p < 0.001$, even though the median age in each of the three groups was 70, 70 and 69 years. Despite the statistical significance, there is no clinical relevance. This shows that the potentially large samples from a registry have to be handled and analysed from a clinical perspective.

**Is there room for randomised clinical trials in future cardiac arrest research?**

Clinical trials are an important source of knowledge in cardiac arrest care [77, 110]. The requirement for informed consent is a cornerstone of research ethics, as is clearly stated in the Swedish Ethical Review Act. The Swedish Ethical Review Act does not leave any room for research including physical interventions in unconscious patients. This is a main issue to address in cardiac arrest trials. A person eligible for a research trial is unable to give consent and consent obtained from a legal surrogate risks delaying interventions.
The importance of clinical trials and the inevitable need for the possibility of exceptions to informed consent in OHCA research has been frequently highlighted in the literature [162-165].

In the observational third paper in this thesis, we found no evidence that PLR improved survival chances in OHCA, when performed within five minutes of EMS arrival. However, it is possible that PLR performed earlier after collapse could be beneficial. Dispatch-assisted PLR in OHCA patients receiving bystander-initiated CPR is one possible way of further exploring this matter. It is unlikely that a randomised clinical trial, comparing dispatch-assisted PLR with conventional bystander-initiated CPR, would be harmful to the patient.

Formulating the practical circumstances in a trial of this kind to make it ethically acceptable might be challenging, but it appears to be feasible.

When an intervention has the potential to be directly beneficial to the research participant and when it is impossible to conduct with informed consent, an exception to the Swedish Ethical Review Act is required. A similar procedure is already applied elsewhere [166].
Designing a national procedure to permit exceptions from informed consent is vital in order to conduct future trials in medical emergencies, like OHCA.





# CONCLUSION

We have explored important survival factors in OHCA in four different studies. First, we demonstrated that the chances of survival after an OHCA decreased for each defibrillatory shock that was administered. In addition, EMS response time was identified as being associated with survival to 30 days, together with ten other factors. An intensified discussion about when to initiate transportation in the OHCA patient with a refractory, or recurrent, shockable rhythm is crucial.

Secondly, we found that a pathway for immediate coronary angiography after OHCA had limited feasibility and that the selection process was extremely demanding for the EMS organisation. The chances of survival were about three times as high in this selected group of patients as in the overall OHCA population in Sweden.

The third survey explored prehospital PLR in OHCA patients. We found no indications that the PLR manoeuvre during CPR was beneficial when performed by the EMS crew within five minutes of arrival on the scene.

Finally, we demonstrated that the chances of survival, after a witnessed OHCA, decrease as ambulance response times increase. This was seen independently of initial rhythm and whether or not CPR was performed before EMS arrival.

Possible actions to reduce EMS response times need to be considered urgently, as this could be lifesaving for future OHCA patients.

# FUTURE PERSPECTIVES

The first moments in a resuscitation attempt in OHCA are based on general guidelines. For the last few decades, these guidelines have been presented in the form of algorithms or flow charts. These are national and have recently been extended to cover OHCA with a shockable rhythm resistant to three or four defibrillatory attempts [130]. These new guidelines are supported by the results of our first study, where we demonstrated that the chances of survival decreased for each shock that was added and the decrease was more marked for the first three defibrillations. Almost half the patients found in a shockable rhythm had more than three shocks and as many as 7.5% required more than 10 shocks, emphasising the clinical importance of management in OHCA patients with a recurrent or a shock-resistant shockable rhythm.

Furthermore, the chances of survival for OHCA patients with an initial shockable rhythm, reported to the SRCR, have increased dramatically over the years and, in 2018, 34% survived to 30 days [10]. Among survivors to 30 days after an OHCA in Sweden, 80% presented with an initial shockable rhythm in 1992-2007 [50]. There are indications that neurological recovery is superior among OHCA survivors presenting with, or turning to, a shockable rhythm compared with those with a non-shockable rhythm [50, 167]. This highlights the importance of continuous future monitoring of the number of defibrillations and their relationship to EMS response time and outcome. We are managing OHCA patients in an era in which the potential of PCI and different types of mechanical circulatory support is rapidly evolving [131, 168]. More invasive procedures, with a long and demanding rehabilitation process, require thoughtful decision-making based on knowledge of the possible risks. Pivotal circumstances during the course of resuscitation and their association with the outcome need to be monitored and described to help guide clinicians in making the right decision for each individual patient suffering an OHCA. The possible association between the number of defibrillations and neurological function on follow-up is still to be explored.

The differentiation of shock-resistant defibrillatory rhythms and re-fibrillation or recurrent episodes of a shockable rhythm is equally interesting. This differentiation is poorly explored and is possibly important for resuscitation interventions, as it might reflect a biological difference in the underlying cause.

The importance of whether CPR is actually on-going during the loading and transportation of the OHCA patient is another crucial circumstance that needs to be explored. We can assume that this affects no-flow/low-flow time and





outcome and further knowledge could be useful in the EMS crew's delicate decision-making relating to when and how to load and transport the OHCA patient and to which destination.

The criteria for selecting OHCA patients for immediate coronary angiography are often discussed, based on ECG characteristics. The current opinion is that patients resuscitated after an OHCA and presenting with a STEMI benefit from emergency coronary angiography. In a large randomised trial, immediate coronary angiography in OHCA patients with an initial shockable rhythm and no ST elevation did not appear to be beneficial compared with angiography within two hours [103].

For OHCA patients presenting with a non-shockable rhythm and with ROSC on hospital arrival, the need for immediate coronary angiography needs to be further explored. In spite of the importance of an initial shockable rhythm, is has been estimated that one in five survivors of an OHCA presents with a non-shockable rhythm [50]. The more exact urgency of the angiography procedure in this group is still unclear and needs to be illuminated.

It is possible that the initial rhythm and prodromal symptoms, combined with patient and resuscitation characteristics, could provide an adequate basis for the decision to perform immediate, EMS-initiated coronary angiography after OHCA, independent of further ECG characteristics. In our second study, we demonstrated that an immediate coronary angiography can be initiated in the prehospital setting and performed within the hour. However, identifying the OHCA patients who would benefit from this kind of a prehospitally initiated pathway is important for resource allocations both prehospitally and in hospital. Follow-up including short- and long-term neurological function, as well as long-term survival, is of great importance in the evaluation of the benefits of future immediate coronary angiography.

Our study of PLR in OHCA and CPR has severe limitations, as already discussed. However, we explored the most practical and feasible form of EMS-initiated PLR. The use of special equipment, for more extreme and standardised PLR, could not easily be explored without affecting other important interventions in CPR. Carrying additional equipment affects the time the crew spends from parking the vehicle to reaching the OHCA patient.

The potential of the earlier performance of EMS-initiated PLR encounters the same obstacle: it could affect other resuscitation factors known to be important for outcome. We assume that, if there were a way to perform EMS-initiated PLR that is beneficial to the OHCA patient, we would have detected an association between PLR, as it was performed in our study, and outcome. Earlier, bystander-initiated PLR in OHCA could still be beneficial and appears to be suitable to evaluate in a randomised trial.

Another potentially interesting approach is the combination of leg elevation and an active decompression phase during CPR. Combining negative pressure in the right atrium, achieved by active decompression in mechanical chest compressions from the LUCAS device, with the increased venous return from PLR could potentially increase cardiac output. Even though our third study included patients receiving both PLR and mechanical chest compressions, we were unable to draw any conclusions relating to the potential benefit of combining these two interventions.

As short-term survival after OHCA improves, the need for further knowledge of the long-term neurological outcome and quality of life after an OHCA crystallises. Patient-reported outcomes and health-related quality of life are now included as supplementary outcomes in the updated Utstein template [9]. Exploring the association between crucial short-term survival factors in OHCA and long-term outcome, or even the time from collapse to death, could add important knowledge to OHCA care.

Establishing causality in observational research is not easy. In spite of this, a great deal is known about what affects survival chances in OHCA and it is reasonable to assume that the EMS response time is important. The key to reducing the EMS response time is improved ambulance availability. This discussion is often brought back to the dispatch centre and different methods for optimising case selection. However, finding criteria and methods to increase specificity in priority-one dispatches has been discussed for a long time and is obviously not easy to achieve. We must not let this discussion stand in the way of other means of improving ambulance availability, such as more numerous vehicles, a continuous discussion about where to place ambulance stations and proximity to citizens.





# A CLINICIAN-RESEARCHER’S THOUGHTS

The number of measurable variables, as well as the solutions for exact measurements and data collection, are making continuous, fantastic progress. Despite this, saving a life goes beyond measured variables and randomised trials, in the sense that population-level knowledge needs to be made useful in the care of each individual OHCA patient.

Resuscitation and saving lives are a chain of interdependent, time-dependent actions. All cardiac arrest situations are different and unique. Knowledge is based on data from large samples and their analysis, but it has to be considered in this context. Even if associations, and even causations, are based on a large number of previous cardiac arrest incidents, their validity in each specific situation can never be taken for granted. This is due to the immense interactions between resuscitation factors and their relationship to time. Very few of the known survival factors are independent of time and these interactions.

The validity of a specific factor in resuscitation therefore has to be considered in each individual cardiac arrest situation. This process relies on healthcare workers continuously considering the value of each resuscitation effort.

Algorithms based on large trials or amounts of historical data provide invaluable guidance to those trying to save lives using CPR and resuscitation. The automation of recommended actions in OHCA might be useful for the very first instances of CPR and resuscitation, but this must not prevent parallel attempts to identify the underlying cause and initiate situational interventions.

Future development in data collection and analysis is likely to be fast and revolutionary. Machine learning and artificial intelligence have the potential to increase our knowledge of OHCA patients and their resuscitation. It is crucial that this development incorporates the perspective that each OHCA situation and patient is unique. Very few actions in OHCA resuscitation can be listed under “always” or “never” and making priorities is a part of CPR and resuscitation. Decision-making in the OHCA situation is not improved by being reduced to mathematics, while research and data collection from cardiac arrest incidents have an important role to play in supporting emergency medical professionals in saving cardiac arrest victims. Knowledge that can be applied through responsible judgement by medical professionals is the heart of cardiac arrest research.

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# APPENDICES

## APPENDIX A

| Beskrivning | värde | Kommentar |
|---|---|---|
| Primary key | Index | |
| Rapporteringsdatum | åååå-mm-dd | |
| Region kod | | |
| Regionsnamn | | |
| Distrikt | PK i tabell tbDistrikt (dID) | |
| Station | PK i tabell tbStation (sID) | |
| Personnummer | ååååmmdd-nnnn | |
| Pnr kvalitet | 1 = Fullständigt<br>2 = Utländskt<br>3 = Ofullständigt | |
| Om ofullständigt, uppskattad ålder | | |
| Uträknad ålder | | |
| Kön | 1 = Man<br>2 = Kvinna | |
| Uppdragsnummer | | |
| Larmdatum | åååå-mm-dd | |
| Plats för hjärtstopp | 1 = Hemmet<br>2 = Allmän plats<br>3 = Annan plats | |
| Allmän plats | 1 = Affärscenter<br>2 = Arbetsplats<br>3 = Badplats<br>4 = Flygplats<br>5 = Gata/torg<br>6 = Park/terräng<br>7 = Kyrka<br>8 = Nöjesplats<br>9 = Sportanläggning<br>10 = Tågstation<br>11 = Vattendrag<br>12 = Övrigt | |
| Annan plats | 1 = Ambulans | |



| | | |
|---|---|---|
| | 2 = Hotellrum<br>3 = Privat kontor<br>4 = Vårdhem<br>5 = Övrigt<br>6 = Vårdcentral<br>7 = Tandvård<br>8 = Sjukhus utan eget/n akutteam/larmorganisation | |
| Inträffade hjärtstoppet i samband med idrottsutövning | 0 = Nej<br>1 = Ja, på motionsnivå<br>2 = Ja, på elitnivå<br>9 = Vet ej | Finns från 2016 |
| Bevittnat hjärtstopp | 0 = Nej<br>1 = Ja | |
| Om Ja, vem bevittnade | 1 = Bystander<br>2 = Ambulans<br>3 = Räddningstjänst<br>4 = Polis<br>5 = Samtidigt ambulans och räddningstjänst<br>6 = Samtidigt ambulans och polis<br>7 = Samtidigt räddningstjänst och polis | Version 2 (inmatat efter 2014) |
| Vem var först på plats vid patientens sida | 2 = Ambulans<br>3 = Räddningstjänst<br>4 = Polis<br>5 = Samtidigt ambulans och räddningstjänst<br>6 = Samtidigt ambulans och polis<br>7 = Samtidigt räddningstjänst och polis | Version 2 (inmatat efter 2014) |
| Gavs behandling av bystander före ankomst av utlarmad enhet | 0 = Nej<br>1 = Ja | Version 2 (inmatat efter 2014) |
| Bystander-HLR | 0 = Nej<br>1 = Ja, enbart bröstkompressioner<br>2 = Ja, enbart ventilation<br>3 = Ja, bröstkompressioner och ventilation<br>9 = Vet ej | Version 2 (inmatat efter 2014) |
| Om Ja, vilken var den högsta utbildningsnivån på den/de som utförde HLR | 1 = Lekman (ej HLR-utbildad)<br>2 = Lekman (HLR-utbildad)<br>3 = Medicinskt utbildad (ej i tjänst)<br>9 = Vet ej | Version 2 (inmatat efter 2014) |

| | | |
|---|---|---|
| Om Ja, utfördes Telefon-HLR enligt instruktion från larmcentralen | 0 = Nej<br>1 = Ja | Version 2 (inmatat efter 2014) |
| Anslöts publik hjärtstartare till patienten | 0 = Nej<br>1 = Ja | Version 2 (inmatat efter 2014) |
| Om Ja, utfördes defibrillering | 0 = Nej<br>1 = Ja | Version 2 (inmatat efter 2014) |
| Gavs behandling av räddningstjänst/polis före ambulans ankomst | 0 = Nej<br>1 = Ja | Version 2 (inmatat efter 2014) |
| Om Ja, utfördes HLR | 0 = Nej<br>1 = Ja, enbart bröstkompressioner<br>2 = Ja, enbart ventilation<br>3 = Ja, bröstkompressioner och ventilation<br>9 = Vet ej | Version 2 (inmatat efter 2014) |
| Om Ja, vem utförde HLR | 1 = Räddningstjänst<br>2 = Polis<br>3 = Räddningstjänst och polis | Version 2 (inmatat efter 2014) |
| Anslöts hjärtstartare till patienten av räddningstjänst/polis | 0 = Nej<br>1 = Ja | Version 2 (inmatat efter 2014) |
| Utfördes defibrillering av räddningstjänst/polis | 0 = Nej<br>1 = Ja | Version 2 (inmatat efter 2014) |
| Bevittnat av | 1 = Bystander<br>2 = Ambulanspersonal | Version 1 (inmatat före 2015) |
| HLR före ambulansens ankomst | 0 = Nej<br>1 = Ja | Version 1 (inmatat före 2015) |
| HLR av vem | 1 = Lekman | Version 1 (inmatat före 2015) |
| HLR av vem | 1 = Ambulanspersonal | Version 1 (inmatat före 2015) |
| HLR av vem | 1 = Polisen | Version 1 (inmatat före 2015) |
| HLR av vem | 1 = Sjukvårdspersonal | Version 1 (inmatat före 2015) |



| | | |
|---|---|---|
| HLR av vem | 1 = Annan | Version 1 (inmatat före 2015) |
| HLR av vem | 1 = Räddningstjänst | Version 1 (inmatat före 2015) |
| Telefon-HLR | 0 = Nej<br>1 = Ja | Version 1 (inmatat före 2015) |
| Hjärtkompression | 0 = Nej<br>1 = Ja | Version 1 (inmatat före 2015) |
| Ventilation | 0 = Nej<br>1 = Ja | Version 1 (inmatat före 2015) |
| Defibrillering | 0 = Nej<br>1 = Ja | Version 1 (inmatat före 2015) |
| Antal defibrilleringar | | Version 1 (inmatat före 2015) |
| Vid medvetande | 0 = Nej<br>1 = Ja | |
| Andning | 1 = Normal<br>2 = Agonal<br>3 = Ingen | |
| Puls | 0 = Nej<br>1 = Ja | |
| Om halvautomatisk defibrillator | 0 = Defibrillera ej<br>1 = Defibrillera | |
| Om information finns om rytm | 1 = VF<br>2 = VT<br>3 = PEA<br>4 = Asystoli | |
| Initial arytmi | 1 = VF/VT<br>2 = PEA<br>3 = Asystoli | |
| Troligaste anledningen till hjärtstopp | 1 = Hjärtsjukdom<br>2 = Överdos läkemedel<br>3 = Olycksfall<br>4 = Lungsjukdom<br>5 = Kvävning<br>6 = Självmord<br>7 = Drunkning<br>8 = Plötslig spädbarnsdöd<br>9 = Annat | |

| | | |
|---|---|---|
| Hjärtstopp | tt:mm | |
| Larm registrerat | tt:mm | |
| Utlarmning | tt:mm | |
| Start av HLR | tt:mm | |
| Amb. ankomst (bil stoppar klocka) | tt:mm | |
| Amb. ankomst (vid patientens sida) | tt:mm | |
| Första EKG/rytm | tt:mm | I version 2 står tiden för ROSC istället för EKG |
| Första defibrillering | tt:mm | |
| Hjärtkompression | 0 = Nej<br>1 = Ja | |
| Mekanisk hjärtkompression | 0 = Nej<br>1 = Ja | |
| Ventilation | 0 = Nej<br>1 = Ja | |
| Intubation | 0 = Nej<br>1 = Ja | |
| Larynxmask | 0 = Nej<br>1 = Ja | |
| Defibrillering | 0 = Nej<br>1 = Ja | |
| Antal defibrilleringar | | |
| Intraosseös infart | 0 = Nej<br>1 = Ja | |
| Adrenalin | 0 = Nej<br>1 = Ja | |
| Cordaron | 0 = Nej<br>1 = Ja | |
| Atropin | 0 = Nej<br>1 = Ja | Togs bort i slutet av 2014. Stockholm har en del inmatat under 2016. |
| Hypotermi | 0 = Nej<br>1 = Ja | |
| Återfått pulsgivande rytm någon gång | 0 = Nej<br>1 = Ja | |
| Körd till sjukhus/annan vårdenhet | 0 = Nej<br>1 = Ja | |
| Sjukhus | PK i tabell tbSjukhus (sID) | |



| | | |
|---|---|---|
| Pulsgivande rytm vid ankomst till sjukhus/annan vårdenhet | 0 = Nej<br>1 = Ja | |
| Vid medvetande vid ankomst till sjukhus/annan vårdenhet | 0 = Nej<br>1 = Ja | |
| Behandling avslutad före ankomst till sjukhus/annan vårdenhet | 0 = Nej<br>1 = Ja | |

# APPENDIX B

| | värde | Rubrik |
|---|---|---|
| Inlagd på avdelning | 0 = Nej<br>1 = Ja<br>9 = Vet ej | |
| Utskriven levande från sjukhus | 0 = Nej<br>1 = Ja<br>9 = Vet ej | |
| Om Ja, utskriven till | 1 = Hemmet<br>2 = Annat sjukhus<br>3 = Annan vårdform<br>9 = Vet ej | |
| ICD | 0 = Nej<br>1 = Ja<br>2 = Planerad<br>9 = Vet ej | |
| PCI | 0 = Nej<br>1 = Ja<br>2 = Planerad<br>9 = Vet ej | |
| CABG | 0 = Nej<br>1 = Ja<br>2 = Planerad<br>9 = Vet ej | |
| Hypotermi | 0 = Nej<br>1 = Ja<br>9 = Vet ej | |
| Betablockad | 0 = Nej<br>1 = Ja<br>9 = Vet ej | |
| Om ja, utskrivningsdatum | | |
| Vet ej utskrivningsdatum | 1 | |
| Om ja, CPC-score vid utskrivningen | 1-5 | |
| Död inom 30 dagar efter hjärtstopp | 0 = Nej<br>1 = Ja<br>9 = Vet ej | |
| Dödsdatum | | |



| | | |
|---|---|---|
| Vet ej dödsdatum | 1 | |
| Rapport klar | 1 = Ja | |
| Versionsnummer | 1 = Inmatat före 2015-01-01<br>2 = Inmatat efter 2014-12-31 | |

# APPENDIX C

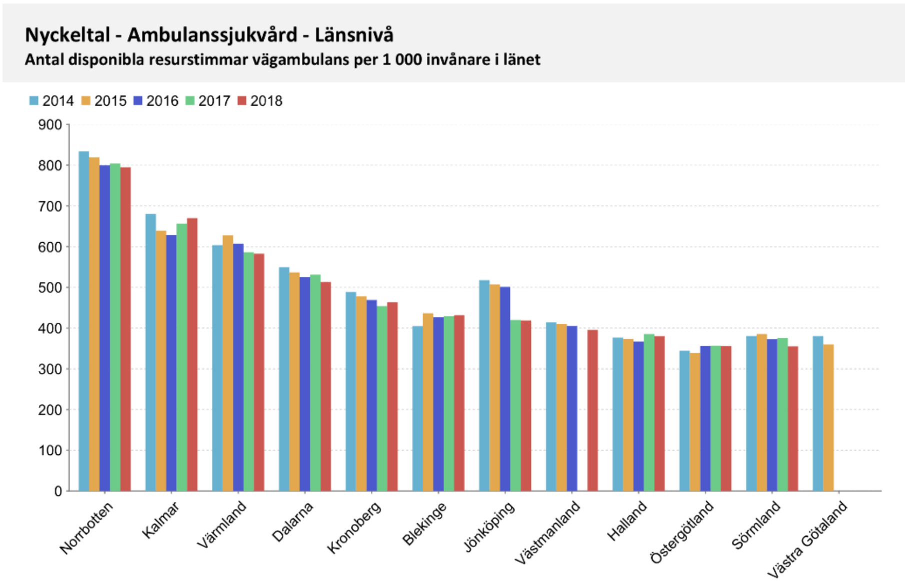


*Figure 14. The hours of ambulance availability per 1,000 inhabitants for 14 of the 21 regions in Sweden [128].*



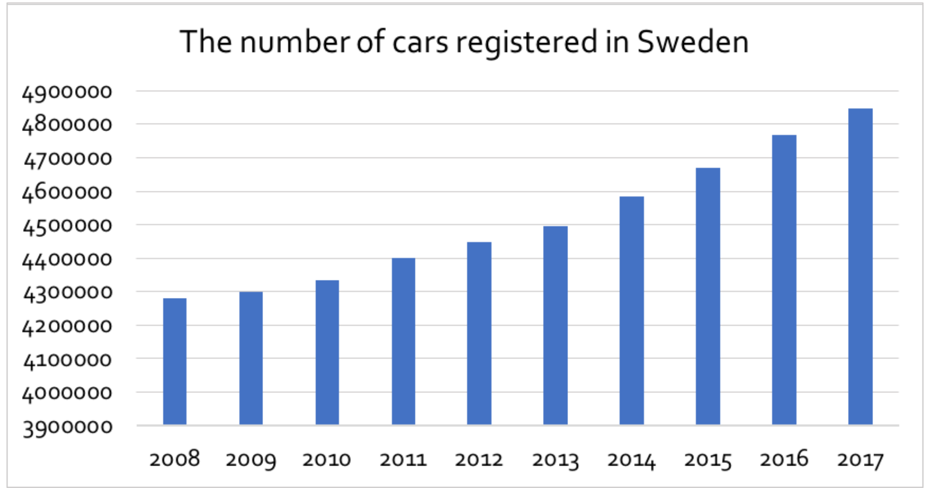


*Figure 15. The number of cars registered in Sweden during the study period for paper IV [145].*

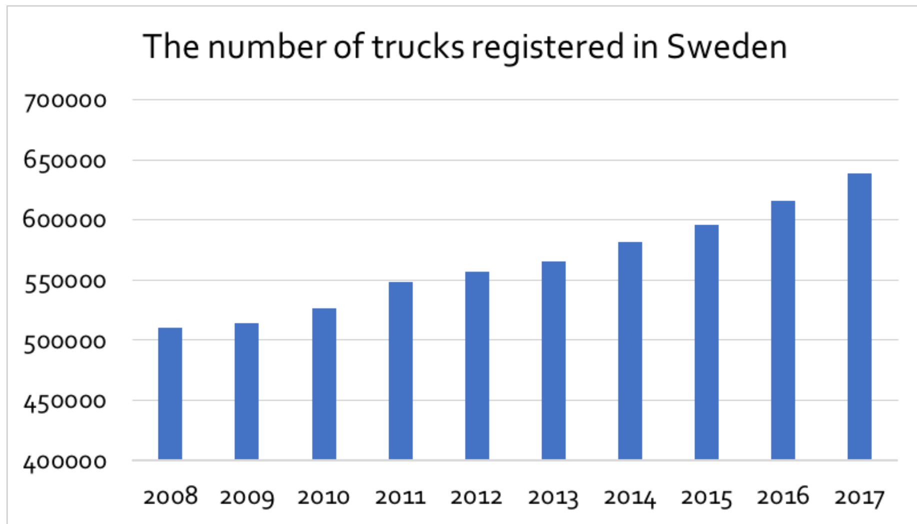


*Figure 16. The number of trucks registered in Sweden during the study period for paper IV [145].*

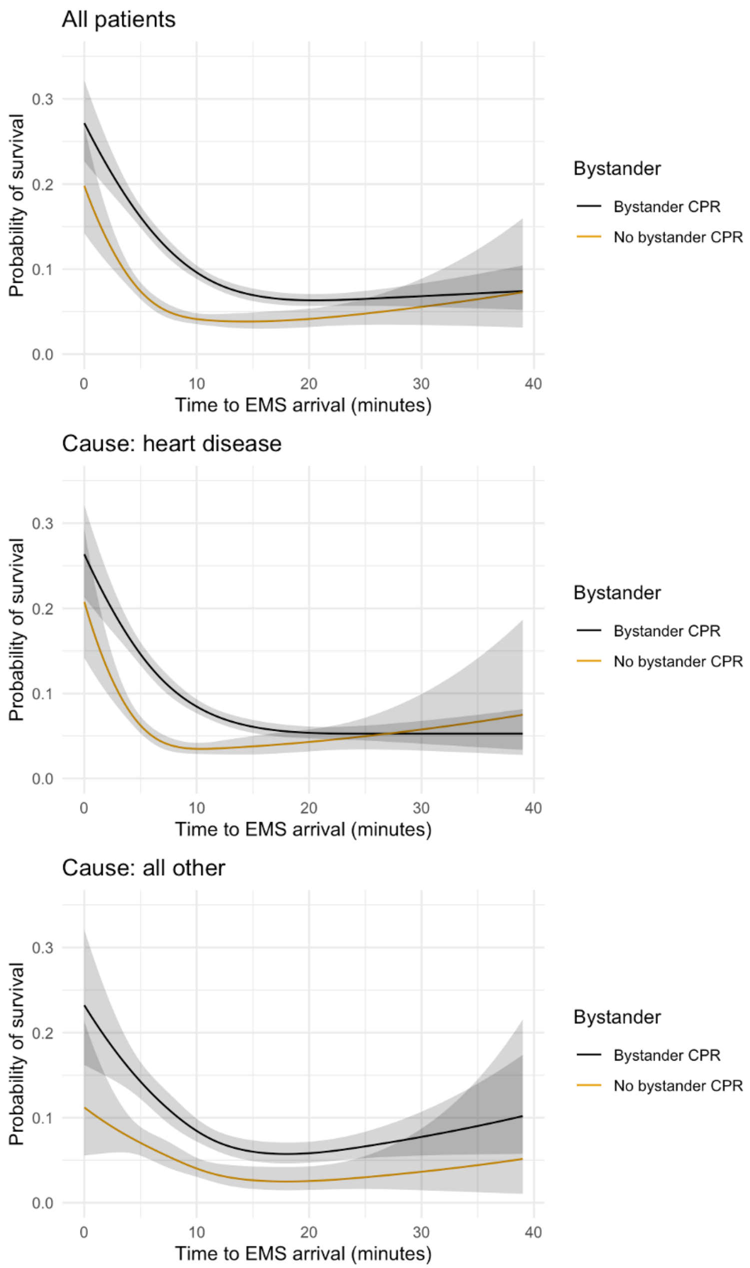


*Figure 17. Adjusted survival to 30 days in relation to EMS response time for patients receiving CPR before EMS arrival and those that did not. Presented for all patients (top), those assessed by the EMS crew as having a cardiac cause (middle) and a non-cardiac cause (bottom) respectively.*